Newer Synthetic Methodologies in Carbohydrate Chemistry and Facile Access to N-Heterocycles Using Multicomponent Reactions

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DOCTOR OF PHILOSOPHY

by

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Dedicated to

My Parents

INDIAN INSTITUTE OF TECHNOLOGY, GUWAHATI

Department of Chemistry

STATEMENT

I do hereby declare that the matter embodied in this thesis entitled *"Newer Synthetic Methodologies in Carbohydrate Chemistry and Facile Access to N-Heterocycles Using Multicomponent Reactions"* is the result of investigations carried out by me under the supervison of Prof. A. T. Khan in the Department of Chemistry, Indian Institute of Technology Guwahati, India.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

IIT Guwahati
March 10, 2011.

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CERTIFICATE

This is to certify that Mr. Md. Musawwer Khan has been working in my research group since 2nd January, 2007 as a regular registered Ph. D. student. I am forwarding his thesis entitled "*Newer Synthetic Methodologies in Carbohydrate Chemistry and Facile Access to N-Heterocycles Using Multicomponent Reactions*" being submitted for the Ph. D. (Science) Degree of this Institute. I certify that he has fulfilled all the requirements according to the rules of this Institute regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

IIT Guwahati
March 10, 2011

Prof. A. T. Khan
(Thesis Supervisor)

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Md. Musawwer Khan

SUMMARY

This dissertation describes the successful efforts on the development of new methodologies in carbohydrate chemistry and synthesis of N-heterocyclic compounds using multicomponent reactions.

The thesis has been divided mainly into two parts namely Part A and Part B. Each part has been further subdivided into three chapters, Chapter 1, 2 and 3 respectively based on the experimental results performed during the complete course of the research work.

Part A

Chapter 1 describes the importance of dialkyldithioacetal and *O*-isopropylidene derivatives of sugar. A brief literature survey for the preparation of dialkyldithioacetal and *O*-isopropylidene derivatives of sugar and their synthetic application are highlighted in this Chapter precisely.

In **Chapter 2**, we have developed an efficient and solvent-free method for preparation of various diethyl dithioacetals of sugar in excellent yields by the treatment of various monosaccharides with ethanethiol in the presence of 3 mol% of bromodimethylsulfonium bromide (BDMS) at 0-5 ^{o}C. Similarly, dipropyl dithioacetal derivatives can also be obtained in very good yields using propanethiol under identical reaction conditions. These dithioacetal derivatives were characterized by per-*O*-acetylation using silica supported perchloric acid. This method is a useful alternative for the large scale preparation of dithioacetal derivatives of sugar in a greener manner.

Chapter 3 illustrates two new methodologies for synthesis of *O*-isopropylidene derivatives of sugar using bromodimethylsulfonium bromide (BDMS) and tetrabutylammonium tribromide (TBATB). **Chapter 3.1** demonstrates a simple and efficient method for the preparation of *O*-isopropylidene derivatives from free sugars as well as from other sugar derivatives by employing BDMS as a catalyst. The salient features of this protocol include operational simplicity and high yields of the products. The products can be obtained by direct recrystallization in case of solid products without going through tedious chromatographic separation as well as by non-aqueous work-up. **Chapter 3.2** describes another new synthetic methodology using tetrabutylammonium tribromide (TBATB) for the preparation of *O*-isopropylidene derivatives from free sugars as well as from acyclic sugar derivatives. The notable advantages of the present

protocol are: good yields, stable and easy to handle catalyst as well as lower amount of catalyst loading. Due to its operational simplicity, generality and efficacy, this method is expected to have wider applicability for the preparation of various *O*-isopropylidene derivatives of sugar.

Part B

Chapter 1 highlights a brief literature survey on the multicomponent reactions and its importance in organic synthesis. In addition, a brief literature survey on the methods preparation for tetra- and dihydropyridine derivatives and its importance as well as synthetic utility are presented in this chapter precisely.

In **Chapter 2** of **Part B** describes the synthesis and mechanistic aspects of highly functionalized tetrahydropyridine derivatives. A mild, efficient and one-pot five-component reaction between aldehydes, amines and 1,3-dicarbonyl compounds is developed for synthesis of highly as well as fully functionalized tetrahydropyridines in presence of iodine at room temperature or at 55 °C . The salient features of this protocol are good yields, mild reaction conditions, environmentally benign, superior atom economy, the readily accessibility of the catalyst and its cost effectiveness. In addition, we propose the possibility for the formation of tetrahydropyridine *via* double Mannich-type intermediates and mechanism is under investigation. The resultant heterocyclic systems have both secondary amine and enamino esters, which enable further modifications leading to molecular diversity.

Chapter 3 describes an interesting multicomponent reaction for the synthesis of dihydropyridines and application in imino-Diels-Alder Reaction. In this Chapter, the trifluoroacetic acid (TFA) catalyzed synthesis of unsymmetrical tetrasubstituted 1,4- and 1,6-dihyropyridines (DHPs) using one-pot three-component reactions of dimethyl acetylenedicarboxylate (DMAD), aliphatic amines and α,β-unsaturated aldehydes have been accomplished. The regioselective synthesis of tetrasubstituted 1,4-DHPs were also achieved in good yields using TfOH. These 1,4-DHPs can be used for new class of dienophiles for imino-Diels-Alder reaction for the construction of highly substituted naphthyridine derivatives. The significant advantages of present protocol are simple experimental procedure, non toxic byproduct, high atom economy, good regioselectivity and diastereoselectivity. The new heterocyclic entities containing β-amino acid skeleton might exhibit interesting pharmacological activities.

In conclusion, the thesis describes some new and effective synthetic methodologies for the preparation of dialkyl dithioacetal and *O*-isopropylidene of sugars as well as for synthesis of highly functionalized tetra- and dihydropyridines. Due to the advantages of these methodologies over existing methods, it is expected that these methodologies will be applicable in target-oriented synthesis as well as valuable additions in the arsenal of synthetic organic chemistry literature.

CONTENTS

GENERAL REMARKS

The present investigations were carried out in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati -781 039, Assam, from January 2, 2007 to March 10, 2011 as a Ph.D. student under the supervision of Prof. Abu T. Khan.

The analytical samples were routinely dried *in vacuo* at 50 ^{o}C for 8 hours. In TLC experiments, silica gel G (SRL) or silica gel GF 254 (SRL) were employed as adsorbent or precoated TLC plates (0.2 mm layer thickness of silica gel 60 F-254) were used. The spots were detected by staining with iodine vapors or under UV light or charring with 10% conc. H_2SO_4 in MeOH or MOSTAIN solution (by dissolving 20 g ammonium heptamolybdate and 0.4 g cerium(IV) sulphate in 400 mL 10% H_2SO_4 solution). Column chromatography was carried out with silica gel (60-120 mesh, Merck, SRL or Qualigen), for purifications of reaction mixture. After purification, the solvent was usually removed in rotavapor using Buechi R-114V instrument. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 243 polarimeter at 25 ºC temperature. IR spectra were recorded on Perkin-Elmer 281 IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian 400 spectrometer TMS as internal reference; chemical shifts (δ scale) are reported in parts per million (ppm). ^{1}H NMR Spectra are reported in the order: multiplicity, no of protons and coupling constant (*J* value) in hertz (Hz); signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), brs (broad singlet), dq (doublet of quartet) and ddt (doublet of doublet of triplet). HRMS spectra were recorded using WATERS MS system, Q-TOF premier and data analyzed using Mass Lynx 4.1. Elemental analyses were carried out using Perkin-Elmer 2400 Series II CHNS/O analyzer at the Department of Chemistry, Indian Institute of Technology, Guwahati. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated MoKα radiation (λ = 0.71073 Å) at 298 K.

ABBREVIATIONS

Ac	acetyl
BDMS	bromodimethylsulfonium bromide
Bn	benzyl
Boc	*t*-butoxycarbonyl
Bu	butyl
Bz	benzoyl
CAN	cerium(IV)ammonium nitrate
Cbz	benzyloxycarbonyl
CCDC	cambridge crystallographic data centre
COSY	correlation spectroscopy
DCE	1,1-dichloroethane
DCM	dichloromethane
DIBAL-H	diisobutylaluminium hydride
DMAD	dimethyl acetylene dicarboxylate
DMAP	*N*,*N*-4-dimethylaminopyridine
DMF	*N*, *N*-dimethylformamide
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
Fmoc	9-fluorenylmethoxycarbonyl
IR	infrared
MCR	multicomponent reaction
Mp	melting point
MS	molecular sieves
MW	microwave
NMR	nuclear magnetic resonance
NOESY	nuclear overhauser enhancement spectroscopy
ORTEP	oak ridge thermal ellipsoid program
PCC	pyridinium chlorochromate
Ph	phenyl
PMB	*p*-methoxy benzyl

ppm	parts per million
Pr	propyl
PTSA	*p*-toluenesulfonic acid
RCM	ring-closing metathesis
rt	room temperature
TBATB	tetrabutylammonium tribromide
TBS	*t*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	*p*-tolyl
Ts	*p*-toluenesulfonyl

PART A

CHAPTER 1

Brief review on dialkyl dithioacetals and *O*-isopropylidene derivatives of sugar

1.1 Introduction

Carbohydrates such as glucose, sucrose, cellulose, chitin and glycogen have long been known and well recognized as structural and energy storage molecules. Recent advances in chemistry and biology have led to identification of a group of complex oligosaccharides either as glycoconjugates namely glycoproteins, glycolipids or free oligosaccharides, which play an essential role in living system.[1] Synthesis of complex carbohydrates and their analogues have been regarded as one of the most challenging area in organic chemistry. During the synthesis of carbohydrates/non-carbohydrates either natural or non-natural molecules, an organic chemist encounters a range of essential regioselective protection and deprotection steps. Dithioacetalization and isopropylidenation of sugars are one of the very beginning steps in carbohydrate chemistry.

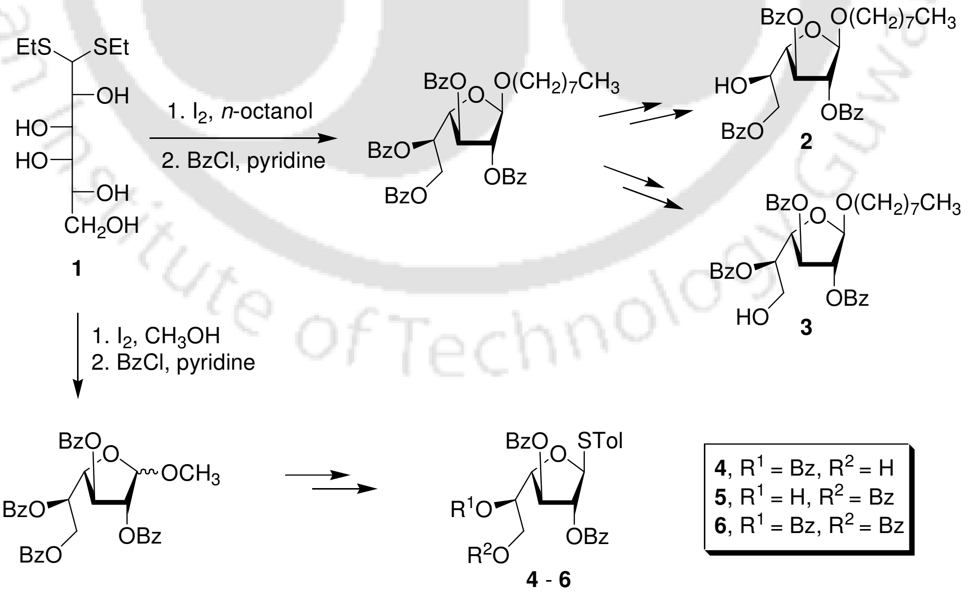
The dialkyl dithioacetals prepared from reducing sugars are well-known precursors for the synthesis of various natural and non-natural products.[2,3] For example, diethyl dithioacetals of D-arabinose and D-xylose have been used for the synthesis of constanolactones A, B[4] and (+)-phorboxazole A,[5] a potent cytostatic agent, respectively. They are extremely important intermediates in carbohydrate chemistry, especially for the preparation of aldehydic-sugar derivatives through protection of the chain hydroxyl groups followed by subsequent deprotection of the dithioacetal group using Hg(II) salts under neutral condition.[6] The acyclic aldehydic-sugar derivatives are widely used in the area of synthetic carbohydrate chemistry for the synthesis of *C*-disaccharides,[7] *C*-arylglycosides[8] and prodrugs.[9]

Similarly, the most common isopropylidenation is the protection of 1,2-diols as *O*-isopropylidene acetal group in carbohydrate chemistry.[10,11] Due to the unique behavior of aldohexose results in the formation of *O*-isopropylidene derivative of sugars with a selective unmasked hydroxyl group depending upon the nature of the sugars and reaction conditions. For example, D-mannose provides 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose on reaction with acetone in presence of a catalyst, unprotected hydroxyl group at the anomeric position. On the other hand, on acetonation D-glucose gives 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose with free -OH group at C-3 position.[12] They serve as a valuable building blocks in carbohydrate chemistry such as glycosyl acceptors[13] and glycosyl donors.[14] In addition, many of them have been used as key starting material for natural product synthesis.[15] For example, 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol has been utilized in the total synthesis of (+)-7-epigoniofufurone[16] and other analogues. Moreover, these sugar derivatives are also important materials for structural and conformational studies.[17] Furthermore, some of them also exhibit important pharmacological properties. For example, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose exhibits anti-inflammatory and antipyretic activities with a very low toxicity.[18]

1.2 Synthetic utility of dithioacetals and *O*-isopropylidene derivatives of sugar

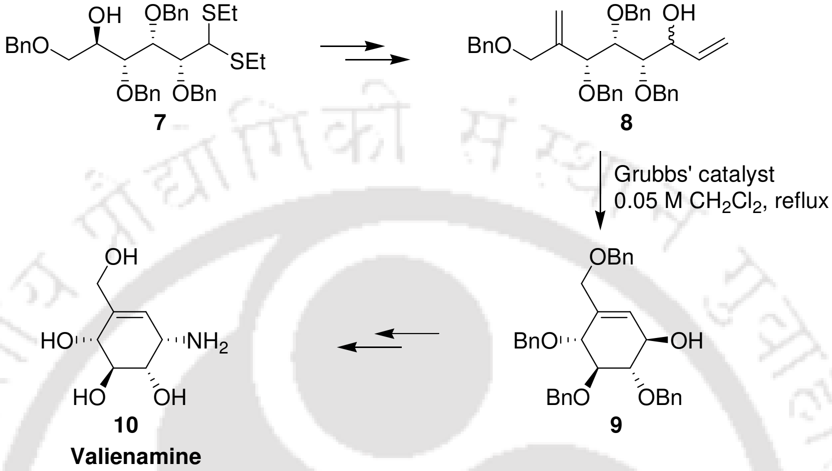
From the literature survey, it has been revealed that both dithioacetal and isopropylidene derivatives of sugar are extremely important building blocks for the synthesis of various sugar, non-sugar, natural and non-natural products. They are also used as chiral synthons in organic synthesis. Some of their useful synthetic applications are presented here:

Completo and Lowary[19] demonstrated the synthesis of various galactofuranose for mycobacterial galactofuranosyltransferases. Galactose diethyl dithioacetal (**1**) was chosen as starting material for the synthesis of galactofuranose derivatives **2-6** by an iodine-promoted cyclization as shown in Scheme 1. These derivatives are important building blocks for glycosylation reaction.



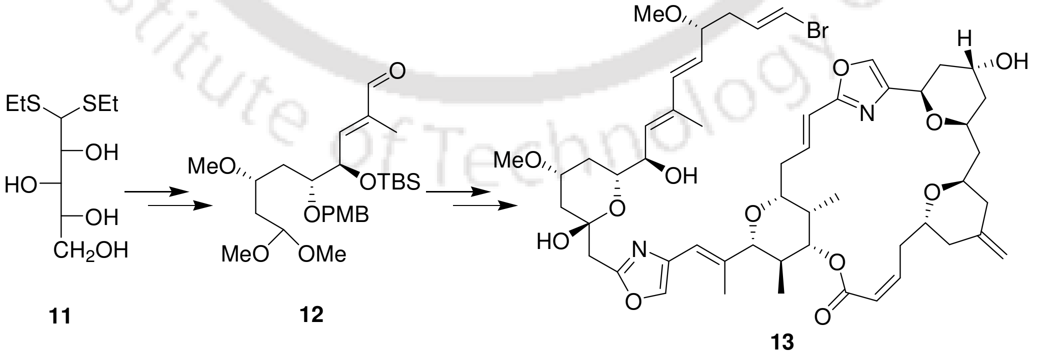
Scheme 1

Chang and co-workers[20a] synthesized the valienamine (**10**), α-glucosidase inhibitor,[20b] from 2,3,4,6-tetra-*O*-benzyl-D-glucose diethyl dithioacetal (**7**) using ring-closing metathesis reaction of compound **8** as shown in Scheme 2, which was first isolated from the microbial degradation of validoxyamine A with *Pseudomonas denitrificans.*[20c]



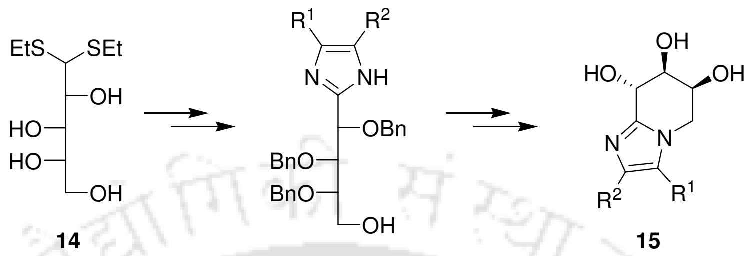
Scheme 2

Phorboxazole A (**13**) isolated from a species of Indian Ocean sponge of the genus *Phorbas* sp.[21] shows cytotoxic activity against the entire panel of human cell lines, in combination with the spongiastatins. They are the most potent naturally occurring cytotoxic agents.[22] Pattenden and his groups[5] reported a convergent total synthesis of phorboxazole A (**13**) from the aldehyde **12**, which is obtained from D-xylose diethyl dithioacetal (**11**) as depicted in Scheme 3.



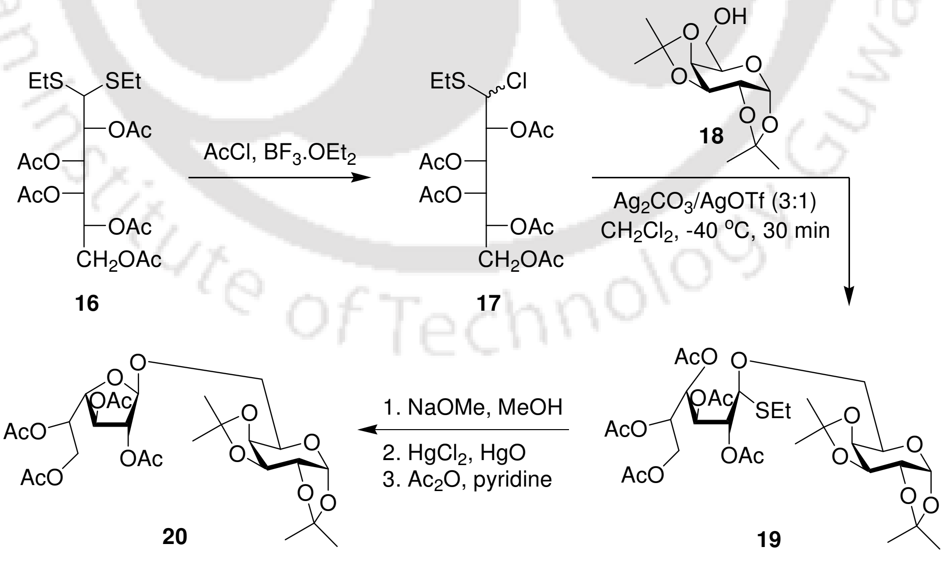
Scheme 3

The synthesis of substituted imidazolo[1,2-a]piperidinoses **15** have been demonstrated by Dubost *et al.*[23] using diethyl dithioacetal of L-arabinose **14** as illustrated in Scheme 4. In addition, these derivatives also demonstrated to have glycosidase inhibitor activity.



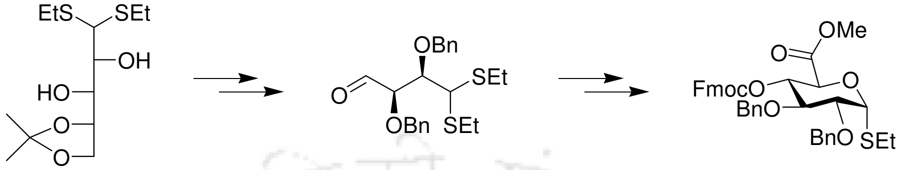
Scheme 4

McAuliffe and Hindsgaul[24] illustrated the efficient glycosylation of 1-chloro-1-(ethylthio)-2,3,4,5,6-penta-*O*-acetyl-D-galactose (**17**) with carbohydrate acceptors such as 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (**18**) promoted by silver trifluoromethane sulfonate which afforded the corresponding acyclic *O,S*-acetal (**19**) in very good yield. Compound **17** was prepared from 2,3,4,5,6-penta-*O*-acetyl-D-galactose diethyl dithioacetal (**16**) on reaction with acetyl chloride in the presence of $BF_3.OEt_2$. The *O,S*-acetal **19** was finally converted into the disaccharide **20** in three-steps as shown in Scheme 5.



Scheme 5

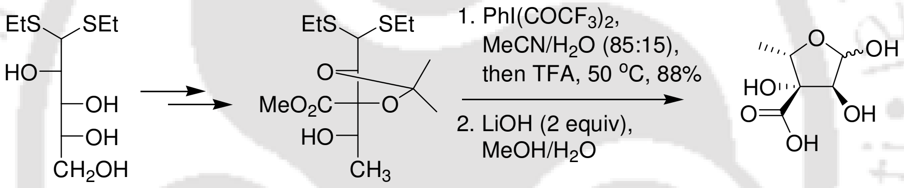
Timmer *et al.*[25] reported the synthesis of uronic acid monosaccharides such as L-glucuronic acid thioglycoside (**23**) from the key thioacetal aldehyde (**22**), which is prepared from L-arabinose derivative **21** as depicted in Scheme 6.



21 **22** **23**

Scheme 6

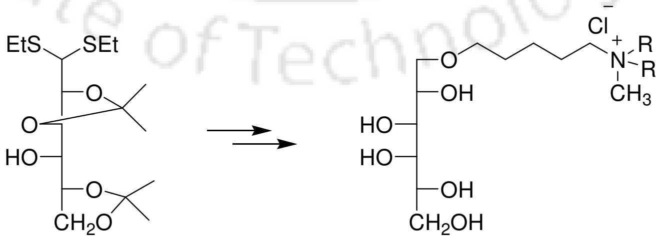
Timmer and his co-workers[26] devised the synthesis of aceric acid (**26**) and related building blocks commenced with D-arabinose diethyl dithioacetal (**24**) *via* intermediate β-hydroxy ester (**25**) as given in Scheme 7.



24 **25** **26**

Scheme 7

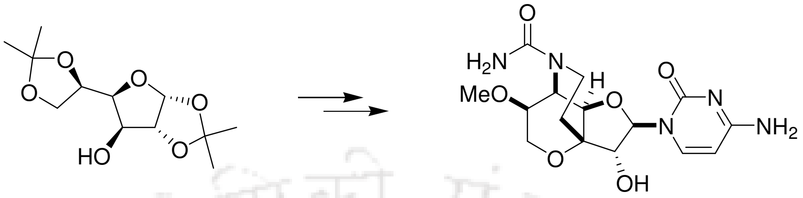
Mahidhar *et al.*[27] synthesized various novel cationic glycolipids (**28**) from a series of reaction started with 2,3:4,5-di-*O*-isopropylidene-D-galactose diethyl dithioacetal (**27**) as represented in Scheme 8. They have also performed in vitro studies for gene delivery efficacy of these compounds.



27 **28**

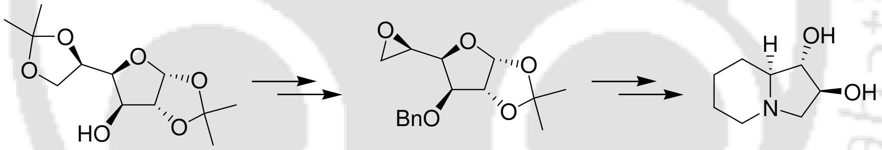
Scheme 8

Hanessian and Ritson[15a] reported the synthesis of *N*-malayamycin A (**30**) from 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (**29**) in a stereoselective manner as depicted in Scheme 9.


29 **30**

Scheme 9

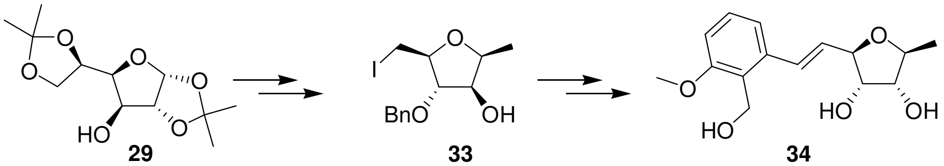
Recently, Alam and Vankar[15b] demonstrated the total synthesis of (+)-lentiginosine (**32**) in an overall yield of 38% from 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (**29**) from the epoxide (**31**) in efficient manner (Scheme 10). (+)-Lentiginosine (**32**) is the most potent and selective amyloglucosidase inhibitor so far, having activity in very low concentration (IC_{50} = 0.43 µg/L),[28] which was isolated from the leaves of *Astragalus lentiginosus* in 1990.


29 **31** **32**

(+)-Lentiginosine

Scheme 10

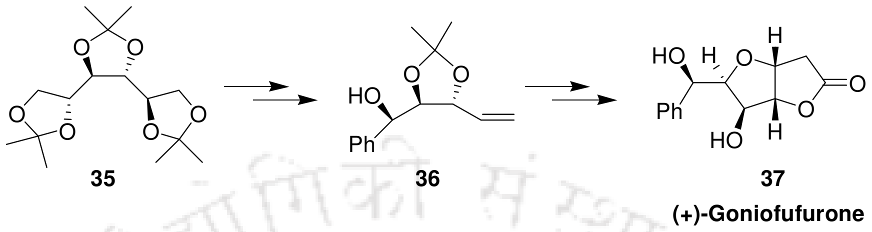
Very recently, Palík *et al.*[29a] demonstrated the formal synthesis of (+)-varitriol (**34**) from the key intermediate **33**, starting from 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (**29**) as illustrated in Scheme 11. The compound **34**, which was isolated from a marine-derived strain of fungus *Emericella variecolor* has been known to have potent cytotoxic activity against several human tumor cell lines.[29b]


29 **33** **34**

(+)-Varitriol

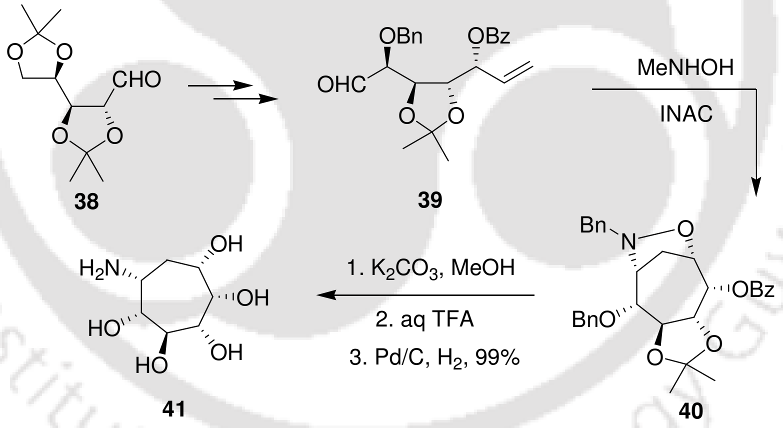
Scheme 11

Yadav and Agrawal[16] accomplished the total synthesis of (+)-goniofufurone (**37**) from the alcohol (**36**). The alcohol **36** is readily accessible from 1,2:3,4:5,6-tri-*O*-isopropylidene-D-(+)-mannitol (**35**) as shown in Scheme 12.



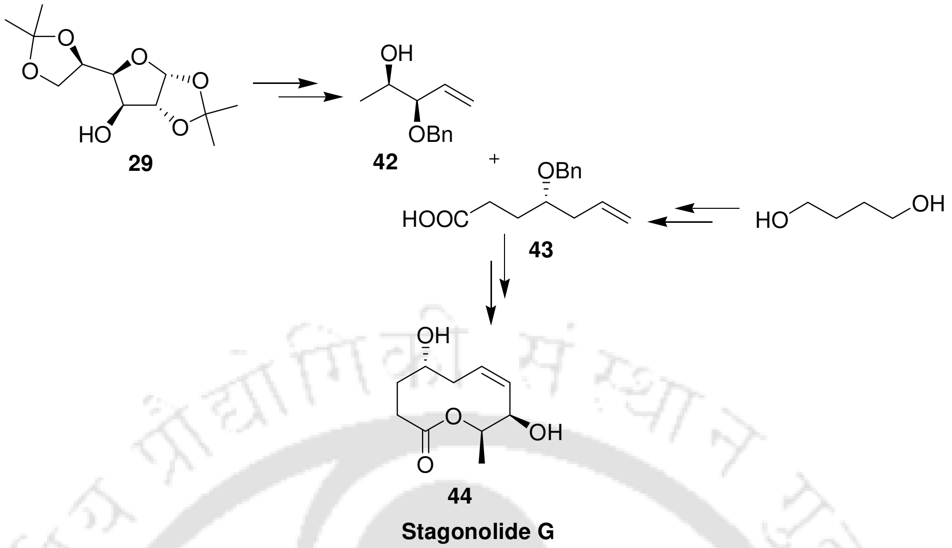
Scheme 12

Shing *et al.*[30] first synthesized bridged bicyclo[4.2.1]isoxazolidine (**40**) controlled by trans-acetonide in high yield *via* intramolecular nitrone-alkene cycloaddition (INAC) reaction of hept-6-enose (**39**). The enose **39** was easily prepared from acetonide of D-xylose (**38**), and the cycloadduct **40** was converted into hydroxylated aminocycloheptane framework (**41**) as represented in Scheme 13.



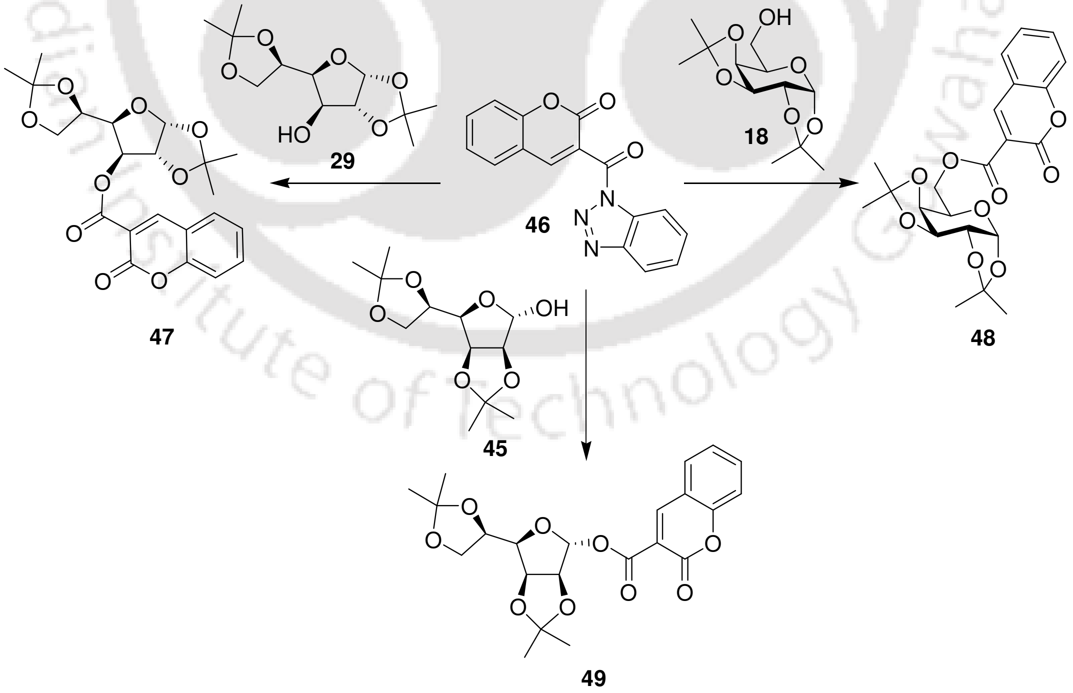
Scheme 13

Very recently, Srihari *et at.*[31] reported the convergent total synthesis of stagonolide G **(44)** involving chiron pool synthesis by the condensation of chiral acid **43** with chiral alcohol **42**. The key steps for this target synthesis are Keck allylation and Grubbs' olefin metathesis reaction. The required alcohol **42** was synthesized from 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (**29**) as depicted in Scheme 14.



Scheme 14

Katritzky *et al.*[32] demonstrated a convenient and efficient synthesis of *O*-fluorescent labeling monosaccharide from N-(coumarin-3-carbonyl)benzotriazole (**46**) on reaction with isopropylidene derivatives of D-galctose, D-glucose and D-mannose as displayed in Scheme 15.

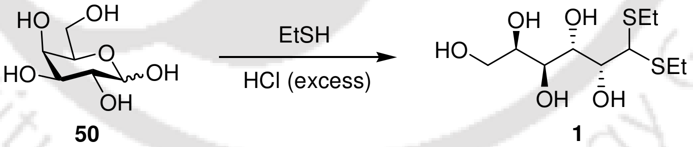


Scheme 15

The above literature highlights the importance of dithioacetal and isopropylidene derivative of carbohydrates. They are one of the most valuable building blocks for the synthesis of various natural and non-natural products. Due to innumerable application of these derivatives, we were interested to explore the method of preparation of these derivatives. The existing procedures for the preparation of dialkyl dithioacetals and *O*-isopropylidenes of carbohydrate are mentioned below:

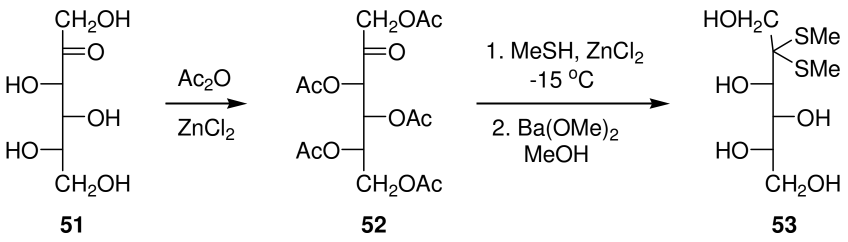
1.3 Methods for preparation of dialkyl dithioacetals and *O*-isopropylidenes of sugar

For the preparation of dialkyl dithioacetal especially diethyl dithioacetal, the most used methods are either the protocol developed by Fischer or a slight modification of Fischer method.[33] The diethyl dithioacetal derivatives of free sugar are conventionally obtained from reducing sugars with ethanethiol in presence of excess amount of concentrated HCl.[25-27,34] This is an exclusive practical method which is used till date since the discovery of Fischer's protocol.[33] A few other methods are also known in the literature for the preparation of dithioacetal derivatives from free sugar using trifluoroacetic acid[20a,35] and anhydrous zinc chloride.[36] For example, Mahidhar *et at.*[27] reported the preparation of D-galactose diethyl dithioacetal (**1**) from D-galactose (**50**) using excess amount of both concentrated HCl and ethanethiol as shown in Scheme 16. The major disadvantage lies in the process is the use of both conc. HCl and thiol in excess amount.



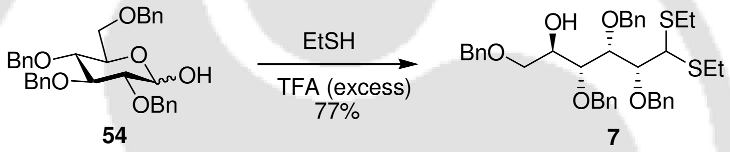
Scheme 16

Zinner and Schneider[36] reported the preparation of L-sorbose dimethyl dithioacetal (**53**) on treatment with methanethiol and 1,3,4,5,6-penta-*O*-acetyl-L-sorbose (**52**) using $ZnCl_2$ as a catalyst at -15 °C followed by deprotection of acetate groups using $Ba(OMe)_2$ in methanol as illustrated in Scheme 17.



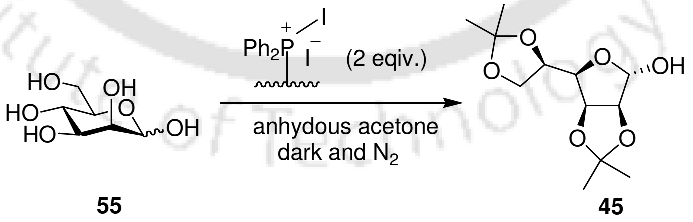
Scheme 17

Chang *et al.*[20a] described the preparation of 2,3,4,6-tetra-*O*-benzyl-D-glucose diethyl dithioacetal (**7**) in 77% yield from 2,3,4,6-tetra-*O*-benzyl-D-glucose (**54**) on reaction with ethanethiol in the presence of excess amount of trifluoroacetic acid at room temperature as displayed in Scheme 18. The drawback of this method is the use of excess amount of expensive trifluoroacetic acid.



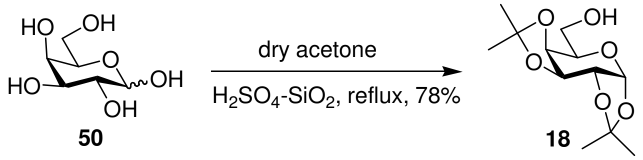
Scheme 18

The preparation of *O*-isopropylidene derivatives of sugar have been demonstrated by Pedatella *et al.*[37] using the Lewis acid and dehydrating agent triphenylphosphine polymer-bound/I_2 complex. This method is clean but not catalytic and it requires equivalent amount of promoter as well as dark and inert atmosphere as depicted in Scheme 19.



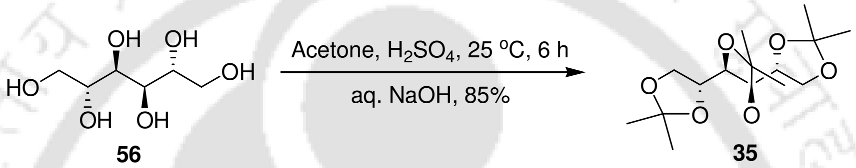
Scheme 19

Recently, Rajput and Mukhopadhyay[38] have demonstrated the preparation of *O*-isopropylidene of carbohydrates using dry acetone catalyzed by H_2SO_4-SiO_2 under reflux condition as shown in Scheme 20. The main disadvantage of this method is that the reaction has to be carried out at reflux temperature.



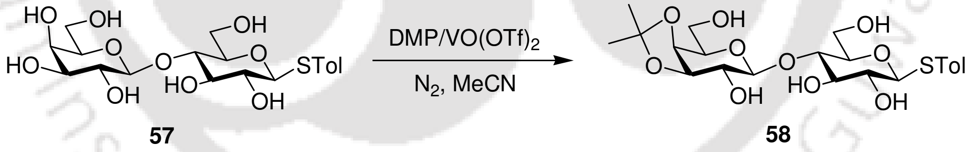
Scheme 20

Yadav and Agrawal[16] reported the preparation of 1,2:3,4;5,6-tri-*O*-isopropylidene-D-mannitol (**35**) from the reaction of D-mannitol (**56**) and acetone in the presence of excess amount of H_2SO_4 followed by neutralization with saturated aqueous NaOH solution as shown in Scheme 21.



Scheme 21

Lin *et al.*[39] recently reported the synthesis of various isopropylidenes using $VO(OTf)_2$. For example, they prepared the isopropylidene derivative **58** from sugar derivative **57** on reaction with methoxypropane catalyzed by $VO(OTf)_2$ at room temperature in inert atmosphere as illustrated in Scheme 22.



Scheme 22

Over the years, some more methods have been reported for the preparation of *O*-isopropylidene derivative of carbohydrates using various reagents such as concentrated H_2SO_4,[40] combination of anhydrous $ZnCl_2$ and H_3PO_4,[41] anhydrous copper(II) sulfate,[42] $FeCl_3$,[43] pyridinium *p*-toluenesulfonate (PPTS),[44] iodine,[45] ceric ammonium nitrate (CAN),[46] Zeolite HY,[47] montmorillonite clay[48] etc. Unfortunately, many of these methods have some drawbacks such as harsh reaction conditions, low yields, requirement of excess, expensive catalysts and inert atmospheric conditions.

The aforementioned discussions revealed that the dialkyl dithioacetals and *O*-isopropylidene derivatives of sugar are used extensively by organic chemists.

Scope of Work

On the basis of brief review presented above, the following problems appear to require serious attention:

(a) The only practical method is known to the chemist for the preparation of dialkyl dithioacetal derivative of sugars in which both the concentrated HCl and thiols were used in excess amount. Two others methods reported in literature are less common because of the use of expensive TFA and metallic $ZnCl_2$ in excessive amount. Hence, an alternative environmentally benign method, which might be practical, efficient and must be catalytic, is highly desirable.

(b) On the other hand, for synthesis of *O*-isopropylidene of carbohydrates a number of methods are reported over the years. However, some of these methods are confronted with serious drawbacks such as harsh reaction conditions, low yields, use of excess and expensive catalyst and inert atmospheric conditions.

The dialkyl dithioacetals and *O*-isopropylidene derivatives of sugar are widely used for the synthesis of various natural products, drugs molecules, molecules related to life process and also used as chiron synthon. In this context, the development of new and efficient catalytic methods that would allow to prepare these derivatives in eco-friendly manners with good yields is extremely important and great demanding.

The work described in the thesis encompasses to develop newer synthetic methodologies in carbohydrates chemistry.

PART A

CHAPTER 2

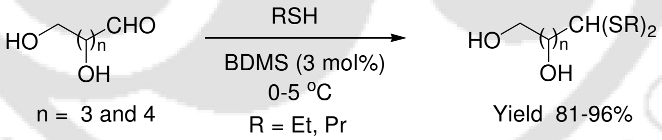
Synthesis of dialkyl dithioacetal derivatives of sugar using bromodimethysulfonium bromide (BDMS)

Results and Discussion

The importance of dithioacetal derivative of sugars and their methods of preparation have been discussed in Chapter 1. Literature survey reveals that the previously reported methods are mainly based on using excess amount of acids. Therefore, there is a further scope to develop a practical and catalytic method for the preparation of dithioacetals, which might work under mild, neat, environmentally benign reaction conditions and can replace the existing procedure.

We envisaged that bromodimethylsulfonium bromide (BDMS) can be used for the preparation of dithioacetal of sugars because it can generate dry HBr in the reaction medium on reaction with thiol.

Last few years, our research group[49,50] and others[51] have demonstrated the extensive use of bromodimethylsulfonium bromide (BDMS) as a useful brominating reagent as well as an efficient catalyst for various organic transformations. In addition, Xiong *et al.* have demonstrated the application of BDMS as a promoter for the glycosylation reaction.[52] Very recently, its application in various organic transformations has also been reviewed by our group.[53] In this Chapter, a practical and efficient method for the preparation of diethyl/dipropyl dithioacetal from reducing sugars using bromodimethylsulfonium bromide (BDMS) as a catalyst has been achieved, which is illustrated in Scheme 23.



Scheme 23

For the present studies, the catalyst bromodimethylsulfonium bromide (BDMS) was prepared by following the literature procedure.[49a] L-arabinose (**59**) was initially chosen as a model substrate. The reaction condition for dithioacetalization of sugars was optimized in terms of yield and amount of catalyst. Several reactions were scrutinized using different amounts of catalyst with various solvents such as DMF, DMSO and H_2O and the results are summarized in Table 1.

Table 1. Optimization of reaction conditions with L-arabinose

Entry	EtSH[a] (mL/mmol)	BDMS (mol%)	Solvent	Time (h)	Yield[b](%)
1	1.9/25	5	DMF	1	51
2	1.9/25	10	DMF	1	59
3	1.9/25	5	DMSO	1	46
4	1.9/25	5	H_2O	1	23
5	1.9/25	5	--	1	63[c]
6	5.5/75	5	--	30 min	95
7	**5.5/75**	**3**	**--**	**30 min**	**95**

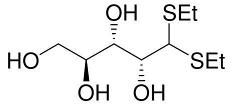
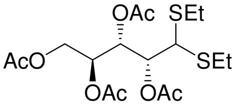
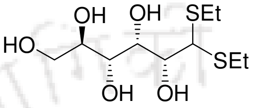
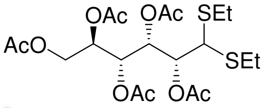
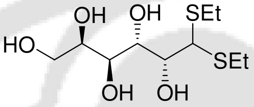
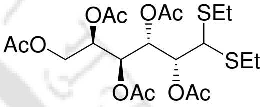
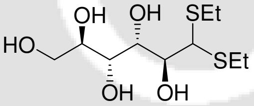
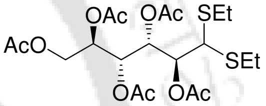
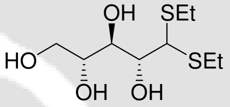
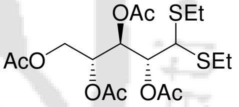
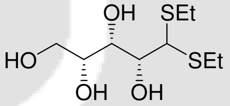
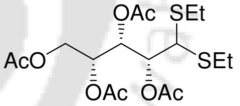
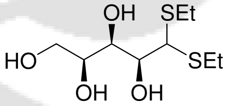
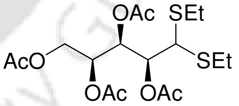
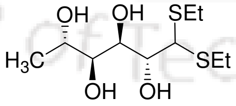
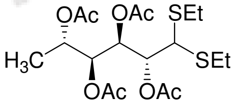
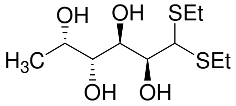
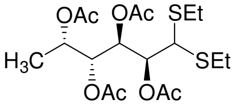
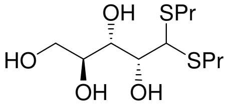
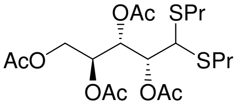
[a]*Unreacted ethanethiol was recovered by short-path distillation.* [b]*Isolated yields.* [c]*Low yield due to improper mixing of sugar and ethanethiol.*

It was noted that the best result was obtained by using 3 mol% of BDMS at 0-5 °C under solvent-free conditions. The product L-arabinose diethyl dthioacetal (**14**) was characterized by recording melting point and specific rotation.

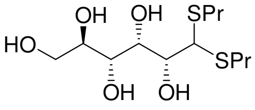
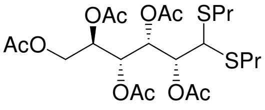
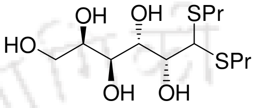
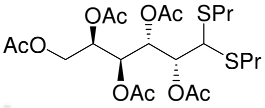
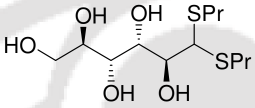
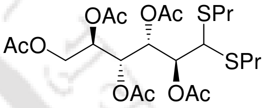
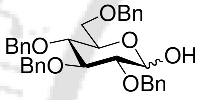
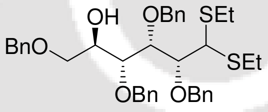
For further characterization, the product L-arabinose diethyl dithioacetal (**14**) was acetylated using silica-supported perchloric acid.[54] The acetylated product 2,3,4,5-tetra-*O*-acetyl-L-arabinose diethyl dithioacetal (**76**) was fully characterized by recording its melting point, IR, ^{1}H NMR, ^{1}H-^{1}H COSY, ^{13}C NMR, specific rotation and by its elemental analysis. The ^{1}H NMR and ^{13}C NMR spectra of compound **76** are given in the Experimental Section (Figure 1).

After optimization of the reaction conditions, the reaction of D-glucose (**60**) with ethanethiol was examined using same mol% catalyst under identical reaction conditions. The product D-glucose diethyl dithioacetal (**66**) was obtained in 92% yield. Encouraged by the above results, D-galactose (**50**) was taken as a substrate under similar reaction conditions and product **1** was isolated in good yield. Likewise, other sugars such as D-xylose (**62**), D-mannose (**55**), D-ribose (**61**), L-xylose (**63**), L-rhamnose (**64**) and L-fucose (**65**) were smoothly converted into their corresponding diethyl dithioacetal derivatives **11** and **67**-**71**, on reaction with ethanethiol in the presence of 3 mol% BDMS, in good to excellent yields as represented in Table 2.

Table 2. Dithioacetalization of various reducing sugars using BDMS as a catalyst[a]

Entry	Substrate	Product	Time (min)/ Yield[b] (%)	Per-*O*-acetylated Product[d]
1	L-Arabinose **59**	 **14**	30/96	 **76**
2	D-Glucose **60**	 **66**	40/91	 **77**
3	D-Galactose **50**	 **1**	40/88	 **16**
4	D-Mannose **55**	 **67**	40/82	 **78**
5	D-Ribose **61**	 **68**	30/72	 **79**
6	D-Xylose **62**	 **11**	35/86	 **80**
7	L-Xylose **63**	 **69**	35/83[c]	 **81**
8	L-Rhamnose **64**	 **70**	45/86	 **82**
9	L-Fucose **65**	 **71**	45/89[c]	 **83**
10	L-Arabinose **59**	 **72**	40/91	 **84**

Continued Table 2

Entry	Substrate	Product	Time (min)/ Yield[b] (%)	Per-*O*-acetylated Product[d]
11	D-Glucose **60**	 **73**	60/88	 **85**
12	D-Galactose **50**	 **74**	55/83	 **86**
13	D-Mannose **55**	 **75**	60/81	 **87**
14	 **54**	 **7**	60/84[c]	--

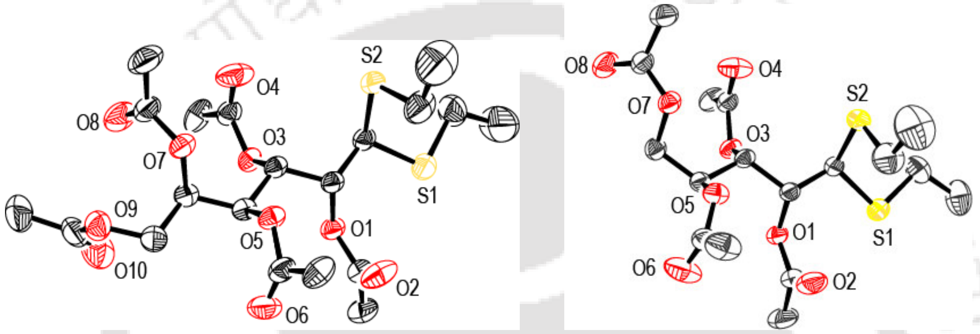
[a]*Sugar (20 mmol) was taken in thiol (10 mL) and BDMS (134 mg, 0.6 mmol) was added in two portions.* [b]*Isolated yield.* [c]*Reaction were carried out with 2 mmol of sugars.* [d]*Per-O-acetylation were performed with 2 mmol of dithioacetal derivative of sugars using $HClO_4$-SiO_2.*

The generality of the protocol was further examined by the reaction of sugars such as L-arabinose (**59**), D-glucose (**60**), D-galactose (**50**) and D-mannose (**55**) with propanethiol under identical conditions. The corresponding dipropyl dithioacetals **72-75** were obtained in good yields (Table 2, entries 10-13). The ^{1}H NMR and ^{13}C NMR spectra compound of compound **86** is given in the Experimental Section (Figure 2).

All the dithioacetal derivatives were per-*O*-acetylated into the corresponding acetate derivatives **16** and **76-87** using $HClO_4$-SiO_2. They were fully characterized by recording their melting points, IR, ^{1}H and ^{13}C NMR spectra and specific rotation as well as by elemental analyses. In addition, the structures of **16** and **76** were also confirmed by single X-ray crystallographic data as shown in Figure 1.

Recently, it was reported[20a] that diethyl dithioacetal derivative of 2,3,4,6-tetra-*O*-benzyl-D-glucose (**54**) is an important starting material for the synthesis of valienamine, which acts as α-glucosidase inhibitor.[20c] To verify our protocol, the substrate 2,3,4,6-tetra-*O*-benzyl-D-glucose (**54**) was subjected with ethanethiol in the presence of 3 mol% catalyst under identical conditions and it provided 2,3,4,6-*O*-benzyl-D-glucose diethyl dithioacetal (**7**) in 84% yield. The ^{1}H NMR and ^{13}C NMR spectra compound **7** given in the Experimental Section (Figure 3).

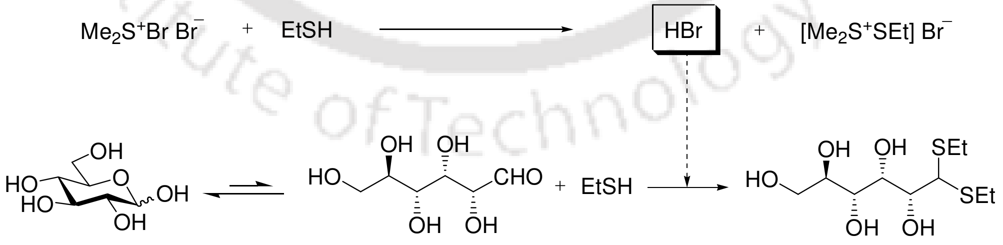
It is worthwhile to mention that the present protocol provides better yield and it also requires less reaction time as compared to the trifluoroacetic acid method.[20a] The formation of the product may be rationalized as follows: BDMS can *in situ* generate dry HBr on reaction with methanol.[55] Similarly, we believe that BDMS reacts with thiol to generate *in situ* dry HBr, which actually catalyzes the conversion of sugars into the corresponding dithioacetals as illustrated in Scheme 24.



16 (CCDC No. 687605) **76** (CCDC No. 687604)

Figure 1. *ORTEP molecular diagram with ellipsoid at 35% probability of* ***16*** *and* ***76***

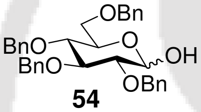
One-pot dithioacetalization followed by per-*O*-acetylation reaction can also be accomplished by just removing excess ethanethiol without further recrystallization or purification of the product, which is generally not feasible with other methods. For example, per-*O*-acetylation of diethyl dithioacetal of L-xylose (**63**) and L-fucose (**65**) were carried out in the same reaction vessel after removing excess ethanethiol.



Scheme 24

This method is highly efficient and suitable for the large scale preparation of dithioacetal derivatives without any difficulty by using only 2 mol% of the catalyst. For example, **14** was obtained in quantitative yield, when a mixture of L-arabinose (**59**) (30 g, 200 mmol) and ethanethiol (100 mL) was treated with bromodimethylsulfonium bromide (0.888 g, 4 mmol) under similar reaction conditions. The efficacy and generality of the present method can be visualized at a glance from the comparison Table 3.

Table 3. Comparison of BDMS with other catalysts for preparation of diethyl dithioacetal of sugars

Entry	Substrate	Catalyst	Catalyst (mol%)	Time (h)	Yield[b](%)
1	L-Arabinose	conc.HCl	Excess	0.50	87[56]
	59	**BDMS**	**3**	**0.50**	**96**
2	D-Glucose	conc. HCl	Excess	0.50	63[2]
	60	**BDMS**	**3**	**0.75**	**92**
3	D-Galactose	conc. HCl	Excess	0.50	47[2]
	50	**BDMS**	**3**	**0.75**	**88**
		CF_3COOH	Excess	12	77[20a]
4	 **54**	**BDMS**	**3**	**1**	**84**

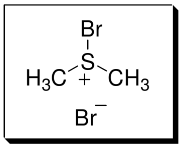
[b] *Isolated yields.*

We have also performed a dithioacetalization reaction with aqueous HBr to verify the efficiency of our protocol. For this purpose, L-arabinose (10 mmol, 1.5 g) was treated with ethanethiol (10 mL) in presence of catalytic amount of aqueous HBr (0.1 mL) at ice-bath temperature. We obtained the desired product **14** in 71% yields, which is lower than BDMS catalyzed reaction.

In conclusion, we have devised a catalytic, efficient and practical synthetic protocol for the preparation of diethyl/dipropyl dithioacetal derivative of sugars using a versatile catalyst bromodimethylsulfonium bromide (BDMS). Simple, mild and clean reaction conditions, good to excellent yields are some of the significant features of this presented method. In addition, this method will be a useful alternative for the large scale preparation of dithioacetal derivatives of sugar.

Experimental

Preparation of bromodimethylsulfonium bromide (BDMS)

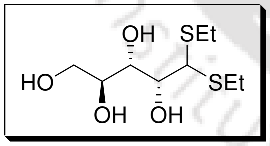


Dimethyl sulfide (1.83 mL, 25 mmol) was dissolved in 5 mL of dry dichloromethane in a 150 mL standard joint conical flask. 1.3 mL of bromine (25 mmol) dissolved in 5 mL of dry dichloromethane was added slowly to the above solution at ice-bath temperature over a period of 5 min. During the addition, light orange crystals of bromodimethylsulfonium bromide begin to separate out. After the complete addition of bromine, the crystals of bromodimethylsulfonium bromide were collected by filtration. The solid material was then washed with dry hexane and dried under vacuum. The yellow crystalline product was obtained 4.3 g in 77% yield, M.p. 80 °C.

General procedure for preparation of dialkyl dithioacetal

To an ice cold stirring suspension of sugar (20.0 mmol) in thiol (10 mL), BDMS (0.134 g, 0.6 mmol) was added in two portions after an interval of 10 minutes. The reaction mixture was allowed to continue for stirring. After completion of reaction, the excess thiol was removed by short-path distillation, which is reused for next set of reaction. The crude residue was recrystallized in hot water or other solvents system, which are mentioned with each compounds.

L-Arabinose diethyl dithioacetal (**14**)

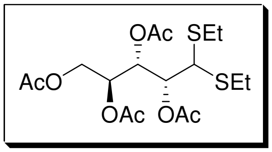


White solid; M.p. 124–126 °C; $[\alpha]_D^{25}$ –8.4 (*c* 1.0, H_2O).

General experimental protocol for per-O-acetylation of dialkyl dithioacetal of sugars

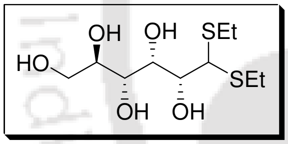
A suspension of dialkyl dithioacetal (2.0 mmol) in Ac_2O (0.94 mL, 10.0 mmol) was placed in an ice bath for stirring. To the cold suspension of the reaction mixture was added $HClO_4–SiO_2$ (50 mg) and stirring was continued further. After completion of the reaction (monitored by TLC), the reaction mixture was passed through a celite pad and washed with toluene. The crude reaction mixture was further co-evaporated with toluene (2 x 10 mL) to remove traces of acetic acid and the crude product was purified by column chromatography on silica gel using 3:1 hexane-EtOAc to furnish pure per-*O*-acetyl of dialkyl dithioacetals.

2,3,4,5-Tetra-O-acetyl-L-arabinose diethyl dithioacetal (**76**)



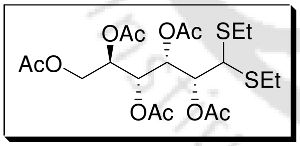
Colorless crystalline solid; M.p. 84 ºC; $[\alpha]_D^{25}$ –34 (*c* 1.0, MeOH); **IR** (KBr): 2968, 1738, 1371, 1229, 1032 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.21 (t, 3H, *J* = 7.6 Hz, SCH_2CH_3), 1.23 (t, 3H, *J* = 7.6 Hz, SCH_2CH_3), 2.03 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 2.11 (s, 3H, $COCH_3$), 2.58–2.76 (m, 4H, 2 × SCH_2CH_3), 3.89 (d, 1H, *J* = 8.0 Hz, H-1), 4.03 (dd, 1H, *J* = 5.6 Hz, *J* = 12.4 Hz, H-5), 4.26 (dd, 1H, *J* = 2.8 Hz, *J* = 12.4 Hz, H-5'), 5.09–5.13 (m, 1H, H-4), 5.27 (dd, 1H, *J* = 2.8 Hz, *J* = 8.0 Hz, H-2), 5.72 (dd, 1H, *J* = 2.8 Hz, *J* = 8.0 Hz, H-3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.2, 14.5, 20.9, 21.06, 21.12, 25.0, 51.9, 62.3, 69.0, 69.7, 70.9, 169.7, 170.1, 170.2, 170.9; **Anal. Calcd** for $C_{17}H_{28}O_8S_2$ (424.54): C, 48.10; H, 6.65; S, 15.11. Found: C, 48.00; H, 6.44; S, 14.95.

D-Glucose diethyl dithioacetal (**66**)



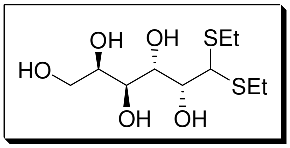
White solid; M.p. 125–126 ºC (recrystallized from hot water); $[\alpha]_D^{25}$ –28 (*c* 1.0, H_2O).

2,3,4,5,6-Penta-O-acetyl-D-glucose diethyl dithioacetal (**77**)



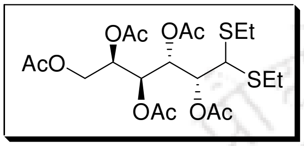
White syrup; $[\alpha]_D^{25}$ +13.6 (*c* 1.0, $CHCl_3$); **IR** (KBr): 2969, 1750, 1372, 1226, 1069, 1031 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.20 (t, 3H, *J* = 7.6 Hz, SCH_2CH_3), 1.30 (t, 3H, *J* = 8.0 Hz, SCH_2CH_3), 2.01 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 2.12 (s, 3H, $COCH_3$), 2.48–2.80 (m, 4H, 2 × SCH_2CH_3), 4.04 (d, 1H, *J* = 4.0 Hz, H-1), 4.10 (dd, 1H, *J* = 4.8 Hz, *J* = 12.4 Hz, H-6), 4.21 (dd, 1H, *J* = 2.8 Hz, *J* = 12.4 Hz, H-6'), 5.02–5.05 (m, 1H, H-5), 5.26 (dd, 1H, *J* = 4.0 Hz, *J* = 7.2 Hz, H-2), 5.40 (dd, 1H, *J* = 2.8 Hz, *J* = 8.4 Hz, H-4), 5.73 (dd, 1H, *J* = 2.8 Hz, *J* = 7.2 Hz, H-3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.3, 14.5, 20.5, 20.6, 20.7, 20.8, 24.8, 25.6, 50.6, 61.4, 68.3, 68.4, 70.0, 72.1, 169.6, 169.8, 169.9, 170.2, 170.5; **Anal. Calcd** for $C_{20}H_{32}O_{10}S_2$ (496.60): C, 48.37; H, 6.49; S, 12.91. Found: C, 48.29; H, 6.43; S, 12.82.

D-Galactose diethyl dithioacetal (**1**)



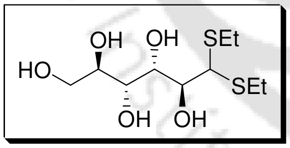
White needles; M.p. 142–143 ºC (recrystallized from methanol); $[\alpha]_D^{25}$ –3.6 (*c* 1.0, H_2O).

2,3,4,5,6-Penta-O-acetyl-D-galactose diethyl dithioacetal (**16**)



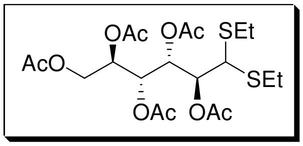
Colorless solid; M.p. 78–80 ºC (recrystallized from ethanol); $[\alpha]_D^{25}$ +11.6 (*c* 1.0, MeOH); **IR** (KBr): 2977, 1747, 1372, 1220, 1025 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 1.19 (t, 3H, *J* = 7.2 Hz, $\mathrm{SCH_2C}H_3$), 1.22 (t, 3 H, *J* = 7.2 Hz, $\mathrm{SCH_2C}H_3$), 1.99 (s, 3H, $\mathrm{COC}H_3$), 2.08 (s, 6H, 2 x $\mathrm{COC}H_3$), 2.09 (s, 3H, $\mathrm{COC}H_3$), 2.09 (s, 3H, $\mathrm{COC}H_3$), 2.54–2.67 (m, 4H, 2 × $\mathrm{SC}H_2\mathrm{CH_3}$), 3.80 (d, 1H, *J* = 6.8 Hz, H-1), 3.83 (dd, 1H, *J* = 7.2 Hz, *J* = 12.0 Hz, H-6), 4.26 (dd, 1H, *J* = 5.2 Hz, *J* = 12.0 Hz, H-6'), 5.14 (dd, 1H, *J* = 1.6 Hz, *J* = 8.0 Hz, H-2), 5.16–5.19 (m, 1H, H-5), 5.22 (dd, 1H, *J* = 2.0 Hz, *J* = 9.6 Hz, H-4), 5.75 (dd, 1H, *J* = 1.6 Hz, *J* = 9.6 Hz, H-3); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 14.2, 14.4, 20.8, 20.9, 21.1, 25.1, 25.4, 28.9, 52.0, 62.3, 67.9, 68.1, 68.4, 70.5, 169.6, 169.9, 170.3, 170.5, 170.6; **Anal. Calcd** for $C_{20}H_{32}O_{10}S_2$ (496.60): C, 48.37; H, 6.49; S, 12.91. Found: C, 48.29; H, 6.41; S, 12.79.

D-Mannose diethyl dithioacetal (**67**)



White solid; M.p. 135–136 ºC (recrystallized from water); $[\alpha]_D^{25}$ +25.2 (*c* 1.0, H_2O).

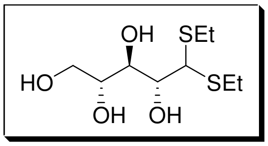
2,3,4,5,6-Penta-O-acetyl-D-mannose diethyl dithioacetal (**78**)



White syrup; $[\alpha]_D^{25}$ +30 (*c* 0.35, MeOH); **IR** (KBr): 2971, 1749, 1371, 1218, 1047 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 1.24 (t, 3H, *J* = 7.6 Hz, $\mathrm{SCH_2C}H_3$), 1.28 (t, 3H, *J* = 7.2 Hz, $\mathrm{SCH_2C}H_3$), 2.06 (s, 3H, $\mathrm{COC}H_3$), 2.08 (s, 3H, $\mathrm{COC}H_3$), 2.09 (s, 6H, 2 × $\mathrm{COC}H_3$), 2.10 (s, 3H, $\mathrm{COC}H_3$), 2.60–2.76 (m, 4H, 2 × $\mathrm{SC}H_2\mathrm{CH_3}$), 3.90 (d, 1H, *J* = 5.6 Hz, H-1), 4.08 (dd, 1H, *J* = 5.2 Hz, *J* = 12.4 Hz, H-6), 4.22 (dd, 1H, *J* = 2.8 Hz, *J* = 12.4 Hz, H-6'), 5.06–5.09 (m, 1H, H-5), 5.29 (dd, 1H, *J* = 5.6 Hz, *J* = 7.2 Hz, H-2), 5.50 (dd, 1H, *J* = 2.0 Hz, *J* = 9.2 Hz, H-4), 5.75 (dd, 1H, *J* = 1.6 Hz, *J* = 7.2 Hz, H-3); **^{13}C NMR** (100 MHz,

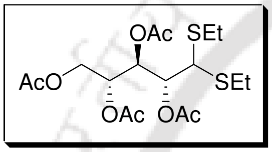
$CDCl_3$): δ 14.3, 14.4, 20.9, 21.0, 21.03, 25.3, 25.6, 51.5, 62.0, 67.4, 68.2, 69.2, 71.2, 169.9, 170.1, 170.7, 170.8; **Anal. Calcd** for $C_{20}H_{32}O_{10}S_2$ (496.60): C, 48.37; H, 6.49; S, 12.91. Found: C, 48.30; H, 6.41; S, 12.82.

D-Ribose diethyl dithioacetal (**68**)



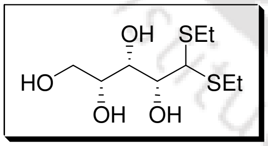
Creamy solid; M.p. 78–80 ºC (recrystallized from water); $[\alpha]_D^{25}$ –38.2 (*c* 1.0, H_2O).

2,3,4,5-Tetra-O-acetyl-D-ribose diethyl dithioacetal (**79**)



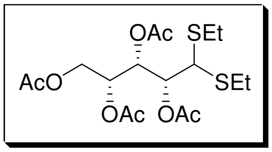
Colorless solid; M.p. 47–48 ºC (recrystallized from ethanol); $[\alpha]_D^{25}$ +29.6 (*c* 1.0, MeOH); **IR** (KBr): 2971, 1749, 1372, 1220, 1049 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.24 (t, 3H, *J* = 7.6 Hz, SCH_2CH_3), 1.25 (t, 3H, *J* = 7.2 Hz, SCH_2CH_3), 2.04 (s, 3H, $COCH_3$), 2.07 (s, 6H, 2 × $COCH_3$), 2.15 (s, 3H, $COCH_3$), 2.58–2.76 (m, 4H, 2 × SCH_2CH_3), 3.95 (d, 1H, *J* = 6.0 Hz, H-1), 4.13 (dd, 1H, *J* = 7.6 Hz, *J* = 12.0 Hz, H-5), 4.42 (dd, 1H, *J* = 2.8 Hz, *J* = 12.0 Hz, H-5'), 5.32 (t, 1H, *J* = 6.0 Hz, H-2), 5.37–5.40 (m, 1H, H-4), 5.64 (dd, 1H, *J* = 4.0 Hz, *J* = 6.0 Hz, H-3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1, 14.3, 20.7, 20.8, 20.9, 25.07, 25.13, 51.6, 62.2, 69.8, 71.2, 72.1, 169.3, 169.7, 169.9, 170.7; **Anal. Calcd** for $C_{17}H_{28}O_8S_2$ (424.53): C, 48.10; H, 6.65; S, 15.11. Found: C, 48.03; H, 6.56; S, 14.92.

D-Xylose diethyl dithioacetal (**11**)



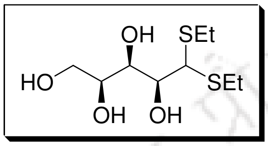
White solid; M.p. 66–68 ºC (recrystallized from toluene),

2,3,4,5-Tetra-O-acetyl-D-xylose diethyl dithioacetal (**80**)



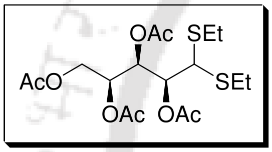
Colorless solid; M.p. 48–49 ºC (recrystallized from ethanol); $[\alpha]_D^{25}$ +9.9 (*c* 0.6, MeOH); **IR** (KBr): 2967, 1751, 1372, 1216, 1052 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.21 (t, 3H, *J* = 7.2 Hz, SCH_2CH_3), 1.26 (t, 3H, *J* = 7.2 Hz, SCH_2CH_3), 2.04 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 2.54–2.73 (m, 4H, 2 × SCH_2CH_3), 3.92 (d, 1H, *J* = 5.2 Hz, H-1), 4.00 (dd, 1H, *J* = 6.8 Hz, *J* = 12.0 Hz, H-5), 4.29 (dd, 1H, *J* = 4.0 Hz, *J* = 12.0 Hz, H-5'), 5.30 (dd, 1H, *J* = 5.2 Hz, *J* = 6.0 Hz, H-2), 5.31–5.33 (m, 1H, H-4), 5.71 (dd, 1H, *J* = 4.4 Hz, *J* = 6.0 Hz, H-3); **^{13}C NMR** (100 MHz, CDCl$_3$): *δ* 14.3, 20.7, 20.8, 25.2, 25.4, 51.1, 62.2, 69.4, 70.5, 71.9, 169.7, 170.1, 170.4, 170.5; **Anal. Calcd** for $C_{17}H_{28}O_8S_2$ (424.53): C, 48.10; H, 6.65; S, 15.11. Found: C, 48.00; H, 6.49; S, 14.88.

L-Xylose diethyl dithioacetal (**69**)



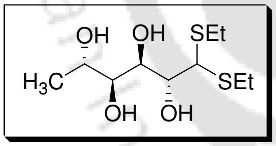
White solid; M.p. 65–67 ºC (recrystallized from toluene).

2,3,4,5-Tetra-O-acetyl-L-xylose diethyl dithioacetal (**81**)



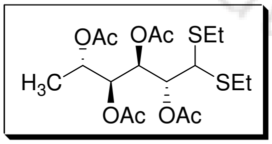
Colorless solid; M.p. 48–50 °C (recrystallized from ethanol); $[\alpha]_D^{25}$ –9.8 (*c* 0.6, CHCl$_3$); **IR** (KBr): 2966, 1754, 1373, 1221, 1049 cm^{-1}; **^{1}H** and **^{13}C NMR** are same as 2,3,4,5-Tetra-*O*-acetyl-D-xylose diethyl dithioacetal (**80**); **Anal. Calcd** for $C_{17}H_{28}O_8S_2$ (424.53): C, 48.10; H, 6.65; S, 15.11. Found: C, 47.98; H, 6.54; S, 14.98.

L-Rhamnose diethyl dithioacetal (**70**)



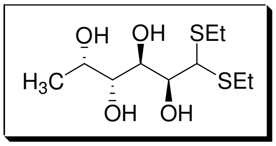
White solid; M.p. 148–150 ºC (recrystallized from ethanol); $[\alpha]_D^{25}$ –10.1 (*c* 1.0, MeOH).

2,3,4,5-Tetra-O-acetyl-L-rhamnose diethyl dithioacetal (**82**)



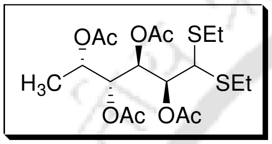
Syrup; $[\alpha]_D^{25}$ –44.6 (*c* 1.0, MeOH); **IR** (KBr): 2974, 1751, 1371, 1224, 1069 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$): *δ* 1.16 (d, 3H, *J* = 6.4 Hz, C*H$_3$*), 1.22 (t, 3H, *J* = 7.2 Hz, SCH$_2$C*H$_3$*), 1.23 (t, 3H, *J* = 7.6 Hz, SCH$_2$C*H$_3$*), 2.03 (s, 3H, COC*H$_3$*), 2.06 (s, 3H, COC*H$_3$*), 2.07 (s, 3H, COC*H$_3$*), 2.08 (s, 3H, COC*H$_3$*), 2.58–2.72 (m, 4H, 2 × SC*H$_2$*CH$_3$), 3.83 (d, 1H, *J* = 4.4 Hz, H-1), 4.85–4.92 (m, 1H, H-5), 5.23 (dd, 1H, *J* = 1.6 Hz, *J* = 8.4 Hz, H-4), 5.28 (dd, 1H, *J* = 4.4 Hz, *J* = 7.6 Hz, H-2), 5.78 (dd, 1H, *J* = 1.6 Hz, *J* = 7.6 Hz, H-3); **^{13}C NMR** (100 MHz, CDCl$_3$): *δ* 14.1, 14.3, 16.5, 20.9, 21.0, 21.2, 25.3, 25.6, 51.5, 67.2, 69.0, 71.0, 71.1, 169.6, 169.9, 170.1, 170.4; **Anal. Calcd** for $C_{18}H_{30}O_8S_2$ (438.56): C, 49.30; H, 6.89; S, 14.62. Found: C, 49.21; H, 6.80; S, 14.49.

L-Fucose diethyl dithioacetal (**71**)



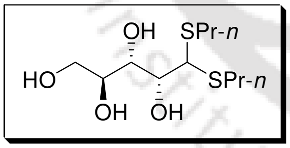
White solid; M.p. 168–170 ºC (recrystallized from ethanol).

2,3,4,5-Tetra-O-acetyl-L-fucose diethyl dithioacetal (**83**)



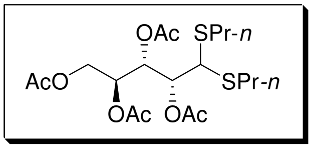
Colorless solid; M.p. 81–82 ºC (recrystallized from ethanol); $[\alpha]_D^{25}$ +7.7 (*c* 0.39, MeOH); **IR** (KBr): 2971, 1748, 1372, 1212, 1030 cm^{-1}; ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 1.14 (d, 3H, J = 6.8 Hz, CH_3), 1.21 (t, 3H, J = 7.6 Hz, SCH$_2$CH_3), 1.24 (t, 3H, J = 7.6 Hz, SCH$_2$CH_3), 2.09 (s, 3H, COCH_3), 2.10 (s, 3H, COCH_3), 2.12 (s, 6H, 2 × COCH_3), 2.52–2.76 (m, 4H, 2 × SCH_2CH$_3$), 3.83 (d, 1H, J = 8.4 Hz, H-1), 4.90–4.96 (m, 1H, H-5), 5.07 (dd, 1H, J = 2.0 Hz, J = 9.6 Hz, H-4), 5.19 (dd, 1H, J = 2.0 Hz, J = 8.4 Hz, H-2), 5.80 (d, 1H, J = 9.6 Hz, H-3); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 14.2, 14.5, 16.6, 20.9, 21.2, 21.3, 25.2, 25.4, 52.2, 67.5, 68.7, 70.8, 71.4, 169.6, 170.4, 170.7; **Anal. Calcd** for $C_{18}H_{30}O_8S_2$ (438.56): C, 49.30; H, 6.89; S, 14.62. Found: C, 49.22; H, 6.71; S, 14.51.

L-Arabinose dipropyl dithioacetal (**72**)



White needles; M.p. 138–139 ºC (recrystallized from water/ethanol/ethyl acetate: 3:1:1); $[\alpha]_D^{25}$ +13.3 (*c* 1.0, MeOH).

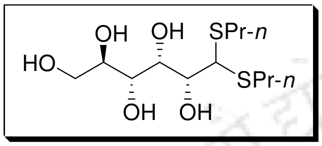
2,3,4,5-Tetra-O-acetyl-L-arabinose dipropyl dithioacetal (**84**)



Syrup; $[\alpha]_D^{25}$ –35 (*c* 1.0, MeOH); **IR** (KBr): 2964, 1749, 1372, 1217, 1044 cm^{-1}; ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 0.96–1.01 (m, 6H, 2 × SCH$_2$CH$_2$CH_3), 1.56–1.63 (m, 4H, 2 × SCH$_2$CH_2), 2.05 (s, 3H, COCH_3), 2.06 (s, 3H, COCH_3), 2.11 (s, 3H, COCH_3), 2.12 (s, 3H, COCH_3), 2.50–2.74 (m, 4H, 2 × SCH_2CH$_2$), 3.86 (d, 1H, J = 8.4 Hz, H-1), 4.01 (dd, 1H, J = 6.0 Hz, J = 12.4 Hz, H-5), 4.27 (dd, 1H, J = 3.2 Hz, J = 12.4 Hz, H-5'), 5.10–

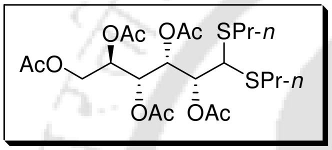
5.13 (m, 1H, H-4), 5.26 (dd, 1H, *J* = 2.8 Hz, *J* = 8.4 Hz, H-2), 5.74 (dd, 1H, *J* = 2.8 Hz, *J* = 8.0 Hz, H-3); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 13.6, 13.8, 20.9, 21.0, 21.1, 22.5, 22.7, 32.9, 33.0, 52.4, 62.3, 68.9, 69.6, 70.9, 169.7, 170.0, 170.2, 170.8; **Anal. Calcd** for $C_{19}H_{32}O_8S_2$ (452.59): C, 50.42; H, 7.13; S, 14.17. Found: C, 50.31; H, 7.00; S, 14.06.

D-Glucose dipropyl dithioacetal (**73**)



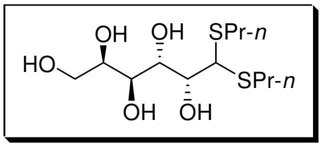
Light yellow solid; M.p. 148–150 ºC (recrystallized from water/ ethanol/ ethyl acetate: 3:1:1); $[\alpha]_D^{25}$ –6.4 (*c* 1.0, MeOH).

2,3,4,5,6-Penta-O-acetyl-D-glucose dipropyl dithioacetal (**85**)



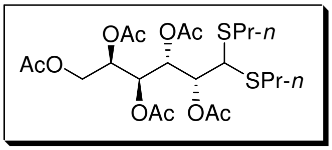
Syrup; $[\alpha]_D^{25}$ –6.3 (*c* 1.0, MeOH); **IR** (KBr): 2961, 1747, 1369, 1215, 1061, 1029 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 0.95 (t, 3H, *J* = 7.2 Hz, $SCH_2CH_2CH_3$), 1.02 (t, 3H, *J* = 7.6 Hz, $SCH_2CH_2CH_3$), 1.51–1.69 (m, 4H, 2 × SCH_2CH_2), 2.02 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 2.07 (s, 3H, $COCH_3$), 2.12 (s, 3H, $COCH_3$), 2.40–2.78 (m, 1H, $SCHHCH_2$), 2.50–2.56 (m, 1H, $SCHHCH_2$), 2.58–2.66 (m, 1H, $SCHHCH_2$), 2.74–2.82 (m, 1H, $SCHHCH_2$), 4.01 (d, 1H, *J* = 4.4 Hz, H-1), 4.11 (dd, 1 H, *J* = 4.8 Hz, *J* = 12.4 Hz, H-6), 4.20 (dd, 1H, *J* = 3.2 Hz, *J* = 12.4 Hz, H-6'), 5.01–5.05 (m, 1H, H-5), 5.25 (dd, 1H, *J* = 4.0 Hz, *J* = 7.6 Hz, H-2), 5.40 (dd, 1H, *J* = 2.8 Hz, *J* = 8.4 Hz, H-4), 5.74 (dd, 1H, *J* = 2.8 Hz, *J* = 7.6 Hz, H-3); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 13.6, 20.7, 20.8, 20.89, 20.9, 22.7, 33.1, 33.8, 51.3, 61.6, 68.4, 68.5, 70.02, 72.3, 169.8, 170.03, 170.04, 170.4, 170.7; **Anal. Calcd** for $C_{22}H_{36}O_{10}S_2$ (524.65): C, 50.37; H, 6.92; S, 12.22. Found: C, 50.28; H, 6.81; S, 12.01.

D-Galactose dipropyl dithioacetal (**74**)



White needles; M.p. 151–154 ºC (recrystallized from water/ ethanol/ethyl acetate: 3:1:1); $[\alpha]_D^{25}$ +10.8 (*c* 1.0, MeOH).

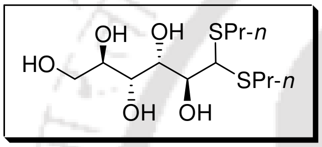
2,3,4,5,6-Penta-O-acetyl-D-galactose dipropyl dithioacetal (**86**)



Syrup; $[\alpha]_D^{25}$ +6.6° (*c* 0.80, MeOH); **IR** (KBr): 2961, 1750, 1371, 1215, 1030 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ*

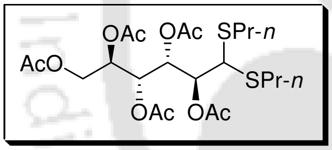
0.98 (t, 3H, *J* = 7.2 Hz, $SCH_2CH_2CH_3$), 0.99 (t, 3H, *J* = 7.6 Hz, $SCH_2CH_2CH_3$), 1.52–1.64 (m, 4H, 2 × SCH_2CH_2), 2.02 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 2.11 (s, 6H, 2 × $COCH_3$), 2.13 (s, 3H, $COCH_3$), 2.60–2.70 (m, 4H, 2 × SCH_2CH_2), 3.79 (d, 1H, *J* = 8.4 Hz, H-1), 3.84 (dd, 1H, *J* = 7.2 Hz, *J* = 12.0 Hz, H-6), 4.28 (dd, 1H, *J* = 5.2 Hz, *J* = 12.0 Hz, H-6'), 5.15 (dd, 1H, *J* = 2.0 Hz, *J* = 8.4 Hz, H-2), 5.17–5.20 (m, 1H, H-5), 5.24 (d, 1H, *J* = 2.0 Hz, *J* = 9.6 Hz, H-4), 5.79 (dd, 1H, *J* = 2.0 Hz, *J* = 9.6 Hz, H-3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.7, 13.8, 20.9, 21.0, 21.2, 22.6, 22.7, 33.1, 33.6, 52.7, 62.4, 68.0, 68.2, 68.5, 70.7, 169.7, 170.1, 170.4, 170.6, 170.7; **Anal. Calcd** for $C_{22}H_{36}O_{10}S_2$ (524.65): C, 50.37; H, 6.92; S, 12.22. Found: C, 50.26; H, 6.85; S, 12.13.

D-Mannose dipropyl dithioacetal (**75**)



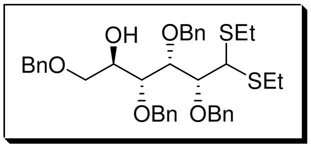
White reddish needles; M.p. 130–132 ºC (recrystallized from water/ethanol/ethyl acetate: 3:1:1); $[\alpha]_D^{25}$ +4.3 (*c* 1.0, MeOH).

2,3,4,5,6-Penta-O-acetyl-D-mannose dipropyl dithioacetal (**87**)



Syrup; $[\alpha]_D^{25}$ +26.1 (*c* 1.2, MeOH); **IR** (KBr): 2964, 1750, 1372, 1218, 1052 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.98 (t, 3H, *J* = 7.6 Hz, $SCH_2CH_2CH_3$), 1.01 (t, 3H, *J* = 7.6, $SCH_2CH_2CH_3$), 1.54–1.66 (m, 4H, 2 × SCH_2CH_2), 2.05 (s, 3H, $COCH_3$), 2.07 (s, 6H, 2 × $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 2.53–2.62 (m, 2H, SCH_2CH_2), 2.64–2.72 (m, 2H, SCH_2CH_2), 3.87 (d, 1H, *J* = 6.0 Hz, H-1), 4.08 (dd, 1H, *J* = 5.2 Hz, *J* = 12.8 Hz, H-6), 4.20 (dd, 1H, *J* = 2.4 Hz, *J* = 12.8 Hz, H-6'), 5.05–5.09 (m, 1H, H-5), 5.28 (dd, 1H, *J* = 6.0 Hz, *J* = 7.2 Hz, H-2), 5.50 (dd, 1H, *J* = 1.6 Hz, *J* = 9.2 Hz, H-4), 5.74 (dd, 1H, *J* = 1.6 Hz, *J* = 7.2 Hz, H-3); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.7, 20.9, 21.0, 22.5, 22.6, 33.2, 33.5, 52.1, 62.0, 67.4, 68.2, 69.2, 71.4, 169.9, 170.1, 170.8; **Anal. Calcd** for $C_{22}H_{36}O_{10}S_2$ (524.65): C, 50.37; H, 6.92; S, 12.22. Found: C, 50.29; H, 6.80; S, 11.97.

2,3,4,6-Tetra-O-benzyl-D-glucose diethyl dithioacetal (**7**)



White syrup; $[\alpha]_D^{25}$ +27 (*c* 1.0, MeOH); **IR** (KBr): 3492, 2925, 1454, 1100, 697 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.17 (t, 3H, *J* = 7.6 Hz, SCH_2CH_3), 1.18 (t, 3H, *J* = 7.2 Hz, SCH_2CH_3), 2.50–2.60 (m, 2H, SCH_2CH_3), 2.66 (q, 2H, *J* = 7.6 Hz, SCH_2CH_3), 3.08 (d, 1H, *J* = 5.2 Hz, OH), 3.61 (dd, 1H, *J* = 5.6 Hz, *J* = 10.0 Hz, H-6), 3.66 (dd, 1H, *J* = 4.0 Hz, *J* = 10.0 Hz, H-6'), 3.71 (dd, 1H, *J* = 3.6 Hz, *J* = 6.8 Hz, H-4), 3.93 (d, 1H, *J* = 4.0 Hz, H-1), 4.03–4.15 (m, 1H, H-5), 4.14 (dd, 1H, *J* = 4.0 Hz, *J* = 6.8 Hz, H-2), 4.27 (dd, 1H, *J* = 3.6 Hz, 6.8 Hz, H-3), 4.49–4.59 (m, 4H, 2 × C*H*$_2$), 4.67 (d, 1H, *J* = 11.6 Hz, *CH*H), 4.79 (d, 1H, *J* = 11.6, CH*H*), 4.80 (d, 1H, *J* = 11.2, *CH*H), 4.89 (d, 1H, *J* = 11.2 Hz, CH*H*), 7.23–7.38 (m, 20H, Ar*H*); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 14.6, 25.5, 25.7, 54.0, 71.1, 71.6, 73.0, 73.7, 75.1, 75.5, 77.5, 80.3, 82.9, 127.6, 127.9, 127.96, 128.0, 128.03, 128.2, 128.3, 128.4, 128.6, 138.1, 138.4, 138.7; **Anal. Calcd** for $C_{38}H_{36}O_5S_2$ (646.28): C, 70.55; H, 7.17; S, 9.91. Found: C, 70.46; H, 7.03; S, 9.82.

*XRD for Compounds **16** and **76***

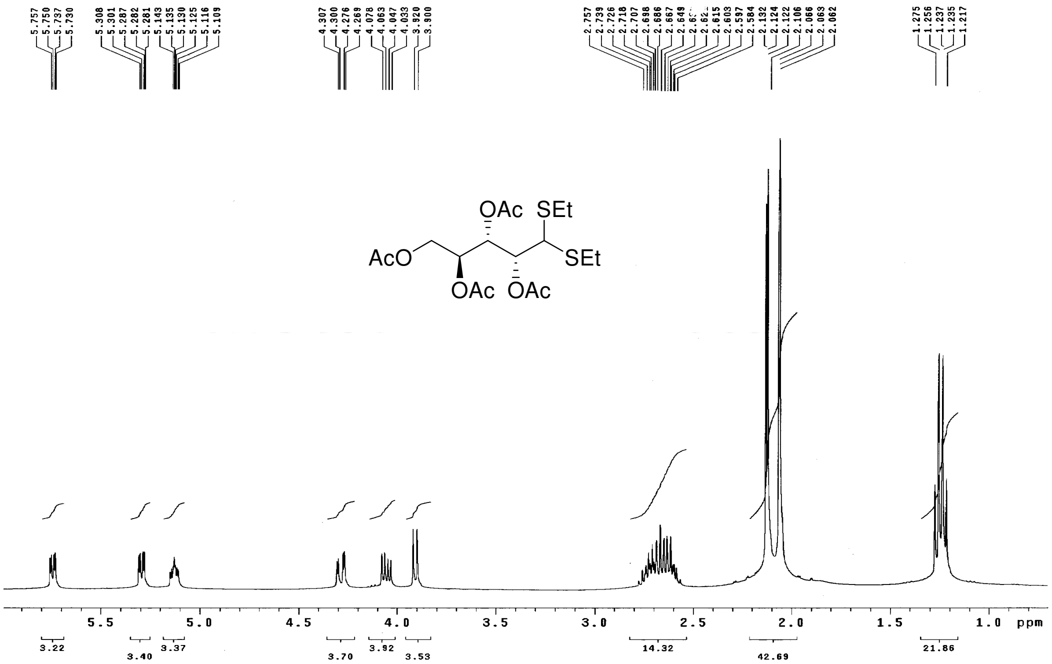
Complete crystallographic data of **16** and **76** for the structural analyses have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. are 687605 and 687604 respectively. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

Table 4. Crystal data and structures refinement for the compounds **16** and **76**, for atomic coordinates and equivalent isotropic displacement parameters and bond angles, please check the CIF.

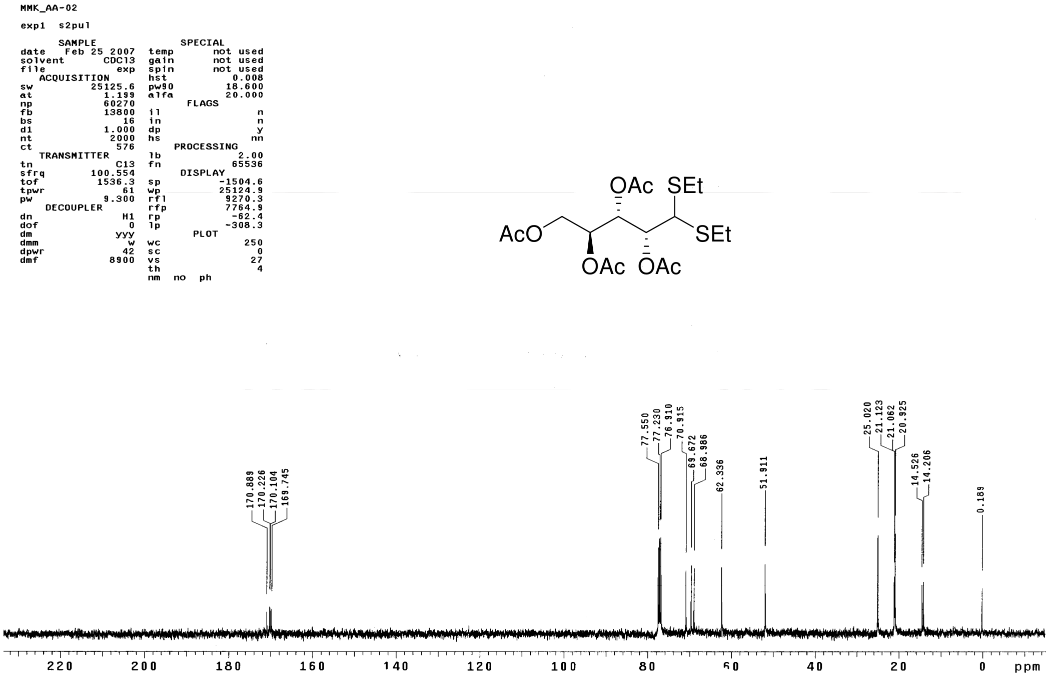
Parameters	**Compound 16**	**Compound 76**
Empirical formula	$C_{20}H_{32}O_{10}S_2$	$C_{17}H_{28}O_8S_2$
Formula weight	496.58	424.51
Temperature	298(2) K	298(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic
Space group	P 21	P 21
Unit cell dimensions		
a	13.10100(10) Å	9.5981(2) Å
b	7.97840(10) Å	8.1725(2) Å
c	14.03080(10) Å	14.3102(3) Å
α	90.00°	90.00°

β	115.6060(10)°	96.5400(10)
γ	90.00°	90.00°
Volume	1322.53(2) Å^3	1115.19(4) Å^3
Z	2	2
Density (calculated)	1.247 g/cm^3	1.264 g/cm^3
Absorption coefficient	0.248 mm^{-1}	0.276 mm^{-1}
F(000)	528	452
Theta range for data collection	1.61 to 28.31°	1.43 to 28.26°
Index ranges	-13<=h<=17, -10<=k<=9, -18<=l<=18	-12<=h<=12, -10<=k<=10, -18<=l<=17
Reflections collected	16439	13789
Independent reflections	5487 R_{int} = 0.0177	5072 R_{int} = 0.0166
Completeness to θ°	92.8% (θ = 28.31°)	97.0% (θ = 28.26°)
Refinement method	Full-matrix least-squares on F2	Full-matrix least-squares on F2
Data / restraints / parameters	5487 / 1 / 296	5072 / 1 / 251
Goodness-of-fit on F2	0.994	1.037
Final R indices [>2sigma(I)]	R_{obs} = 0.0397, wR_{obs} = 0.1096	R_{obs} = 0.0390, wR_{obs} = 0.0991
R indices (all data)	R_{all} = 0.0485, wR_{all} = 0.1155	R_{all} = 0.0476, wR_{all} = 0.1061

***^{1}H NMR (400 MHz, CDCl$_3$):** 2,3,4,5-Tetra-O-acetyl-L-arabinose diethyl dithioacetal* (**76**)



***^{13}C NMR (100 MHz, CDCl$_3$):** 2,3,4,5-Tetra-O-acetyl-L-arabinose diethyl dithioacetal* (**76**)



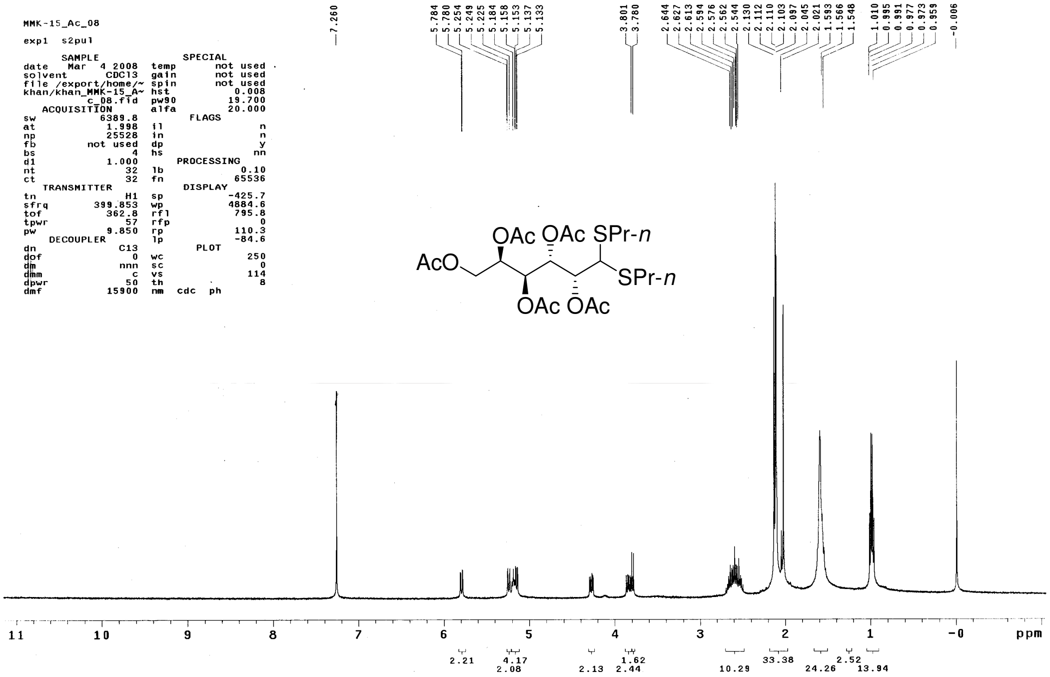
```
MMK_AA-02

exp1  s2pul

      SAMPLE               SPECIAL
date   Feb 25 2007   temp        not used
solvent      CDC13   gain        not used
file           exp   spin        not used
   ACQUISITION       hst            0.008
sw         25125.6   pw90          18.600
at           1.199   alfa          20.000
np           60270           FLAGS
fb           13800   il                 n
bs              16   in                 n
d1           1.000   dp                 y
nt            2000   hs                nn
ct             576         PROCESSING
   TRANSMITTER       lb              2.00
tn             C13   fn             65536
sfrq       100.554           DISPLAY
tof         1536.3   sp           -1504.6
tpwr            61   wp           25124.9
pw           9.300   rfl           9270.3
    DECOUPLER        rfp           7764.9
dn              H1   rp             -62.4
dof              0   lp            -308.3
dm             yyy            PLOT
dmm              w   wc               250
dpwr            42   sc                 0
dmf           8900   vs                27
                     th                 4
                     nm  no  ph
```

Figure 1

***¹H NMR (400 MHz, CDCl₃):** 2,3,4,5,6-Penta-O-acetyl-D-galactose dipropyl dithioacetal* (**86**)



***¹³C NMR (100 MHz, CDCl₃):** 2,3,4,5,6-Penta-O-acetyl-D-galactose dipropyl dithioacetal* (**86**)

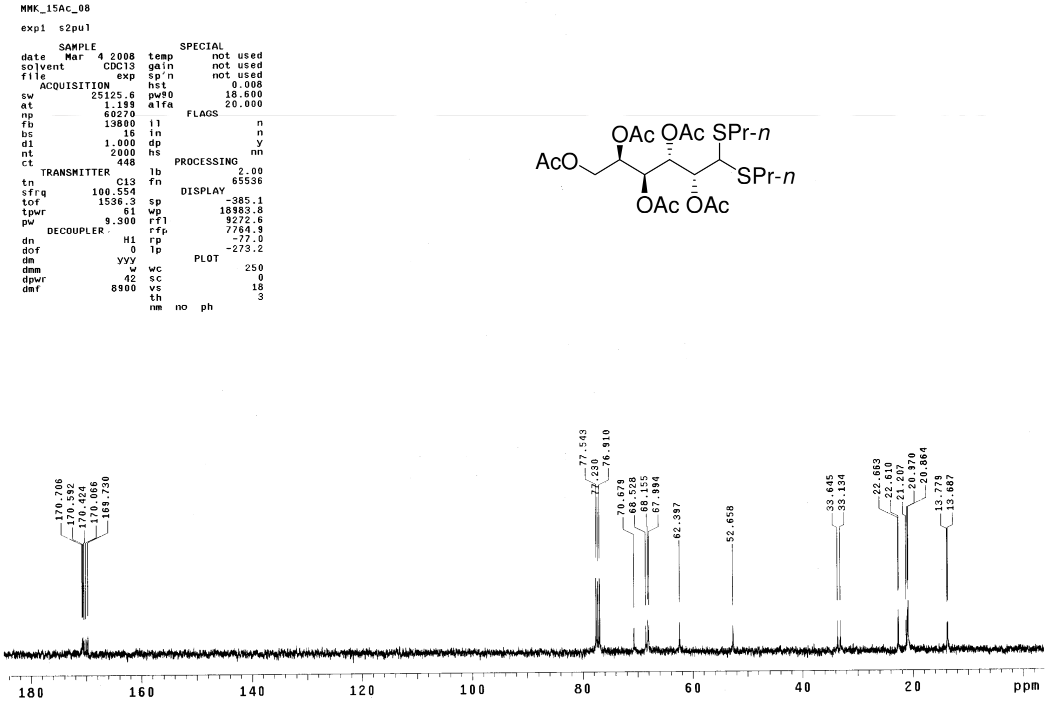
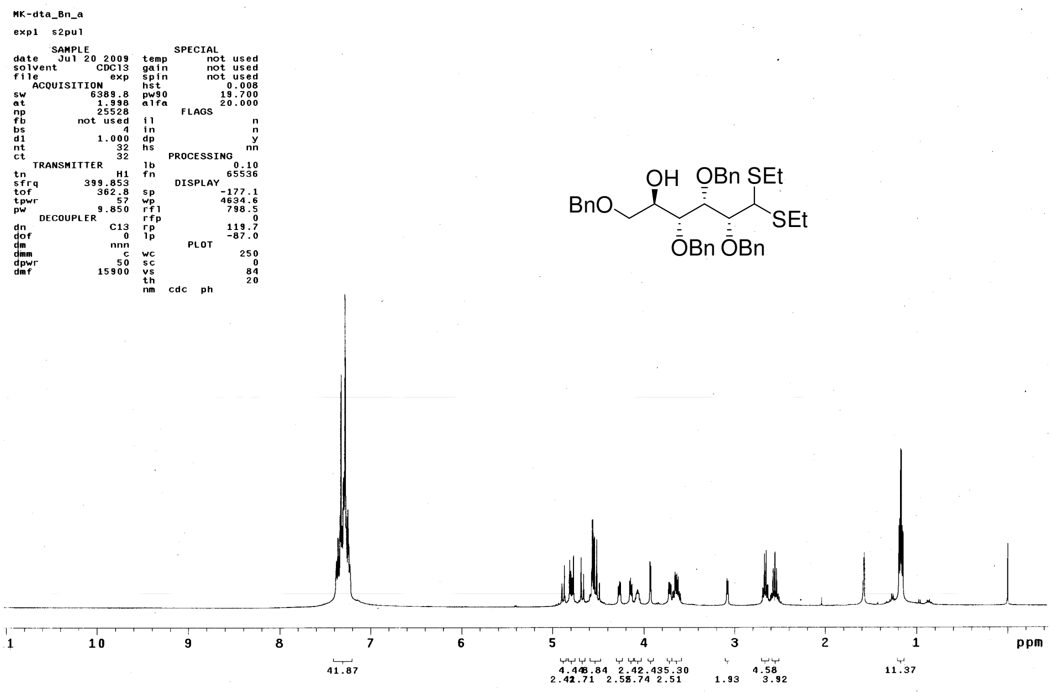


Figure 2

***^{1}H NMR (400 MHz, CDCl$_3$):** 2,3,4,6-Tetra-O-benzyl-D-glucose diethyl dithioacetal* (**7**)

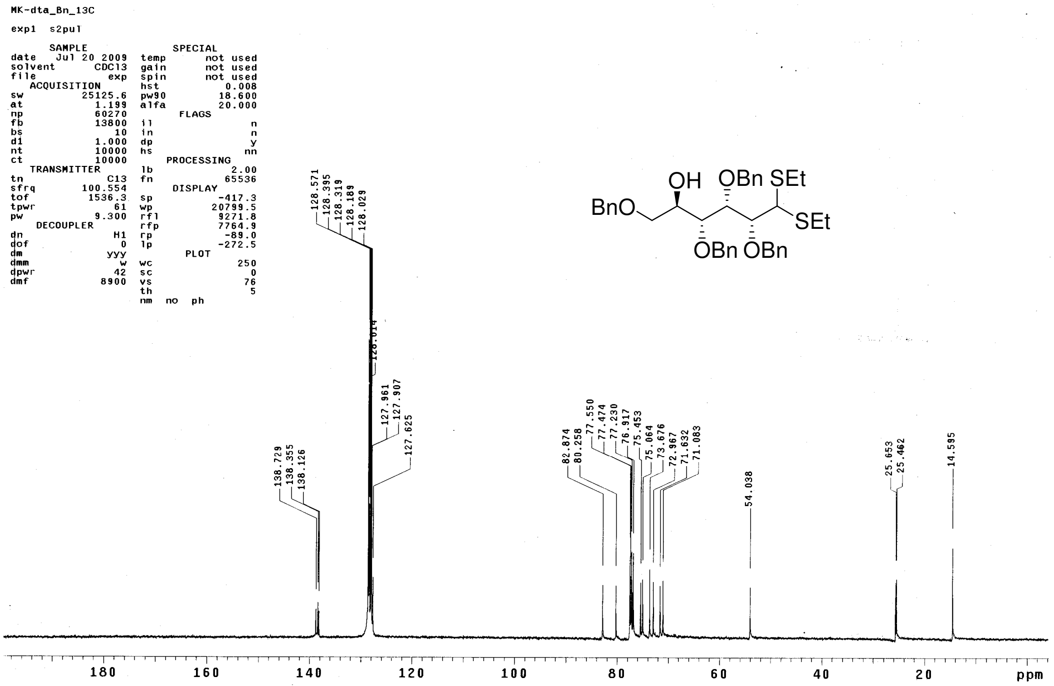


```
MK-dta_Bn_a

exp1  s2pul

      SAMPLE              SPECIAL
date   Jul 20 2009  temp        not used
solvent      CDCl3  gain        not used
file           exp  spin        not used
   ACQUISITION      hst            0.008
sw          6389.8  pw90          19.700
at           1.998  alfa          20.000
np           25528         FLAGS
fb        not used  il                 n
bs               4  in                 n
d1           1.000  dp                 y
nt              32  hs                nn
ct              32        PROCESSING
   TRANSMITTER      lb              0.10
tn              H1  fn             65536
sfrq       399.853         DISPLAY
tof          362.8  sp            -177.1
tpwr            57  wp            4634.6
pw           9.850  rfl            798.5
    DECOUPLER       rfp                0
dn             C13  rp             119.7
dof              0  lp             -87.0
dm             nnn           PLOT
dmm              c  wc               250
dpwr            50  sc                 0
dmf          15900  vs                84
                    th                20
                    nm  cdc  ph
```

***^{13}C NMR (100 MHz, CDCl$_3$):** 2,3,4,6-Tetra-O-benzyl-D-glucose diethyl dithioacetal* (**7**)



```
MK-dta_Bn_13C

exp1  s2pul

      SAMPLE              SPECIAL
date   Jul 20 2009  temp        not used
solvent      CDCl3  gain        not used
file           exp  spin        not used
   ACQUISITION      hst            0.008
sw         25125.6  pw90          18.600
at           1.199  alfa          20.000
np           60270         FLAGS
fb           13800  il                 n
bs              10  in                 n
d1           1.000  dp                 y
nt           10000  hs                nn
ct           10000        PROCESSING
   TRANSMITTER      lb              2.00
tn             C13  fn             65536
sfrq       100.554         DISPLAY
tof         1536.3  sp            -417.3
tpwr            61  wp           20799.5
pw           9.300  rfl           9271.8
    DECOUPLER       rfp           7764.9
dn              H1  rp             -89.0
dof              0  lp            -272.5
dm             yyy           PLOT
dmm              w  wc               250
dpwr            42  sc                 0
dmf           8900  vs                76
                    th                 5
                    nm  no  ph
```

Figure 3

PART A

CHAPTER 3

O-Isopropylidenation of Sugars

PART A

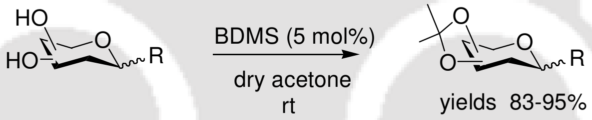
CHAPTER 3.1

Synthesis of *O*-isopropylidene derivatives of carbohydrate using bromodimethylsulfonium bromide (BDMS)

Results and Discussion

In the previous Chapter, we have demostrated the efficiency and catalytic activity of the bromodimethylsulfonium bromide (BDMS) for preparation of dithioacetal derivatives of sugar. On the basis of our experience and continuation of our research program, we conceived that the same reagent can be implemented for *O*-isopropylidenation of carbohydrates. As a matter of fact, the *O*-isopropylidene derivatives of sugars, which are also known as acetonides of aldoses and ketoses, has been used extensively in carbohydrate chemistry to protect selectively the hydroxyl groups of the different sugars.[11] Some of the applications of *O*-isopropylidene derivatives of sugars and their methods of preparation have already been discussed in Chapter 1. Therefore, it seems to us that there is a further research interest to develop a new methodology for *O*-isopropylidenation of carbohydrates, which might be simple, efficient and economic.

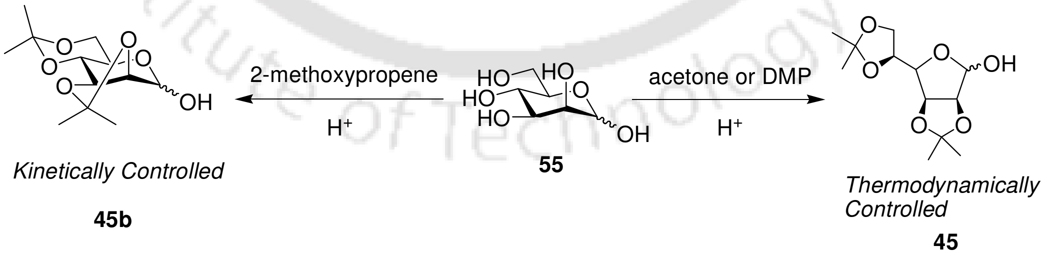
In Chapter 3, a practical and efficient method for the synthesis of *O*-isopropylidene derivatives of sugars at room temperature by involving bromodimethylsulfonium bromide (BDMS) as a catalyst has been achieved which illustrated in Scheme 25.



Scheme 25

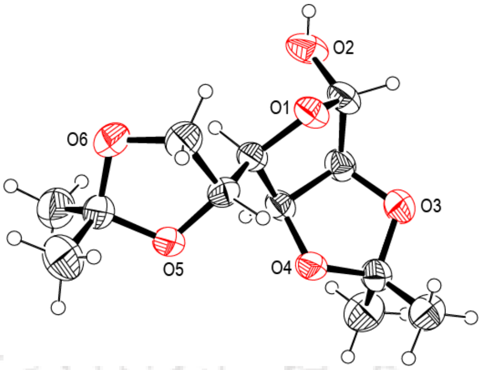
The preparation of catalyst bromodimethylsulfonium bromide (BDMS) already mentioned in the Experimental Section in Chapter 2. When a mixture of D-glucose (0.360 g, 2 mmol) in dry acetone (10 mL) was treated with BDMS (0.10 mmol) at room temperature, it gave 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose (**29**) in 84% yield, as per our expectation. The product **29** was fully characterized by recording melting point, IR, ^{1}H and ^{13}C NMR spectra, optical rotation and elemental analysis. ^{1}H NMR spectrum gives the signals at δ 1.32 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 2.58 (d, 1H, J = 3.6 Hz, OH), 3.99 (dd, 1H, J = 5.6 Hz, J = 8.4 Hz, H-6), 4.08 (dd, 1H, J = 2.8 Hz, J = 7.6 Hz, H-4), 4.18 (dd, 1H, J = 6.4 Hz, J = 8.4 Hz, H-6'), 4.32–4.37 (m, 2H, H-3 and H-5), 4.54 (d, 1H, J = 3.6 Hz, H-2), 5.95 (d, 1H, J = 3.6 Hz, H-1) ppm. The four signals of methyl groups at 1.32, 1.37, 1.45 and 1.50 clearly indicate the formation of di-*O*-isopropylidine derivative. Similary, ^{13}C NMR spectrum exhibit peaks at δ 25.3, 26.3, 26.9, 27.0, 67.8, 73.4, 75.2, 81.3, 85.2, 105.4, 109.8 and 112.0. The spectral data were compared and found to be in good agreement with the earlier reported data.[37] Then the same reaction was carried out with 2,2-dimethoxypropane (DMP) in acetonitrile by employing the same amount of catalyst at room temperature. In this case we obtained the product **29** in 90% yield. The important feature is that it took relatively much less reaction time than using dry acetone, which is shown in Table 4.

From the outcome of this reaction, we conclude that we have obtained only thermodynamically controlled product. Next, we have studied the reactions of D-galactose (**50**) with acetone as well as DMP using same mol% catalyst under identical reaction conditions. In both the cases, we got thermodynamically controlled product 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (**18**) in 85% and 91%, respectively. After these encouraging results, D-mannose (**55**) was kept for isopropylidenation with acetone as well as with DMP individually under similar reaction conditions. The furnished product was 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**45**) from both the reactions in good yields. The ^{1}H NMR and ^{13}C NMR spectra of compounds **18** and **45** are shown in the Experimental Section (Figures 1 and 2). From the literature, it reveals[12] that isopropylidenation of D-mannose usually provides thermodynamically controlled product **45** preferably on reaction with acetone or DMP in presence of acid catalyst instead of **45b** as shown in Scheme 26. However, recently Mukhopadhyay *et al.* wrongly reported[38] the formation of 2,3:4,5-di-*O*-isopropylidene-D-mannopyranose (**45b),** a kinetically controlled product, using dry acetone in presence of silica supported sulfuric acid though the spectral data are closely matched with our compound.



Scheme 26

To resolve the ambiguity of the structure**,** we have collected single XRD data of the product and it was found that the structure of the product was 2,3:4,5-di-*O*-isopropylidene-D-α-mannofuranose (**45)** instead of kinetically controlled product **45b**, which is shown in Figure 2.



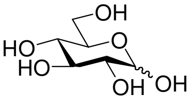
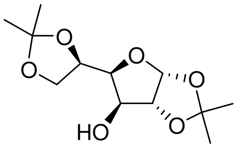
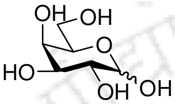
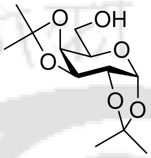
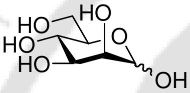
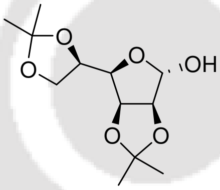
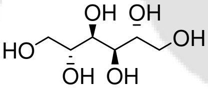
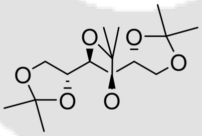
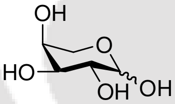
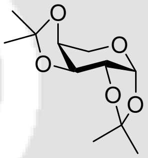
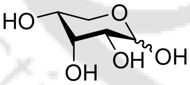
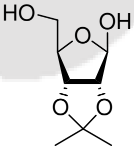
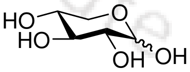
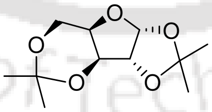
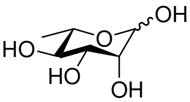
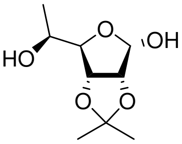
45b (CCDC no. 685637)

Figure 2. *ORTEP molecular diagram with ellipsoid at 35% probability of **45b***

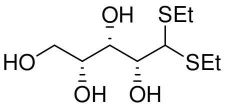
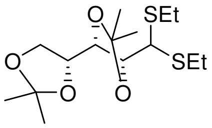
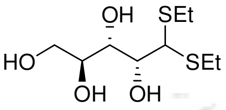
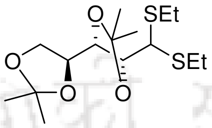
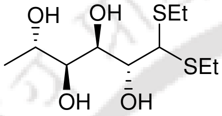
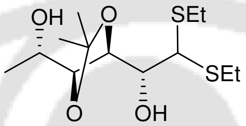
Likewise, D-mannitol (**56**) was converted into the corresponding 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol (**35**) in very good yields. Similarly, various aldopentoses such as L-arabinose (**59**), D-ribose (**61**), D-xylose (**62**) and L-rhamnose (**64**) were converted to the corresponding *O*-isopropylidene derivatives **88-91** in good yields using dry acetone in the presence of 5 mol% BDMS as shown in Table 4.

To show the generality of our protocol, a series of diethyl dithioacetals of sugar such as D-xylose, L-arabinose and L-rhamnose were further examined using identical conditions. The products **92-94** were obtained in good yields from the corresponding dithioacetals derivative. The results are summarized in Table 4 and all these products were characterized by recording ^{1}H NMR, ^{13}C NMR spectra as well as elemental analysis. Interestingly, the diethyl dithioacetal group remains unaffected during the experimental conditions. Notably, we have also verified that the conversion of the various free sugars to the corresponding *O*-isopropylidene derivatives even in a larger scale (100 mmol) without any difficulty by using 3 mol% of the catalyst instead of required 5 mol% catalyst. For instance, when a mixture of D-mannitol (**56**, 18.22 g, 100 mmol) and dry acetone (400 mL) was treated with bromodimethylsulfonium bromide (0.670 g, 3 mmol), it was smoothly converted within 3 h to the *O*-isopropylidene derivative **35** in 92% yield. The following work up procedure was followed for the large scale reaction. After completing the reaction, the reaction mixture was neutralized with solid $NaHCO_3$ and then it was passed through a celite pad. Acetone was removed in rotatory evaporator and the crude solid residue was recrystallized from ethanol to obtain the pure product. The product **35** was obtained 27.82 g from the reaction. In this reaction, we have obtained much better yield as well as reaction time is shorter than concentrated H_2SO_4 method.[16]

Table 4. Preparation of *O*-isopropylidene derivatives of sugar using BDMS

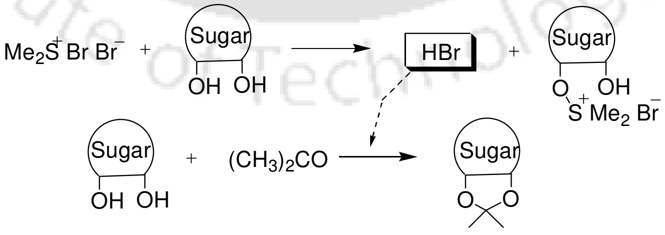
Substrate No.	Substrate	Product	Product No.	Method/ Time (h)	Yield[a,b] (%)
60			**29**	A / 10 B / 4	84[c] 90
50			**18**	A / 10 B / 4	85[c] 91
55			**45**	A / 2 B / 1	90 95
56			**35**	A / 3 B / 1	86[c] 89
59			**88**	A / 10	86
61			**89**	A / 2	86
62			**90**	A / 2	91
64			**91**	A / 2	88

Continued Table 4

Substrate No.	Substrate	Product	Product No.	Method/ Time (h)	Yield[a,b] (%)
11			**92**	A / 2	83
14			**93**	A / 2	86
70			**94**	A / 2	89

Method A: *Sugar (2 mmol) in dry acetone (10 mL) using BDMS (22 mg, 0.1 mmol).* ***Method B:*** *Sugar (2 mmol) in dry acetonitrile (10 mL) and 2,2-dimethoxypropane (1.0 mL, 8.14 mmol) using BDMS (22 mg, 0.1 mmol.).* [a]*Isolated yield.* [b]*All products were characterized by recording* ^{1}*H NMR,* ^{13}*C NMR, specific rotation and elemental analysis.* [c]*The trace amount of sugar remains undissolved.*

The formation of the products can be rationalized as follows. It has been proposed that BDMS may generate dry HBr in the medium on reaction with sugars. We believe that *in situ* generated dry HBr catalyzes the *O*-isopropylidenation reaction of sugars or sugar derivatives into the corresponding *O*-isopropylidene derivatives as shown in Scheme 27. It is also noted that the pH of the solution is ~2-3 during the reaction. The reaction of D-mannitol (**56**) and dry acetone was also examined with equivalent amount of aqueous 48% HBr at room temperature. It was observed that it took much longer reaction time (5h) as well as provides relatively low yield (70%).



Scheme 27

In summary, we have developed a simple, efficient and catalytic method for the preparation of *O*-isopropylidene derivatives from free sugar as well as from other sugar derivatives by employing BDMS as a catalyst. The notable advantages of the present protocol are good yields, clean reaction and short reaction times. The reaction products can be obtained by direct recrystallization in case of solid products without going through tedious chromatographic separation as well as by non-aqueous work-up. Due to its operational simplicity, generality and efficacy, this method is expected to have much wider applicability for the preparation of *O*-isopropylidene sugar derivatives on a large scale in future.

Experimental

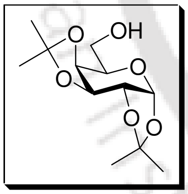
Method A: *By using anhydrous acetone*

Bromodimethylsulfonium bromide (BDMS) (22 mg, 0.10 mmol) was added to a stirred solution of sugar (2 mmol) in dry acetone (10 mL) at room temperature. The reaction time was monitored by TLC as mentioned in Table 4. After completion of the reaction, the reaction mixture was concentrated in rotary evaporator. The crude residue was recrystallized in ethanol to obtain the desire product. However, in case of liquid product or low melting solid product, the crude residue was passed through a silica gel column to get the pure product.

Method B: *By using 2,2-dimethoxypropane*

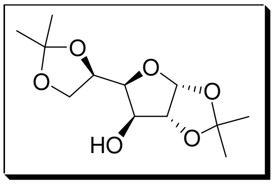
Into a mixture of sugar (2 mmol) in dry acetonitrile (10 mL) and 2,2-dimethoxypropane (1.0 mL, 8.14 mmol), bromodimethylsulfonium bromide (BDMS) (22 mg, 0.1 mmol) was added at room temperature. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated in rotary evaporator. The similar procedure was followed as above to obtain the desire product in pure form.

1,2:3,4-Di-O-isopropylidene-α-D-galactopyranose (**18**)



Colorless oil; $[\alpha]_D^{25}$ –52.6° (*c* 2.0, $CHCl_3$); **IR** (KBr): 3500, 2988, 1382, 1213, 1071, 898 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.34 (s, 6H, 2 × C*H*$_3$), 1.47 (s, 3H, C*H*$_3$), 1.54 (s, 3H, C*H*$_3$), 2.09 (s, 1H, O*H*), 3.75 (q, 1H, *J* = 8.0 Hz, H-5), 3.84–3.90 (m, 2H, H-6 and H-6'), 4.28 (d, 1H, *J* = 8.0 Hz, H-4), 4.35 (dd, 1H, *J* = 2.4 Hz, *J* = 5.2 Hz, H-2), 4.62 (dd, 1H, *J* = 2.4, *J* = 8.0 Hz, H-3), 5.58 (d, 1H, *J* = 5.2 Hz, H-1); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 24.4, 25.0, 26.0, 26.1, 62.1, 68.4, 70.6, 70.8, 71.5, 96.4, 108.8, 109.6; **Anal. Calcd** for $C_{12}H_{20}O_6$ (260.28) : C, 55.37; H, 7.74. Found: C, 55.15; H, 7.65.

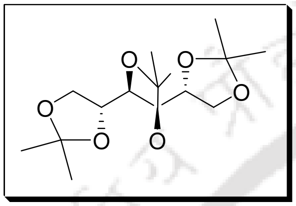
1,2:5,6-Di-O-isopropylidene-α-D-glucofuranose (**29**)



White solid; M.p. 107–109 ºC; $[\alpha]_D^{25}$ –17.8° (*c* 2.0, H_2O); **IR** (KBr): 3430, 2984, 1375, 1221, 1031, 847 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.32 (s, 3H, C*H*$_3$), 1.37 (s, 3H, C*H*$_3$), 1.45 (s, 3H, C*H*$_3$), 1.50 (s, 3H, C*H*$_3$), 2.58 (d, 1H, *J* = 3.6 Hz, O*H*), 3.99

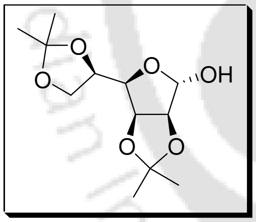
(dd, 1H, *J* = 5.6 Hz, *J* = 8.4 Hz, H-6), 4.08 (dd, 1H, *J* = 2.8 Hz, *J* = 7.6 Hz, H-4), 4.18 (dd, 1H, *J* = 6.4 Hz, *J* = 8.4 Hz, H-6'), 4.32–4.37 (m, 2H, H-3 and H-5), 4.54 (d, 1H, *J* = 3.6 Hz, H-2), 5.95 (d, 1H, *J* = 3.6 Hz, H-1); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 25.3, 26.3, 26.9, 27.0, 67.8, 73.4, 75.2, 81.3, 85.2, 105.4, 109.8, 112.0; **Anal. Calcd** for $C_{12}H_{20}O_6$ (260.28): C, 55.37; H, 7.74. Found: C, 55.07; H, 7.68.

1,2:3,4;5,6-Tri-O-isopropylidene-D-mannitol (**35**)



White solid; M.p. 70–71 ºC; $[\alpha]_D^{25}$ +13.4° (*c* 1.0, MeOH); **IR** (KBr): 2983, 1371, 1256, 1064, 749 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.36 (s, 6H, 2 × C*H*$_3$), 1.40 (s, 6H, 2 × C*H*$_3$), 1.43 (s, 6H, 2 × C*H*$_3$), 3.95 (dd, 2H, *J* = 2.0 Hz, *J* = 4.8 Hz), 3.99 (dd, 2H, *J* = 6.0 Hz, *J* = 8.4 Hz), 4.06 (dd, 2H, *J* = 6.0 Hz, *J* = 8.4 Hz), 4.18 (dd, 1H, *J* = 2.0 Hz, *J* = 6.0 Hz), 4.22 (dd, 1H, *J* = 1.6 Hz, *J* = 6.4 Hz); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 25.5, 26.7, 27.7, 66.5, 76.5, 79.6, 109.8, 110.4; **Anal. Calcd** for $C_{15}H_{26}O_6$ (302.36): C, 59.58; H, 8.67. Found: C, 59.30; H, 8.60.

2,3:5,6-Di-O-isopropylidene-α-D-mannofuranose (**45**)



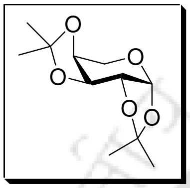
White solid; M.p. 122–123 ºC; $[\alpha]_D^{25}$ +16.1° (*c* 2.0, EtOH); **IR** (KBr): 3435, 2978, 2948, 1373, 1226, 1203, 1068, 976, 839 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.33 (s, 3H, C*H*$_3$), 1.38 (s, 3H, C*H*$_3$), 1.46 (s, 3H, C*H*$_3$), 1.47 (s, 3H, C*H*$_3$), 2.83 (d, 1H, *J* = 2.4 Hz, O*H*, D_2O exchangeable), 4.05 (dd, 1H, *J* = 4.8 Hz, *J* = 8.8 Hz, H-6), 4.09 (dd, 1H, *J* = 6.4 Hz, *J* = 8.8 Hz, H-6'), 4.19 (dd, 1H, *J* = 3.6 Hz, *J* = 7.2 Hz, H-4), 4.38–4.43 (m, 1H, H-5), 4.62 (d, 1H, *J* = 6.0 Hz, H-2), 4.82 (dd, 1H, *J* = 3.6 Hz, *J* = 6.0 Hz, H-3), 5.38 (d, 1H, *J* = 2.0 Hz, H-1); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 24.6, 25.3, 26.0, 26.9, 66.7, 73.5, 79.8, 80.3, 85.7, 101.4, 109.3, 112.8; **Anal. Calcd** for $C_{12}H_{20}O_6$ (260.28): C, 55.37; H, 7.74. Found: C, 55.29; H, 7.72.

X-ray crystallographic data for compound ***45***

2:3;5:6-Di-*O*-isopropylidene-α-D-mannofuranose (**45**): Empirical formula $C_{12}H_{20}O_6$, colorless prismatic crystal, formula wt. 260.28, orthorhombic, P2(1), *a* = 6.6693(9), *b* = 10.8368(18), *c* = 18.904(3) Å, *V* = 1366.3(4) Å^3 , *Z* = 4, μ (λ Mo-K$_\alpha$ 0.71073 Å) = 0.101 mm^{-1}. *F*(000) = 560, *GOF*(S) = 0.986. Final indices *R1*= 0.0418, *wR2*=

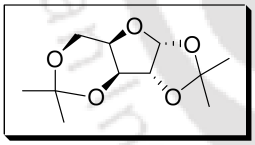
0.0899 with $I > 2\sigma(I)$; $R1$= 0.0857, $wR2$= 0.1060 for all data. Complete crystallographic data of **45** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC no. 685637. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

1,2:3,4-Di-O-isopropylidene-L-arabinopyranose (**88**)



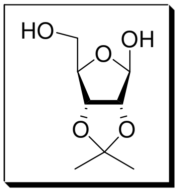
White solid; M.p. 41–43 ºC; $[\alpha]_D^{25}$ +6.4° (*c* 1.5, H_2O); **IR** (KBr): 2987, 2937, 1381, 1251, 1212, 1078, 879 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.34 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.54 (s, 3H, CH_3), 3.68 (dd, 1H, *J* = 1.2 Hz, *J* = 12.8 Hz, H-5), 3.84 (dd, 1H, *J* = 2.0 Hz, *J* = 12.8 Hz, H-5'), 4.24 (dt, 1H, *J* = 1.2 Hz, *J* = 8.0 Hz, H-4), 4.31 (dd, 1H, *J* = 2.4 Hz, *J* = 5.2 Hz, H-2), 4.57 (dd, 1H, *J* = 2.4 Hz, *J* = 8.0 Hz, H-3), 5.51 (d, 1H, *J* = 5.2 Hz, H-1); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 24.3, 25.1, 26.1, 26.2, 60.3, 70.0, 70.7, 70.9, 96.0, 108.5, 109.0; **Anal. Calcd** for $C_{11}H_{18}O_5$ (230.26): C, 57.38; H, 7.88. Found: C, 57.20; H, 7.81.

1,2:3,5-Di-O-isopropylidene-α-D-xylofuranose (**89**)



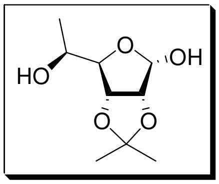
White solid; M.p. 42–44 ºC; $[\alpha]_D^{25}$ +12.2° (*c* 1.5, H_2O); **IR** (KBr): 2990, 2938, 1375, 1200, 1165, 1081, 824 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.33 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 4.03–4.04 (m, 1H), 4.08–4.10 (m, 2H), 4.30 (d, 1H, *J* = 2.4 Hz), 4.53 (d, 1H, *J* = 4.0 Hz), 6.01 (d, 1H, *J* = 4.0 Hz, H-1); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 18.8, 26.3, 26.9, 29.0, 60.3, 71.7, 73.3, 84.8, 97.6, 105.3, 111.8; **Anal. Calcd** for $C_{11}H_{18}O_5$ (230.26): C, 57.38; H, 7.88. Found: C, 57.16; H, 7.80.

2,3-O-Isopropylidene-D-ribofuranose (**90**)



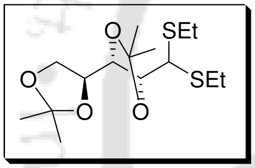
Colorless oil; $[\alpha]_D^{25}$ –25.2° (*c* 1.0, $CHCl_3$); **IR** (KBr): 3418, 2942, 1377, 1212, 1068, 869 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.33 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 3.40 (br s, 1H, OH), 3.70–3.78 (m, 2H), 4.42 (s, 1H, H-4), 4.59 (d, 1H, *J* = 6.0 Hz, H-2), 4.85 (d, 1H, *J* = 6.0 Hz, H-3), 5.43 (d, 1H, *J* = 6.0 Hz, H-1); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 24.9, 26.5, 63.7, 81.8, 86.9, 87.9, 102.9, 112.3; **Anal. Calcd** for $C_8H_{14}O_5$ (190.19): C, 50.52; H, 7.42. Found: C, 50.29; H, 7.30.

2,3-O-Isopropylidene-L-rhamnofuranose (**91**)



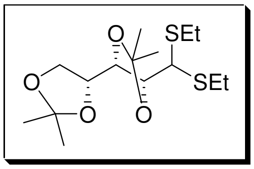
Colorless oil; $[\alpha]_D^{25}$ +16.2 (*c* 2.0, water); IR (Neat): 3434, 2923, 1489, 1071, 1021, 825 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.31 (s, 3H, C*H_3*), 1.32 (s, 3H, C*H_3*), 1.46 (s, 3H, C*H_3*), 2.61 (d, 1H, *J* = 6.0 Hz, O*H*), 2.80 (br s, 1H, O*H*), 3.93 (dd, 1H, *J* = 3.6 Hz, *J* = 7.2 Hz), 4.00–4.05 (m, 1H), 4.60 (d, 1H, *J* = 6.0 Hz), 4.87 (dd, 1H, *J* = 6.0, 3.6 Hz), 5.40 (d, 1H, *J* = 1.6 Hz, H-1); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 20.6, 24.7, 26.1, 66.8, 80.3, 83.6, 85.6, 101.1, 112.9; **Anal. Calcd** for $C_9H_{16}O_5$ (204.22): C, 52.93; H, 7.90. Found: C, 52.73; H, 7.81.

2,3:4,5-Di-O-isopropylidene-L-arabinose diethyldithioacetal (**92**)



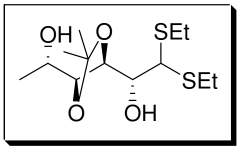
Colorless oil; $[\alpha]_D^{25}$ –80.8° (*c* 1.0, MeOH); **IR** (KBr): 2986, 2931, 1455, 1372, 1219, 1064, 847 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.23 (t, 3H, *J* = 7.6 Hz, SCH_2C*H_3*), 1.26 (t, 3H, *J* = 7.6 Hz, SCH_2C*H_3*), 1.31 (s, 3H, C*H_3*), 1.35 (s, 3H, C*H_3*), 1.39 (s, 3H, C*H_3*), 1.42 (s, 3H, C*H_3*), 2.66–2.78 (m, 4H, 2 × SC*H_2*CH_3), 3.94 (dd, 1H, *J* = 4.4 Hz, *J* = 8.4 Hz, H-5), 4.01 (d, 1H, *J* = 2.4 Hz, H-1), 4.03 (t, 1H, *J* = 4.8 Hz, H-3), 4.06–4.12 (m, 2H, H-4 and H-5'), 4.11 (dd, 1H, *J* = 2.8 Hz, *J* = 4.8 Hz, H-2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.4, 14.5, 25.0, 25.2, 25.3, 26.8, 27.2, 27.4, 52.4, 67.8, 77.2, 79.2, 84.6, 109.8, 110.2; **Anal. Calcd** for $C_{15}H_{28}O_4S_2$ (336.51): C, 53.54; H, 8.39; S, 19.06. Found: C, 53.31; H, 8.30; S, 18.86.

2,3:4,5-Di-O-isopropylidene-D-xylose diethyldithioacetal (**93**)



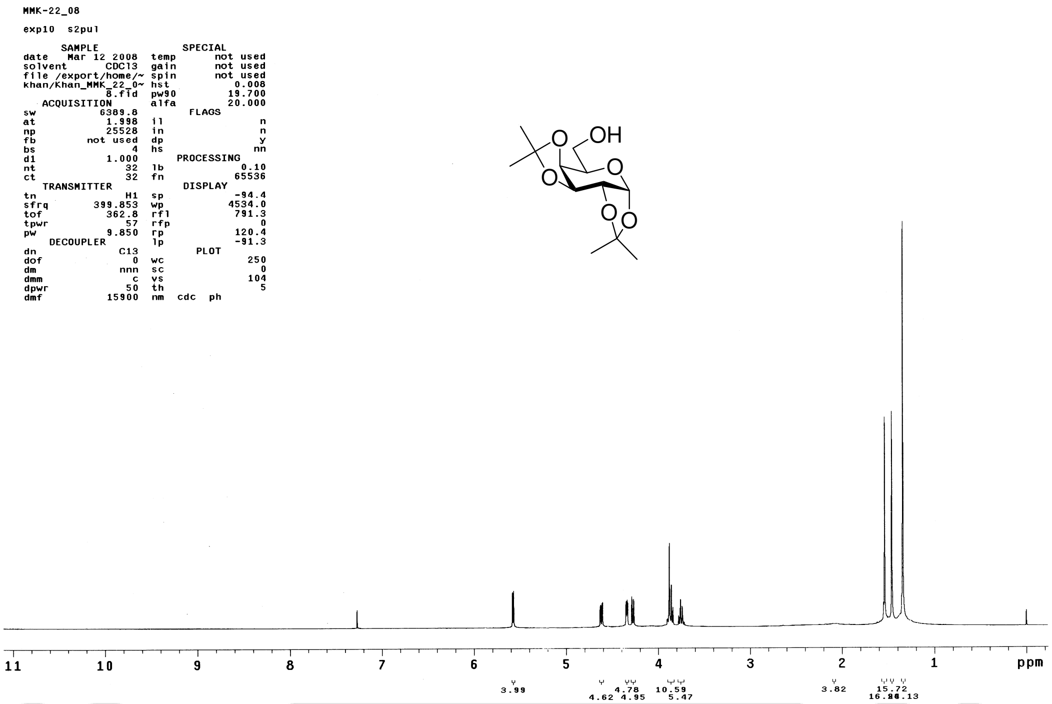
Colourless oil; $[\alpha]_D^{25}$ –68.6° (*c* 2.0, Me_2CO); **IR** (KBr): 2981, 2935, 1453, 1370, 1229, 1063, 841 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.27 (t, 3H, *J* = 7.6 Hz, SCH_2C*H_3*), 1.28 (t, 3H, *J* = 7.6 Hz, SCH_2C*H_3*), 1.38 (s, 3H, C*H_3*), 1.43 (s, 3H, C*H_3*), 1.44 (s, 3H, C*H_3*), 1.47 (s, 3H, C*H_3*), 2.69–2.81 (m, 4H, 2 × SC*H_2*CH_3), 3.91 (d, 1H, *J* = 5.6 Hz), 3.95 (d, 1H, *J* = 8.0 Hz), 4.06 (dd, 1H, *J* = 6.8 Hz, *J* = 8.0 Hz), 4.15 (dd, 1H, *J* = 3.2 Hz, *J* = 7.2 Hz), 4.32–4.36 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.5, 14.6, 25.2, 25.6, 25.8, 26.4, 27.4, 27.6, 53.3, 66.1, 75.5, 78.9, 80.3, 109.8, 110.3; **Anal. Calcd** for $C_{15}H_{28}O_4S_2$ (336.51): C, 53.54; H, 8.39; S, 19.06. Found: C, 53.28; H, 8.32; S, 19.22.

2,3-O-Isopropylidene-L-rhamnose diethyldithioacetal (**94**)



Colorless oil; $[\alpha]_D^{25}$ –30° (*c* 2.0, $CHCl_3$); **IR** (KBr): 3350, 2972, 2929, 1453, 1373, 1259, 1071, 873 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.29 (t, 3H, *J* = 7.2 Hz, SCH_2CH_3), 1.30 (t, 3H, *J* = 7.6 Hz, SCH_2CH_3), 1.31 (d, 3H, *J* = 5.6 Hz, CH_3), 1.38 (s, 6H, 2 × CH_3), 2.09 (s, 1H, O*H*), 2.68 (q, 2H, *J* = 7.6 Hz, SCH_2CH_3), 2.73 (q, 2H, *J* = 7.6 Hz, SCH_2CH_3), 3.71 (t, 1H, *J* = 7.6 Hz), 3.79 (dd, 1H, *J* = 6.4 Hz, *J* = 7.6 Hz), 3.84 (dd, 1H, *J* = 2.0 Hz, *J* = 8.8 Hz, H-2), 4.07 (dd, 1H, *J* = 7.2 Hz, *J* = 8.8 Hz, H-3), 4.19 (d, 1H, *J* = 2.0 Hz, H-1); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.6, 14.9, 20.3, 25.9, 26.2, 27.0, 54.8, 69.3, 75.6, 80.0, 84.5, 109.2; **Anal. Calcd** for $C_{13}H_{26}O_4S_2$ (310.47): C, 50.29; H, 8.44; S, 20.66. Found: C, 50.18; H, 8.36; S, 20.46.

^{1}H NMR (400 MHz, CDCl$_3$): *1,2:3,4,5-Di-O-isopropylidene-D-galactopyranose* (**18**)

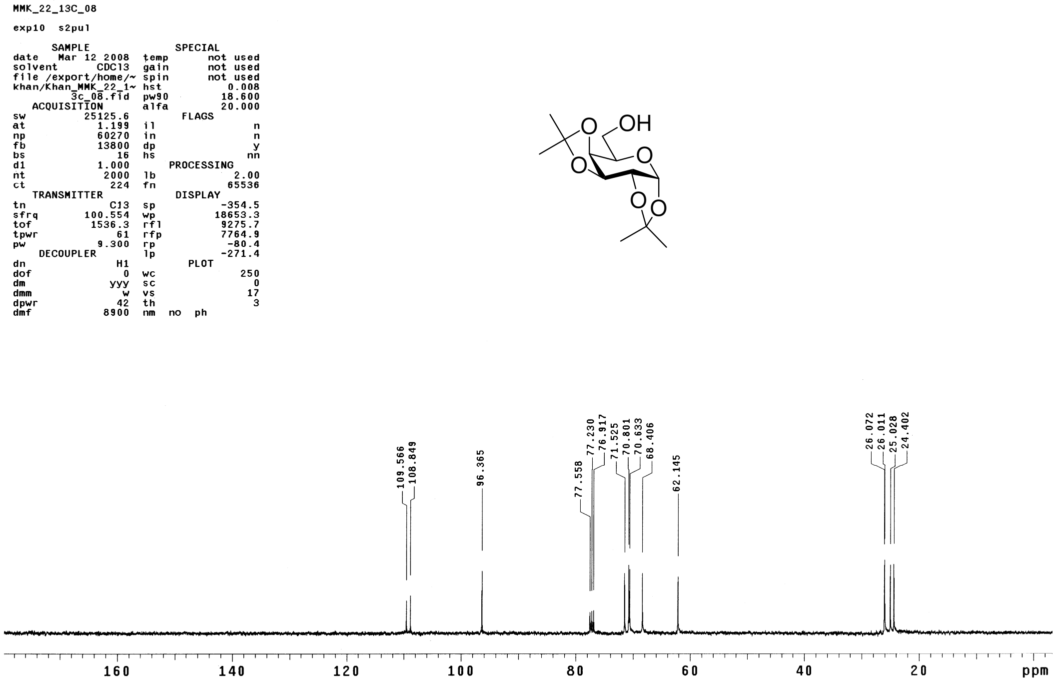


```
MMK-22_08

exp10  s2pul

      SAMPLE                SPECIAL
date   Mar 12 2008  temp       not used
solvent       CDCl3  gain       not used
file /export/home/~ spin       not used
khan/Khan_MMK_22_0~ hst           0.008
           8.fid  pw90         19.700
  ACQUISITION       alfa         20.000
sw          6389.8          FLAGS
at           1.998  il                n
np           25528  in                n
fb        not used  dp                y
bs               4  hs               nn
d1           1.000        PROCESSING
nt              32  lb             0.10
ct              32  fn            65536
  TRANSMITTER             DISPLAY
tn              H1  sp            -94.4
sfrq       399.853  wp           4534.0
tof          362.8  rfl           791.3
tpwr            57  rfp               0
pw           9.850  rp            120.4
   DECOUPLER        lp            -91.3
dn             C13           PLOT
dof              0  wc              250
dm             nnn  sc                0
dmm              c  vs              104
dpwr            50  th                5
dmf          15900  nm  cdc  ph
```

^{13}C NMR (100 MHz, CDCl$_3$): *1,2:3,4,5-Di-O-isopropylidene-D-galactopyranose* (**18**)



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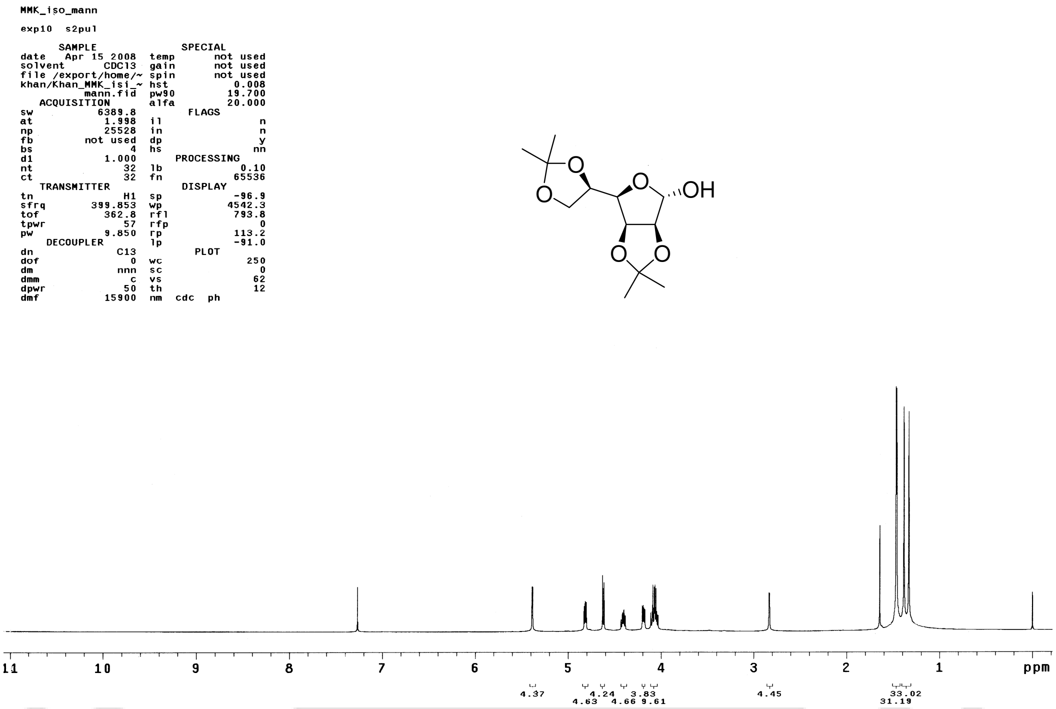
MMK_22_13C_08

exp10  s2pul

      SAMPLE                SPECIAL
date   Mar 12 2008  temp       not used
solvent       CDCl3  gain       not used
file /export/home/~ spin       not used
khan/Khan_MMK_22_1~ hst           0.008
        3c_08.fid  pw90         18.600
  ACQUISITION       alfa         20.000
sw         25125.6          FLAGS
at           1.199  il                n
np           60270  in                n
fb           13800  dp                y
bs              16  hs               nn
d1           1.000        PROCESSING
nt            2000  lb             2.00
ct             224  fn            65536
  TRANSMITTER             DISPLAY
tn             C13  sp           -354.5
sfrq       100.554  wp          18653.3
tof         1536.3  rfl          9275.7
tpwr            61  rfp          7764.9
pw           9.300  rp            -80.4
   DECOUPLER        lp           -271.4
dn              H1           PLOT
dof              0  wc              250
dm             yyy  sc                0
dmm              w  vs               17
dpwr            42  th                3
dmf           8900  nm  no  ph
```

Figure 1

^{1}H NMR (400 MHz, CDCl$_3$): *2,3:5,6-Di-O-isopropylidene-D-mannofuranose* (**45**)

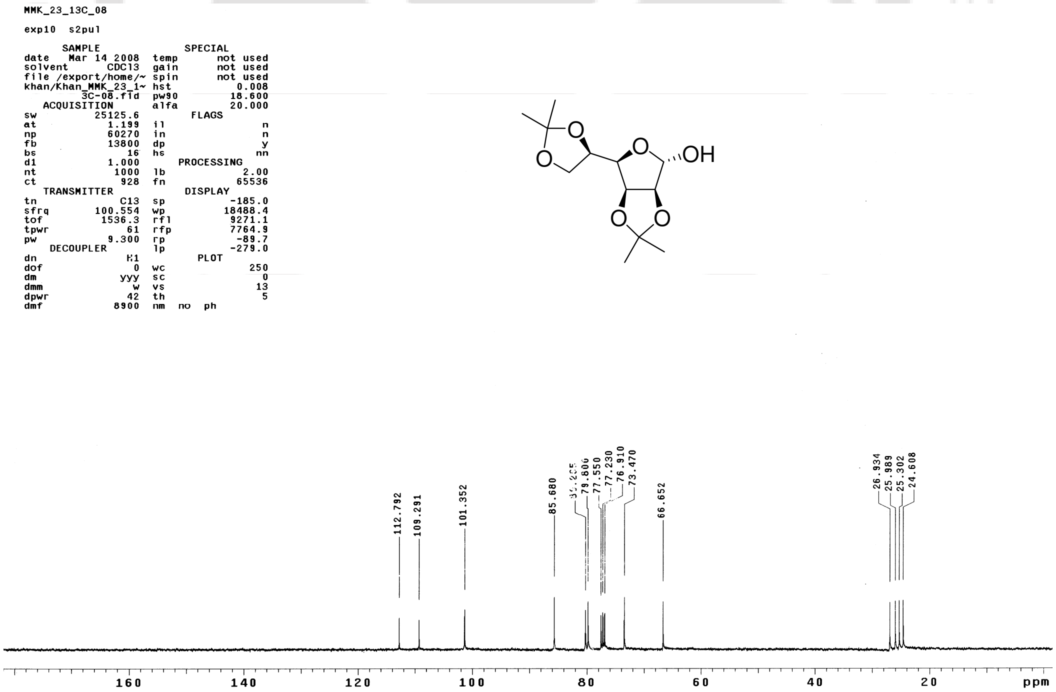


```
MMK_iso_mann

exp10  s2pul

       SAMPLE              SPECIAL
date   Apr 15 2008  temp       not used
solvent       CDCl3  gain       not used
file /export/home/~ spin       not used
khan/Khan_MMK_isi_~ hst           0.008
          mann.fid  pw90         19.700
   ACQUISITION      alfa         20.000
sw           6389.8           FLAGS
at            1.998  il               n
np            25528  in               n
fb         not used  dp               y
bs                4  hs              nn
d1            1.000        PROCESSING
nt               32  lb            0.10
ct               32  fn           65536
   TRANSMITTER              DISPLAY
tn               H1  sp           -96.9
sfrq        399.853  wp          4542.3
tof           362.8  rfl          793.8
tpwr             57  rfp              0
pw            9.850  rp           113.2
    DECOUPLER        lp           -91.0
dn              C13           PLOT
dof               0  wc             250
dm              nnn  sc               0
dmm               c  vs              62
dpwr             50  th              12
dmf           15900  nm  cdc  ph
```

^{13}C NMR (100 MHz, CDCl$_3$): *2,3:5,6-Di-O-isopropylidene-D-mannofuranose* (**45**)



```
MMK_23_13C_08

exp10  s2pul

       SAMPLE              SPECIAL
date   Mar 14 2008  temp       not used
solvent       CDCl3  gain       not used
file /export/home/~ spin       not used
khan/Khan_MMK_23_1~ hst           0.008
         3C-08.fid  pw90         18.600
   ACQUISITION      alfa         20.000
sw          25125.6           FLAGS
at            1.199  il               n
np            60270  in               n
fb            13800  dp               y
bs               16  hs              nn
d1            1.000        PROCESSING
nt             1000  lb            2.00
ct              928  fn           65536
   TRANSMITTER              DISPLAY
tn              C13  sp          -185.0
sfrq        100.554  wp         18488.4
tof          1536.3  rfl         9271.1
tpwr             61  rfp         7764.9
pw            9.300  rp           -89.7
    DECOUPLER        lp          -279.0
dn               H1           PLOT
dof               0  wc             250
dm              yyy  sc               0
dmm               w  vs              13
dpwr             42  th               5
dmf            8900  nm  no  ph
```

Figure 2

PART A

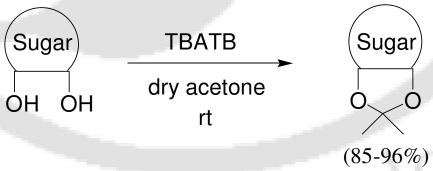
CHAPTER 3.2

Synthesis of *O*-isopropylidene derivatives of carbohydrate catalyzed by tetrabutylammonium tribromide (TBATB)

Results and Discussion

In the previous section of this Chapter, we have developed a highly efficient method for *O*-isopropylidene of carbohydrates by employing bromodimethylsulfonium bromide (BDMS) as a catalyst. Due to moisture sensitive nature of the reagent and requirement of excess amount of BDMS, this method has some limitations though we have successfully achieved the isopropylidenation of sugars using BDMS. Therefore we look for an alternative protocol which is free from these shortcomings.

A few years ago, Chaudhuri *et al.* have reported[57] the environmentally benign synthesis of various organic ammonium tribromides and their application in bromination reactions. Later on, our group have shown the efficacy of these solid organic ammonium tribromides in various organic transformations such as deprotection of dithioacetals,[58] interconversion of carbonyl compounds into 1,3-oxathiolanes and vice-versa,[59] synthesis of α-bromo enones[60] and various naturally occurring flavone derivatives.[61] The usefulness and efficacy of solid tetrabutylammonium tribromide (TBATB) have also been demonstrated by others in a wide variety of organic transformations.[62-67] Knowing the unique behavior, properties and stability of these organic ammonium tribromides, we conceived the idea that tetrabutylammonium tribromide (TBATB) might be a useful catalyst for the preparation of various *O*-isopropylidene derivatives from sugars. In this Chapter, we would like to discuss our successful results as depicted in Scheme 28.



Scheme 28

As per requirement, we have prepared TBATB by following the standard literature procedure.[57] For our present study, the reaction of D-mannose (**55**) was carried out with anhydrous acetone in presence of 0.5 mol% TBATB. We have noted incomplete conversion even after 8 h of stirring due to insufficient amount of catalyst. Therefore, the same reaction was performed with 1 mol%, 2 mol% and 5 mol% catalyst, respectively and the results are summarized in Table 5. The best result was obtained using 2 mol% catalysts with complete conversion within 2 h and furnished 96% yield, which is characterized by usual spectroscopy, melting point and specific rotation. These data are closely matched with our data mentioned in Experimental Section of Chapter 3.1 as well as other reported data.[37] The product was obtained as 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**45**), a thermodynamically controlled product. It is worthwhile to mention that the same transformation was also achieved within 1 h using 5 mol% of catalyst.

Table 5. Screening of amount of TBATB for *O*-isopropylidation of D-mannose conditions at room temperature

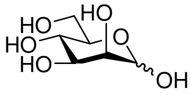
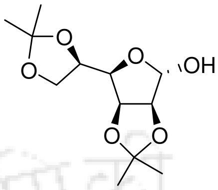
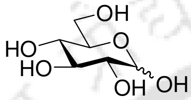
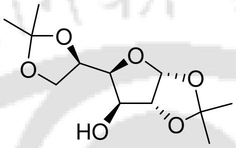
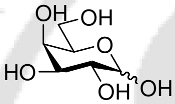
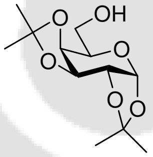
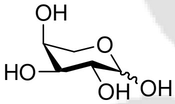
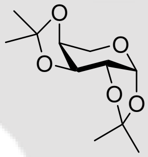
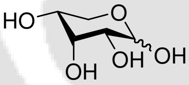
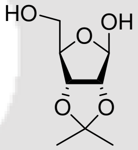
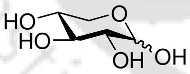
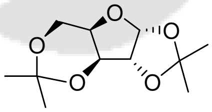
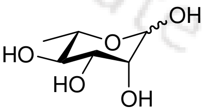
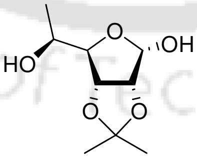
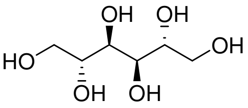
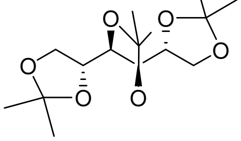
Entry	Catalyst (mol %)	Time (h)	Conversion[a] (%)	Yield[b] (%)
1	No catalyst	12	0	0
2	0.5	8	50	75
3	1	5	70	80
4	2	2	100	96
5	5	1	100	94

[a]*The reactions were performed with 2 mmol scale in 10 mL dry acetone.* [b]*Isolated yield based on starting material recovery.*

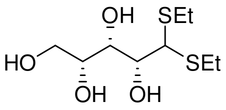
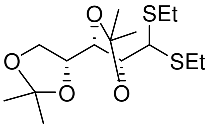
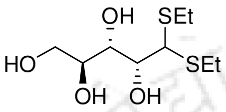
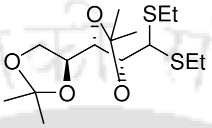
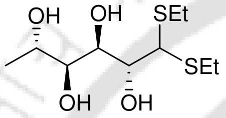
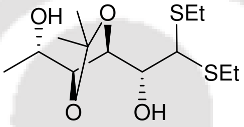
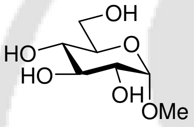
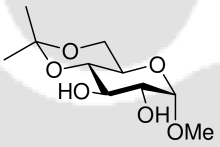
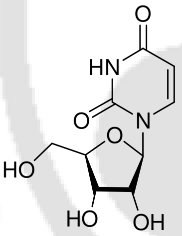
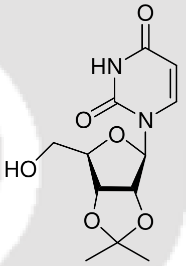
After optimizing the reaction condition, the other aldohexoses such as D-glucose and D-galactose were tried for isopropylidenation and yielded the products **29** (88%) and **18** (89%) respectively. Next, a range of aldopentoses such as L-arabinose, D-ribose and D-xylose were smoothly converted into the corresponding *O*-isopropylidene derivatives **88-90** in good yield.

To explore further scope of this protocol, L-rhamnose (**64**) and D-mannitol (**56**) were transformed into the corresponding acetonides **91** and **35** under similar reaction conditions. It is important to mention here that a wide variety of diethyl dithioacetal of various sugars such as D-xylose, L-arabinose and L-rhamnose were also converted into the corresponding products **92-94** in good yields without any effect on dithioacetal group. Further, we have extended our protocol for *O*-isopropylidenation of α-methyl glucopyranoside (**95**) and uridine (**96**) and provided the desired products **97** and **98** in good yields as shown in Table 6. Unfortunately, we did not get the desired product while the reaction was carried out with disaccharide derivative such as thioglycoside of celleboise in acetone using TBATB as catalyst under identical reaction reactions.

Table 6. Results of *O*-isopropylidenation of free sugar and their derivatives using TBATB as catalyst

Substrate No.	Substrate	Product	Product No.	Time (h)	Yield[a,b] (%)
55			**45**	2	96
60			**29**	8	88[c]
50			**18**	8	89[c]
59			**88**	5	86
61			**89**	1.5	86
62			**90**	3	89
64			**91**	1	88
56			**35**	2	94

Continued Table 6

Substrate No.	Substrate	Product	Product No.	Time (h)	Yield[a,b] (%)
11			**92**	1.5	85
14			**93**	1.5	91
70			**94**	1	87
95			**97**	10	72[c]
96			**98**	6	76

[a]*Isolated yield.* [b]*All products were characterized by recording* ^{1}*H NMR,* ^{13}*C NMR, specific rotation and elemental analysis.* [c]*The trace amount of sugar remains undissolved.*

Interestingly, we have noticed that the conversion of the various free sugars to the respective *O*-isopropylidene derivatives can be achieved even in a larger scale (100 mmol) without any difficulty by using only 1 mol% of the catalyst. For example, the reaction of diethyl dithioacetal of L-arabinose (25.6 g, 100 mmol) was investigated in dry acetone (400 mL) in presence of TBATB (1 mmol). The reaction was complete within 2 h and the desired product **93** was obtained in 91% yield. The above result indicates that a large-scale reaction is also feasible using less amount of the catalyst.

The formation of the product may be explained as follows: It was proposed earlier that benzyltrimethyl ammonium tribromide can react with alcohol to generate dry HBr in the medium.[68] Analogues, we propose that, *in situ* generated dry HBr catalyzes the *O*-

isopropylidenation reaction of sugars or other sugar derivatives into the corresponding *O*-isopropylidene compounds. The reaction of D-mannose (**55**) and acetone was also examined with aqueous 48% HBr (5 μL) at room temperature. It was found that it requires longer reaction time as well as provides relatively low yield (64%). Furthermore, the efficiency of TBATB can be visualized by comparison with other catalysts as shown in Table 7. All the products were fully characterized by IR, ^{1}H and ^{13}C NMR, specific rotation and elemental analysis. The ^{1}H NMR and ^{13}C NMR spectra of compound **93** and **97** are given in the Experimental Section (Figure 1 and 2).

Table 7. Comparison table for *O*-isopropylidenation using various catalysts and their amount of loading

Entry	Substrate	Catalyst	Amount (mol%)	Time (h)	Yield^b (%)
1	D-Glucose	$FeCl_3$	>10	6	83[43]
		Iodine	>10	4	80[45]
		)–Ph$_2$P–I$_2$	200	30 (min)	95[37]
		VO(OTf)$_2$	5	10	89[39]
		BDMS	5	10	84
		TBATB	**2**	**8**	**88** (in this work)
2	D-Mannose	$FeCl_3$	>10	1	90[43]
		Iodine	>10	25 min	85[45]
		)–Ph$_2$P–I$_2$	200	30 (min)	95[37]
		VO(OTf)$_2$	5	3	92[39]
		BDMS	5	2	90
		TBATB	**2**	**2**	**96** (in this work)

^{b}*Isolated yields.*

In summary, we have demonstrated a simple and efficient method for the preparation of *O*-isopropylidene derivatives from free sugars as well as from acyclic sugar derivatives by employing TBATB as catalyst. The notable advantages of the present protocol are: good yields, short reaction time, stable and easy to handle catalyst as well as lower amount of catalyst loading. Due to its operational simplicity, generality and efficacy, this method is expected to have wider applicability for the preparation of various *O*-isopropylidene derivatives of sugar.

Experimental

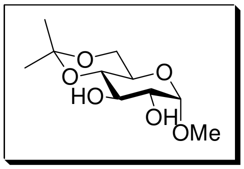
Preparation of tetrabutylammonium tribromide (TBATB)

An amount of 0.05 g (0. 27 mmol) of vanadium pentoxide (V_2O_5), was added to 5 mL (44.12 mmol) of 30% hydrogen peroxide (H_2O_2) taken in a pre-cooled 250 mL beaker (care should be taken to maintain ice-cold condition as the reaction between V_2O_5 and H_2O_2 is exothermic). The reaction mixture was stirred at 0 – 5 °C temperature in an ice-water bath till all the V_2O_5 dissolved and the solution became reddish-brown. To it was added a solution of 5.67 g (47.65 mmol) potassium bromide (KBr) and 7.7 g (23.81 mmol) of tetrabutylammonium bromide (TBAB), dissolved in 25 mL of 1M H_2SO_4. An orange-yellow precipitate started to appear after 5 minutes of stirring. The mixture was stirred continuously for about 30 minutes subsequent upon which the whole was kept standing in an ice-bath for 1h, to give a bright orange colored compound. The isolated yield was 80%, M.p. 75 °C.

General procedure for preparation of O-isopropylidenation of sugars

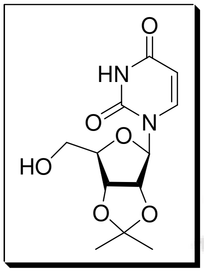
To a stirred solution of the sugar (2 mmol) in dry acetone (10 mL) tetrabutylammonium tribromide (TBATB) (19 mg, 0.04 mmol) was added at room temperature. The reaction was monitored by TLC as mentioned in Table 2. After completion of the reaction, one-drop of NEt_3 was added to reaction mixture and then acetone was removed in a rotary evaporator. Then the crude residue was passed through a silica gel column to obtain the desired product in pure form. The spectral data of the compounds **18**, **29**, **35**, **45** and **88-94** are reported previously in the Experimental Section of Chapter 3.1.

Methyl 4,6-O-isopropylidene-α-D-glucopyranoside (**97**)



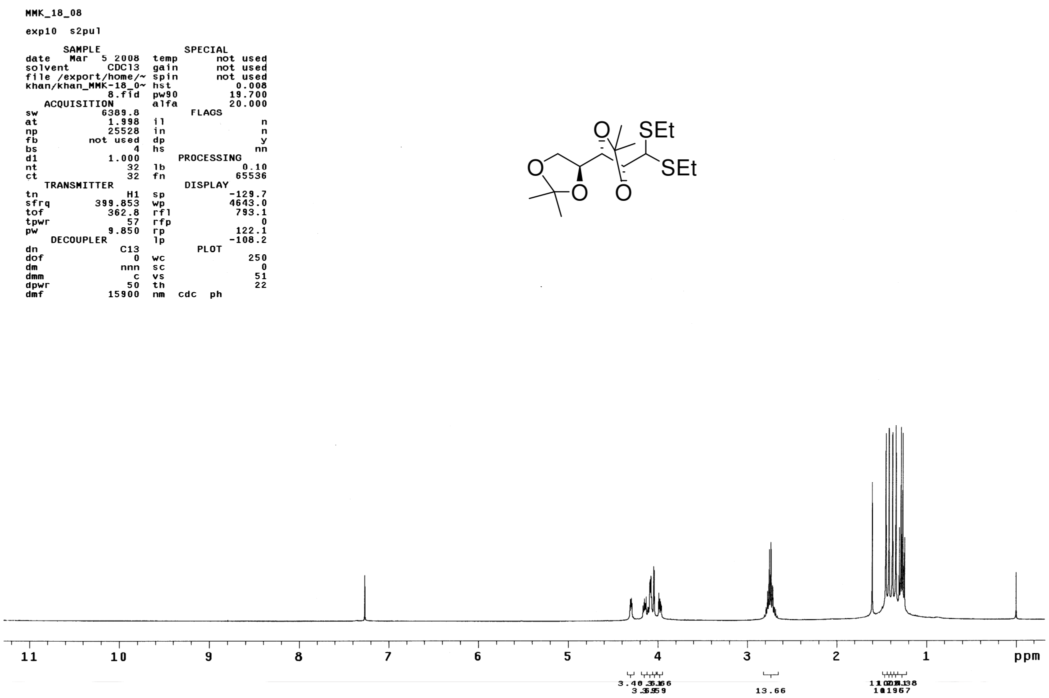
White solid; M.p. 112-114 ºC; $[\alpha]_D^{25}$ +108.6° (*c* 1.0, H_2O); **IR** (KBr): 3436, 2975, 2948, 1371, 1228, 1201, 1068, 974, 835 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.42 (s, 3H, C*H*$_3$), 1.49 (s, 3H, C*H*$_3$), 2.59 (d, 1H, *J* = 2.0 Hz, O*H*), 3.41 (s, 3H, C*H*$_3$), 3.52 (q, 1H, *J* = 9.6 Hz, H-5), 3.54–3.64 (m, 2H, H-2 and H-4), 3.73 (t, 1H, *J* = 10.8 Hz, H-6), 3.77 (t, 1H, *J* = 10.0 Hz, H-3), 3.86 (dd, 1H, *J* = 5.6 Hz, *J* = 10.8 Hz, H-6'), 4.74 (d, 1H, *J* = 3.6 Hz, H-1); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.3, 29.3, 55.6, 62.5, 63.5, 72.1, 73.2, 73.7, 99.9, 100.0; **Anal. Calcd** for $C_{10}H_{18}O_6$ (234.25): C, 51.27; H, 7.75. Found: C, 51.16; H, 7.58.

2',3'-O-Isopropylideneuridine (**98**)



White solid; M.p. 145-146 ºC; **IR** (KBr): 3430, 3316, 2984, 1691, 1586, 1375, 1221, 1031, 847 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.37 (s, 3H, C*H*$_3$), 1.58 (s, 3H, C*H*$_3$), 2.99 (br s, 1H, N*H*), 3.81 (br d, 1H, *J* = 11.6 Hz, H-5'), 3.92 (br d, 1H, *J* = 11.6 Hz, H-5'), 4.30 (d, 1H, *J* = 3.2 Hz, H-4'), 4.96 (dd, 1H, *J* = 3.6 Hz, *J* = 6.4 Hz, H-2'), 5.04 (dd, 1H, *J* = 2.8 Hz, *J* = 6.4 Hz, H-3'), 5.59 (d, 1H, *J* = 1.6 Hz, H-1'), 5.74 (d, 1H, *J* = 8.0 Hz, H-5), 7.39 (d, 1H, *J* = 8.0 Hz, H-6), 9.11 (br s, 1H, O*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 25.3, 27.2, 62.1, 80.6, 84.4, 86.9, 94.2, 102.3, 114.4, 142.4, 150.7, 164.3; **Anal. Calcd** for $C_{12}H_{16}N_2O_6$ (284.27): C, 50.70; H, 5.67; N, 9.85. Found: C, 50.53; H, 5.51, N, 9.96.

^{1}H NMR (400 MHz, $CDCl_3$): *2,3:4,5-Di-O-isopropylidene-L-arabinose diethyl dithioacetal* (**93**)



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MMK_18_08

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solvent       CDC13  gain        not used
file /export/home/~ spin        not used
khan/khan_MMK-18_0~ hst            0.008
             8.fid  pw90          19.700
   ACQUISITION      alfa          20.000
sw           6389.8            FLAGS
at            1.998  il                n
np            25528  in                n
fb         not used  dp                y
bs                4  hs               nn
d1            1.000          PROCESSING
nt               32  lb             0.10
ct               32  fn            65536
   TRANSMITTER              DISPLAY
tn               H1  sp           -129.7
sfrq        399.853  wp           4643.0
tof           362.8  rfl           793.1
tpwr             57  rfp               0
pw            9.850  rp            122.1
    DECOUPLER        lp           -108.2
dn              C13             PLOT
dof               0  wc              250
dm              nnn  sc                0
dmm               c  vs               51
dpwr             50  th               22
dmf           15900  nm  cdc  ph
```
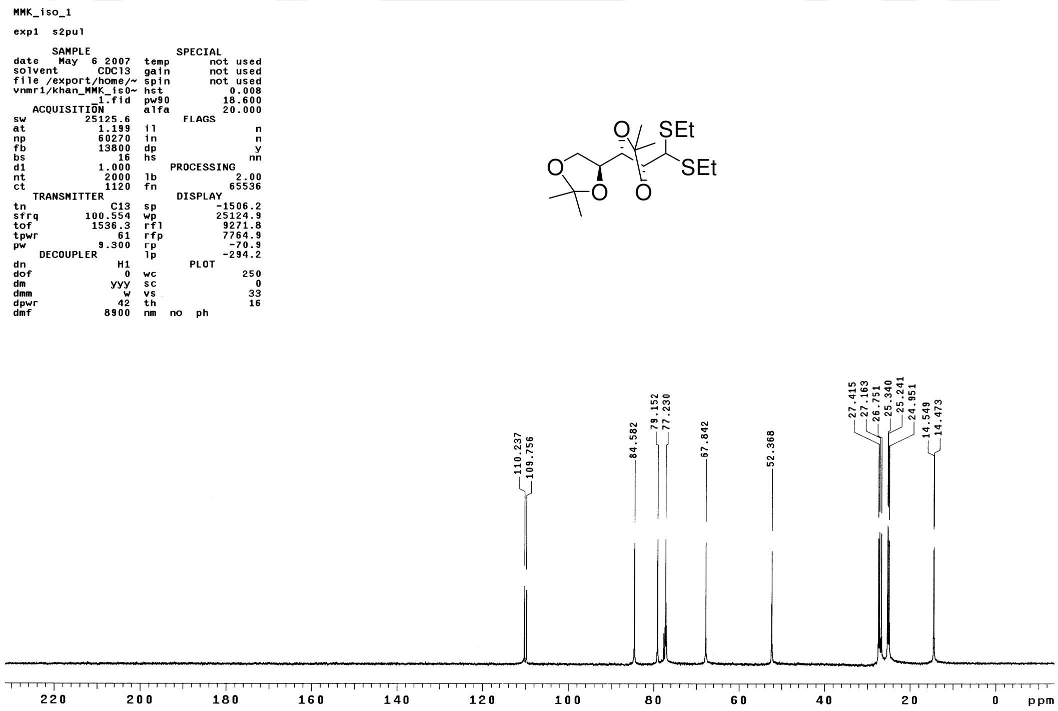

^{13}C NMR (100 MHz, $CDCl_3$): *2,3:4,5-Di-O-isopropylidene-L-arabinose diethyl dithioacetal* (**93**)



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MMK_iso_1

exp1  s2pul

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solvent       CDC13  gain        not used
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vnmr1/khan_MMK_is0~ hst            0.008
            _1.fid  pw90          18.600
   ACQUISITION      alfa          20.000
sw          25125.6            FLAGS
at            1.199  il                n
np            60270  in                n
fb            13800  dp                y
bs               16  hs               nn
d1            1.000          PROCESSING
nt             2000  lb             2.00
ct             1120  fn            65536
   TRANSMITTER              DISPLAY
tn              C13  sp          -1506.2
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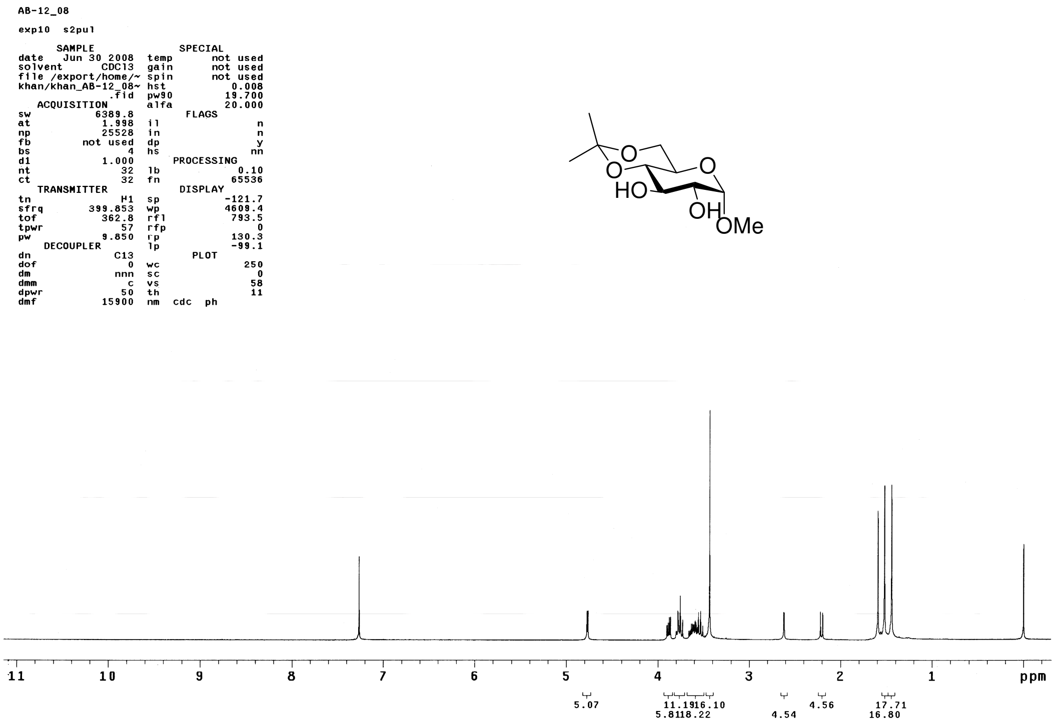
tof          1536.3  rfl          9271.8
tpwr             61  rfp          7764.9
pw            9.300  rp            -70.9
    DECOUPLER        lp           -294.2
dn               H1             PLOT
dof               0  wc              250
dm              yyy  sc                0
dmm               w  vs               33
dpwr             42  th               16
dmf            8900  nm  no  ph
```

Figure 1

^{1}H NMR (400 MHz, CDCl$_3$): *Methyl 4,6-O-isopropylidene-α-D-glucopyranoside* (**97**)



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AB-12_08

exp10  s2pul

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solvent      CDC13  gain       not used
file /export/home/~ spin       not used
khan/khan_AB-12_08~ hst           0.008
              .fid  pw90         19.700
   ACQUISITION      alfa         20.000
sw          6389.8           FLAGS
at           1.998  il                n
np           25528  in                n
fb        not used  dp                y
bs               4  hs               nn
d1           1.000         PROCESSING
nt              32  lb             0.10
ct              32  fn            65536
   TRANSMITTER              DISPLAY
tn              H1  sp           -121.7
sfrq       399.853  wp           4609.4
tof          362.8  rfl           793.5
tpwr            57  rfp               0
pw           9.850  rp            130.3
    DECOUPLER       lp            -99.1
dn             C13             PLOT
dof              0  wc              250
dm             nnn  sc                0
dmm              c  vs               58
dpwr            50  th               11
dmf          15900  nm  cdc  ph
```
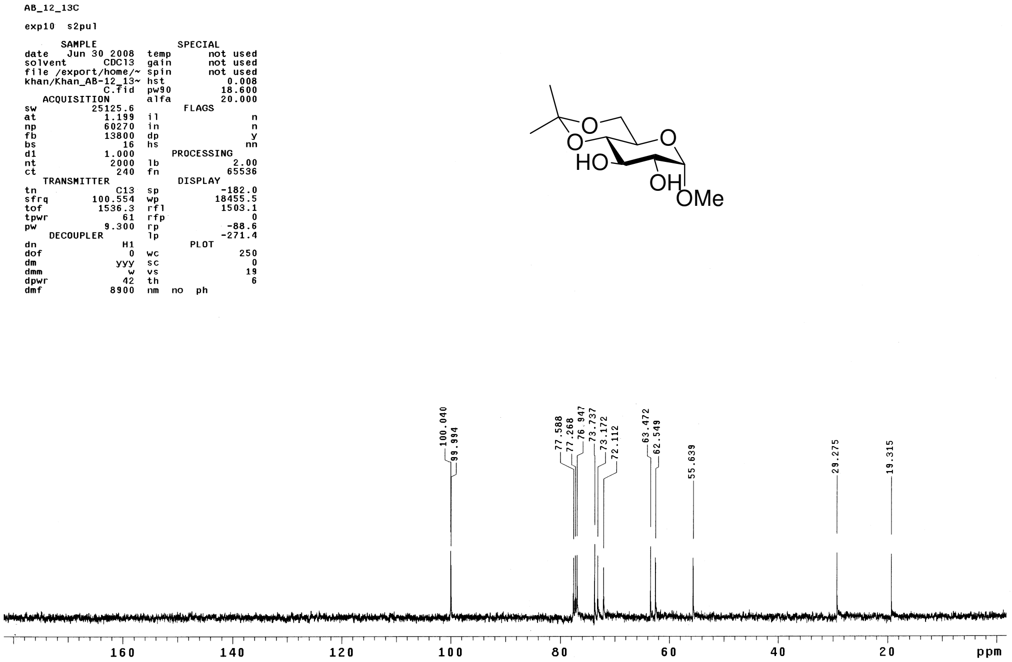

^{13}C NMR (100 MHz, CDCl$_3$): *Methyl 4,6-O-isopropylidene-α-D-glucopyranoside* (**97**)



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AB_12_13C

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solvent      CDC13  gain       not used
file /export/home/~ spin       not used
khan/Khan_AB-12_13~ hst           0.008
            C.fid   pw90         18.600
   ACQUISITION      alfa         20.000
sw         25125.6           FLAGS
at           1.199  il                n
np           60270  in                n
fb           13800  dp                y
bs              16  hs               nn
d1           1.000         PROCESSING
nt            2000  lb             2.00
ct             240  fn            65536
   TRANSMITTER              DISPLAY
tn             C13  sp           -182.0
sfrq       100.554  wp          18455.5
tof         1536.3  rfl          1503.1
tpwr            61  rfp               0
pw           9.300  rp            -88.6
    DECOUPLER       lp           -271.4
dn              H1             PLOT
dof              0  wc              250
dm             yyy  sc                0
dmm              w  vs               19
dpwr            42  th                6
dmf           8900  nm  no  ph
```

Figure 2

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Part A (Chapter 1-3)

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PART B

CHAPTER 1

Brief introduction on multicomponent reactions, tetra- and dihydropyridine derivatives

1.1 Introduction

Multicomponent reactions (MCRs) can be defined as the processes in which three or more reactants are combined together through covalent bonds regardless of their mechanistic nature in a single chemical operation to produce products that incorporate substantial portions of all the reactants (Figure 1). They are sometimes referred to as *multiple-component condensations*.[1]

Multicomponent reactions have inherent convergence and high productivity in combination with their exploratory and complexity generating power. They have significant advantages over conventional reactions in several aspects, such as (a) reduced cost and reaction time; (b) readily available starting materials; (c) operationally simple; (d) variable and high bond forming efficiency; (e) resource effective; (f) atom economy and (g) eco-compatibility.[1,2]

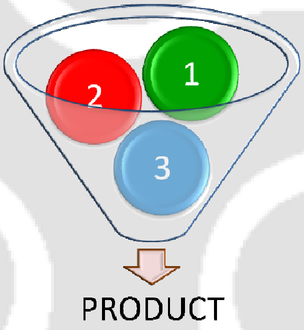


Figure 1

Most of the known MCRs are *domino reactions*, a sequence of elementary steps in which subsequent transformations are determined by the functionalities produced in the previous step.

"A domino reaction is a process involving two or more bond-forming transformations which take place under the same reaction conditions without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed in the previous step" L. F. Tietze.[3]

MCRs are an especially attractive synthetic strategy comprises to provide easy and rapid access to large libraries of organic compounds with diverse substitution patterns. As MCRs are one-pot reactions, they are easier to carry out than multistep syntheses as shown in Figure 2. Coupled with high-throughput library screening, this strategy is an important development in the ties of drug discovery in the context of rapid identification and optimization of biologically active compounds. Libraries of small organic molecule are perhaps the most desired class of potential drug candidates. With a small set of starting materials, very large libraries can be built up within a short time, which may then be used in pharmaceuticals. Therefore, MCRs have become a rapidly evolving field in the context of drug discovery for the preparation of libraries of molecules in a time- and cost-effective manner, and they are now key tools in industrial and academic research.[4]

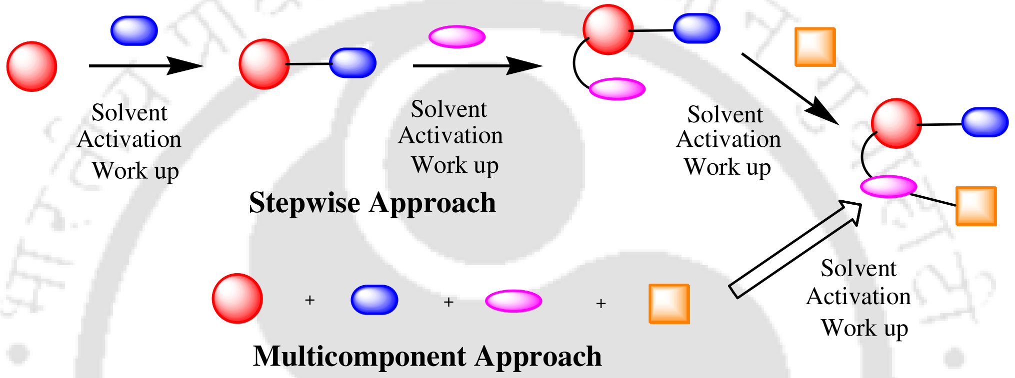
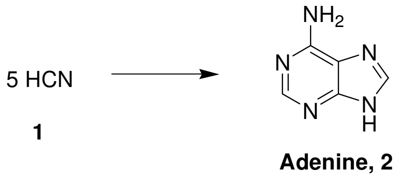


Figure 2. *Stepwise vs Multicomponent Approach*

1.2 Development and Synthetic Application of MCRs

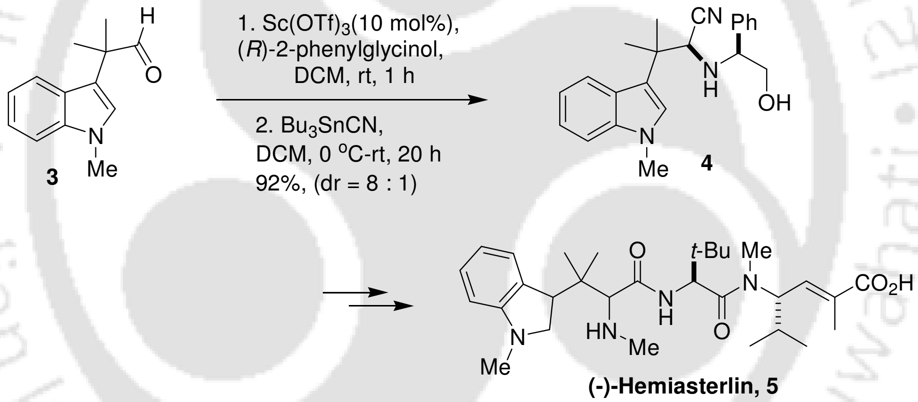
The history of multicomponent reactions began mainly in 1850 by the publication of the Strecker reaction[5] and arriving in the age of its apex after long journey of Hantzsch,[6] Biginelli[7] and Ugi reaction.[8] Multicomponent reactions have emerged as a powerful synthetic strategy only after the discovery of Ugi reaction even though the history of MCRs started in the second half of 19th century with the reactions of Strecker. In recent years, it has become a promising tool for the efficient synthesis of natural products and screening of compounds for the discovery of biological probes and drugs.[9]

Nature plays an important role in evolution of MCR and it has made significant contribution to the synthesis of various organic compounds. For example, adenine (**2**), one of the major constituents of DNA and RNA, was prebiotically formed by the condensation of five molecules of HCN as shown in Scheme 1.[10]



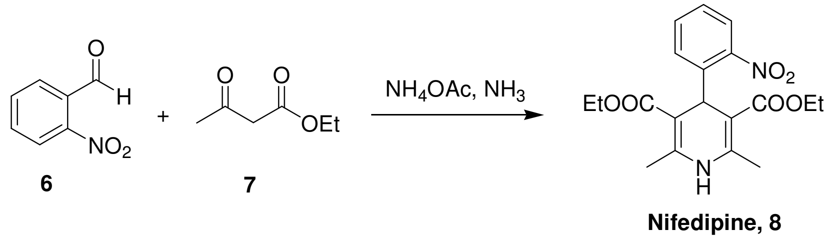
Scheme 1

The first modern contribution to the development of multicomponent chemistry by Strecker[5] was the synthesis of α-amino nitrile derivatives which involves condensation of an aldehyde or a ketone with amine and hydrogen cyanide or their equivalents. Vedejs and co-workers[11] utilized the asymmetric Streker reaction for the construction of the key intermediate tetramethyltryptophan **4** for the enantioselective total synthesis of (-)-hemiasterlin (**5**), a marine tripeptide having cytotoxic and antimitotic activity as illustrated in Scheme 2.



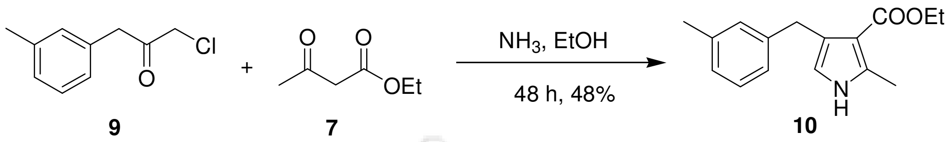
Scheme 2

Hantzsch[6] in 1882 developed a one-pot four-component condensation reaction between aldehydes, two equivalents of a β-keto ester and ammonium acetate or ammonia to synthesize symmetrically substituted dihydropyridines (**8**) as shown in Scheme 3.[12]



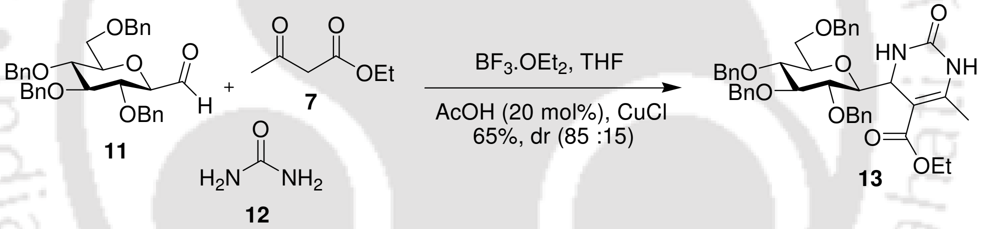
Scheme 3

Another important contribution made by Hantzsch to MCRs was the synthesis of pyrroles (**10**), by reacting β-ketoesters and α-halogenated β-ketoesters in presence of ammonia as mentioned in Scheme 4.[13]



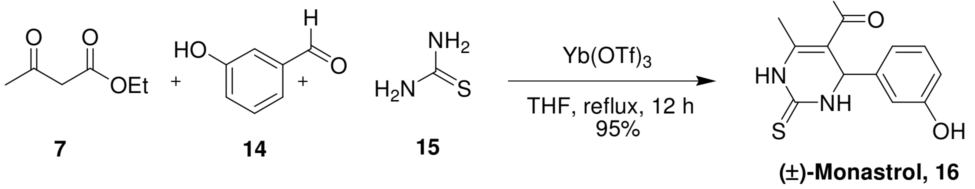
Scheme 4

In the late nineties, Biginelli was the first to synthesize functionalized 3,4-dihydropyrimidin-2(1*H*)-ones by one-pot three-component reaction of an aldehyde, urea and ethyl acetoacetate in the presence of a catalyst.[7] Aparicio *et al.* then synthesized compound **13** using sugar aldehyde (**11**) by modifying Biginelli method as depicted in Scheme 5.[14]



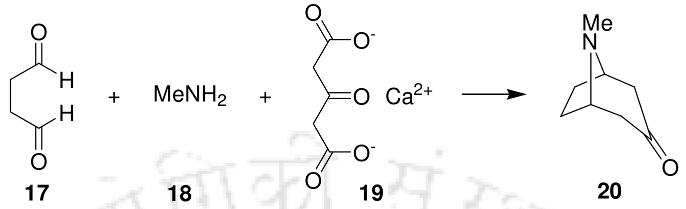
Scheme 5

Dondoni and co-workers reported an improved synthesis of racemic monastrol (**16**) by utilizing the traditional three-component version of the Biginelli reaction. The one-pot three-component reaction between 3-hydroxybenzaldehyde, ethyl acetoacetate and thiourea catalyzed by $Yb(OTf)_3$ resulted in 95% racemic monastrol (**16**) as given in Scheme 6.[15]



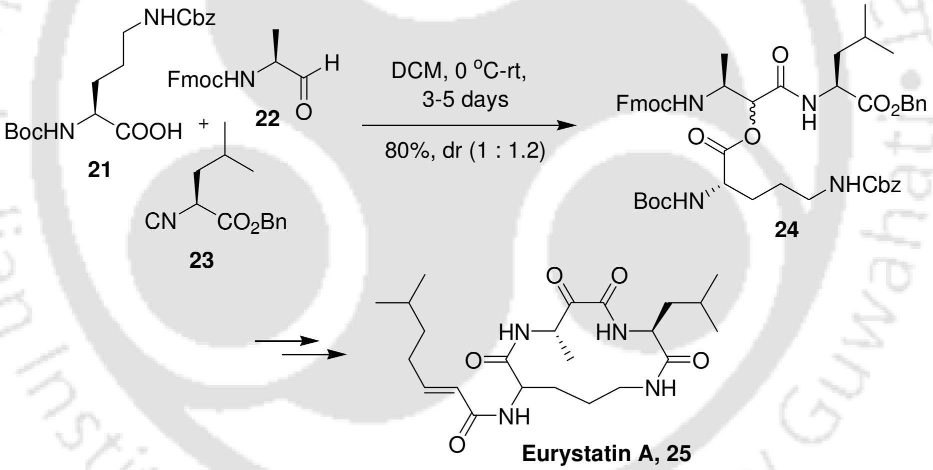
Scheme 6

In 1917, the first important application of MCR in natural product was reported by Robinson for the synthesis of alkaloid tropinone (**20**) from succinic dialdehyde, methylamine and calcium salt of acetonedicarboxylic acid as illustrated in Scheme 7.[16]



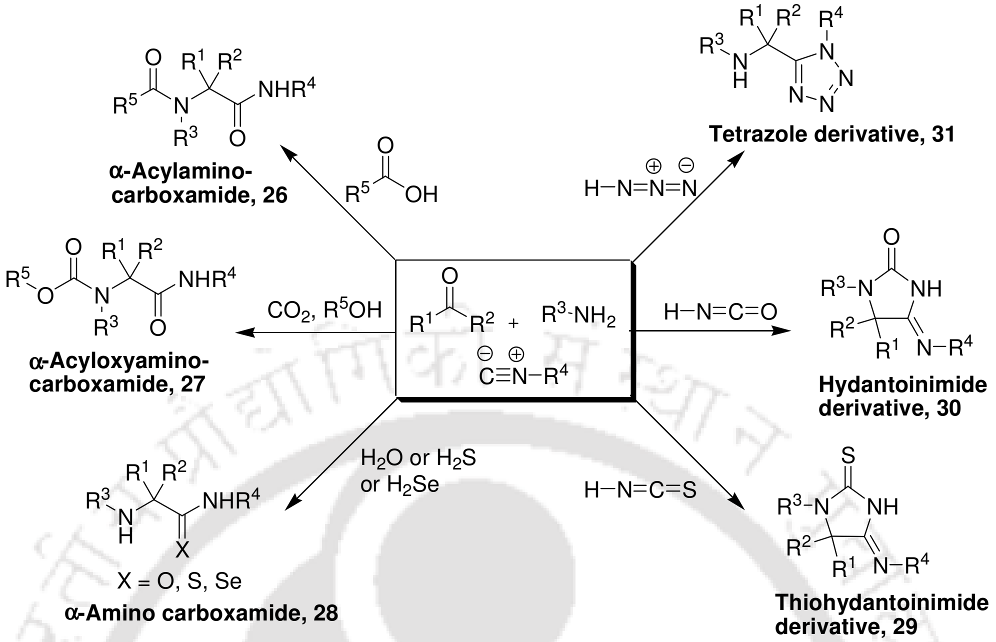
Scheme 7

Passerini in 1921 demonstrated a MCR involving isocyanide in which one-pot reaction of carboxylic acid, carbonyl compound and isocyanide afforded α-acyloxy carboxamide.[17a] Owens *et al.* utilized this reaction for the synthesis of eurystatine A (**25**), which is a 13-membered macrocyclic natural product as depicted in Scheme 8.[17b]



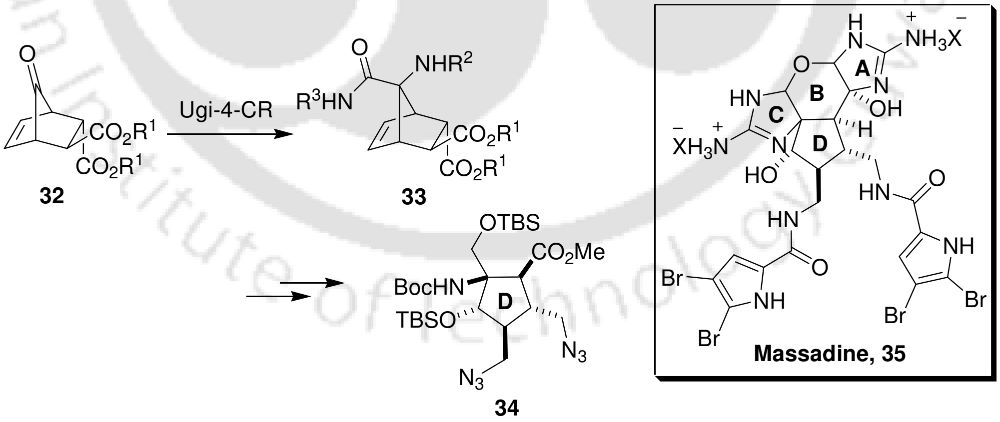
Scheme 8

In 1959, Ugi and co-workers discovered one of the most utilized multicomponent reactions. The isocyanides undergo a four-component reaction (4-CR) in the presence of an amine, aldehyde or ketone and a nucleophile to afford a single condensation product. The most commonly used nucleophiles are carboxylic acids, hydrazoic acid, cyanates, thiocyanates, carbonic acid monoesters, water, hydrogen sulfide and hydrogen selenide. Therefore, Ugi reaction found a widespread application in combinatorial chemistry as represented in Scheme 9.[8]



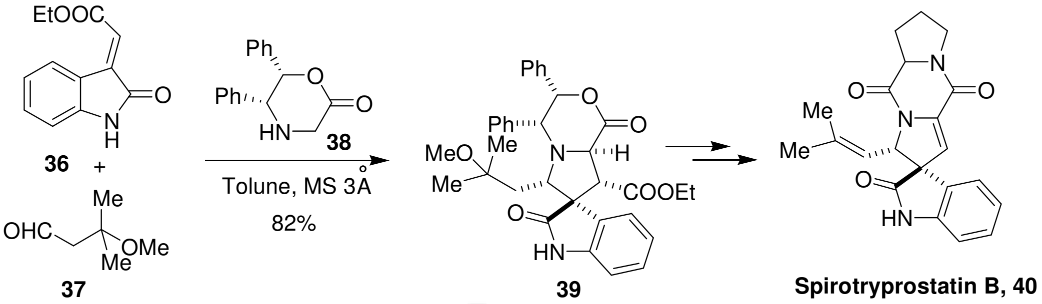
Scheme 9

This synthetic strategy of Ugi reaction was utilized for the synthesis of various natural products and biologically active molecules. Chinigo *et al.* recently utilized Ugi-4-CR as a key reaction for the synthesis of the D-ring sub-unit (**34**), which rapidly gives functionalized core structure of massadine (**35**) as shown in Scheme 10.[18]



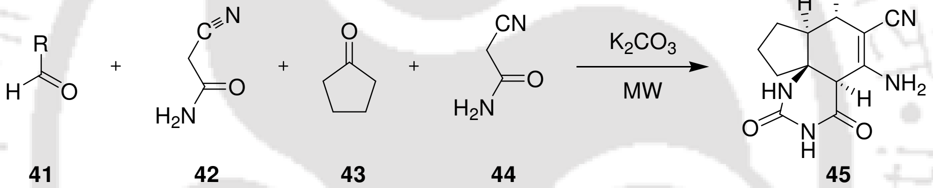
Scheme 10

The key intermediate **39** of spirotryprostatin B (**40**) was achieved through MCR employing the reaction of oxindole (**36**), aldehyde (**37**) and oxazinone (**38**) afforded in 82% yield.[19] The synthesis of spirotryprostatin B (**40**) was achieved utilizing this key intermediate **39** as depicted in Scheme 11.



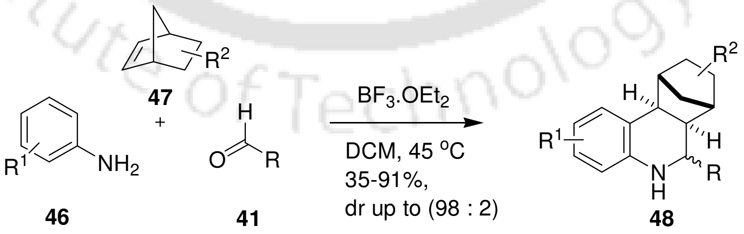
Scheme 11

Jiang *et al.*[20] established a novel multicomponent domino reaction by condensing aldehydes, cycloketones and cyanoamides, which act as both substrates and nucleophiles to give important scaffolds with highly substituted quinazoline derivatives (**45**) as illustrated in Scheme 12.



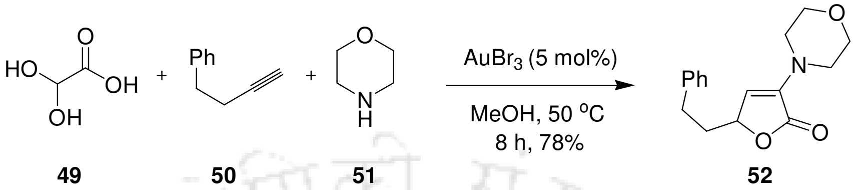
Scheme 12

Recently, Smith *et al.*[21] synthesized highly functionalized natural product like tetra cyclic system **48** from the reaction of aldehydes, amines and bicycle [2.2.1] hepta-5-en using three-component Povarov reaction catalyzed by $BF_3.OEt_2$ in DCM as shown in Scheme 13.



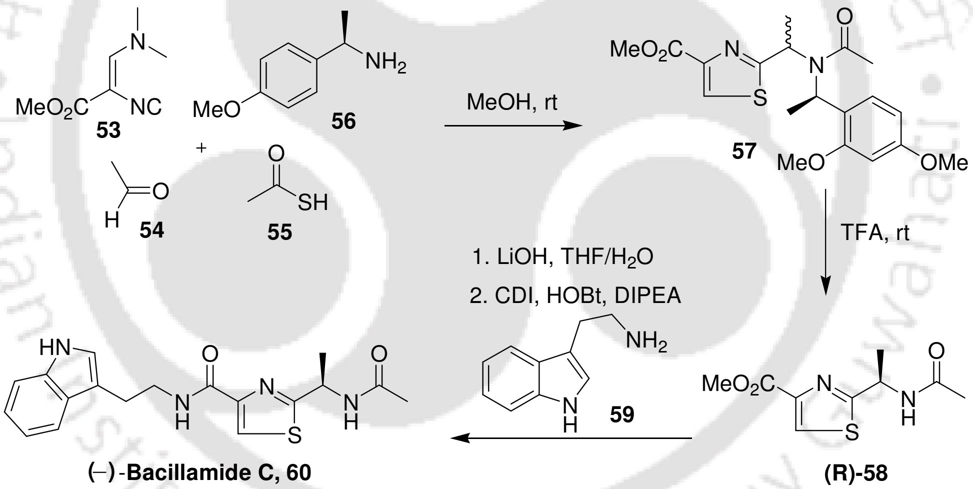
Scheme 13

Zhang and co-workers[22] accomplished a practical gold-catalyzed multicomponent reaction for the preparation of polysubstituted butenolides (**52**) in a tandem manner. This MCR consists of a novel direct alkyne-amine-glyoxylic acid coupling reaction. For example, the three-component domino reaction of glyoxylic acid, alkyne and morpholine in the presence of catalytic amount of $AuBr_3$ in MeOH at 50 °C gives butenolide derivative (**52**) in 78% yield as represented in Scheme 14.



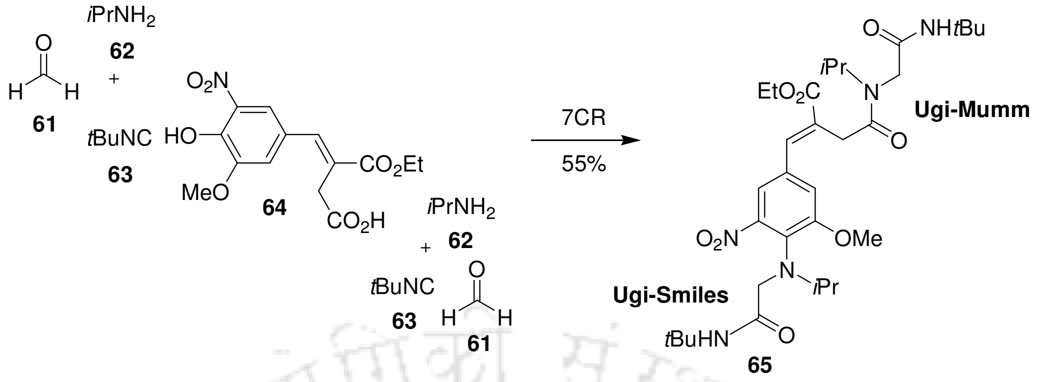
Scheme 14

Dömling and co-workers[23] described an enantioselective synthesis leading to the algicidal natural product such as bacillamide C (**60**) and its derivatives as shown in Scheme 15. This synthesis is convergent and the key step involve is the modification of the Ugi reaction leading to highly substituted thiazoles (**57**) as depicted in Scheme 15.



Scheme 15

Brauch *et al.*[24] reported a seven-component reaction by utilizing the different chemoselectivities of the Ugi–Mumm and the Ugi–Smiles reaction. The sequential multicomponent reaction has led to highly diverse peptide and glycopeptide like structures (**65**) from formaldehyde, isopropyl amine and *tert*-butyl isonitrile. The Ugi–Mumm/Ugi–Smiles product was formed in 55% yield and the yield for each bond forming step exceeds 90% as depicted in Scheme 16.



Scheme 16

From this survey it is apparent that development of novel multicomponent reactions is a challenging area in synthetic organic chemistry. MCRs are of particular interest for three reasons: efficiency, diversity and their large unexplored chemical space. The number of steps needed for generating a particular chemical structure or chemical diversity is a measure of the efficiency of chemical synthesis. MCRs have been found to be most efficient approach to a variety of chemical synthetic problems, especially for the synthesis of natural products and analogues. Thus, we were motivated to work on this promising field of chemistry. In this part of my research work aimed at the synthesis of N-heterocycles such as tetra- and dihydropyridine derivatives. I would like to address their importance as well as some recently developed synthetic methods as described below.

1.3 Tetrahydropyridines and its importance

Pyridines and its derivatives such as tetrahydropyridines, dihydropyridines and piperidines are the most common structural motifs found in natural products and drugs. Especially, functionalized tetrahydropyridine and piperidine rings are featured in a variety of biologically active alkaloids and pharmaceuticals.[25,26] Very recently, new alkaloids such as **66** (Figure 3) and four others were isolated from the stem-bark extract of *Leuconotis griffithii* by Gan *et al.*. These alkaloids exhibit moderate cytotoxicity against drug-sensitive and vincristine-resistant human KB cells.[27] The steroidal alkaloids having tetrahydropyridine ring were isolated from *Eclipta alba*. The alkaloid **67** showed good activity against *Candida allbicans* and weak cytotoxicity against the M-109 cell lines.[28] The compound **68** acts as potent inhibitors of protein geranylgeranyltransferase type I having submicromolar IC_{50} values.[29] Blockade of postsynaptic dopamine (DA) D_2 receptors is a characteristically common to all effective antipsychotics in clinical use today. For example, roxindole (**69**) and analogues showed potential antipsychotic activity.[30] Thurmond *et al.*[31] have demonstrated the synthesis of compound **70** exhibited IC_{50} of 1.0 μM against Cat S, is the first nonpeptidic and non-covalent inhibitors of the cysteine protease cathepsin S (Cat S). Tetrahydropyridine units are also present in various other medicinally important compounds with diverse range of biological activities such as anticancer,[32] proteasome inhibitors,[33] selective antagonists for 5-hydroxytryptamine[34] and muscarinic receptor.[35] Interestingly, 1,4-disubstituted tetrahydropyridines are also used for probing the active sites of monoamine oxidase A and B to understand better structural insights of these enzymes.[36]

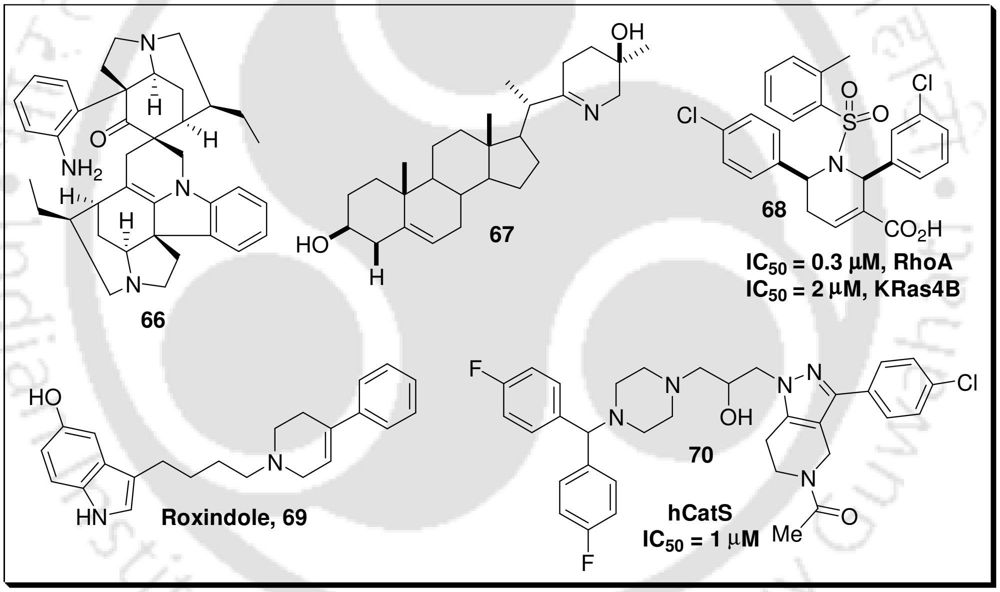
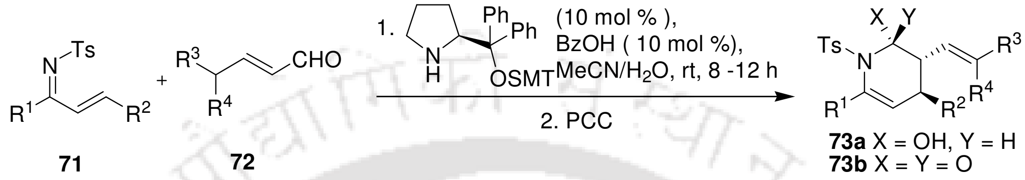


Figure 3. *Some Biologically Active Tetrahydropyridines*

1.4 Synthetic Methods and Utility of Tetrahydropyridines

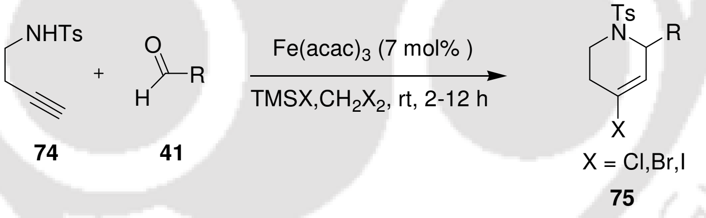
Over the years, several strategies were developed for the synthesis of tetrahydropyridine derivatives with different substitution pattern.[37] Some approaches to construct these nitrogen containing six-membered heterocycles are: aza-Diels-Alder reaction,[38] aza-Prins cyclization,[39] annulations,[40] ring-closing metathesis[41] and various multicomponent reactions.[42-46]

Han *et al.*[47] demonstrated the synthesis of tetrahydropyridine derivatives (**73**) using regio- and stereoselective aza-Diels-Alder reaction of α,β-unsaturated aldehydes and N-tosyl-1-aza-1,3-butadienes promoted by an organocatalyst. These enantiomerically pure functionalized tetrahydropyridine derivatives are useful in the total synthesis of natural products and in medicinal chemistry as shown in Scheme 17.[48]



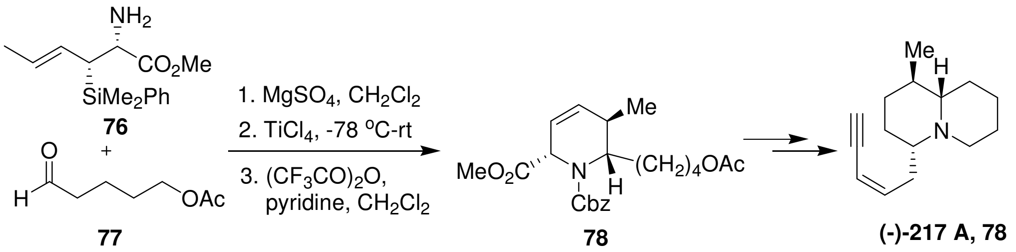
Scheme 17

Miranda *et al.*[49] developed iron(III) promoted alkyne aza-Prins cyclization between homopropargyl tosylamines and aldehydes to give 2-alkyl-4-halo-1-tosyl-1,2,5,6-tetrahydropyridines (**75**) in good yields as depicted in Scheme 18. The catalytic system comprises of Fe(acac)$_3$ and trimethylsilyl halide for Prins cyclization which leads to easy access of C-C, C-N and C-halogen bonds. This method can be applied for a wide range of substrates and also for other heterocyclic systems.



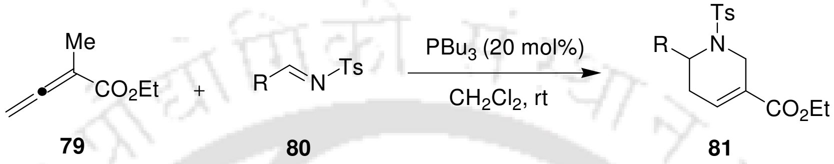
Scheme 18

Huang *et al.*[50] achieved the synthesis of trisubstituted tetrahydropyridines *via* an enantioselective [4 + 2] annulation, which relies on the reaction of chiral organosilane and aldehyde. The utility of this methodology was further extended for the synthesis of quinolizidine alkaloid (-)-217 A (7**8**) as shown in Scheme 19.



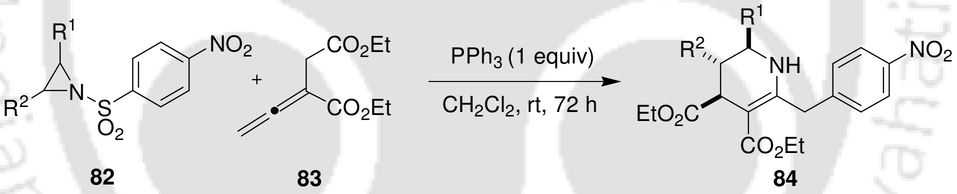
Scheme 19

Zhu and his co-workers[51] demonstrated an expedient phosphine-catalyzed [4 + 2] annulation reaction of allenoate with N-tosylaldamines to form tetrahydropyridine derivatives (**81**) in excellent yields with complete regioselectivity and high diastereoselectivities as represented in Scheme 20.



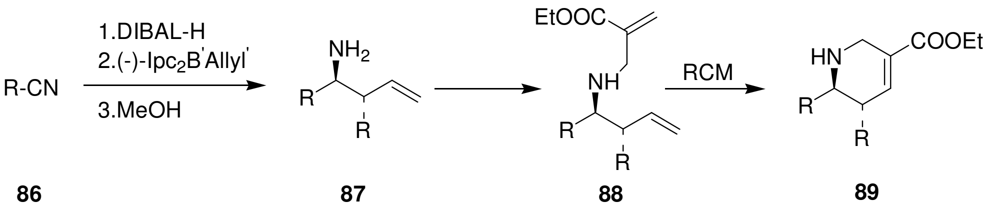
Scheme 20

Guo *et al.*[52] synthesized highly functionalized tetrahydropyridines (**84**) using phosphine-promoted [3 + 3] anuulation of aziridines with allenoates. The reaction is operationally simple and provides good to excellent yield with high level of diastereoselectivity as illustrated in Scheme 21.



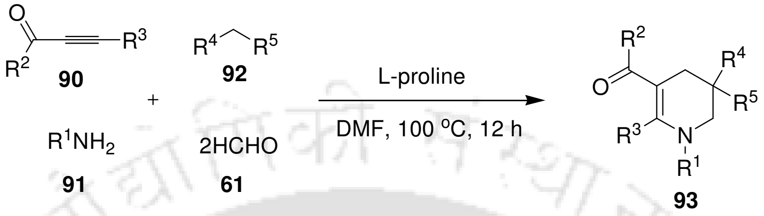
Scheme 21

Ramachandran and co-workers[53] accomplished the synthesis of chiral tetrahydropyridine-3-carboxylates (**89**) commenced with nitriles. This synthesis passes through steps such as allylboration, conjugate addition-elimination and ring-closing metathesis as given in Scheme 22. These derivatives also showed γ-aminobutyric acid (GABA)-inhibiting properties at low concentrations.



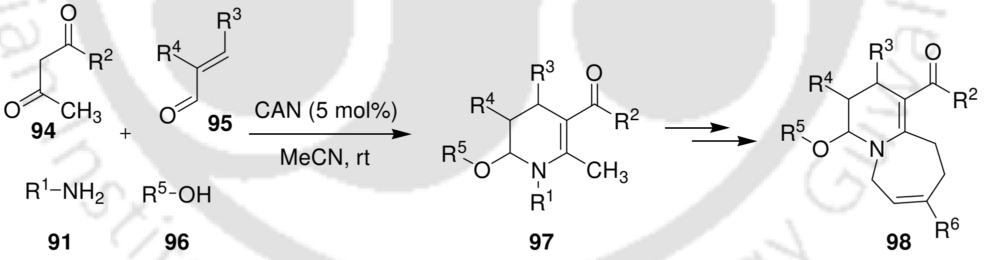
Scheme 22

Very recently, Jiang *et al.*[42] reported L-proline catalyzed synthesis of substituted tetrahydropyridines **93** using one-pot multicomponent reaction as illustrated in Scheme 23. This domino MCR includes hydroamination, Prins reaction, Mannich-type reaction and intramolecular dehydration-cyclization process.



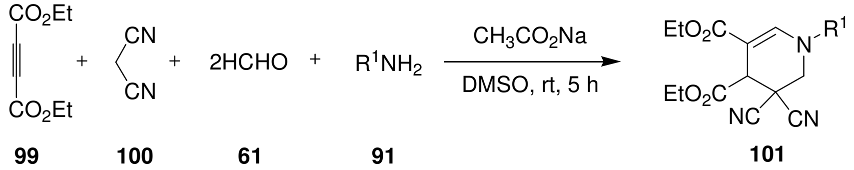
Scheme 23

Recently, Sridharan *et al.*[43] demonstrated the synthesis of functionalized 6-alkoxy-2-methyl-1,4,5,6-tetrahydropyridines through a four-component rection between primary aliphatic amines, β-ketoesters or β-ketothioesters, α,β-unsaturated aldehydes and alcohols catalyzed by cerium(IV) ammonium nitrate (CAN). Further, a two-step sequential reaction comprising of regioselective, γ-deprotonation-allylation and ring closing metathesis of tetrahydropyridines leads to substituted homoquinolizine derivatives **98** in excellent yields as shown in Scheme 24.



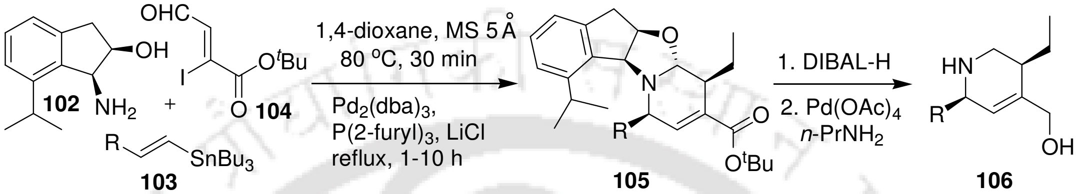
Scheme 24

Liu *et al.*[44] developed a new procedure for the synthesis of functionalized 1,2,3,4-tetrahydropyridines (**101**) through multicomponent reaction promoted by sodium acetate as depicted in Scheme 25.



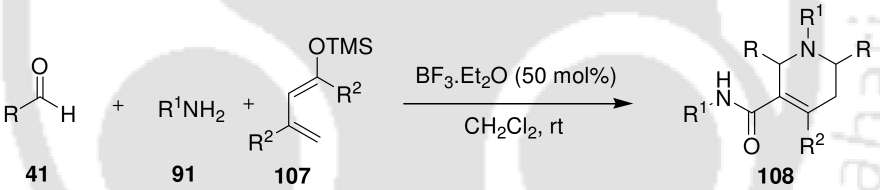
Scheme 25

Kobayashi *et al.*[45] demonstrated the stereocontrolled synthesis of trisubstituted 1,2,5,6-tetrahydropyridines **106** using a one-pot tandem 6π-azaelectrocyclization. The products were obtained by multicomponent reaction of vinyl stannanes, tetrasubstituted vinyl iodide having *tert*-ester groups and 7-isopropyl-*cis*-aminoindanol with an excellent stereoselectivity using Pd-catalyst as shown in Scheme 26.



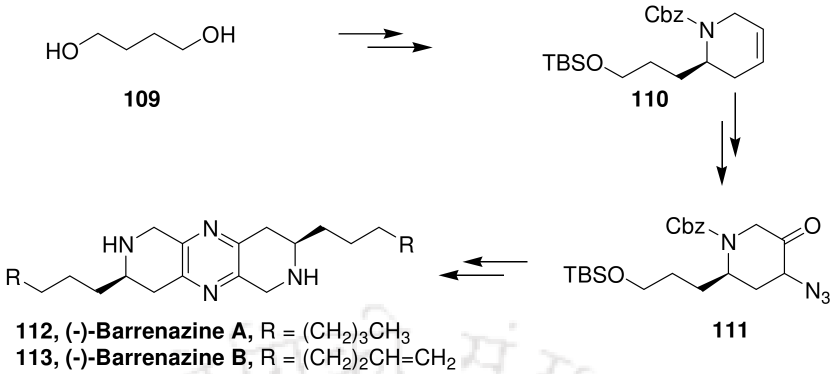
Scheme 26

Xiao and his group[46] reported $BF_3.OEt_2$-mediated synthesis of tetrahydropyridines **108** through a one-pot multicomponent reaction of aldehydes, anilines and Brassard's diene under mild and solvent-free reaction conditions *via* the Aldol and aza Diels-Alder condensation as represented in Scheme 27.



Scheme 27

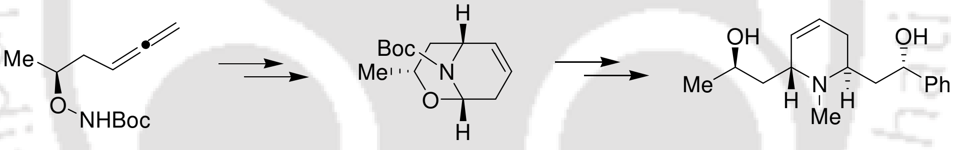
Peña-López and his group[54] demonstrated the enantioselective total synthesis of barrenazines A and B (**112** and **113**) starting from 1,4-butanediol through the tetrahydropyridine intermediates **110**. The construction of tetrahydropyridine ring **112** and **113** were achieved by sequential allylboration and ring-closing metathesis as shown in Scheme 28.



112, (-)-Barrenazine A, R = $(CH_2)_3CH_3$
113, (-)-Barrenazine B, R = $(CH_2)_2CH=CH_2$

Scheme 28

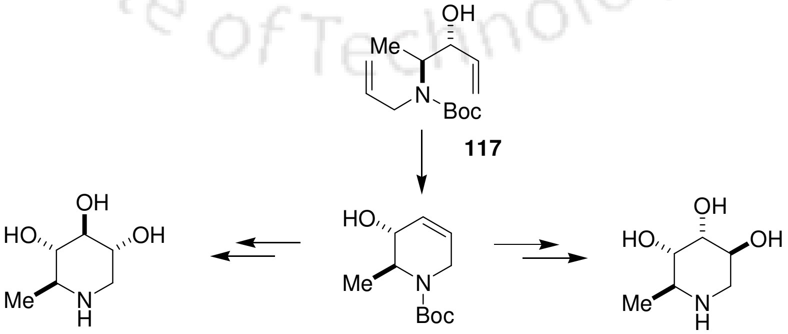
Recently, Bates and Lu[55] demonstrated the synthesis of (-)-sedinine (**116**), an important class of sedum alkaloid due to their interesting biological activities. Initially the intermediate bicyclic *N,O*-acetal was constructed using silver(I)-catalyzed allenic hydroxylamines. The natural product was obtained by ring opening of *N,O*-acetal with a silyl enolether under Lewis acidic conditions followed by reduction as illustrated in Scheme 29.



114 **115** **116**

Scheme 29

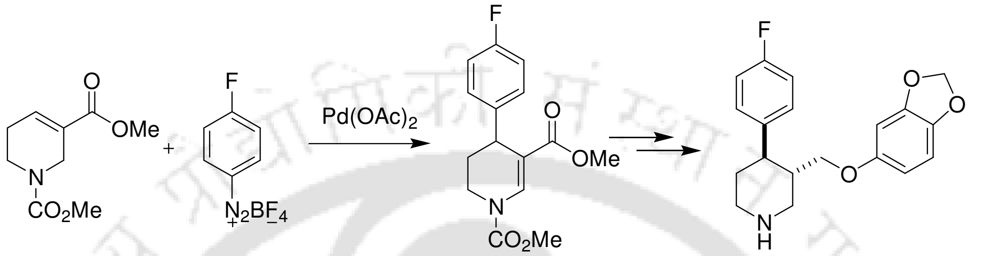
Rengasamy *et al.*[56] developed an efficient route for the synthesis of tetrahydropyridine **118**, which was used as a precursor for the synthesis of polyhydroxylated piperidines **119** and **120** as shown in Scheme 30.



***ent*-1,6-dDNJ, 119** **118** **120**

Scheme 30

Pastre and Correia described[57] the Heck arylation of acyclic and cyclic substituted acrylates using various arenediazonium tatrafluoroborate under aerobic and ligand free conditions to give moderate to high yields of substituted acrylates **123**. The compound **123** was further employed in the synthesis of antidepressant drug (±)-paroxetine (**124**) as illustrated in Scheme 31.



121 **122** **123** **(±)-Paroxetine, 124**

Scheme 31

1.5 Dihyropyridines and its importance

Nitrogen-containing heterocyclic motifs are ubiquitous in pharmaceuticals and biologically functional molecules. Especially molecules containing 1,4-dihydropyridine (1,4-DHP) skeleton is one of the most attractive target molecules because of their wide range of pharmacological activities and also acts as central fragment in many clinical pharmaceuticals.[58] The 1,4-DHPs embraces both potent calcium channel antagonist such as nifedipine (**8**), nimodipine (**125**) and other potent calcium channel agonist (**126** and **127**), respectively as shown Figure 4.[59] In addition, they have overwhelming utilization in the cardiovascular pharmacology as Ca^{2+} channel blockers (CCBs),[60] NMDA receptor antagonism (anticonvulsant)[61] and adenosine-A_3 receptor antagonism.[62] Recently, 1,4-DHPs have been found with some new pharmacological activities such as neuromodulatory (anticonvulsant),[63] HIV-I protease inhibition,[64] nitric oxide-like activities,[65] antidiabetic, antiviral, antibacterial, membrane protecting, anticancer[66] antitubercular[67] and antimicrobial.[68] Further, dihydropyridines have been reported to be potent R_{1a}-adrenoreceptor antagonists acting as inhibitors of human prostate contraction and hence are useful for treatment of benign prostate hyperplasia[69] and they are also useful NADH models.[70]

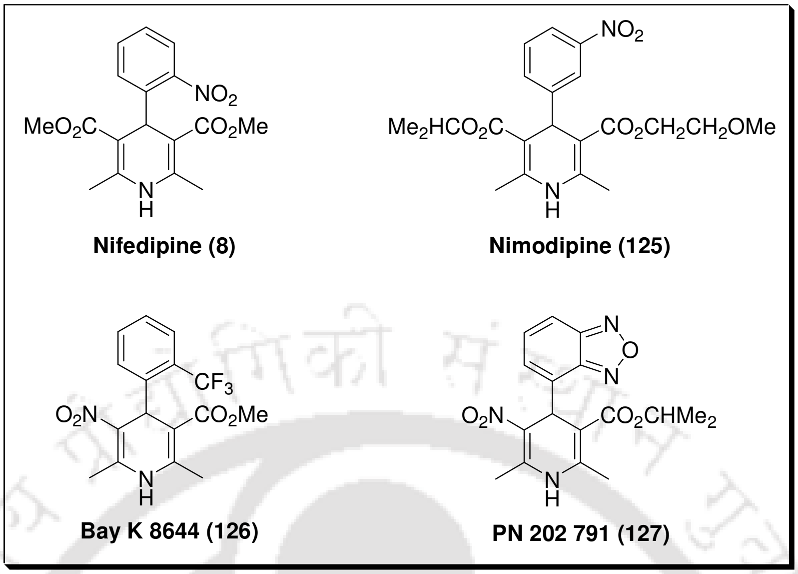


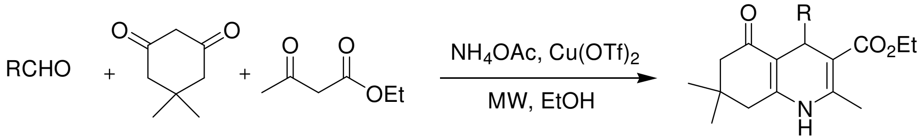
Figure 4. *Some biologically active compounds*

The unsymmetrical 1,4-DHPs represent effective drug moiety or sometime display even better pharmacological activities.[71] Therefore, the synthesis of unsymmetrical 1,4-DHPs justifies equal importance like symmetrical 1,4-DHPs in terms of drug discovery.

The literature exposing synthetic methods of dihydropyridines and their applications represented here:

1.6 General Approaches for the Construction of Dihydropyridines

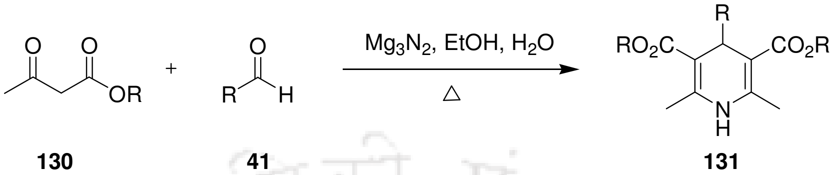
In 1882, Hantzsch[6] developed an important multicomponent condensation reaction for synthesis of 1,4-dihydropyridines known as Hantzsch 1,4-dihydropyridines (1,4-DHP). The classical method for the synthesis of 1,4-dihydropyridines is the one-pot condensation of aldehydes with ethyl acetoacetate and ammonia either in acetic acid or by refluxing them in alcohol. Recently, Pasunooti *et al.*[72] accomplished highly efficient copper-catalyzed multicomponent synthesis of 1,4-dihydropyridines **129** under microwave irradiation in excellent yields as shown in Scheme 32.



41 **128** **7** **129**

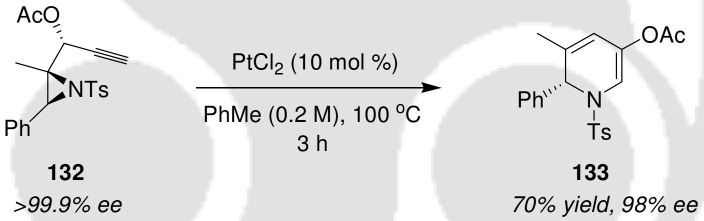
Scheme 32

Recently, Bridgwood *et al.*[73] illustrated the synthesis of Hantzsch 1,4-dihydropyridines (**131**) using magnesium nitride in place of ammonium acetate. In this method there is no need of additional catalyst as depicted in Scheme 33.



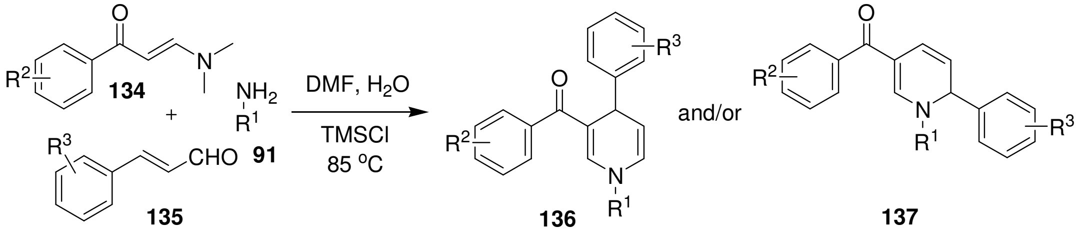
Scheme 33

Aziridinyl propargylic esters (**132**) were found to be an important precursor for the synthesis of 1,2-dihydropyridines (**133**). Motamed and his co-workers[74] demonstrated a novel Pt(II)-catalyzed cycloisomerization approach to access 1,2-DHPs using readily prepared aziridinyl propargylic esters as given in Scheme 34. The important feature of this reaction is the substituents installation which occurs in a regiodefined manner of aziridinyl propargylic esters.



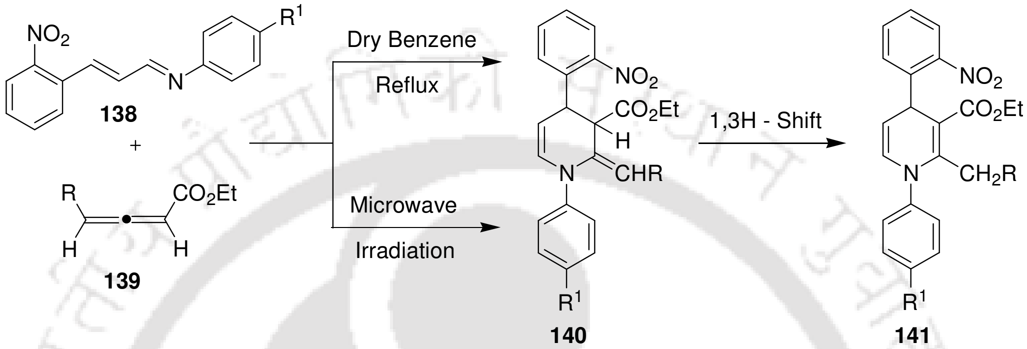
Scheme 34

Wan and his group[75] demonstrated the synthesis of usymmetrical 1,4- and 1,2-dihydropyridines **136** and **137** by the three-component sequential reaction of α,β-unsaturated aldehydes, amines and enaminones in presence of TMSCl. In this approach, 1,2-DHPs have been obtained in unexpected regioselective manner as depicted in Scheme 35.



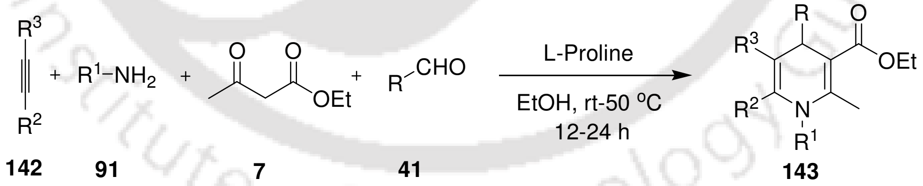
Scheme 35

Singh *et al.*[76] developed the synthesis of unsymmetrically substituted 1,4-DHPs through thermal and microwave promoted [4 + 2] cycloadditions of 1,4-diaryl-1-aza-1,3-butadiene with allenic ester. The substituted unsymmetrical 2-alkyl-1,4-diaryl-3-ethoxy-carbonyl-1,4-dihydropyridines (**141**) were obtained in good yields *via* 1,3-H shift from [4 + 2] cycloadducts as shown in Scheme 36.



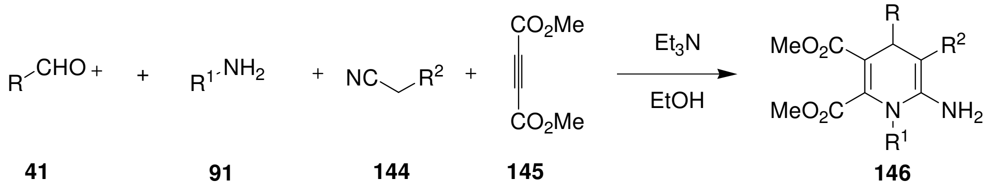
Scheme 36

Jiang *et al.*[77] reported the one-pot multicomponent reactions (MCRs) of alkynoates or alkynones, amines, β-dicarbonyl compounds and aldehyde catalyzed by L-proline to give highly functionalized multisubstituted 1,4-dihydropyridines (**143**) as represented in Scheme 37. Hydroamination, Knoevenagel condensation, Michael-type addition and intramolecular cyclization are the key steps in this MCRs leading to the formation of 1,4-dihydropyridines.



Scheme 37

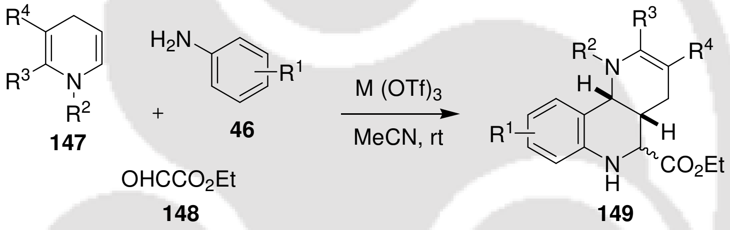
Very recently, Sun and his co-workers[78] have illustrated a practical and efficient one-pot four-component reaction of aromatic aldehydes, malonitrile, arylamines and acetylene dicarboxylate catalyzed by triethylamine in ethanol for the synthesis of polysubstituted dihydropyridines (**146**) as shown in Scheme 38.



Scheme 38

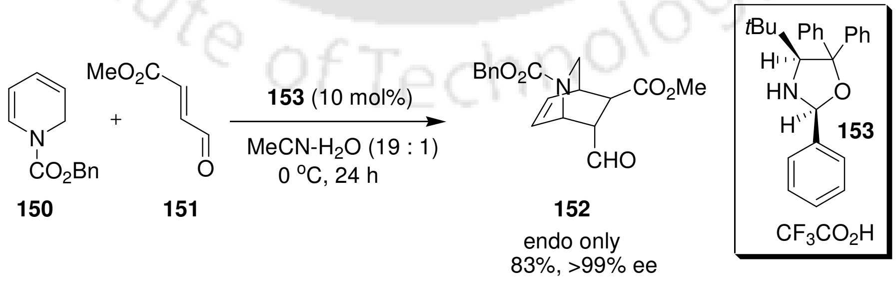
1.7 Synthetic utility of dihydropyridines

Maiti *et al.*[79] and Lavilla and co-workers[80] independently used dihydropyridines as dienophilic component in Povarov reaction to generate molecular diversity. Both groups have synthesized naphthyridine derivatives **149** by the reaction of dihydropyridine, anilines and ethyl glyoxylate in presence of metal triflate as catalyst in acetonitrile at room temperature as shown in Scheme 39.



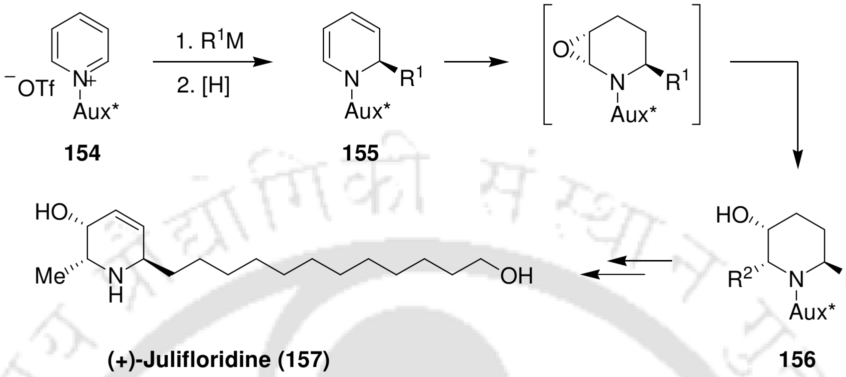
Scheme 39

Recently, Nakano *et al.*[81] reported an interesting application of 1,2-dihydropyridines as a diene in enantioselective Diels-Alder reaction with acrolein using a chiral oxazolidine organocatalyst for the synthesis of isoquinuclidine derivative **152** as depicted in Scheme 40.



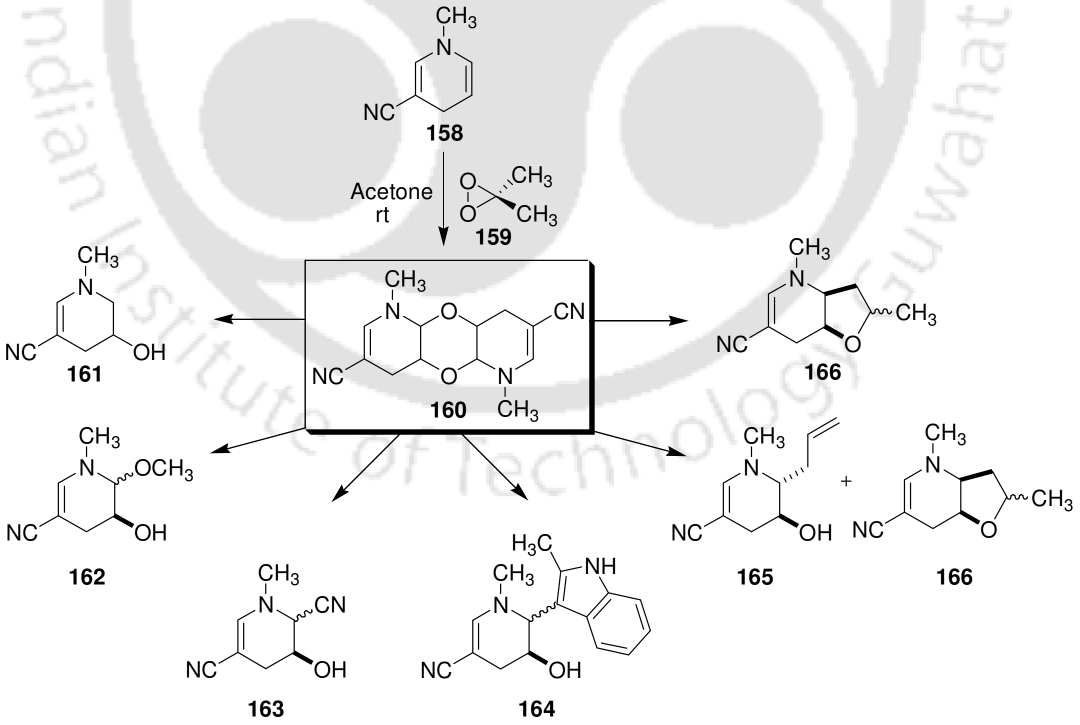
Scheme 40

Lemire and Charette demonstrated[82] the asymmetric synthesis of 2,6-disubstituted-3-piperidinols. This strategy was applied to the expedient asymmetric total synthesis of (+)-julifloridine (**157**) as depicted in Scheme 41.



Scheme 41

Lavilla *et al.*[83] reported "nonbiomimetic" oxidations of dihydropyridines to the intermediate dioxanes (**160**), which readily converted into various tetrahydropyridine derivatives having different functionalities as displayed in Scheme 42.



Scheme 42

From the literature it is evident that the tetra- and di- hydropyridine derivatives are present in natural products and exhibits diverse range of biological activities. Although, several methods have been reported for the synthesis of dihydropyridines over the years[84,85] but some of these methods are associated with certain limitations. The development of new methodologies related to synthesis of tetra- and di- hydropyridines is a challenging task. Thus, the second part of my thesis work is to develop new synthetic methodologies for the preparation of N-hetrocyclic compounds such as highly functionalized tetra- and dihydropyridine derivatives. In an endeavor to achieve our target, we have developed newer methodologies using Lewis acid and Brønsted acid catalysts. In the subsequent Chapters 2 and 3 of Part B, we have described multicomponent reactions leading to construction of tetra- and dihydropyridine derivatives.

PART B

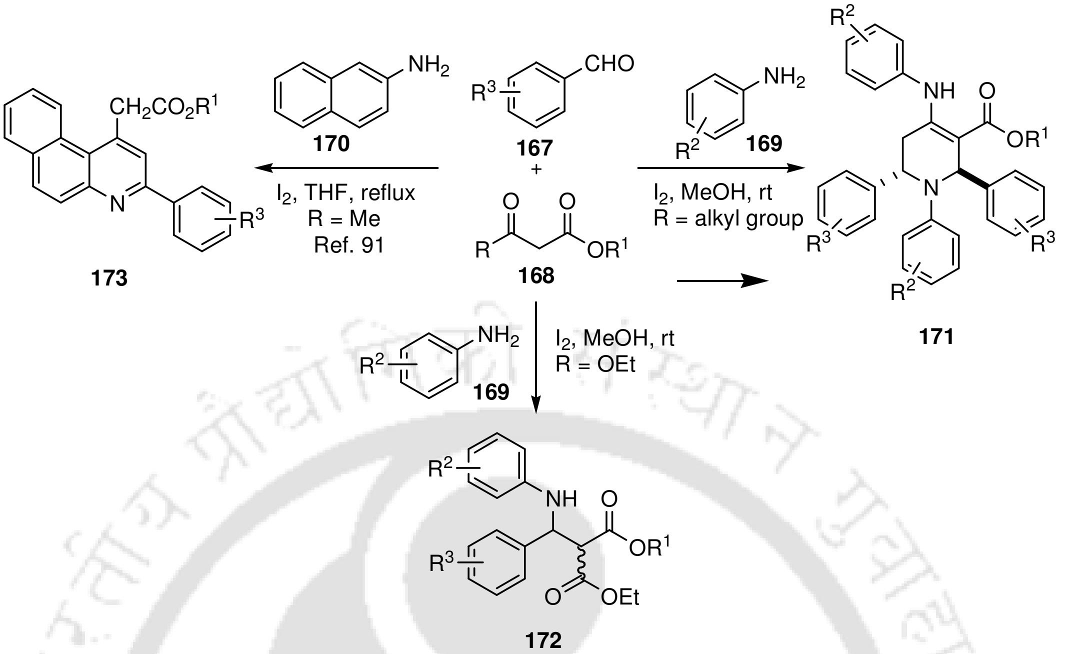
CHAPTER 2

Synthesis of functionalized tetrahydropyridines using one-pot five-component reaction catalyzed by iodine

Results and Discussion

In continuation of our endeavour to explore the application of new reagents in organic synthesis, we sought to test the catalytic activity of iodine as a Lewis acid for the development of new methodology in multicomponent reactions leading to functionalized tetrahydropyridine derivatives. The importance, synthetic utility and some recent strategies for the synthesis of tetrahydropyridines have been discussed in previous Chapter 1 Part B. We perceived that a new methodology is always welcome for the synthesis of tetrahydropyridine derivatives due to their medicinal and synthetic importance. In addition, the review of literatures also revealed the gradual development of multicomponent reactions (MCRs) in organic synthesis. Recently, MCRs have emerged as a powerful synthetic tool in organic synthesis due to their advantages over the conventional multi-step synthesis, which is highlighted in the previous Chapter. Recently, some more methods have also been developed by using MCR strategy for the synthesis of highly functionalized tetrahydropyridine derivatives employed catalysts such as $InCl_3$,[86] bromodimethylsulfonium bromide (BDMS),[87] L-Proline/TFA,[88] tetrabutylammonium tribromide (TBATB).[89] However, the aforesaid methods have some disadvantages such as use of metallic, expensive and excess amount of catalysts and failure in some of the cases to obtain the desired product. Therefore, there is a need for simpler and greener method, which are applicable to a broad range of substrates for the construction of these compounds.

On the other hand, molecular iodine has emerged as an inexpensive, non-toxic, non-metallic, readily available and environmentally benign catalyst for various organic transformations, which has been reviewed recently.[90] From the current literature survey it is also evident that molecular iodine can be used as an efficient catalyst for a diverse range of multicomponent reactions as well as synthesis of various heterocycles.[91-93] We envisaged that molecular iodine is to be an ideal Lewis acid for the one-pot synthesis of highly substituted tetrahydropyridine derivatives from aromatic aldehydes, amines and β-keto esters. In this Chapter, we have demonstrated the synthesis and mechanistic aspects of densely functionalized tetrahydropyridine derivatives (**171**) using MCRs as illustrated in Scheme 43.



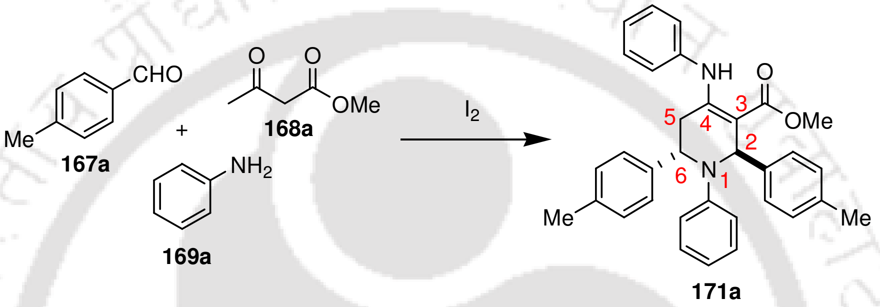
Scheme 43. *Direction of product formation in iodine catalyzed MCRs*

Initially, the mixture of 4-methylbenzaldehyde (1 mmol), aniline (1 mmol) and methyl acetoacetate (1 mmol) in acetonitrile (5 mL) was catalyzed by iodine (10 mol%) at room temperature. We obtained a highly functionalized tetrahydropyridine **171a** in 36% yield along with un-reacted methyl acetoacetate. The product was fully characterized by IR, ^{1}H NMR, ^{13}C NMR spectra, HRMS and elemental analysis. Appearance of a strong absorption peak at 1685 cm^{-1} in IR spectrum indicates the presence of carbonyl group. In ^{1}H NMR spectra the characteristic signals for tetrahydropyridine ring exhibited at δ 2.75 (dd, 1H, J = 2.4 Hz, J = 15.2 Hz, H-5), 2.86 (dd, 1H, J = 5.6 Hz, J = 15.2 Hz, H-5'), 5.11 (d, 1H, J = 3.2 Hz, H-6), 6.39 (s, 1H, H-2) and 10.25 (s, 1H, NH). Similarly, appearance of the peaks at δ 33.8 (C-5), 55.0 (C-2), 58.1 (C-6), 98.2 (C-3), 156.5 (C-4) and 168.8 (C=O) in ^{13}C NMR support the formation of tetrahydropyridine derivative. Finally, HRMS (ESI) was found at m/z = 489.2556 against the calculated m/z = 489.2542 for $C_{33}H_{32}N_2O_2$ $[M + H]^+$ is also evident for the product **171a** formation. From the above, it is quite clear that the substituted tetrahydropyridine derivative **171a** was obtained via five-component reaction.

For optimization of the amount of catalyst and choosing the suitable solvent, various trial reactions were investigated with a combination of 4-methylbenzaldehyde, aniline and methyl acetoacetate to obtain the best yield of product **171a**, which is summarized in

Table 1. We have noted that 10 mol% of the iodine furnished the best result for the formation of product. It has also been observed that MeOH was the best solvents for the present reaction among various other solvents such as MeCN, DCM, EtOH and EtOAc. For this transformation, ethanol can be a second choice of solvent. Under solvent-free conditions, the product was obtained in a moderate yield (48%) that may be due to lack of effective interaction of reactants with the catalyst.

Table 1. Optimization of reaction conditions for the synthesis of functionalized tetrahydropyridine **171a**

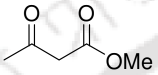
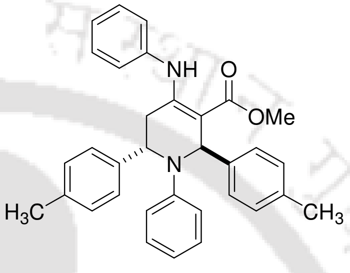
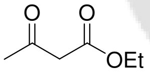
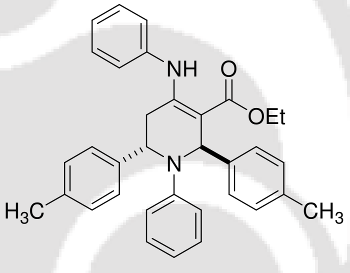
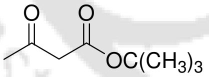
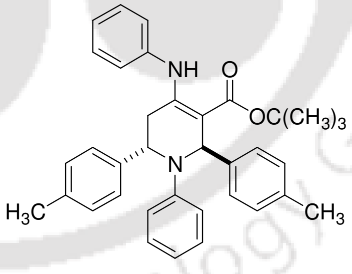
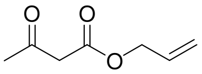
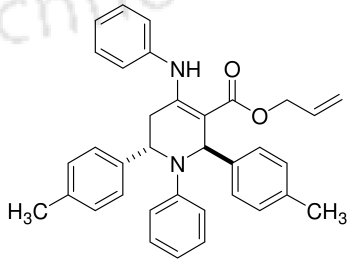


Entry	Solvent	Catalyst (mol %)	Time (h)	Yield^b (%)
1	CH_3CN	No catalyst	12	0
2	CH_3CN	5	12	52
3	CH_3CN	10	12	72
4	CH_3CN	20	12	69
5	CH_2Cl_2	10	12	60
6	C_2H_5OH	10	10	78
7	CH_3OH	10	8	84
8	EtOAc	10	12	62
9	Neat	10	12	48

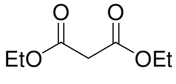
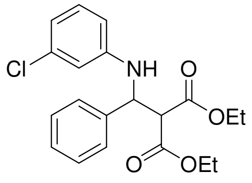
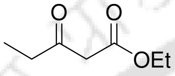
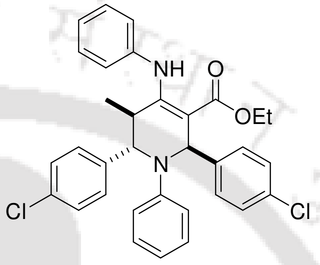
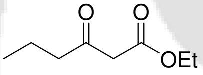
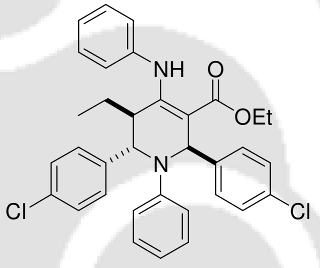
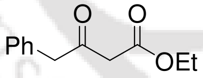
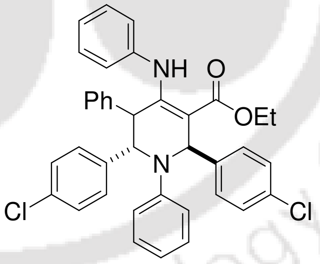
[b] *Isolated yields.*

Having established the optimal reaction conditions, the mixture of 4-methylbenzaldehyde, aniline and ethyl acetoacetate (**168b**) in methanol was treated with 10 mol% iodine to obtain the desired tetrahydropyridine derivative **171b**. Similarly, various other β-keto esters like *tert*-butyl acetoacetate (**168c**) and allyl acetoacetate (**168d**) also provided the corresponding tetrahydropyridine derivatives **171c** and **171d** in good yields as shown in Table 2. From these observations, we may conclude that the alkoxy (-OR) moiety present in the β-keto ester does not have any significant role in determining the course of the reaction. However, reaction of diethyl malonate (**168e**) yielded the corresponding β-amino carbonyl compound (**172**) under identical reaction conditions (Table 2, entry 5). This can be attributed to the lack of enolizable alkyl group in the β-position.

Table 2. Scope of β-keto esters in the formation of product with aromatic aldehydes and amines using iodine as catalyst[a]

Entry	β-Keto esters	Time (h)	Product	Yield[b] (%)
1	 **168a**	8	 **171a**	84
2	 **168b**	8	 **171b**	78
3	 **168c**	10	 **171c**	68
4	 **168d**	10	 **171d**	66

Continued Table 2

Entry	β-Keto esters	Time (h)	Product	Yield[b] (%)
5	 **168e**	8	 **172**	88[c]
6	 **168f**	48	 **171e**	42
7	 **168g**	48	 **171f**	36
8	 **168h**	48	 **171g**	0[d]

[a]*Reactions were performed in the ratio of 2:2:1 (aldehydes: amines: β-keto esters) in presence of 10 mol% iodine in 5 mL methanol at rt.* [b]*Isolated yields.* [c]*Unreacted imine (0.150 g) was recovered from the reaction.* [d]*Determined by crude* ^{1}H *NMR.*

In addition, the effect of an alkyl group was also studied by varying the substitutents at the β-position of the β-keto esters. The reaction of ethyl propionylacetate (**168f**) with 4-chlorobenzaldehyde and aniline afforded fully substituted tetrahydropyridine **171e** in 42% yield. Similarly, the reaction of ethyl butyrylacetate (**168g**) with 4-chlorobenzaldehyde and aniline also provided the desired compound **171f** in 36% yield under similar reaction conditions (Table 2, entry 7). The ^{1}H NMR and ^{13}C NMR spectra of compound **171c** and **171f** are given in Figure 1 and 2 of the Experimental Section. The fully substituted tetrahydropyridine derivatives were not reported earlier.[86-88] From these observations, it is clear that methyl and ethyl group can be introduced easily at the 5-position of the tetrahydropyridine ring by choosing a suitable β-keto ester.

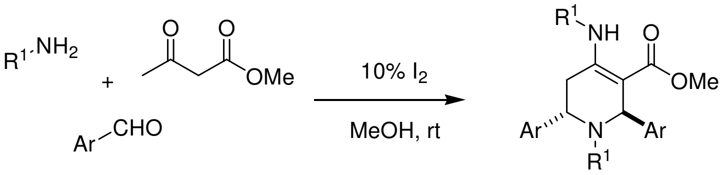
Next, we wanted to incorporate a phenyl group at the 5-position in the pyridine ring. For this purpose, the required β-keto ester (ethyl 3-oxo-4-phenylbutanoate, **168h**) was prepared by following the literature procedure.[94] Then, it was subjected to react with 4-chlorobenzaldehyde and aniline in presence of 10 mol% catalyst under identical reaction conditions (Table 2, entry 8). Unfortunately, we did not get the desired tetrahydropyridine derivative **171g** even after 48 h of stirring.

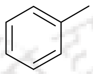
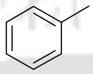
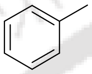
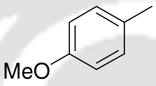
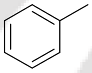
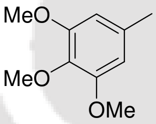
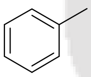
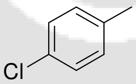
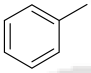
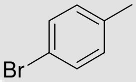
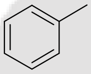
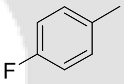
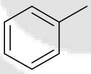
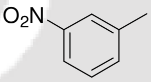
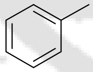
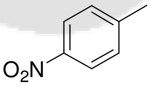
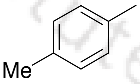
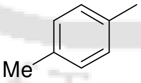
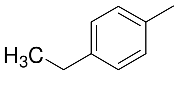
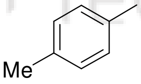
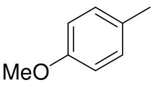
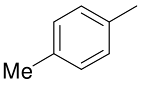
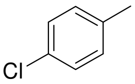
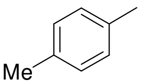
These investigation suggests that not only methyl group but also any enolizable alkyl group present in the β position of β-keto esters, is a necessary and sufficient condition for the formation of highly substituted tetrahydropyridines using MCRs (Table 2).

We proceeded further to investigate the reaction of various aromatic aldehydes having substituents such as OMe, Cl, Br, F and NO_2 with aniline and methyl acetoacetate under the similar reaction conditions. The reaction time and yield of the products **171h-o** are shown in Table 3, entries 1-8. The low yields obtained in case of entries 7 and 8 attributed to the (i) formation of more stable imine due to extra conjugation in the presence of nitro group, which is less reactive and (ii) partial or less solubility in methanol. Unfortunately, some of the aldehydes such as β-naphthaldehyde and *n*-butanal, did not give the corresponding functionalized tetrahydropyridines.

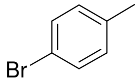
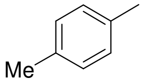
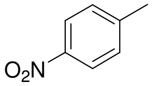
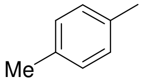
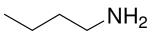
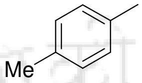
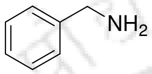
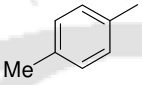
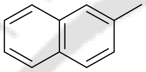
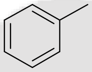
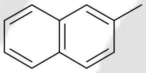
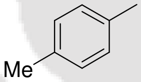
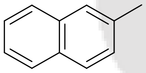
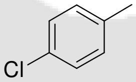
In some cases of aldehydes such as benzaldehyde, 4-chlorobenzaldehyde and 4-nitrobenzaldehyde a small quantity of enol-piperidines were formed along with the desired tetrahydropyridines as shown in Scheme 44. For example, the reaction of benzaldehyde with aniline and methyl acetoacetate in presence of iodine at room temperature provided a mixture of desired tetrahydropyridines **171h** and enol-piperidine **174h** in 53% and 27% respectively**.** It is speculated that the formation of **174** may be due to either hydrolysis of the enamine-piperidines **171** or through a four-component reaction. If the product **174** is formed from hydrolysis of **171**, then we expected that enol-piperidine derivative **174** should have obtained in more quantities at elevated temperature.

Table 3. Scope for one-pot five-component reactions of methyl acetoacetate with aromatic aldehydes and amines[a]

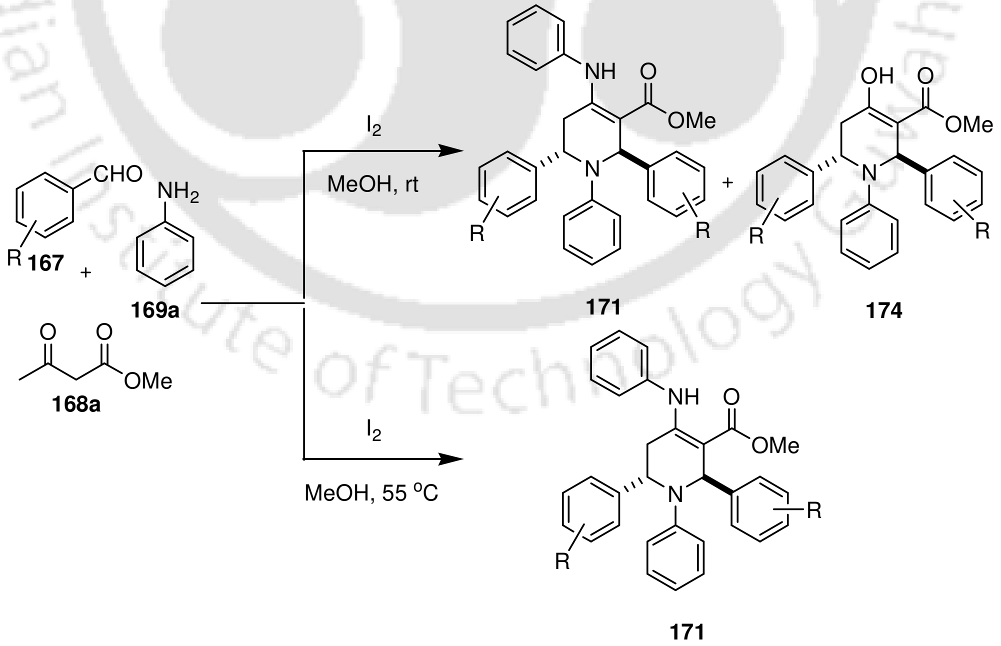


Entry	R¹	Ar	Time (h)	Product	Yield[b] (%)
1			8	**171h**	81[c]
2			8	**171i**	74
3			18	**171j**	68
4			6	**171k**	85[c]
5			6	**171l**	81
6			8	**171m**	74
7			6	**171n**	36
8			6	**171o**	38[c]
9			8	**171p**	68
10			10	**171q**	65
11			8	**171r**	74
12			6	**171s**	79[c]

Continued Table 3

Entry	R^1	Ar	Time (h)	Product	Yield^b (%)
13			8	**171t**	68
14			38	**171u**	57
15			48	**171v**	48
16			48	**171w**	55
17			8	**171x**	53
18			8	**171y**	51
19			6	**171z**	55^c

[a] *Aldehyde, amine and methyl acetoacetate were taken in 2:2:1 ratio in presence of 10 mol% iodine at rt.* [b] *Isolated yields.* [c] *Reaction was carried out at 55 °C.*



Scheme 44. *Formation of product at different reaction conditions*

To investigate this, the reaction was carried out at 55 °C and surprisingly, we isolated the tetrahydropyridines **171h** exclusively in 81% yield not enol-piperidine after 5 h. Further, we did not obtain the hydrolysed product **174h** from **171h** even upon hydrolysis under both acidic and basic reaction conditions. From these observations, we may conclude that the enol-piperidine **174h** is obtained exclusively through a four-component reaction rather than hydrolysis of **171**. The ^{1}H NMR and ^{13}C NMR spectra of compound **174h** are given in Figure 5 of the Experimental Section.

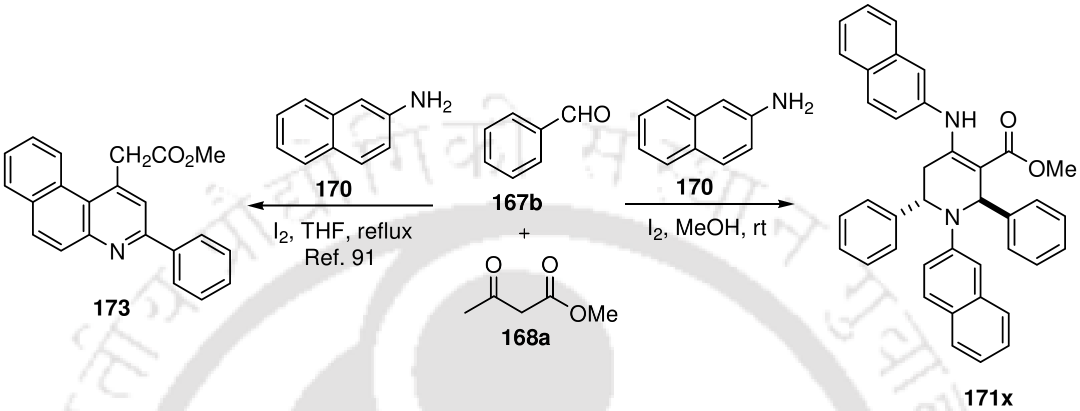
Table 4. Visualization of products at different reaction conditions

Entry	R	Reaction at rt		Reaction at 55 °C	
		Time (h)	Product Ratio[a] **171** : **174**	Time (h)	Product[b] **171**
1	4-H	8	65:35	6	81
2	4-Cl	8	79:21	6	85
3	4-NO_2	10	81:19	8	38

[a]*Ratio determined by crude* ^{1}*H NMR.* [b]*Isolated yields.*

To find the generality and scope of this MCR, various amines aromatic as well as aliphatic were also examined. A wide variety of anilines bearing substituents such as Me, Et, OMe, Br, NO_2 were treated with 4-methylbenzaldehyde and methyl acetoacetate under identical reaction conditions. All the reactions underwent smoothly to provide the corresponding tetrahydropyridines derivative **171p**-**u**, in moderate to good yields (Table 3, entries 9-13). Likewise, aliphatic amines *viz* *n*-butylamine and benzylamine also afforded the corresponding tetrahydropyridines **171v** and **171w** respectively in moderate yields. The ^{1}H NMR and ^{13}C NMR spectra of compound **171w** are given in Figure 3 of the Experimental Section. It is worthwhile to mention that 4-nitroaniline and aliphatic amines do not give the corresponding tetrahydropyridine derivatives by using $InCl_3$.[86]

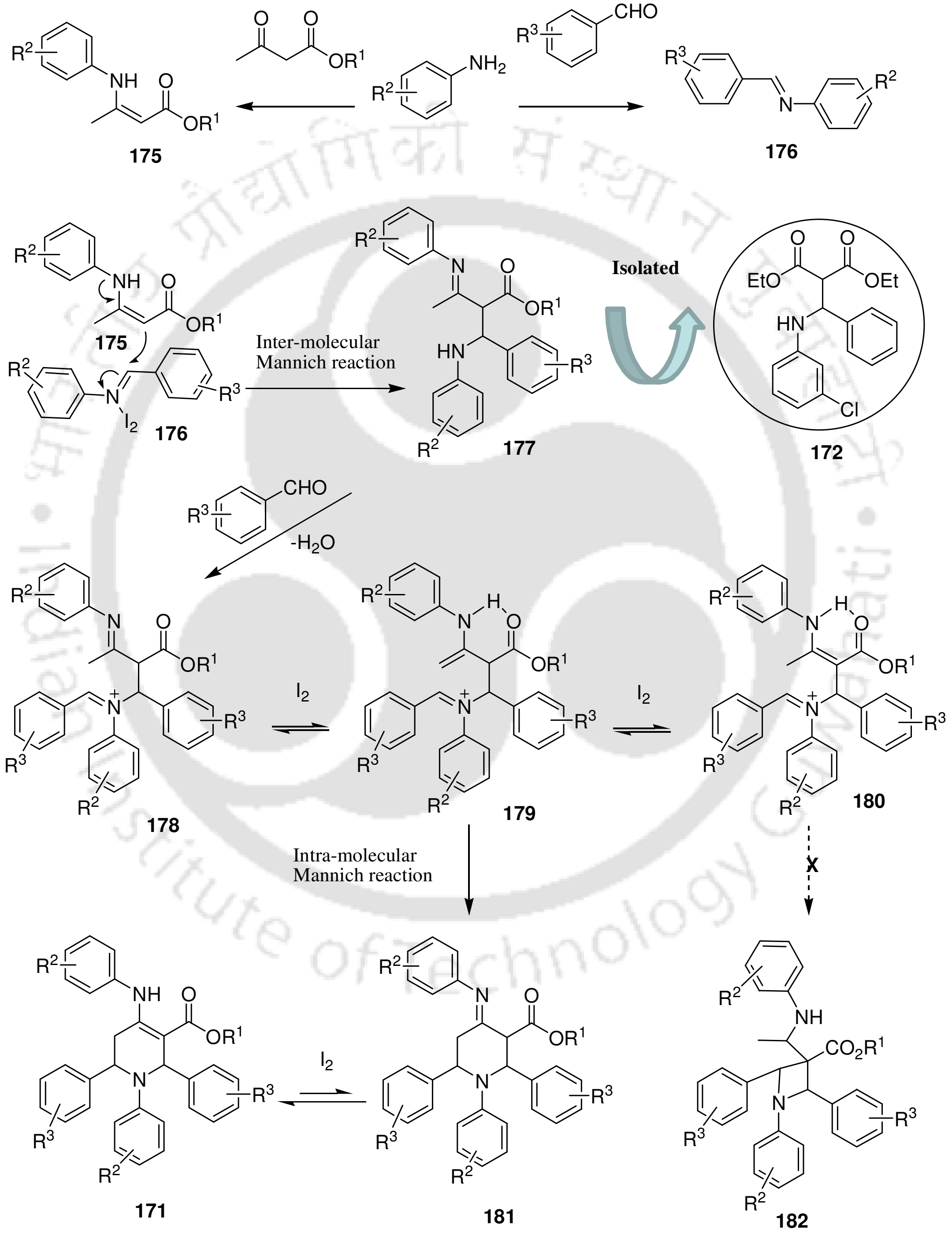
It is interesting to point out that, in our experimental conditions when 2-naphthylamine was treated with methyl acetoacetate and benzaldehyde to give the desired tetrahydropyridine derivatine **171x** in 53%. However, Wang *et al.* recently reported[91] that same combination of 2-naphthylamine and benzaldehyde with methyl acetoacetate catalyzed by molecular iodine in THF at reflux temperature provided 3-aryl-1-substituted benzo[*f*]quinoline derivative **173** in good yield as represented in Scheme 45. Further, we performed the reaction of 2-naphthylamine, methyl acetoacetate and other aldehydes such as 4-methylbenzaldehyde and 4-chlorobenzaldehyde under identical reaction conditions and results are summarized in Table 2. The ^{1}H NMR and ^{13}C NMR spectra of compound **171y** are given in Figure 4 of the Experimental Section. Unfortunately, 1-naphthylamine did not give the expected piperidine derivative under similar reaction conditions. This may be due to the steric hindrance of the bulky naphthyl group.



Scheme 45. *Role of reaction condition towards different product formation*

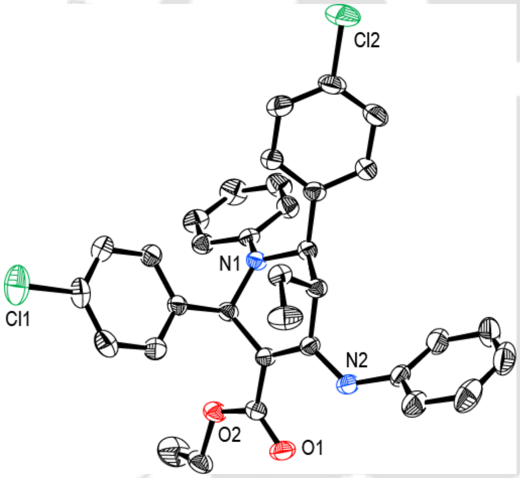
The products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectra, HRMS and by elemental analysis. The assignment of the tetrahydropyridines ring protons and carbons were made by using ^{1}H-^{1}H-COSY and ^{1}H-^{13}C-COSY spectra. Finally, the structures as well as the relative stereochemistry of tetrahydropyridines **171f** and **171l** were confirmed by X-ray crystallographic analysis as shown in Figure 5. From the structures, it was found that the ring adopted a boat conformation in case of compound **171f** in which flag pole positions 2 and 5 of the tetrahydropyridines ring, as well as the CO group of the ester and the -NH are on the same side of the plane and having intramolecular hydrogen bonding.

Finally, we turned our attention towards mechanistic studies for this transformation. Earlier, reported papers[86-88] proposed that the formation of tetrahydropyridines is going through [4 + 2] aza-Diels-Alder reaction. It was expected that β-keto ester reacts with amine to give enamine **175** and then it reacts with aldehyde to provide Knoevenagel type product, which acts as the reactive diene. Finally, it undergoes Diels-Alder reaction with imine **176** to give the desired product. To prove this mechanism, we had tried to trap the intermediate diene with other reactive dienophiles such as maleic anhydride, dihydropyran and dimethyl acetylenedicarboxylate. Unfortunately, we did not get any desired cycloaddition products. However, in the case of diethylmalonate on reaction with imine **176** furnished the Mannich-type product **172** (Table 2, entry 5). Therefore, we would like to propose an alternate plausible mechanism in which the product formed *via* double Mannich-type reactions. The enamine **175** and imine **176** were formed initially in the presence of iodine as illustrated in Scheme 46.

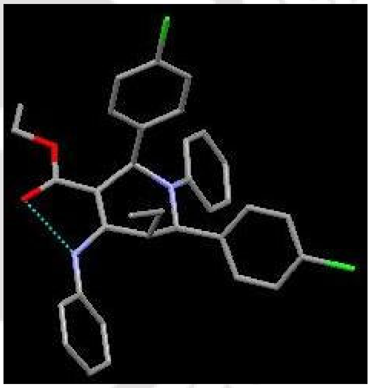


Scheme 46. *A plausible mechanism for the formation of highly substituted piperidine in the presence of iodine*

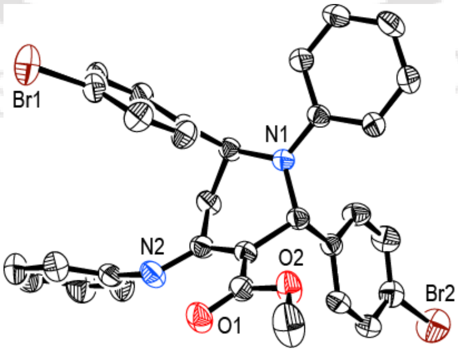
It is well known that enamine **175** would be a better nucleophile as compared to diethylmalonate. So, it is quite obvious that the nucleophilic attack by enamine **175** will take place preferentially on the iodine-activated imine **176** to give Mannich-type intermediate **177** with diethyl malonate. Then the intermediate **177** reacts with aldehyde to give **178** by elimination of water molecule. Further, there will be a spontaneous tendency in the presence of iodine for tautomerization to give the intramolecular hydrogen bonded species either **179** or **180**. However, the tautomer **179** immediately undergoes intramolecular Mannich-type reaction to form intermediate **181**. The tautomer **180** would have given a four membered ring product **182**, which is unfavourable. Finally, the intermediate **181** tautomerizes to give the final tetrahydropyridines derivative **171** due to conjugation with the ester group. However, the exact explanation is not yet clear and under investigation.



171f (CCDC No. 756203)



171f



171l (CCDC No. 756204)

Figure 5. *ORTEP molecular diagram with ellipsoid at 35% probability of **171f** and **171l***

The formation of four-component product in a few cases discussed earlier (Scheme 45) may be explained as follows: the enol form of methyl acetoacetate reacts with imine **176** instead of enamine **175** to form a Mannich-type intermediate, which is analogue to **177**. The remaining steps may be similar as depicted in Scheme 46.

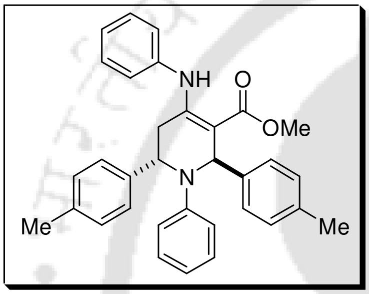
In summary, a general methodology is reported for the formation of highly as well as fully functionalized tetrahydropyridines in presence of iodine as catalyst *via* one-pot five component reaction from common available starting materials. The salient features of this protocol are good yields, mild reaction conditions, environmentally benign, superior atom economy, the readily accessibility of the catalyst and its cost effectiveness. In addition, we propose the possibility for the formation of functionalized tetrahydropyridines *via* double Mannich-type intermediates and mechanism is under investigation.

Experimental Section

General procedure for the synthesis of highly functionalized tetrahydropyridines **171**

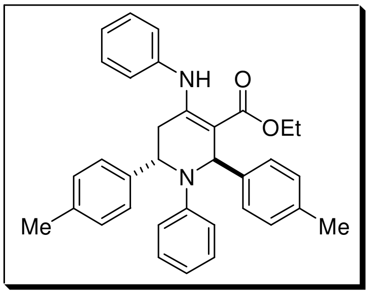
To a solution of amines (2 mmol) and β-keto esters (1 mmol) in 5 mL of methanol was added iodine (0.1 mmol) and stirred at room temperature. After 20 min, aromatic aldehyde (2 mmol) was added to the reaction mixture and stirred till completion. The thick precipitate was filtered off and washed with ethanol to give the pure products.

Methyl 2,6-bis(4-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171a**)



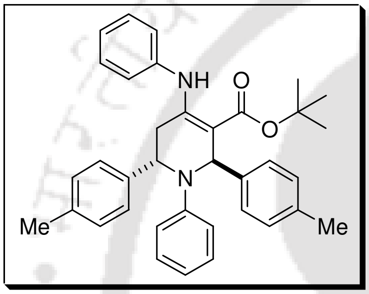
White solid; M.p. 215–217 °C; **IR** (KBr): 2922, 1657, 1591, 1504, 1250, 1074 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 2.32 (s, 3H, ArCH_3), 2.33 (s, 3H, ArCH_3), 2.75 (dd, 1H, J = 2.4 Hz, J = 15.2 Hz, H-5), 2.86 (dd, 1H, J = 5.6 Hz, J = 15.2 Hz, H-5'), 3.92 (s, 3H, OCH_3), 5.11 (d, 1H, J = 3.2 Hz, H-6), 6.30 (d, 2H, J = 8.0 Hz, Ar*H*), 6.39 (s, 1H, H-2), 6.52 (d, 2H, J = 8.0 Hz, Ar*H*), 6.59 (t, 1H, J = 7.2 Hz, Ar*H*), 7.02–7.10 (m, 11H, Ar*H*), 7.19 (d, 2H, J = 8.0 Hz, Ar*H*), 10.25 (s, 1H, N*H*); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 21.2, 21.3, 33.8 (C-5), 51.2, 55.0 (C-2), 58.1 (C-6), 98.2 (C-3), 113.0, 116.1, 125.8, 126.0, 126.5, 126.7, 128.9, 129.0, 129.1, 129.4, 136.0, 136.8, 138.1, 139.8, 141.1, 147.2, 156.5 (C-4), 168.8 (C=O); **HRMS** (ESI): Calcd for $C_{33}H_{32}N_2O_2$ [M + H]$^+$: *m/z* = 489.2542; found: 489.2556; **Anal. Calcd** for $C_{33}H_{32}N_2O_2$ (488.62): C, 81.12; H, 6.60; N, 5.73. Found: C 80.96, H, 6.55, N, 5.80.

Ethyl 2,6-bis(4-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171b**)



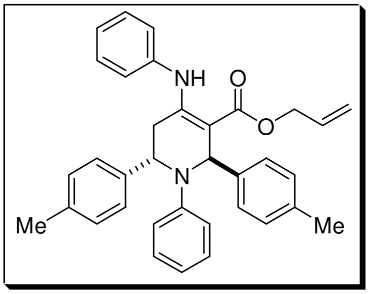
White solid; M.p. 228–231 °C; **IR** (KBr): 2922, 1649, 1592, 1500, 1256, 1071 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.46 (t, 3H, J = 7.2 Hz, OCH$_2$CH_3), 2.32 (s, 3H, ArCH_3), 2.33 (s, 3H, ArCH_3), 2.76 (dd, 1H, J = 2.4 Hz, J = 15.2 Hz, H-5), 2.86 (dd, 1H, J = 5.6 Hz, J = 15.2 Hz, H-5'), 4.26–4.36 (m, 1H, OC*H*H), 4.40–4.51 (m, 1H, OCH*H*), 5.11 (d, 1H, J = 2.4 Hz, H-6), 6.30 (d, 2H, J = 7.6 Hz, Ar*H*), 6.40 (s, 1H, H-2), 6.53 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.59 (t, 1H, *J* = 7.2 Hz, Ar*H*), 7.02–7.10 (m, 11H, Ar*H*), 7.22 (d, 2H, *J* = 8.0 Hz, Ar*H*), 10.29 (s, 1H, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 15.0, 21.2, 21.3, 33.8 (C-5), 55.0 (C-2), 58.1 (C-6), 59.8, 98.5 (C-3), 113.1, 116.1, 125.7, 125.9, 126.5, 126.7, 128.9, 129.0, 129.1, 129.4, 135.9, 136.8, 138.2, 139.9, 141.2, 147.2, 156.2 (C-4), 168.4 (C=O); **HRMS** (ESI): Calcd for $C_{34}H_{34}N_2O_2$ $[M + H]^+$: *m/z* = 503.2699; found: 503.2683; **Anal. Calcd** for $C_{34}H_{34}N_2O_2$ (502.65): C, 81.24; H, 6.82; N, 5.57. Found C, 81.13; H, 6.76; N, 5.69.

Tert-butyl 2,6-bis(4-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171c**)



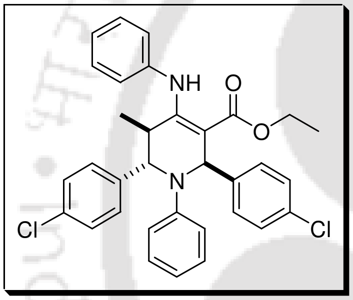
Light yellow solid; M.p. 171–173 °C; **IR** (KBr): 3447, 2923, 1648, 1592, 1500, 1274, 1251, 1152, 1064 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 1.64 (s, 9H, C(CH_3)$_3$), 2.31(s, 3H, ArCH_3), 2.33 (s, 3H, ArCH_3), 2.74 (dd, 1H, *J* = 2.8 Hz, *J* = 15.2 Hz, H-5), 2.82 (dd, 1H, *J* = 5.6 Hz, *J* = 15.2 Hz, H-5'), 5.08 (d, 1H, *J* = 3.2 Hz, H-6), 6.29 (d, 2H, *J* = 7.2 Hz, Ar*H*), 6.35 (s, 1H, H-2), 6.51 (d, 2H, *J* = 8.4 Hz, Ar*H*), 6.58 (t, 2H, *J* = 7.2 Hz, Ar*H*), 7.03–7.09 (m, 11H, Ar*H*), 7.23 (d, 2H, *J* = 8.0 Hz, Ar*H*), 10.25 (s, 1H, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 21.2, 21.3, 29.0, 33.8 (C-5), 55.4 (C-2), 58.2 (C-6), 80.1, 100.2 (C-3), 113.1, 116.1, 125.4, 125.7, 126.6, 126.7, 128.9, 129.1, 129.4, 135.8, 136.7, 138.5, 140.0, 141.5, 147.4, 155.3 (C-4), 168.4 (C=O); **HRMS** (ESI): Calcd for $C_{36}H_{38}N_2O_2$ $[M +H]^+$: *m/z* = 531.3012; found: 531.3013; **Anal. Calcd** for $C_{36}H_{38}N_2O_2$ (530.71): C, 81.47; H, 7.22; N, 5.28. Found C, 81.32; H, 7.31; N, 5.37.

Allyl 2,6-bis(4-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171d**)



Light yellow solid; M.p. 186–188 °C; **IR** (KBr): 3242, 3022, 2921, 1658, 1591, 1499, 1326, 1255, 1064 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 2.31 (s, 3H, ArCH_3), 2.32 (s, 3H, ArCH_3), 2.76 (dd, 1H, *J* = 2.4 Hz, *J* = 15.2 Hz, H-5), 2.86 (dd, 1H, *J* = 5.6 Hz, *J* = 15.2 Hz, H-5'), 4.80 (ddt, 1H, *J* = 1.6 Hz, *J* = 5.6 Hz, *J* = 13.6 Hz, C*H*H), 4.87 (ddt, 1H, *J* = 1.6 Hz, *J* = 5.6 Hz, *J* = 13.6 Hz, CH*H*), 5.10 (d, 1H, *J* = 3.6 Hz, H-6), 5.31 (dq, 1H, J = 1.2 Hz, J = 10.4 Hz, =C*H*H), 5.45 (dq, 1H, J = 1.2 Hz, J = 17.2 Hz, =CH*H*), 6.06–6.15 (m, 1H, =C*H*), 6.30 (dd, 2H, J = 2.4 Hz, J = 8.0 Hz, Ar*H*), 6.43 (s, 1H, H-2), 6.52 (d, 2H, J = 8.4 Hz, Ar*H*), 6.58 (t, 1H, J = 7.2 Hz, Ar*H*), 7.02–7.15 (m, 11H, Ar*H*), 7.21 (d, 2H, J = 8.0 Hz, Ar*H*), 10.26 (s, 1H, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 21.3, 33.9 (C-5), 55.1 (C-2), 58.1 (C-6), 64.5, 98.2 (C-3), 113.1, 116.2, 117.8, 125.8, 126.0, 126.5, 126.8, 128.98, 129.04, 129.1, 129.4, 133.3, 136.0, 136.8, 138.1, 139.8, 141.2, 147.2, 156.8 (C-4), 168.0 (C=O); **HRMS** (ESI): Calcd for $C_{35}H_{34}N_2O_2$ $[M + H]^+$: m/z = 515.2699; found: 515.2697; **Anal. Calcd** for $C_{35}H_{34}N_2O_2$ (514.66): C, 81.68; H, 6.66; N, 5.44. Found C, 81.56; H, 6.57; N, 5.51.

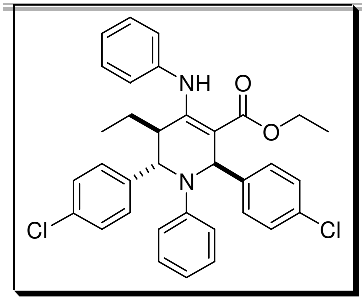
Ethyl 2,6-bis(4-chlorophenyl)-5-methyl-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171e**)



White solid; M.p. 198–199 °C; **IR** (KBr): 3445, 1651, 1594, 1254, 1089 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.04 (d, 3H, J = 7.2 Hz, CHC*H*$_3$), 1.37 (t, 3H, J = 7.2 Hz, CH_2C*H*$_3$), 3.01 (dq, 1H, J = 1.6 Hz, J = 7.2 Hz, H-5), 4.24–4.32 (m, 1H, C*H*HCH_3), 4.35–4.43 (m, 1H, CH*H*CH_3), 4.87 (s, 1H, H-6), 6.20 (s, 1H, H-2), 6.50–6.52 (m, 2H, Ar*H*), 6.57 (d, 2H, J = 8.4 Hz, Ar*H*), 6.68 (t, 1H, J = 7.2 Hz, Ar*H*), 7.00 (d, 2H, J = 8.4 Hz, Ar*H*), 7.09 (t, 2H, J = 7.6 Hz, Ar*H*), 7.18–7.27 (m, 9H, Ar*H*), 10.38 (s, 1H, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.8, 19.2, 38.7 (C-5), 55.7, 60.1 (C-2), 64.0 (C-6), 96.1 (C-3), 115.5, 117.9, 126.7, 127.1, 128.1, 128.7, 128.8, 129.0, 129.3, 129.4, 132.2, 132.8, 138.2, 141.8, 142.8, 147.4, 159.8 (C-4), 169.0 (C=O); **Anal. Calcd** for $C_{33}H_{30}N_2O_2Cl_2$ (557.51): C, 71.09; H, 5.42; N, 5.02. Found C, 71.01; H, 5.33; N, 5.12.

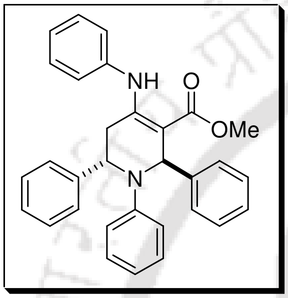
Ethyl 2,6-bis(4-chlorophenyl)-5-ethyl-1-phenyl-4-(phenylamino)-5-ethyl-1,2,5,6-tetrahydropyridine-3-carboxylate (**171f**)

White solid; M.p. 239–241 °C; **IR** (KBr): 2972, 1655, 1594, 1498, 1252, 1104, 1045 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.18 (t, 3H, J = 7.2 Hz, CH_2C*H*$_3$), 0.67–0.76 (m, 1H, C*H*HCH_3), 0.77–0.85 (m, 1H, CH*H*CH_3), 1.22 (t, 3H, J = 7.2 Hz, CH_2C*H*$_3$), 3.04 (m, 1H, H-5), 4.07–4.15 (m, 1H, C*H*HCH_3), 4.25–4.33 (m, 1H, CH*H*CH_3), 4.86 (d, 1H, J = 4.0 Hz, H-6), 5.99 (s, 1H, H-2), 6.78 (d, 2H, J = 8.0 Hz, Ar*H*), 7.12–7.25 (m, 10H, Ar*H*), 7.34 (d, 2H, J = 8.4 Hz, Ar*H*), 7.38–7.43 (m, 4H, Ar*H*), 10.78 (s, 1H, N*H*); **^{13}C NMR**



(100 MHz, $CDCl_3$): δ 12.1, 14.6, 22.2, 43.1 (C-5), 60.0, 61.7 (C-2), 63.8 (C-6), 95.6 (C-3), 116.8, 119.2, 126.3, 126.6, 128.4, 128.5, 128.9, 129.0, 129.6, 132.4, 132.7, 139.1, 139.9, 145.8, 151.2, 161.8 (C-4), 169.2 (C=O); **Anal. Calcd** for $C_{34}H_{32}N_2O_2Cl_2$ (571.54): C, 71.45; H, 5.64; N, 4.90. Found: C, 71.34; H, 5.53; N, 5.02.

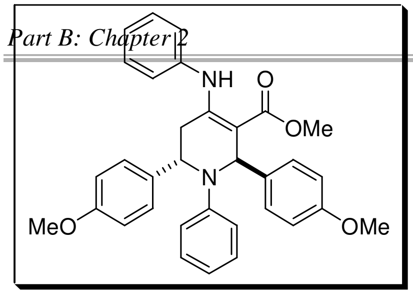
Methyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171h**)



To a solution of aniline (2 mmol) and methyl acetoacetate (1 mmol) in 5 mL of methanol, iodine (0.1 mmol) was added and stirred at 55 °C. After 10 min, benzaldehyde (2 mmol) was added to the reaction mixture and stirring was continued till completion at the same temperature. The reaction mixture was cooled to room temperature. The thick precipitate was filtered off and washed with ethanol to give pure products **171h** as white solid; M.p. 185–186 °C; **IR** (KBr): 3444, 3025, 2950, 1661, 1591, 1503, 1255, 1077 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 2.75 (dd, 1H, *J* = 2.4 Hz, *J* = 15.2 Hz, H-5), 2.86 (dd, 1H, *J* = 5.6 Hz, *J* = 15.2 Hz, H-5'), 3.93 (s, 3H, OCH_3), 5.14 (d, 1H, *J* = 4.4 Hz, H-6), 6.27 (d, 2H, *J* = 8.0 Hz, Ar*H*), 6.44 (s, 1H, H-2), 6.51 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.59 (t, 1H, *J* = 7.2 Hz, Ar*H*), 7.03–7.10 (m, 5H, Ar*H*), 7.16 (d, 2H, *J* = 8.0 Hz, Ar*H*), 7.24–7.32 (m, 8H, Ar*H*), 10.24 (s, 1H, N*H*); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 33.8 (C-5), 51.2, 55.2 (C-2), 58.3 (C-6), 98.0 (C-3), 113.0, 116.3, 125.9, 126.0, 126.5, 126.8, 127.3, 128.4, 128.8, 128.9, 129.0, 137.9, 142.9, 144.0, 147.1, 156.4 (C-4), 168.7 (C=O); **HRMS** (ESI): Calcd for $C_{31}H_{28}N_2O_2$ $[M + H]^+$: *m/z* = 461.2229; found: 461.2256; **Anal. Calcd** for $C_{31}H_{28}N_2O_2$ (460.57): C, 80.84; H, 6.13; N, 6.08. Found: C, 80.72; H, 6.07; N, 6.09.

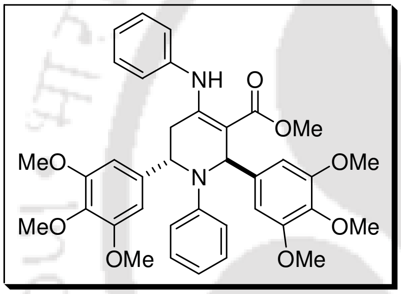
Methyl 2,6-bis(4-methoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171i**)

White solid; M.p. 186–188 °C; **IR** (KBr): 2949, 1654, 1609, 1593, 1508, 1246, 1033 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 2.75 (dd, 1H, *J* = 2.4 Hz, *J* = 15.2 Hz, H-5), 2.85 (dd, 1H, *J* = 5.6 Hz, *J* = 15.2 Hz, H-5'), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 5.07 (d, 1H, *J* = 3.2 Hz, H-6), 6.34–6.38 (m, 3H, H-2 and Ar*H*), 6.52 (d, 2H, *J* = 8.0 Hz, Ar*H*), 6.60 (t, 1H, *J* = 7.2 Hz, Ar*H*), 6.81 (d, 4H, *J* = 8.8 Hz, Ar*H*), 7.05 (d, 2H, *J*



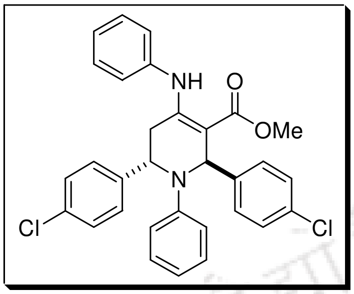
= 8.4 Hz, Ar*H*), 7.06 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.07 (t, 1H, *J* = 7.2 Hz, Ar*H*), 7.11 (d, 2H, *J* = 7.2 Hz, Ar*H*), 7.21 (d, 2H, *J* = 8.8 Hz, Ar*H*), 10.27 (s, 1H, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.9 (C-5), 51.2, 54.7 (C-2), 55.4, 57.7 (C-6), 98.2 (C-3), 113.1, 113.7, 114.1, 116.2, 125.8, 125.9, 127.6, 127.8, 129.0, 134.8, 136.0, 138.1, 147.1, 156.5 (C-4), 158.2, 158.8, 168.8 (C=O); **HRMS** (ESI): Calcd for $C_{33}H_{32}N_2O_4$ $[M + H]^+$: *m/z* = 521.2440; found: 521.2449; **Anal. Calcd** for $C_{33}H_{32}N_2O_4$ (520.62): C, 76.13; H, 6.20; N, 5.38. Found C, 76.01; H, 6.11; N, 5.49.

Methyl 2,6-bis(3,4,5-trimethoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171j**)



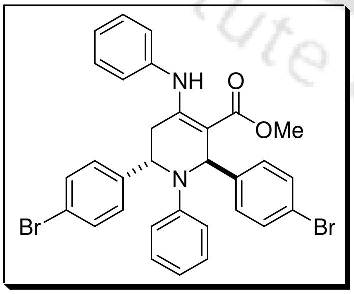
Light yellow solid; M.p. 197–199 °C; **IR** (KBr): 2938, 1655, 1594, 1500, 1415, 1322, 1254, 1125 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.77 (dd, 1H, *J* = 2.4 Hz, *J* = 15.2 Hz, H-5), 2.95 (dd, 1H, *J* = 5.6 Hz, *J* = 15.2 Hz, H-5'), 3.70 (s, 6H, 2 × OCH_3), 3.74 (s, 6H, 2 × OCH_3), 3.84 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.03 (d, 1H, *J* = 3.2 Hz, H-6), 6.34 (s, 1H, H-2), 6.35 (s, 2H, Ar*H*), 6.39 (d, 2H, *J* = 7.7 Hz, Ar*H*), 6.53 (s, 2H, Ar*H*), 6.57 (d, 2H, *J* = 8.0 Hz, Ar*H*), 6.65 (t, 1H, *J* = 7.6 Hz, Ar*H*), 7.09 (d, 2H, *J* = 8.0 Hz, Ar*H*), 7.12 (t, 1H, *J* = 7.2 Hz, Ar*H*), 7.15 (d, 2H, *J* = 7.6 Hz, Ar*H*), 10.26 (s, 1H, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.8 (C-5), 51.1, 55.6 (C-2), 56.0, 58.3 (C-6), 61.0, 97.3 (C-3), 103.2, 103.9, 113.1, 116.6, 126.2, 126.3, 128.9, 136.5, 137.0, 137.8, 138.5, 139.7, 147.0, 153.1, 153.4, 157.0, 168.5 (C=O); **HRMS** (ESI): Calcd for $C_{37}H_{40}N_2O_8$ $[M + H]^+$: *m/z* = 641.2863; found: 641.2800; **Anal. Calcd** for $C_{37}H_{40}N_2O_8$ (640.72): C, 69.36; H, 6.29; N, 4.37. Found C, 69.28; H, 6.24; N, 4.46.

Methyl 2,6-bis(4-chlorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171k**)



To a solution of aniline (2 mmol) and methyl acetoacetate (1 mmol) in 5 mL of methanol, iodine (0.1 mmol) was added and stirred at 55 °C. After 10 min, 4-chlorobenzaldehyde (2 mmol) was added to the reaction mixture and stirring was continued till completion at the same temperature. The reaction mixture was cooled to room temperature. The thick precipitate was filtered off and washed with ethanol to give pure product **171k** as white solid; M.p. 225–227 °C; **IR** (KBr): 2948, 1660, 1591, 1498, 1250, 1070 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 2.74 (dd, 1H, J = 2.4 Hz, J = 15.2 Hz, H-5), 2.82 (dd, 1H, J = 5.6 Hz, J = 15.2 Hz, H-5'), 3.92 (s, 3H, OCH_3), 5.09 (d, 1H, J = 2.4 Hz, H-6), 6.35 (s, 1H, H-2), 6.40 (d, 2H, J = 8.0 Hz, Ar*H*), 6.45 (d, 2H, J = 8.0 Hz, Ar*H*), 6.64 (t, 1H, J = 7.2 Hz, Ar*H*), 7.05 (d, 2H, J = 8.0 Hz, Ar*H*), 7.07 (d, 2H, J = 8.4 Hz, Ar*H*), 7.10 (t, 2H, J = 7.6 Hz, Ar*H*), 7.15 (d, 2H, J = 7.2 Hz, Ar*H*), 7.24 (m, 5H, Ar*H*), 10.25 (s, 1H, N*H*); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 33.8 (C-5), 51.3, 54.8 (C-2), 57.5 (C-6), 97.6 (C-3), 113.1, 116.9, 125.9, 126.2, 127.9, 128.2, 128.6, 128.9, 129.2, 132.3, 133.0, 137.7, 141.0, 142.5, 146.6, 156.2 (C-4), 168.4 (C=O); **HRMS** (ESI): Calcd for $C_{31}H_{26}N_2O_2Cl_2$ $[M + H]^+$: m/z = 529.1450; found: 529.1445; **Anal. Calcd** for $C_{31}H_{26}Cl_2N_2O_2$ (529.46): C, 70.32; H, 4.95; N, 5.29. Found: C, 70.29; H, 4.83; N, 5.34.

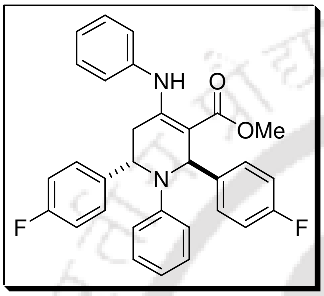
Methyl 2,6-bis(4-bromophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171l**)



Light yellow solid; M.p. 245–247 °C; **IR** (KBr): 2947, 1661, 1590, 1498, 1249, 1072 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 2.74 (dd, 1H, J = 2.4 Hz, J = 15.2 Hz, H-5), 2.82 (dd, 1H, J = 5.6 Hz, J = 15.2 Hz, H-5'), 3.93 (s, 3H, OCH_3), 5.08 (d, 1H, J = 3.6 Hz, H-6), 6.34 (s, 1H, H-2), 6.40 (d, 2H, J = 7.6 Hz, Ar*H*), 6.45 (d, 2H, J = 8.8 Hz, Ar*H*), 6.65 (t, 1H, J = 7.2 Hz, Ar*H*), 7.00 (d, 2H, J = 8.4 Hz, Ar*H*), 7.08 (t, 2H, J = 7.2 Hz, Ar*H*), 7.15 (t, 1H, J = 7.2 Hz, Ar*H*), 7.16 (d, 2H, J = 8.0 Hz, Ar*H*), 7.18 (d, 2H, J = 8.4 Hz, Ar*H*), 7.39 (d, 2H, J = 8.4 Hz, Ar*H*), 7.40 (d, 2H, J = 8.4 Hz, Ar*H*), 10.24 (s, 1H, N*H*); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 33.8 (C-5), 51.3, 54.9 (C-2), 57.5 (C-6), 97.6

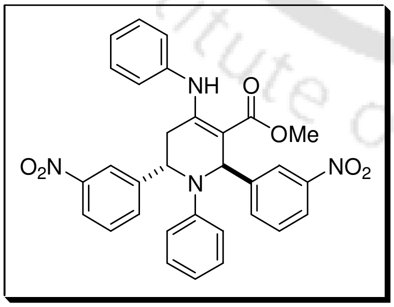
(C-3), 113.0, 116.9, 120.4, 121.1, 125.9, 126.2, 128.3, 128.6, 129.18, 129.2, 131.5, 131.9, 137.7, 141.6, 143.0, 146.5, 156.1 (C-4), 168.4 (C=O); **HRMS** (ESI): Calcd for $C_{31}H_{26}N_2O_2Br_2$ $[M + H]^+$: *m/z* = 617.0439; found: 617.0433; **Anal. Calcd** for $C_{31}H_{26}Br_2N_2O_2$ (618.37): C, 60.21; H, 4.24; N, 4.53. Found: C, 60.45; H, 4.15; N, 4.97.

Methyl 2,6-bis(4-fluorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171m**)



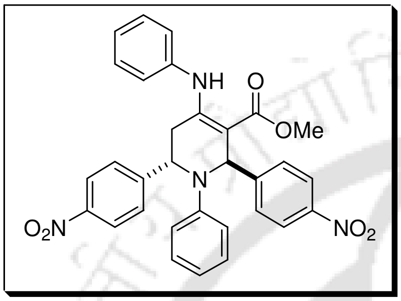
White solid; M.p. 193–195 °C; **IR** (KBr): 2945, 1657, 1592, 1502, 1255, 1071, 744 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.75 (dd, 1H, J = 2.4 Hz, J = 15.2 Hz, H-5), 2.83 (dd, 1H, J = 5.6 Hz, J = 15.2 Hz, H-5'), 3.93 (s, 3H, OCH_3), 5.11 (d, 1H, J = 2.8 Hz, H-6), 6.37 (s, 1H, H-2), 6.39 (d, 2H, J = 8.0 Hz, Ar*H*), 6.47 (d, 2H, J = 8.4 Hz, Ar*H*), 6.64 (t, 1H, J = 7.2 Hz, Ar*H*), 6.96 (t, 4H, J = 8.4 Hz, Ar*H*), 7.06–7.17 (m, 7H, Ar*H*), 7.25 (t, 2H, J = 8.4 Hz, Ar*H*), 10.23 (s, 1H, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.9 (C-5), 51.4, 54.7 (C-2), 57.5 (C-6), 97.9 (C-3), 113.1, 115.1, 115.3, 115.6, 115.8, 116.7, 125.9, 126.2, 128.0, 128.1, 128.3, 128.4, 129.2, 137.8, 138.2, 139.5, 146.7, 156.3 (C-4), 160.5, 163.4, 168.6 (C=O); **HRMS** (ESI): Calcd for $C_{31}H_{26}N_2O_2F_2$ $[M + H]^+$: *m/z* = 497.2241; found: 497.2245; **Anal. Calcd** for $C_{31}H_{26}F_2N_2O_2$ (496.55): C, 74.98; H, 5.28; N, 5.64. Found: C, 74.91; H, 5.11; N, 5.84.

Methyl 2,6-bis(3-nitrophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171n**)



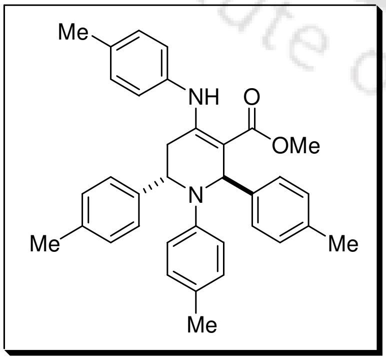
Yellow solid; M.p. 182–183 °C; **IR** (KBr): 3436, 2953, 1655, 1595, 1531, 1351, 1262, 1067 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.88 (d, 2H, J = 4.0 Hz, CH_2), 3.99 (s, 3H, OCH_3), 5.33 (t, 1H, J = 4.0 Hz, H-6), 6.38–6.41 (m, 2H, Ar*H*), 6.44 (d, 2H, J = 8.8 Hz, Ar*H*), 6.48 (s, 1H, H-2), 6.70 (t, 1H, J = 7.2 Hz, Ar*H*), 7.10 (t, 2H, J = 7.2 Hz, Ar*H*), 7.14–7.16 (m, 3H, Ar*H*), 7.45–7.50 (m, 3H, Ar*H*), 7.66 (d, 1H, J = 7.6 Hz, Ar*H*), 7.94 (s, 1H, Ar*H*), 8.10–8.15 (m, 2H, Ar*H*), 8.22 (s, 1H, Ar*H*), 10.30 (s, 1H, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 33.9 (C-5), 51.6, 55.3 (C-2), 57.2 (C-6), 96.9 (C-3), 113.2, 117.9, 121.5, 121.7, 122.0, 122.6, 125.8, 126.7, 129.3, 129.5, 129.8, 132.7, 137.3, 144.6, 145.9, 146.5, 148.7, 148.8, 155.7 (C-4), 168.2 (C=O); **Anal. Calcd** for $C_{31}H_{26}N_4O_6$ (550.56): C, 67.63; H, 4.76; N, 10.18. Found C, 67.51; H, 4.68; N, 10.29.

Methyl 2,6-bis(4-nitrophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171o**)



The reaction was carried out at 55 °C, after completion, the reaction mixture was cooled to room temperature. The thick precipitate was filtered off and washed with ethanol to give pure product **171o** as light yellow solid; M.p. 239–241 °C; **IR** (KBr): 3356, 2957, 1660, 1593, 1529, 1258, 1066 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 2.85 (d, 2H, J = 4.0 Hz, CH_2), 3.95 (s, 3H, OCH_3), 5.24–5.25 (m, 1H, H-6), 6.37–6.42 (m, 4H, Ar*H*), 6.46 (s, 1H, H-2), 6.68 (t, 1H, J = 7.2 Hz, Ar*H*), 7.07 (d, 1H, J = 7.2 Hz, Ar*H*), 7.09 (d, 1H, J = 7.2 Hz, Ar*H*), 7.13–7.17 (m, 3H, Ar*H*), 7.27 (d, 2H, J = 8.8 Hz, Ar*H*), 7.48 (d, 2H, J = 8.4 Hz, Ar*H*), 8.12 (d, 2H, J = 8.8 Hz, Ar*H*), 8.14 (d, 2H, J = 8.8 Hz, Ar*H*), 10.26 (s, 1H, N*H*); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 33.7 (C-5), 51.6, 55.4 (C-2), 57.5 (C-6), 96.8 (C-3), 113.1, 117.8, 123.9, 124.1, 125.7, 126.6, 127.5, 127.6, 129.4, 129.5, 137.3, 145.9, 146.9, 147.5, 149.9, 151.8, 155.7 (C-4), 168.1 (C=O); **Anal. Calcd** for $C_{31}H_{26}N_4O_6$ (550.56): C, 67.63; H, 4.76; N, 10.18. Found C, 67.51; H, 4.69; N, 10.31.

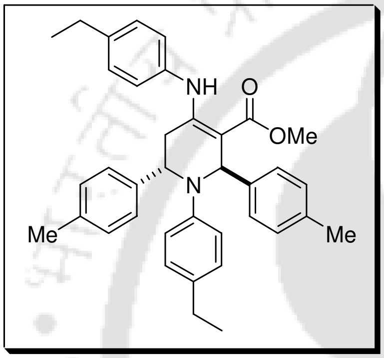
Methyl 2,6-bis(4-methylphenyl)-1-(4-methylphenyl)-4-(4-methylphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171p**)



Light yellow solid; M.p. 206–208 °C; **IR** (KBr): 3249, 2918, 1655, 1594, 1514, 1313, 1259, 1072 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 2.15 (s, 3H, $ArCH_3$), 2.27 (s, 3H, $ArCH_3$), 2.32 (s, 3H, $ArCH_3$), 2.34 (s, 3H, $ArCH_3$), 2.72 (dd, 1H, J = 2.4 Hz, J = 15.2 Hz, H-5), 2.82 (dd, 1H, J = 5.6 Hz, J = 15.2 Hz, H-5'), 3.91 (s, 3H, OCH_3), 5.07 (d, 1H, J = 4.0 Hz, H-6), 6.18 (d, 2H, J = 8.0 Hz, Ar*H*), 6.35 (s, 1H, H-2), 6.43 (d, 2H, J = 8.0 Hz, Ar*H*), 6.87 (d, 2H, J = 8.8 Hz, Ar*H*), 6.89 (d, 2H, J = 8.0 Hz, Ar*H*), 7.03–7.09

(m, 6H, Ar*H*), 7.20 (d, 2H, *J* = 8.0 Hz, Ar*H*), 10.17 (s, 1H, N*H*); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 20.3, 21.0, 21.2, 21.3, 33.7 (C-5), 51.0, 55.1 (C-2), 58.0 (C-6), 97.7 (C-3), 113.0, 125.0, 126.1, 126.5, 126.7, 129.0, 129.4, 129.5, 135.4, 135.6, 135.8, 136.6, 140.1, 141.4, 145.1, 156.8 (C-4), 168.8 (C=O); **HRMS** (ESI): Calcd for $C_{35}H_{36}N_2O_2$ $[M + H]^+$: *m/z* = 517.2855; found: 517.2847; **Anal. Calcd** for $C_{35}H_{36}N_2O_2$ (516.68): C, 81.36; H, 7.02; N, 5.42. Found C, 81.24; H, 7.01; N, 5.53.

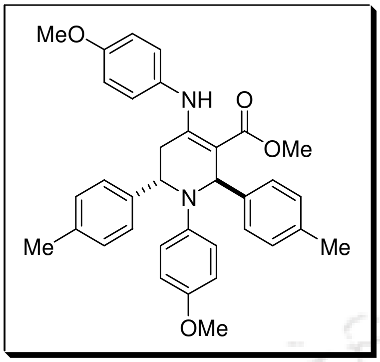
Methyl 2,6-bis(4-methylphenyl)-1-(4-ethylphenyl)-4-(4-ethylphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171q**)



Light yellow solid; M.p. 177–178 °C; **IR** (KBr): 3264, 2960, 1653, 1593, 1514, 1252, 1075 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.11 (t, 3H, *J* = 7.6 Hz, CH_3), 1.18 (t, 3H, *J* = 7.6 Hz, CH_3), 2.31(s, 3H, ArCH_3), 2.34 (s, 3H, ArCH_3), 2.45 (q, 2H, *J* = 7.6 Hz, CH_2), 2.56 (q, 2H, *J* = 7.6 Hz, CH_2), 2.73 (dd, 1H, *J* = 2.4 Hz, *J* = 15.2 Hz, H-5), 2.82 (dd, 1H, *J* = 5.6 Hz, *J* = 15.2 Hz, H-5'), 3.90 (s, 3H, OCH_3), 5.07 (d, 1H, *J* = 3.6 Hz, H-6), 6.19 (d, 2H, *J* = 8.4 Hz, Ar*H*), 6.35 (s, 1H, H-2), 6.44 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.88 (d, 2H, *J* = 8.8 Hz, Ar*H*), 6.91 (d, 2H, *J* = 8.4 Hz, Ar*H*), 7.03–7.09 (m, 6H, Ar*H*), 7.19 (d, 2H, *J* = 8.4 Hz, Ar*H*), 10.17 (s, 1H, N*H*); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 15.7, 15.9, 21.2, 21.3, 27.8, 28.4, 33.8 (C-5), 51.1, 55.2 (C-2), 58.2 (C-6), 97.8 (C-3), 113.0, 126.2, 126.6, 126.8, 128.3, 129.1, 129.4, 131.5, 135.6, 135.8, 136.7, 140.2, 141.5, 142.0, 145.3, 156.8 (C-4), 168.8 (C=O); **HRMS** (ESI): Calcd for $C_{37}H_{40}N_2O_2$ $[M + H]^+$: *m/z* = 545.3168; found: 545.3151; **Anal. Calcd** for $C_{37}H_{40}N_2O_2$ (544.73): C, 81.58; H, 7.40; N, 5.14. Found C, 81.49; H, 7.07; N, 5.24.

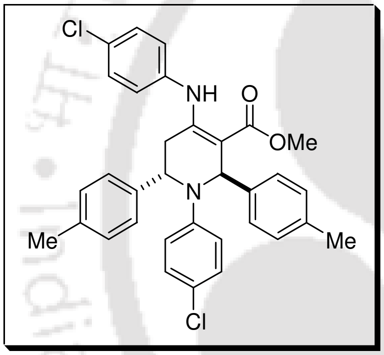
Methyl 2,6-bis(4-methylphenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171r**)

White solid; M.p. 230–231 °C; **IR** (KBr): 3442, 2918, 1657, 1611, 1512, 1248, 1073 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 2.31 (s, 3H, ArCH_3), 2.33 (s, 3H, ArCH_3), 2.62 (dd, 1H, *J* = 2.8 Hz, *J* = 15.2 Hz, H-5), 2.77 (dd, 1H, *J* = 5.6 Hz, *J* = 15.2 Hz, H-5'), 3.65 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 5.00 (d, 1H, *J* = 2.8 Hz, H-6), 6.21 (d, 2H, *J* = 9.2 Hz, Ar*H*), 6.26 (s, 1H, H-2), 6.43 (d, 2H, *J* = 9.2 Hz, Ar*H*), 6.60 (d, 2H, *J* = 9.2 Hz, Ar*H*), 6.64 (d, 2H, *J* = 9.2 Hz, Ar*H*), 7.02–7.09 (m, 6H, Ar*H*), 7.16 (d, 2H, *J* =



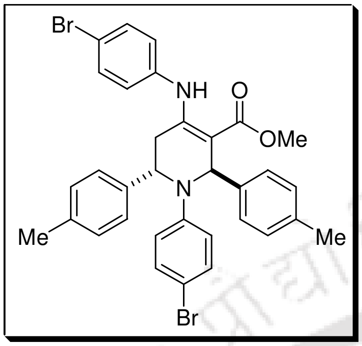
8.0 Hz, Ar*H*), 10.08 (s, 1H, N*H*); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 21.2, 21.3, 33.8 (C-5), 51.0, 55.6, 55.7, 55.8 (C-2), 58.1 (C-6), 97.3 (C-3), 114.1, 114.2, 114.3, 114.7, 126.6, 126.9, 128.0, 129.0, 129.4, 131.0, 135.9, 136.7, 140.4, 141.5, 141.9, 151.0 (C-4), 157.2, 157.9, 168.9 (C=O); **HRMS** (ESI): Calcd for $C_{35}H_{36}N_2O_4$ [M + H]$^+$: *m/z* = 549.2753; found: 549.2753; **Anal. Calcd** for $C_{35}H_{36}N_2O_4$ (548.67): C, 76.62; H, 6.61; N, 5.11. Found C, 76.56; H, 6.55; N, 5.26.

Methyl 2,6-bis(4-methylphenyl)-1-(4-chlorophenyl)-4-(4-chlorophenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171s**)



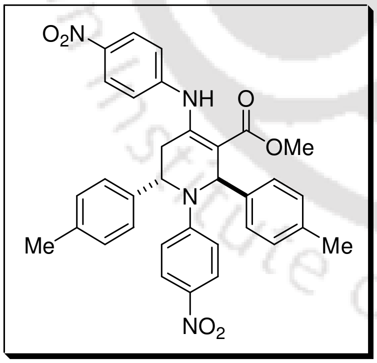
The reaction was carried out at 55 °C, after completion, the reaction mixture was cooled to room temperature. The thick precipitate was filtered off and washed with ethanol to give pure product **171s** as light yellow solid; M.p. 204–206 °C; **IR** (KBr): 3443, 2918, 1655, 1601, 1255, 1071 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 2.32 (s, 3H, ArC*H$_3$*), 2.34 (s, 3H, ArC*H$_3$*), 2.68 (dd, 1H, *J* = 2.4 Hz, *J* = 15.2 Hz, H-5), 2.84 (dd, 1H, *J* = 5.6 Hz, *J* = 15.2 Hz, H-5'), 3.93 (s, 3H, OC*H$_3$*), 5.06 (d, 1H, *J* = 4.0 Hz, H-6), 6.18 (d, 2H, *J* = 8.4 Hz, Ar*H*), 6.32 (s, 1H, H-2), 6.42 (d, 2H, *J* = 9.2 Hz, Ar*H*), 6.98 (d, 2H, *J* = 9.2 Hz, Ar*H*), 7.02 (d, 2H, *J* = 8.4 Hz, Ar*H*), 7.05 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.07–7.12 (m, 7H, Ar*H*), 7.14 (d, 2H, *J* = 8.0 Hz, Ar*H*), 10.19 (s, 1H, N*H*); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 21.2, 21.3, 33.7 (C-5), 51.3, 55.3 (C-2), 58.2 (C-6), 98.8 (C-3), 114.2, 121.2, 126.4, 126.6, 127.2, 128.8, 129.1, 129.2, 129.6, 131.4, 136.3, 136.6, 137.2, 139.3, 140.3, 145.7, 155.7 (C-4), 168.7 (C=O); **HRMS** (ESI): Calcd for $C_{33}H_{30}N_2O_2Br_2$ [M + H]$^+$: *m/z* = 645.0752; found: 645.0753; **Anal. Calcd** for $C_{33}H_{30}Cl_2N_2O_2$ (557.51): C, 71.09; H, 5.42; N, 5.02. Found C, 71.01; H, 5.33; N, 4.92.

Methyl 2,6-bis(4-methylphenyl)-1-(4-bromophenyl)-4-(4-bromophenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171t**)



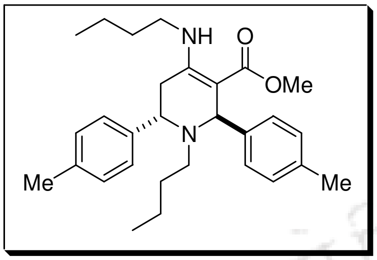
Light yellow solid; M.p. 230–232 °C; **IR** (KBr): 3446, 2919, 1650, 1605, 1491, 1320, 1257, 1070 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 2.32 (s, 3H, ArCH_3), 2.34 (s, 3H, ArCH_3), 2.70 (dd, 1H, J = 2.4 Hz, J = 15.2 Hz, H-5), 2.84 (dd, 1H, J = 5.6 Hz, J = 15.2 Hz, H-5'), 3.93 (s, 3H, OCH_3), 5.06 (d, 1H, J = 3.6 Hz, H-6), 6.13 (d, 2H, J = 8.4 Hz, Ar*H*), 6.31 (s, 1H, H-2), 6.38 (d, 2H, J = 9.2 Hz, Ar*H*), 7.02 (d, 2H, J = 8.0 Hz, Ar*H*), 7.07–7.15 (m, 8H, Ar*H*), 7.20 (d, 2H, J = 8.4 Hz, Ar*H*), 10.17 (s, 1H, N*H*); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 21.2, 21.3, 33.6 (C-5), 51.3, 55.2 (C-2), 58.1 (C-6), 98.9 (C-3), 108.4, 114.7, 119.2, 126.4, 126.6, 127.4, 129.2, 129.6, 131.7, 132.1, 136.3, 137.1, 137.2, 139.2, 140.2, 146.1, 155.6 (C-4), 168.6 (C=O); **HRMS** (ESI): Calcd for $C_{33}H_{30}N_2O_2Br_2$ [M + H]$^+$: m/z = 645.0752; found: 645.0753; **Anal. Calcd** for $C_{33}H_{30}Br_2N_2O_2$ (646.41): C, 61.32; H, 4.68; N, 4.33. Found C, 61.23; H, 4.57; N, 4.46.

Methyl 2,6-bis(4-methylphenyl)-1-(4-nitrophenyl)-4-(4-nitrophenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171u**)



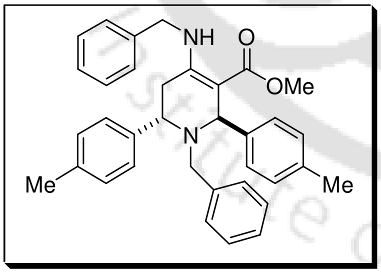
Yellow solid; M.p. 253–255 °C; **IR** (KBr): 1658, 1587, 1504, 1334, 1256, 1113, 1070 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 2.34 (s, 6H, 2 × ArCH_3), 2.94 (dd, 1H, J = 2.4 Hz, J = 15.2 Hz, H-5), 3.06 (dd, 1H, J = 5.6 Hz, J = 15.2 Hz, H-5'), 3.99 (s, 3H, OCH_3), 5.27 (d, 1H, J = 3.2 Hz, H-6), 6.43 (d, 2H, J = 9.2 Hz, Ar*H*), 6.48 (s, 1H, H-2), 6.54 (d, 2H, J = 9.6 Hz, Ar*H*), 7.02 (d, 2H, J = 8.0 Hz, Ar*H*), 7.13 (s, 6H, Ar*H*), 7.97 (d, 2H, J = 9.6 Hz, Ar*H*), 8.00 (d, 2H, J = 9.2 Hz, Ar*H*), 10.55 (s, 1H, N*H*); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 21.2, 21.3, 33.8 (C-5), 52.0, 55.8 (C-2), 58.5 (C-6), 102.0 (C-3), 112.3, 123.1, 125.1, 125.9, 126.1, 126.2, 129.7, 130.0, 137.2, 137.5, 137.9, 138.1, 138.3, 144.1, 151.9, 153.3 (C-4), 168.3 (C=O); **HRMS** (ESI): Calcd for $C_{33}H_{30}N_4O_6$ [M + H]$^+$: m/z = 579.2244; found: 579.2244; **Anal. Calcd** for $C_{33}H_{30}N_4O_6$ (578.61): C, 68.50; H, 5.23; N, 9.68. Found C, 68.39; H, 5.14; N, 9.88.

Methyl 2,6-bis(4-methylphenyl)-1-butyl-4-(butylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171v**)



Light yellow solid; M.p. 158–160 °C; **IR** (KBr): 3428, 2931, 1649, 1597, 1455, 1243 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 0.79 (t, 3H, J = 7.2 Hz, CH_3), 0.98 (t, 3H, J = 7.2 Hz, CH_3), 1.10–1.23 (m, 2H, CH_2), 1.26–1.36 (m, 2H, CH_2), 1.43–1.52 (m, 2H, CH_2), 1.60–1.68 (m, 2H, CH_2), 2.08–2.15 (m, 2H, CH_2), 2.30 (s, 3H, ArCH_3), 2.32 (s, 3H, ArCH_3), 2.51 (dd, 1H, J = 5.2 Hz, J = 17.2 Hz, H-5), 2.60 (dd, 1H, J = 11.2 Hz, J = 17.2 Hz, H-5'), 3.24–3.38 (m, 2H, CH_2), 3.55 (s, 3H, OCH_3), 3.85 (dd, 1H, J = 5.2 Hz, J = 11.6 Hz, H-6), 4.92 (s, 1H, H-2), 7.08 (t, 4H, J = 7.6 Hz, ArH), 7.17 (d, 2H, J = 8.0 Hz, ArH), 7.31 (d, 2H, J = 8.0 Hz, ArH), 9.22 (t, 1H, J = 4.8 Hz, NH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 14.1, 14.3, 20.5, 20.6, 21.3, 25.6, 31.1, 32.5 (C-5), 42.1, 44.7, 50.6, 52.5 (C-2), 58.6 (C-6), 87.9 (C-3), 127.3, 128.4, 128.8, 128.9, 135.6, 136.4, 139.3, 142.4, 159.7 (C-4), 171.4 (C=O); **HRMS** (ESI): Calcd for $C_{29}H_{40}N_2O_2$ [M + H]$^+$: m/z = 449.3168; found: 449.3160; **Anal. Calcd** for $C_{29}H_{40}N_2O_2$ (448.64): C, 77.64; H, 8.99; N, 6.24. Found C, 77.51; H, 8.91; N, 6.37.

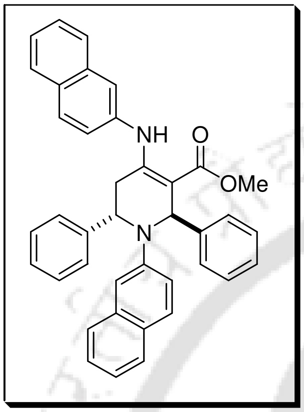
Methyl 2,6-bis(4-methylphenyl)-1-benzyl-4-(benzylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171w**)



Light yellow solid; M.p. 172–173 °C; **IR (KBr):** 3272, 2925, 1650, 1594, 1450, 1237, 1073 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 2.28 (s, 3H, ArCH_3), 2.30 (s, 3H, ArCH_3), 2.62 (dd, 1H, J = 5.2 Hz, J = 17.2 Hz, H-5), 2.73 (dd, 1H, J = 11.6 Hz, J = 17.2 Hz, H-5'), 3.32 (d, 1H, J = 13.6 Hz, CHH), 3.37 (d, 1H, J = 13.6 Hz, CHH), 3.46 (s, 3H, OCH_3), 4.02 (dd, 1H, J = 5.2 Hz, J = 11.2 Hz, CHH), 4.57 (dd, 1H, J = 6.0 Hz, J = 15.6 Hz, CHH), 4.63 (dd, 1H, J = 6.4 Hz, J = 15.6 Hz, H-6), 4.73 (s, 1H, H-2), 7.08 (t, 4H, J = 8.0 Hz, ArH), 7.20 (d, 2H, J = 8.4 Hz, ArH), 7.24 (d, 2H, J = 8.4 Hz, ArH), 7.32 (t, 4H, J = 8.0 Hz, ArH), 7.37–7.40 (m, 6H, ArH), 9.67 (t, 1H, J = 6.0 Hz, NH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 21.3, 25.5, 46.3, 49.7, 50.6, 52.2, 58.1, 89.3, 126.9, 127.0, 127.4, 127.6, 128.3, 128.4, 128.8, 129.0, 129.1, 135.8, 136.7, 138.7, 139.1, 140.5, 141.9, 159.0 (C-4), 171.3; **HRMS** (ESI): Calcd for $C_{35}H_{36}N_2O_2$ [M + H]$^+$: m/z =

517.2855; found: 517.2872; **Anal. Calcd** for $C_{35}H_{36}N_2O_2$ (516.67): C, 81.36; H, 7.02; N, 5.42. Found C, 81.22; H, 7.07; N, 5.57.

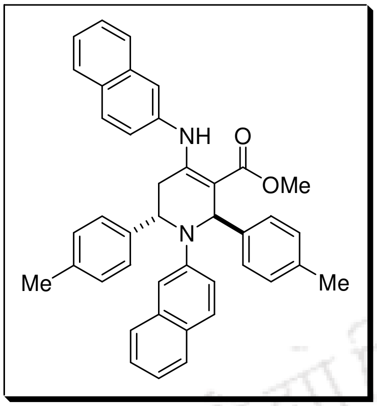
Methyl 1-(2-naphthyl)-4-(2-naphthylamino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (**171x**)



Reaction was carried out with 2-naphthylamine (1 mmol), methyl acetoacetate (0.5 mmol) and benzaldehyde (1 mmol) in methanol (3 mL) in the presence of 10 mol% iodine at room temperature or at 55 °C. After completion of reaction, solid precipitate formed was filtered and washed with ethanol to give **171x** (0.297 g, 53%) as white solid; M.p. 196–198 °C; **IR** (KBr): 3421, 2923, 1657, 1626, 1594, 1251, 1073; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 2.93 (d, 2H, J = 4.0 Hz, CH_2), 3.99 (s, 3H, OCH_3), 5.30 (br s, 1H, H-6), 6.55 (dd, 1H, J = 2.4 Hz, J = 8.8 Hz, Ar*H*), 6.59 (s, 1H, H-2), 6.66 (s, 1H, Ar*H*), 6.77 (d, 1H, J = 2.4 Hz, Ar*H*), 6.97 (dd, 1H, J = 2.4 Hz, J = 9.2 Hz, Ar*H*), 7.11 (t, 1H, J = 8.0 Hz, Ar*H*), 7.20–7.31 (m, 7H, Ar*H*), 7.33–7.34 (m, 4H, Ar*H*), 7.41–7.47 (m, 3H, Ar*H*), 7.52–7.56 (m, 2H, Ar*H*), 7.59 (t, 2H, J = 8.4 Hz, Ar*H*), 7.75 (dd, 1H, J = 2.0 Hz, J = 8.0 Hz, Ar*H*), 10.45 (s, 1H, N*H*); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 33.7 (C-5), 51.4, 55.4 (C-2), 58.6 (C-6), 98.4 (C-3), 107.2, 116.2, 122.0, 123.3, 125.0, 125.9, 126.2, 126.5, 126.6, 126.7, 126.9, 127.4, 127.5, 127.7, 127.8, 128.5, 128.8, 129.1, 131.8, 133.5, 135.0, 135.5, 143.1, 144.0, 145.1, 156.4 (C-4), 168.8 (C=O); **Anal. Calcd** for $C_{39}H_{32}N_2O_2$ (560.68): C, 83.54; H, 5.75; N, 5.00. Found: C, 83.38; H, 5.63; N, 5.10.

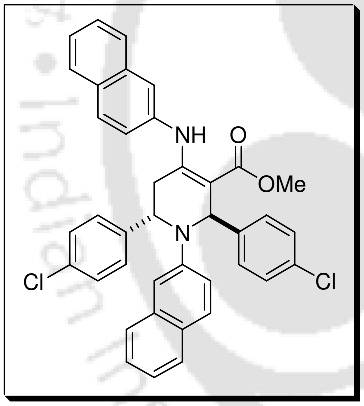
Methyl 2,6-bis(4-methylphenyl)-1-(2-naphthyl)-4-(2-naphthylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171y**)

Reaction was carried out with 2-naphthylamine (1 mmol), methyl acetoacetate (0.5 mmol) and methylbenzaldehyde (1 mmol) in methanol (3 mL) in the presence of 10 mol% iodine at room temperature. After completion, solid precipitate formed was filtered and washed with ethanol to give **171y** (0.300 g, 51%) as white solid; M.p. 220–222 °C; **IR** (KBr): 3445, 2923, 1656, 1627, 1593, 1509, 1250, 1074 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 2.32 (s, 3H, ArCH_3), 2.39 (s, 3H, ArCH_3), 2.91 (d, 2H, J = 4.0 Hz, CH_2), 3.98 (s, 3H, OCH_3), 5.26 (br s, 1H, H-6), 6.57–6.59 (m, 2H, Ar*H*), 6.60 (s, 1H, H-



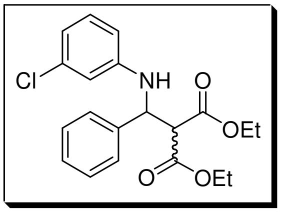
2), 6.77 (d, 1H, *J* = 2.0 Hz, Ar*H*), 6.98 (dd, 1H, *J* = 2.4 Hz, *J* = 9.2 Hz, Ar*H*), 7.09 (t, *J* = 8.0 Hz, 3H, Ar*H*), 7.14 (s, 4H, Ar*H*), 7.23–7.25 (m, 3H, Ar*H*), 7.42–7.47 (m, 3H, Ar*H*), 7.50–7.54 (m, 2H, Ar*H*), 7.60 (t, 2H, *J* = 8.8 Hz, Ar*H*), 7.75 (d, 2H, *J* = 7.2 Hz, Ar*H*), 10.45 (s, 1H, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 21.2, 21.4, 33.7 (C-5), 51.3, 55.2 (C-2), 58.4 (C-6), 98.5 (C-3), 107.1, 116.2, 121.9, 123.2, 125.0, 125.8, 126.1, 126.4, 126.5, 126.6, 126.8, 127.5, 127.6, 127.8, 128.7, 129.0, 129.2, 129.7, 131.5, 133.6, 135.0, 135.6, 136.1, 137.0, 140.1, 141.0, 145.2, 156.4 (C-4), 168.9 (C=O); **Anal. Calcd** for $C_{41}H_{36}N_2O_2$ (588.74): C, 83.64; H, 6.16; N, 4.76. Found: C, 83.49; H, 5.91; N, 4.71.

Methyl 2,6-bis(4-chlorophenyl)-1-(2-naphthyl)-4-(2-naphthylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171z**)



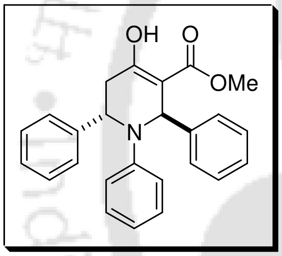
Reaction was carried out with 2-naphthylamine (1 mmol), methyl acetoacetate (0.5 mmol) and benzaldehyde (1 mmol) in methanol (3 mL) in the presence of 10 mol% iodine at 55 °C. After completion of reaction, solid precipitate formed was filtered and washed with ethanol to give **117z** (0.346 g, 55%) as white solid; M.p. 210–212 °C; **IR** (KBr): 3442, 2921, 1653, 1626, 1591, 1507, 1249, 1071 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 2.82–2.92 (m, 2H, CH_2), 3.98 (s, 3H, OCH_3), 5.23 (br s, 1H, H-6), 6.55 (s, 1H, H-2), 6.64 (dd, 1H, *J* = 2.0 Hz, *J* = 8.8 Hz, Ar*H*), 6.69–6.70 (m, 2H, Ar*H*), 6.89 (dd, 1H, *J* = 2.4 Hz, *J* = 9.2 Hz, Ar*H*), 7.11 (d, 2H, *J* = 8.4 Hz, Ar*H*), 7.15 (t, 1H, *J* = 8.4 Hz, Ar*H*), 7.23–7.29 (m, 6H, Ar*H*), 7.44–7.50 (m, 4H, Ar*H*), 7.55 (d, 1H, *J* = 9.2 Hz, Ar*H*), 7.60 (d, 2H, *J* = 8.0 Hz, Ar*H*), 7.66 (d, 1H, *J* = 8.8 Hz, Ar*H*), 7.78 (d, 1H, *J* = 8.0 Hz, Ar*H*), 10.43 (s, 1H, N*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 33.8 (C-5), 51.5, 55.1 (C-2), 57.7 (C-6), 97.9 (C-3), 107.3, 115.9, 122.4, 123.4, 124.8, 126.1, 126.4, 126.5, 126.7, 126.9, 127.5, 127.6, 127.8, 128.0, 127.3, 128.7, 129.0, 129.1, 129.2, 131.6, 132.5, 133.2, 133.5, 134.9, 135.2, 141.2, 142.4, 144.5, 156.2 (C-4), 168.5 (C=O); **Anal. Calcd** for $C_{39}H_{30}N_2O_2$ (629.57): C, 74.40; H, 4.80; N, 4.45. Found: C, 74.33; H, 4.71; N, 4.32.

Diethyl 2-{[(3-chlorophenyl)amino](phenyl)methyl}malonate (**172**)



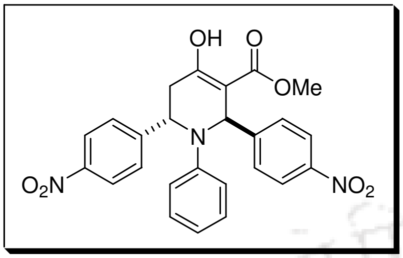
White solid; M.p. 112–114 °C; **IR (KBr):** 3369, 2981, 1752, 1602, 1285, 1148, 785 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.13 (t, 3H, J = 7.2 Hz, CH_3), 1.17 (t, 3H, J = 7.2 Hz, CH_3), 3.88 (d, 1H, J = 5.2 Hz, CH), 4.07–4.17 (m, 4H, 2 × CH_2CH$_3$), 5.18 (br s, 1H, NH), 5.49 (d, 1H, J = 6.0 Hz, CH), 6.46 (d, 1H, J = 8.4 Hz, ArH), 6.58 (s, 1H, ArH), 6.61 (d, 1H, J = 8.0 Hz, ArH), 6.99 (t, 1H, J = 8.0 Hz, ArH), 7.20–7.35 (m, 5H, ArH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 14.0, 14.1, 57.0, 58.1, 61.8, 62.1, 112.1, 113.6, 117.9, 126.8, 128.0, 128.9, 130.3, 135.0, 139.3, 148.0, 167.3, 168.2; **Anal. Calcd** for $C_{20}H_{22}ClNO_4$ (375.85): C, 63.91; H, 5.90; N, 3.73. Found: C, 63.73; H, 5.79; N, 3.63.

Methyl 4-hydroxy-1,2,6-triphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (**174h**)



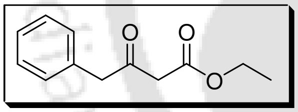
To a solution of amine (2 mmol) and methyl acetoacetate (1 mmol) in 5 mL of methanol was added iodine (0.1 mmol) and stirred at room temperature. After 20 min, benzaldehyde (2 mmol) was added to the reaction mixture and stirring was continued for completion. The thick precipitate was filtered off and washed with ethanol to give mixture of two products of R_f (5% EtOH/hexane) 0.38 and 0.49 respectively. Products were purified by column chromatography using ethyl acetate/hexane (98:2)) furnished **174h** (0.124 g, 29%) as white solid; M.p. 166–168 °C; **IR** (KBr): 3465, 1658, 1595, 1252, 1073 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 2.73 (dd, 1H, J = 4.8 Hz, J = 16.4 Hz, H-5), 3.08 (dd, 1H, J = 5.6 Hz, J = 16.2 Hz, H-5'), 3.87 (s, 3H, OCH_3), 5.12 (t, 1H, J = 5.2 Hz, H-6), 5.99 (s, 1H, H-2), 6.55 (d, 2H, J = 8.4 Hz, ArH), 6.67 (t, 1H, J = 7.6 Hz, ArH), 7.03 (t, 2H, J = 7.2 Hz, ArH), 7.16–7.28 (m, 10H, ArH), 11.94 (br s, 1H, OH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 36.8, 52.2, 56.9, 57.6, 102.2, 116.5, 118.3, 126.6, 127.0, 127.1, 127.3, 128.5, 128.8, 128.9, 142.3, 142.7, 170.8, 170.5; **Anal. Calcd** for $C_{25}H_{23}NO_3$ (385.46): C, 77.90; H, 6.01; N, 3.63. Found C, 77.78; H, 5.91; N, 3.45.

Methyl 4-hydroxy-2,6-bis(4-nitrophenyl)-1-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (**174o**)



Purification was performed by column chromatography using ethyl acetate/hexane (95:5) to furnished **174o** (0.057 g, 12%) as light yellow solid; M.p. 173–175 °C; **IR** (KBr): 3478, 1638, 1595, 1517, 1344, 1240, 1025 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 2.76 (dd, 1H, J = 5.2 Hz, J = 17.2 Hz, H-5), 3.07 (dd, 1H, J = 4.8 Hz, J = 17.2 Hz, H-5'), 3.85 (s, 3H, OCH_3), 5.13 (t, 1H, J = 5.2 Hz, H-6), 5.95 (s, 1H, H-2), 6.46 (d, 2H, J = 8.0 Hz, Ar*H*), 6.76 (t, 1H, J = 7.2 Hz, Ar*H*), 7.04 (t, 2H, J = 7.6 Hz, Ar*H*), 7.33 (d, 2H, J = 8.4 Hz, Ar*H*), 7.36 (d, 2H, J = 8.4 Hz, Ar*H*), 8.11 (t, 4H, J = 7.2 Hz, Ar*H*), 11.99 (br s, 1H, O*H*); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 36.9, 52.4, 56.5, 58.4, 101.0, 118.2, 120.7, 123.9, 124.3, 127.8, 128.1, 129.3, 147.5, 149.4, 170.7; **Anal. Calcd** for $C_{25}H_{21}N_3O_7$ (475.45): C, 63.15; H, 4.45; N, 8.84. Found C, 63.02; H, 4.31; N, 8.71.

Ethyl 3-oxo-4-phenylbutanoate (**168h**)



It was prepared according to the literature procedure[94] from phenylacetyl chloride. To a solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (1.44 g, 10 mmol) in CH_2Cl_2 (6 mL) at 0°C in 100 mL round-bottomed flask equipped with a dropping funnel was added pyridine (2 mL) over 5 min. To this solution was then added a solution of phenylacetyl chloride (1.33 mL, 10 mmol) in CH_2Cl_2 (14 mL) over 10 min. This resulted in the formation of an orange solution. The reaction was stirred at 0°C for 30 min and at RT for 1h. CH_2Cl_2 (20 mL) was added and the solution was washed with water (30 mL × 4). The organic phase was dried over $MgSO_4$ and the solvent was removed to give as orange oil (2.2 g). This was dissolved in EtOH (30 mL) and heated at reflux for 3h. Evaporation of the solvent afforded crude as an orange oil, which was purified by column chromatography using ethyl acetate/hexane (98:2)) furnished **168h** (1.65 g, 80%) as a colourless oil; **IR** (KBr): 2983, 1744, 1716, 1315, 1030, 699 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.26 (t, 3H, J = 7.2 Hz, CH_3), 3.45 (s, 2H, COCH_2CO), 3.83 (s, 3H, PhCH_2), 4.17 (q, 2H, J = 7.2 Hz, OCH_2), 7.21 (d, 2H, J = 7.2 Hz, Ar*H*), 7.36–7.28 (m, 3H, Ar*H*); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.2, 48.4, 50.1, 61.5, 127.5, 129.0, 129.7, 133.4, 167.2, 200.6.

*XRD for Compounds **171f** and **171l***

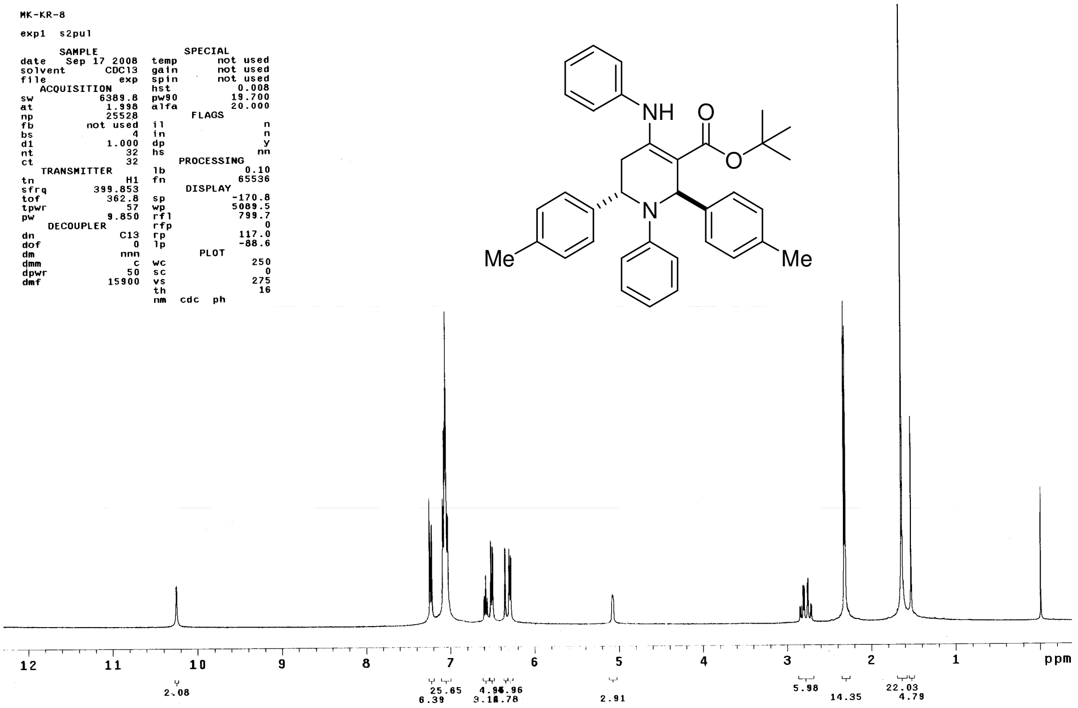
Complete crystallographic data of **171f** and **171l** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, as supplementary publication CCDC No. are 756203 and 756204. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

Table 5. Crystal data and structure refinement for **171f** and **171l,** for atomic coordinates and equivalent isotropic displacement parameters and bond angles, please check the CIF.

Paramrters	**Compound 171f**	**Compound 171l**
Empirical formula	$C_{34}H_{32}Cl_2N_2O_2$	$C_{31}H_{26}Br_2N_2O_2$
Formula weight	571.52	618.36
Temperature	296(2) K	296(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Triclinic
Space group	P2(1)/n	P-1
Unit cell dimensions		
a	11.2764(3) Å	10.1710(5) Å
b	12.9186(4) Å	10.7901(5) Å
c	20.6225(6) Å	13.9201(6) Å
α	90.00º	103.532(2)º
β	97.746 (2)°	106.538(2)º
γ	90.00º	98.517(2)º
Volume	2976.78(15) Å^3	1385.53(11) Å^3
Z	4	2
Density (calculated)	1.275 g/cm^3	1.482 g/cm^3
Absorption coefficient	0.251 mm^{-1}	2.956 mm^{-1}

F(000)	1200	624
Theta range for data collection	2.41 to 22.96º	2.90 to 21.70º
Index ranges	-15<=h<=15, -17<=k<=11, -27<=l<=27	-13<=h<=13, -14<=k<=12, -12<=l<=18
Reflections collected	37289	17414
Independent reflections	7315 R_{int} = 0.0567	6284 R_{int} = 0.0362
Completeness to θº	97.8% (θ = 28.42º)	98.4% (θ = 27.55º)
Data / restraints / parameters	7315 / 0 / 367	6284 / 0 / 339
Goodness-of-fit on F2	0.958	0.994
Final R indices [>2sigma(I)]	R_{obs} = 0.0545, wR_{obs} =0.1747	R_{obs} = 0.0434,wR_{obs}=0.1026
R indices (all data)	R_{all} = 0.1118, wR_{all} = 0.1924	R_{all}=0.1047, wR_{all} = 0.1289
Largest diff. peak and hole	0.221 and -0.420 e.Å^{-3}	0.625 and -0.705 e.Å^{-3}

^{1}H NMR (400 MHz, CDCl$_3$): *Tert-butyl 2,6-bis(4-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate* (**171c**)



```
MK-KR-8

exp1  s2pul

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solvent      CDCl3  gain       not used
file           exp  spin       not used
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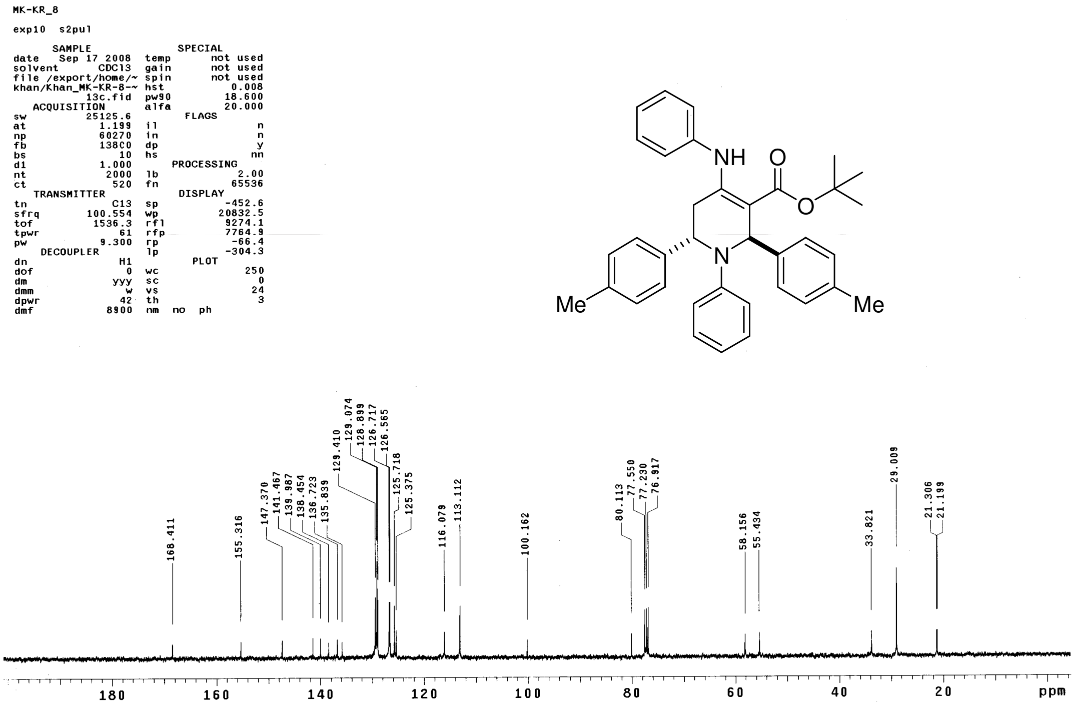
sw          6389.8  pw90         19.700
at           1.998  alfa         20.000
np           25528         FLAGS
fb        not used  il                n
bs               4  in                n
d1           1.000  dp                y
nt              32  hs               nn
ct              32       PROCESSING
   TRANSMITTER      lb             0.10
tn              H1  fn            65536
sfrq       399.853        DISPLAY
tof          362.8  sp           -170.8
tpwr            57  wp           5089.5
pw           9.850  rfl           799.7
    DECOUPLER       rfp               0
dn             C13  rp            117.0
dof              0  lp            -88.6
dm             nnn          PLOT
dmm              c  wc              250
dpwr            50  sc                0
dmf          15900  vs              275
                    th               16
                    nm  cdc  ph
```

^{13}C NMR (100 MHz, CDCl$_3$): *Tert-butyl 2,6-bis(4-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate* (**171c**)



```
MK-KR_8

exp10  s2pul

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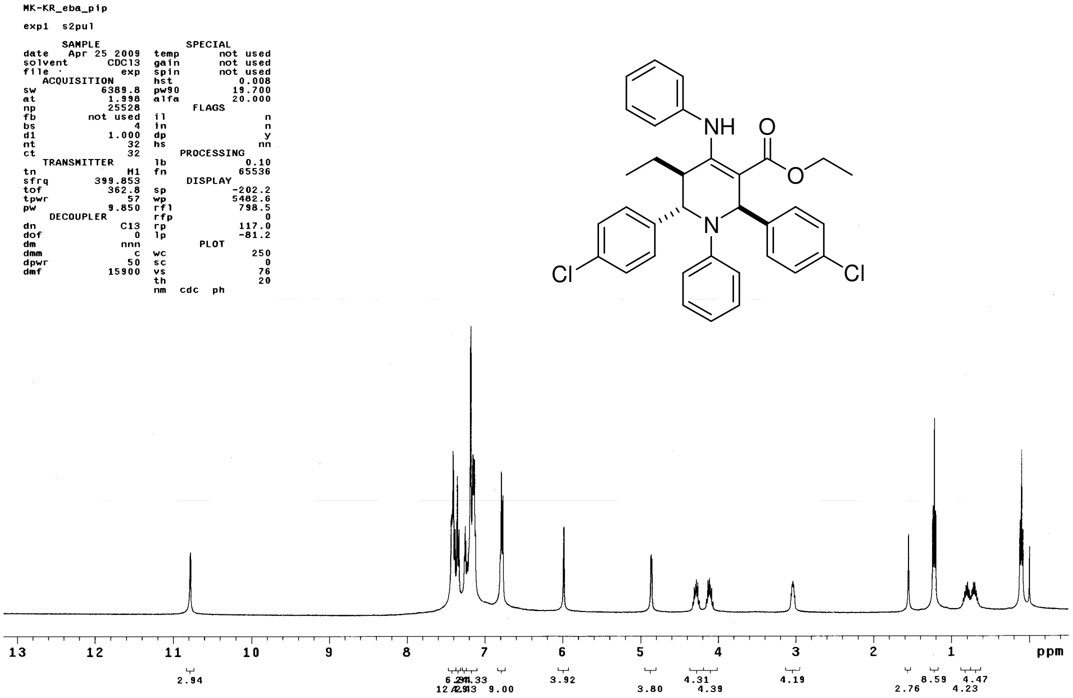
solvent      CDCl3  gain       not used
file /export/home/~ spin       not used
khan/Khan_MK-KR-8-~ hst           0.008
           13c.fid  pw90         18.600
   ACQUISITION      alfa         20.000
sw         25125.6         FLAGS
at           1.199  il                n
np           60270  in                n
fb           13800  dp                y
bs              10  hs               nn
d1           1.000       PROCESSING
nt            2000  lb             2.00
ct             520  fn            65536
   TRANSMITTER            DISPLAY
tn             C13  sp           -452.6
sfrq       100.554  wp          20832.5
tof         1536.3  rfl          9274.1
tpwr            61  rfp          7764.9
pw           9.300  rp            -66.4
    DECOUPLER       lp           -304.3
dn              H1          PLOT
dof              0  wc              250
dm             yyy  sc                0
dmm              w  vs               24
dpwr            42  th                3
dmf           8900  nm  no   ph
```

Figure 1

^{1}H NMR (400 MHz, $CDCl_3$): *Ethyl 2,6-bis(4-chlorophenyl)-1-phenyl-4-(phenylamino)-5-ethyl-1,2,5,6-tetrahydropyridine-3-carboxylate* (**171f**)



```
MK-KR_eba_pip

exp1  s2pul

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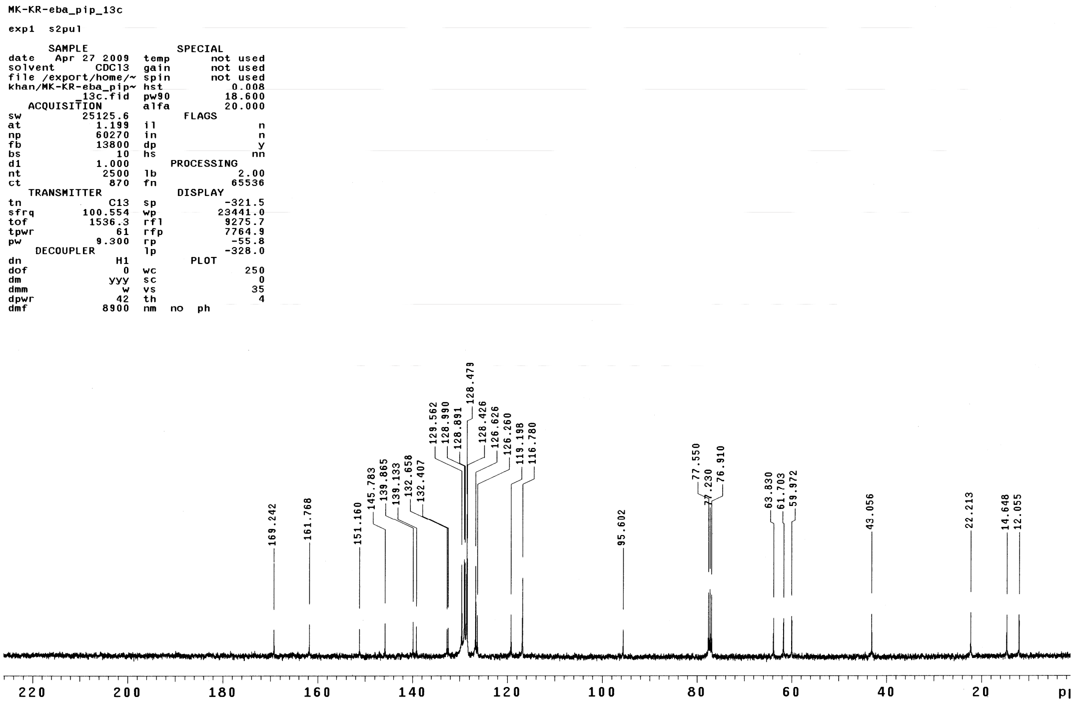
date   Apr 25 2009  temp       not used
solvent      CDCl3  gain       not used
file           exp  spin       not used
   ACQUISITION      hst           0.008
sw          6389.8  pw90         19.700
at           1.998  alfa         20.000
np           25528          FLAGS
fb        not used  il                n
bs               4  in                n
d1           1.000  dp                y
nt              32  hs               nn
ct              32        PROCESSING
   TRANSMITTER      lb             0.10
tn              H1  fn            65536
sfrq       399.853          DISPLAY
tof          362.8  sp           -202.2
tpwr            57  wp           5482.6
pw           9.850  rfl           798.5
    DECOUPLER       rfp               0
dn             C13  rp            117.0
dof              0  lp            -81.2
dm             nnn           PLOT
dmm              c  wc              250
dpwr            50  sc                0
dmf          15900  vs               76
                    th               20
                    nm  cdc  ph
```

^{13}C NMR (100 MHz, $CDCl_3$): *Ethyl 2,6-bis(4-chlorophenyl)-1-phenyl-4-(phenylamino)-5-ethyl-1,2,5,6-tetrahydropyridine-3-carboxylate* (**171f**)



```
MK-KR-eba_pip_13c

exp1  s2pul

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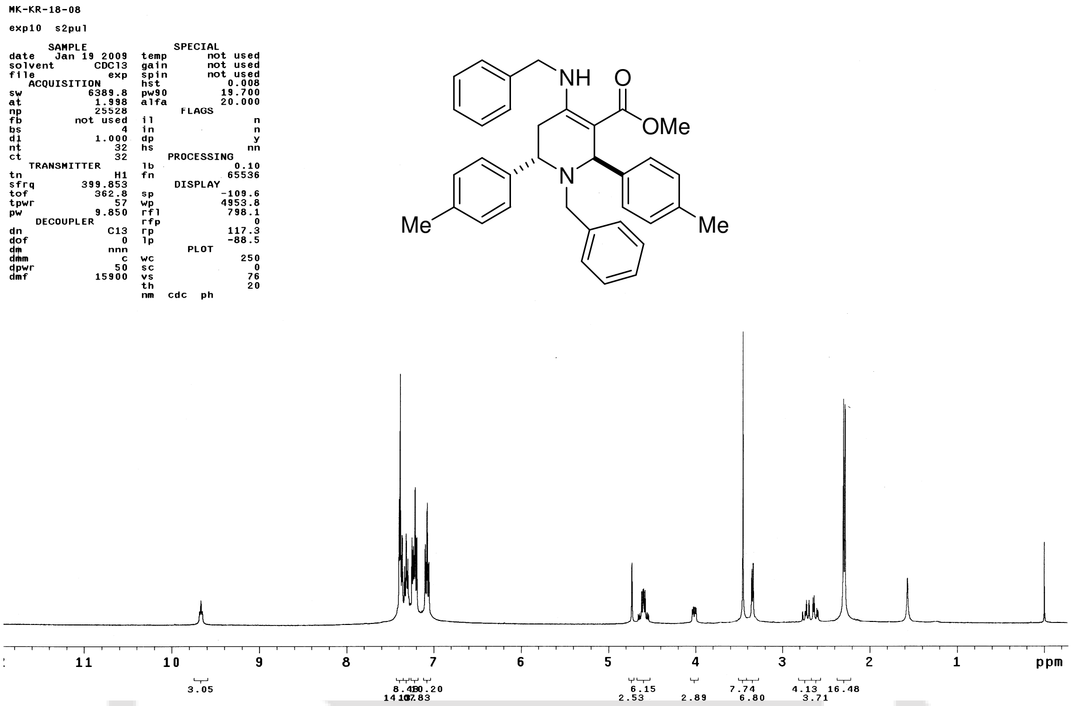
date   Apr 27 2009  temp       not used
solvent      CDCl3  gain       not used
file /export/home/~ spin       not used
khan/MK-KR-eba_pip~ hst           0.008
         _13c.fid   pw90         18.600
   ACQUISITION      alfa         20.000
sw         25125.6          FLAGS
at           1.199  il                n
np           60270  in                n
fb           13800  dp                y
bs              10  hs               nn
d1           1.000        PROCESSING
nt            2500  lb             2.00
ct             870  fn            65536
   TRANSMITTER             DISPLAY
tn             C13  sp           -321.5
sfrq       100.554  wp          23441.0
tof         1536.3  rfl          9275.7
tpwr            61  rfp          7764.9
pw           9.300  rp            -55.8
    DECOUPLER       lp           -328.0
dn              H1           PLOT
dof              0  wc              250
dm             yyy  sc                0
dmm              w  vs               35
dpwr            42  th                4
dmf           8900  nm  no  ph
```

Figure 2

^{1}H NMR (400 MHz, CDCl$_3$): Methyl 2,6-bis(4-methylphenyl)-1-benzyl-4-(benzylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171w**)

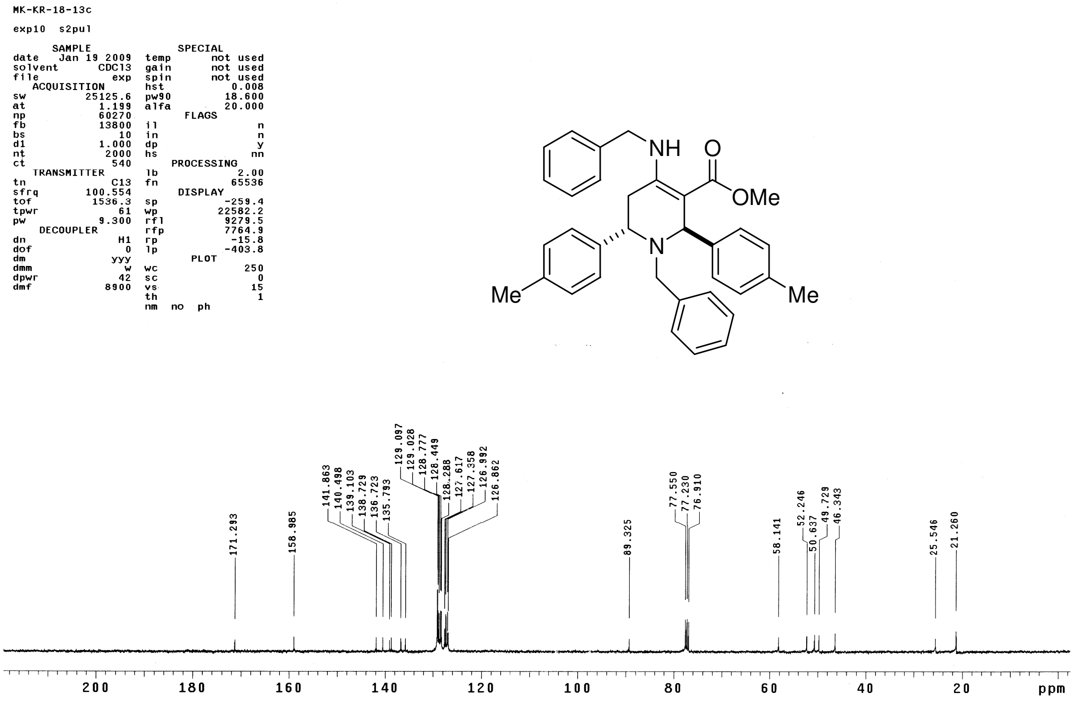


```
MK-KR-18-08

exp10  s2pul

      SAMPLE                SPECIAL
date   Jan 19 2009  temp       not used
solvent      CDC13  gain       not used
file           exp  spin       not used
   ACQUISITION      hst           0.008
sw          6389.8  pw90         19.700
at           1.998  alfa         20.000
np           25528          FLAGS
fb        not used  il                n
bs               4  in                n
d1           1.000  dp                y
nt              32  hs               nn
ct              32        PROCESSING
   TRANSMITTER      lb             0.10
tn              H1  fn            65536
sfrq       399.853          DISPLAY
tof          362.8  sp           -109.6
tpwr            57  wp           4953.8
pw           9.850  rfl           798.1
    DECOUPLER       rfp               0
dn             C13  rp            117.3
dof              0  lp            -88.5
dm             nnn            PLOT
dmm              c  wc              250
dpwr            50  sc                0
dmf          15900  vs               76
                    th               20
                    nm  cdc  ph
```

^{13}C NMR (100 MHz, CDCl$_3$): Methyl 2,6-bis(4-methylphenyl)-1-benzyl-4-(benzylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**171w**)



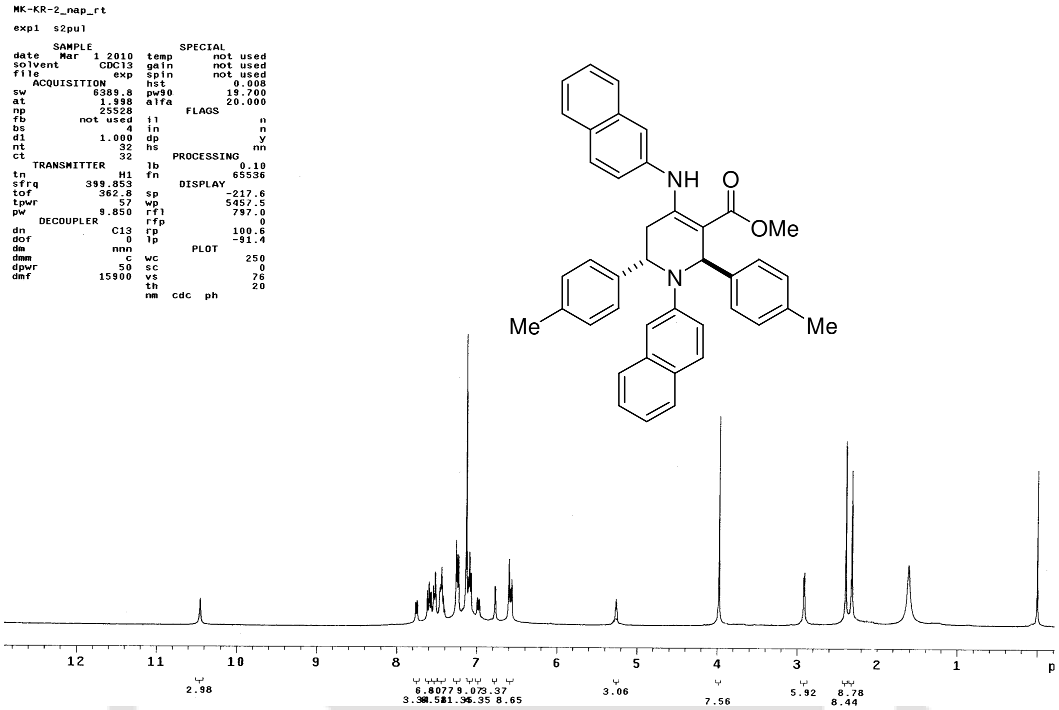
```
MK-KR-18-13c

exp10  s2pul

      SAMPLE                SPECIAL
date   Jan 19 2009  temp       not used
solvent      CDC13  gain       not used
file           exp  spin       not used
   ACQUISITION      hst           0.008
sw         25125.6  pw90         18.600
at           1.199  alfa         20.000
np           60270          FLAGS
fb           13800  il                n
bs              10  in                n
d1           1.000  dp                y
nt            2000  hs               nn
ct             540        PROCESSING
   TRANSMITTER      lb             2.00
tn             C13  fn            65536
sfrq       100.554          DISPLAY
tof         1536.3  sp           -259.4
tpwr            61  wp          22582.2
pw           9.300  rfl          9279.5
    DECOUPLER       rfp          7764.9
dn              H1  rp            -15.8
dof              0  lp           -403.8
dm             yyy            PLOT
dmm              w  wc              250
dpwr            42  sc                0
dmf           8900  vs               15
                    th                1
                    nm  no  ph
```

Figure 3

^{1}H NMR (400 MHz, CDCl$_3$): *Methyl 2,6-bis(4-methylphenyl)-1-(2-naphthyl)-4-(2-naphthylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate* (**171y**)

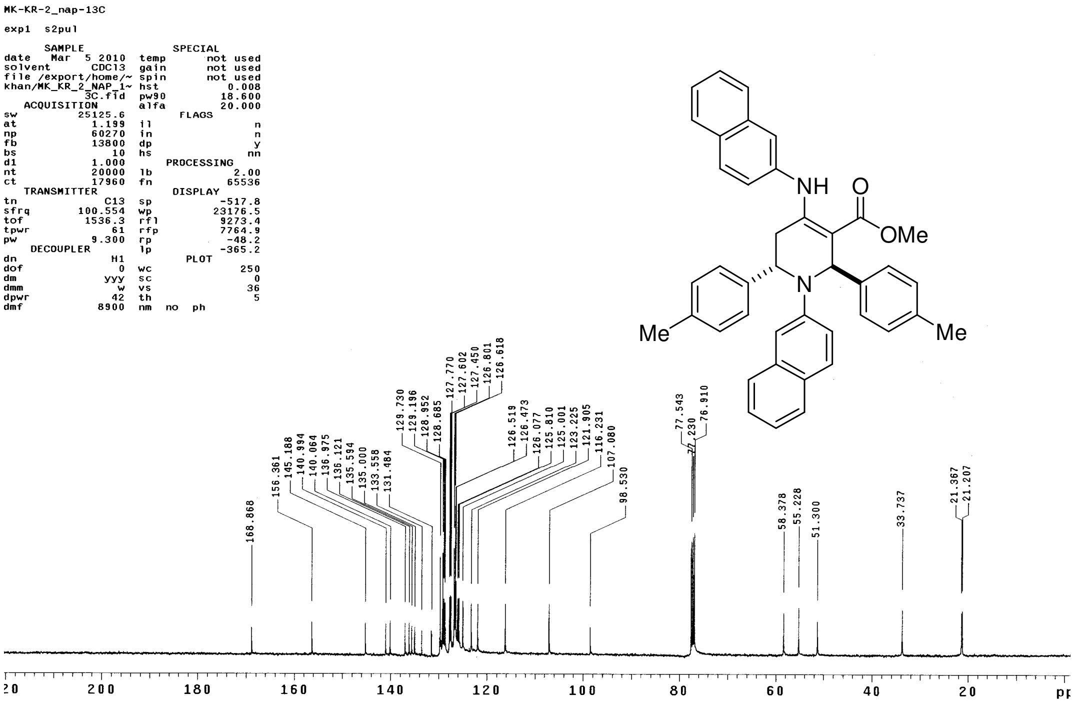


```
MK-KR-2_nap_rt

exp1  s2pul

     SAMPLE              SPECIAL
date   Mar  1 2010  temp       not used
solvent      CDC13  gain       not used
file           exp  spin       not used
   ACQUISITION      hst           0.008
sw          6389.8  pw90         19.700
at           1.998  alfa         20.000
np           25528          FLAGS
fb        not used  il                n
bs               4  in                n
d1           1.000  dp                y
nt              32  hs               nn
ct              32       PROCESSING
   TRANSMITTER      lb             0.10
tn              H1  fn            65536
sfrq       399.853         DISPLAY
tof          362.8  sp           -217.6
tpwr            57  wp           5457.5
pw           9.850  rfl           797.0
    DECOUPLER       rfp               0
dn             C13  rp            100.6
dof              0  lp            -91.4
dm             nnn           PLOT
dmm              c  wc              250
dpwr            50  sc                0
dmf          15900  vs               76
                    th               20
                    nm   cdc   ph
```

^{13}C NMR (100 MHz, CDCl$_3$): *Methyl 2,6-bis(4-methylphenyl)-1-(2-naphthyl)-4-(2-naphthylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate* (**171y**)



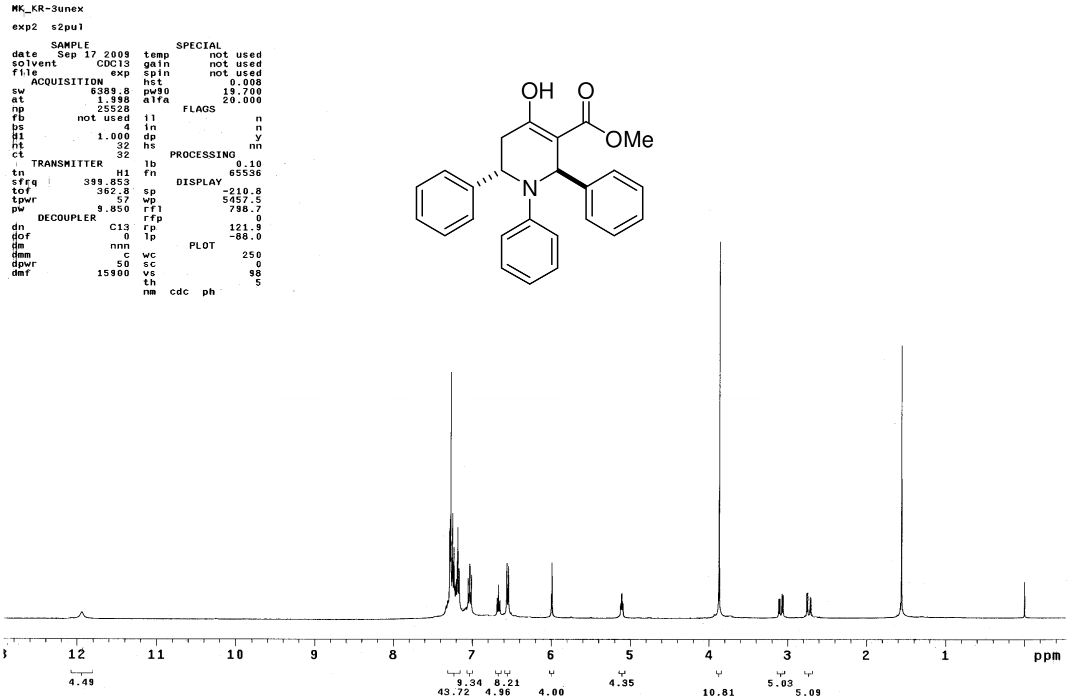
```
MK-KR-2_nap-13C

exp1  s2pul

     SAMPLE              SPECIAL
date   Mar  5 2010  temp       not used
solvent      CDC13  gain       not used
file /export/home/~ spin       not used
khan/MK_KR_2_NAP_1~ hst           0.008
            3C.fid  pw90         18.600
   ACQUISITION      alfa         20.000
sw         25125.6          FLAGS
at           1.199  il                n
np           60270  in                n
fb           13800  dp                y
bs              10  hs               nn
d1           1.000       PROCESSING
nt           20000  lb             2.00
ct           17960  fn            65536
   TRANSMITTER             DISPLAY
tn             C13  sp           -517.8
sfrq       100.554  wp          23176.5
tof         1536.3  rfl          9273.4
tpwr            61  rfp          7764.9
pw           9.300  rp            -48.2
    DECOUPLER       lp           -365.2
dn              H1           PLOT
dof              0  wc              250
dm             yyy  sc                0
dmm              w  vs               36
dpwr            42  th                5
dmf           8900  nm   no    ph
```

Figure 4

^{1}H NMR (400 MHz, CDCl$_3$): *Methyl 4-hydroxy-1,2,6-triphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate* (**174h**)

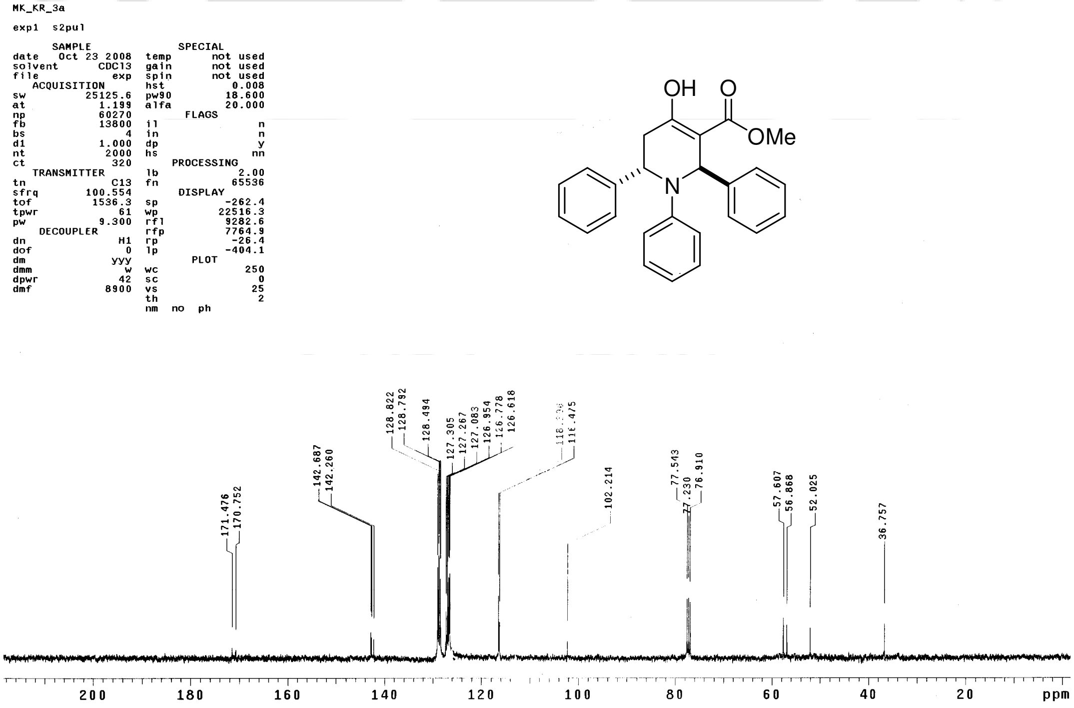


```
MK_KR-3unex

exp2  s2pul

      SAMPLE                  SPECIAL
date   Sep 17 2009   temp        not used
solvent       CDCl3   gain        not used
file            exp   spin        not used
   ACQUISITION        hst            0.008
sw           6389.8   pw90          19.700
at            1.998   alfa          20.000
np            25528          FLAGS
fb         not used   il                 n
bs                4   in                 n
d1            1.000   dp                 y
nt               32   hs                nn
ct               32       PROCESSING
   TRANSMITTER        lb              0.10
tn               H1   fn             65536
sfrq        399.853          DISPLAY
tof           362.8   sp            -210.8
tpwr             57   wp            5457.5
pw            9.850   rfl            798.7
    DECOUPLER         rfp                0
dn              C13   rp             121.9
dof               0   lp             -88.0
dm              nnn           PLOT
dmm               c   wc               250
dpwr             50   sc                 0
dmf           15900   vs                98
                      th                 5
                      nm  cdc  ph
```

^{13}C NMR (100 MHz, CDCl$_3$): *Methyl 4-hydroxy-1,2,6-triphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate* (**174h**)



```
MK_KR_3a

exp1  s2pul

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date   Oct 23 2008   temp        not used
solvent       CDCl3   gain        not used
file            exp   spin        not used
   ACQUISITION        hst            0.008
sw          25125.6   pw90          18.600
at            1.199   alfa          20.000
np            60270          FLAGS
fb            13800   il                 n
bs                4   in                 n
d1            1.000   dp                 y
nt             2000   hs                nn
ct              320       PROCESSING
   TRANSMITTER        lb              2.00
tn              C13   fn             65536
sfrq        100.554          DISPLAY
tof          1536.3   sp            -262.4
tpwr             61   wp           22516.3
pw            9.300   rfl           9282.6
    DECOUPLER         rfp           7764.9
dn               H1   rp             -26.4
dof               0   lp            -404.1
dm              yyy           PLOT
dmm               w   wc               250
dpwr             42   sc                 0
dmf            8900   vs                25
                      th                 2
                      nm  no  ph
```

Figure 5

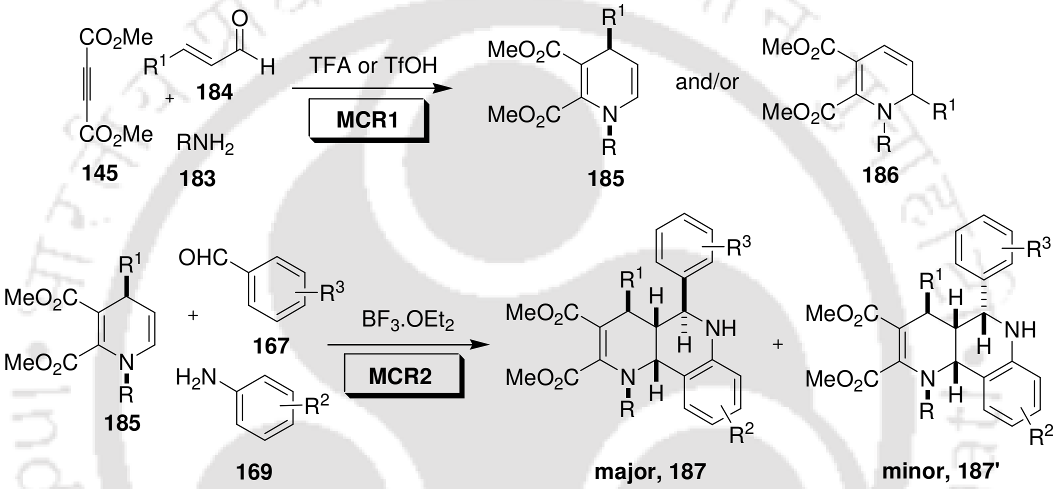
PART B

CHAPTER 3

Dihydropyridines: Synthesis, regioselectivity and its application for the synthesis of naphthyridines

Results and Discussion

The synthetic strategies and importance of dihydropyridines have already been described in Chapter 1 of Part B. In this Chapter, we would like to present a three-component domino reaction for the synthesis of unsymmetrically highly substituted 1,4- and 1,6-dihydropyridines (DHPs), an improved method for regioselective synthesis of 1,4-DHPs and its utility for the synthesis of naphthyridine derivatives through imino-Diels-Alder reaction as illustrated in Scheme 47.

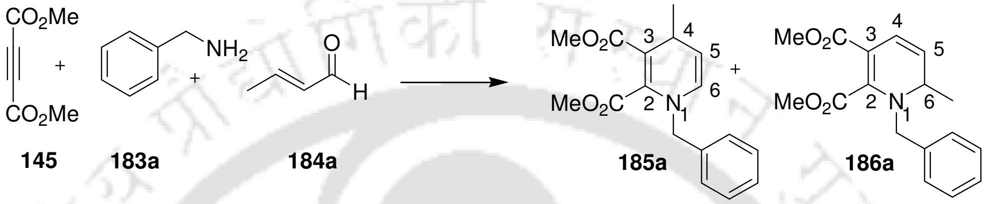


Scheme 47. Sequential multicomponent reactions

For the preparation of unsymmetrical dihydropyridines, the reaction of dimethyl acetylenedicarboxylate (DMAD, **145**, 1 mmol), benzylamine (**183a**, 1 mmol) and crotonaldehyde (**184a**, 1 mmol) was carried out with 20 mol% of trifluoroacetic acid (TFA) in dicholoromethane. The reaction afforded two products i.e. **185a** and **186a** in the ratio of about 56:44 with a combined yield of 62%. The disappearance of peaks at 3399 and 3088 cm^{-1} for benzylamine and 1699 $cm^{-1}$for α,β-unsaturated aldehyde in the IR spectra clearly indicated the formation of product. The structure of compounds **185a** and **186a** were determined by recording IR, ^{1}H NMR, ^{13}C NMR spectra and their elemental analysis. The compound **185a** showed the strong absorbance peaks at 1739 and 1694 cm^{-1}, which is expected to be due to presence of ester and double bond functionalities. The ^{1}H NMR spectrum of compound **185a** showed the signals at δ 1.08 (d, 3H, $J = 6.4$ Hz), 3.32–3.39 (m, 1H), 3.68 (s, 3H), 3.78 (s, 3H), 4.28 (d, 1H, $J = 16.4$ Hz), 4.36 (d, 1H, $J = 16.4$ Hz), 4.87 (dd, 1H, $J = 5.6$ Hz, $J = 7.2$ Hz), 5.75 (d, 1H, $J = 7.2$

Hz) and 7.24–7.36 (m, 5H) and ^{13}C signals at δ 25.3, 27.1, 51.6, 52.9, 54.6, 101.2, 110.6, 127.3, 127.6, 128.0, 128.9, 137.0, 144.3, 166.1, 167.9 respectively. The appearance of peaks at δ 4.87 (dd, 1H, J = 5.6 Hz, J = 7.2 Hz) and 5.75 (d, 1H, J = 7.2 Hz) in the ^{1}H NMR spectrum and ^{13}C signals at δ 25.3, 27.1 is the characteristic for 1,4-dihydropyridine **185a**.

Table 5. Optimization Studies



Entry	Solvent	Catalyst (mol%)	Time (h)	Ratio[a] (185a : 186a)	Yield[b] (%)	Remark
1	DCM	CF_3COOH (20)	30	56 : 44	62	
2	DCM	CF_3COOH (30)	12	56 : 44	80	
3	DCM	CF_3COOH (40)	12	52 : 48	79	
4	MeCN	CF_3COOH (30)	18	59 : 41	76	
5	$C_2H_4Cl_2$	CF_3COOH (30)	24	58 : 42	62	
6	**THF**	**CF_3COOH (30)**	**12**	**51 : 49**	**82**	**Method A**
7	MeOH	CF_3COOH (30)	18	complex	..	
8	DCM	pTSA (30)	30	66 : 34	42	
9	DCM	CH_3COOH (50)	30	65 : 35	36	
10	DCM	TfOH (20)	24	85 : 15	63	
11	**THF**	**TfOH (30)**	**10**	**88 : 12**	**86**	**Method B**
12	DCM	TfOH (30)	16	88 : 12	81	
13	MeCN	TfOH (30)	10	90 : 10	74	
14	Toluene	TfOH (30)	30	62 : 38	61	
15	THF	None	30	no reaction	--	

[a]*Product ratio determined by crude ^{1}H NMR.* [b]*Combined yield of* ***185a*** *and* ***186a****.*

Similarly, the compound **186a** exhibited strong absorbance peaks in the IR spectrum at 1739 and 1693 cm^{-1}. ^{1}H NMR signals at δ 1.14 (d, 3H, J = 6.4 Hz), 3.71 (s, 3H), 3.87 (s, 3H), 3.93–3.98 (m, 1H), 4.30 (d, 1H, J = 15.6 Hz), 4.37 (d, 1H, J = 15.6 Hz), 5.02 (dd, 1H, J = 5.2 Hz, J = 9.6 Hz), 6.41 (d, 1H, J = 9.6 Hz) and 7.37–7.29 (m, 5H) confirms the formation of 1,6-dihydropyridine, which was further supported by ^{13}C NMR in which peaks appeared at δ 19.2, 51.3, 52.7, 53.1, 54.4, 97.8, 114.9, 121.3, 127.7, 128.2, 128.9, 136.4, 147.9, 166.0 and 166.3. The regioisomer **186a** can be easily distinguished from **185a** using ^{13}C signals. In compound **186a** (1,6-DHP), the characteristic signal for C-4 appeared at δ 51.3 instead of δ 27.1. Finally, the structure of other 1,4-dihydropyridine **185i** having similar NMR spectra was confirmed by X-ray crystallographic data analysis as shown in Figure 6. The ^{1}H NMR and ^{13}C NMR spectra of the two isomer **185a** and **186a** are given in the Experimental Section (Figure 1 and 2).

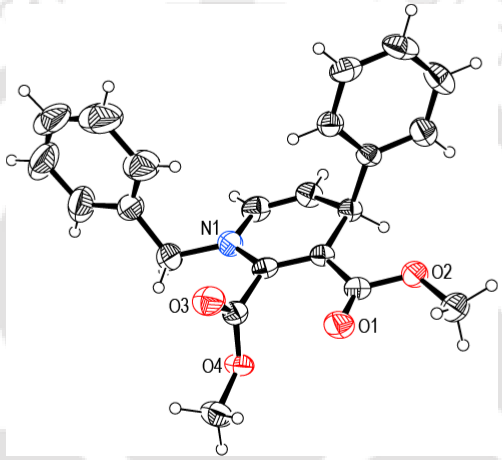
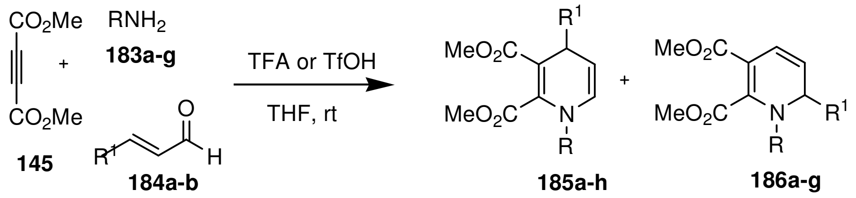


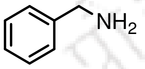
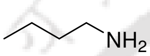
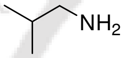
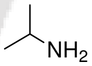
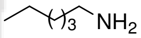
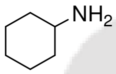
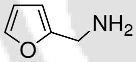
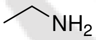
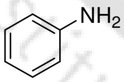
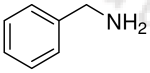
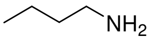
Figure 6. *ORTEP diagram with ellipsoid at 35% probability of **185i***

After establishing the structure of the products, a series of experiments were performed with various catalysts such as TFA, acetic acid, PTSA and triflic acid (TfOH) by varying the amounts of catalysts in order to find out a suitable catalyst which would give good selectivity and high yields of the product. Different solvents such as DCM, DCE, MeOH, MeCN, THF and toluene were also screened in affecting this condensation. The results for the optimization of the reaction conditions are summarized in Table 5.

From these experiments, two optimized reaction conditions were obtained. Method A in which both the products **185a** and **186a** were obtained nearly in equal amounts with a combined yield of 82% from the reaction of **145**, **183a** and **184a** using 30 mol% of TFA in THF. In method B a regioselective 1,4-dihydropyridine **185a** was obtained in 76% yield using TfOH acid (30 mol%) in THF.

Table 6. *Synthesis of various 1,2,3,4- and/or 1,2,3,6-tetrasubstituted dihydropyridines*



Entry	RNH$_2$	R^1	Method A		Method B	
			Ratio[a] (**185** : **186**)	Yield[b](%)	Ratio[a] (**185** : **186**)	Yield[c](%)
1		Me	51 : 49	82	88 : 12	**185a**, 76
2		Me	55 : 45	83	86 : 14	**185b**, 72
3		Me	58 : 42	83	87 : 13	**185c**, 75
4		Me	60 : 40	82	83 : 17	**185d**, 69
5		Me	55 : 45	82	86 : 14	**185e**, 72
6		Me	54 : 46	81	88 : 12	**185f**, 73
7		Me	48 : 52	83	86 : 14	**185g**, 72
8		Me			78 : 22	**185h**, 57
9		Me	no reaction	--	--	no reaction
10		Ph	80 : 20	59	82 : 18	**185i**, 62
11		Ph	75 : 25	56	80 : 20	**185j**, 58

Method A: DMAD (1 mmol), Amines (1 mmol), enals (1.2 mmol) and TFA (0.3 mmol) in THF at rt. Method B: DMAD (1 mmol), Amines (1 mmol), enals (1.2 mmol) and TfOH (0.3 mmol) in THF at rt. [a]*Product ratio determined by crude ^1H NMR.* [b]*Combined yields of* ***185*** *and* ***186****.* [c]*Isolated yields.*

With these optimized reaction condition (method A) in hand, we have reacted DMAD (**145**, 1 mmol), *n*-butylamine (**183b**, 1 mmol) and crotonaldehyde (**184a**, 1.2 mmol).

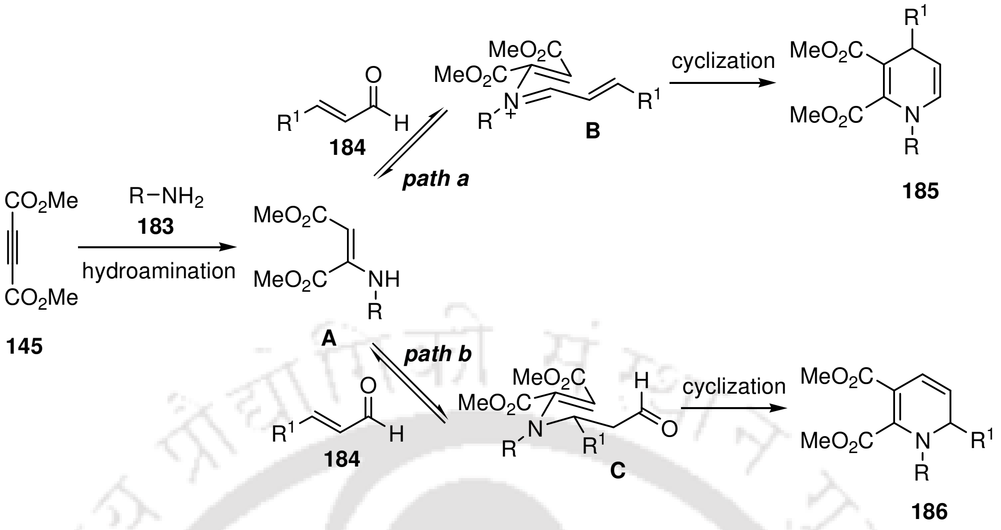
Both the products **185b** and **186b** were obtained in the ratio 55:45 respectively with 83% of the total yield of products. The scope of this protocol was further examined with various aliphatic amines such as *iso*-butylamine, *iso*-propylamine, *n*-hexylamine, cyclohexylamine and furfurylamine. In each case, the corresponding dihydropyridine derivatives **185c**-**g** and **186c**-**g** were obtained in good yields and the ratio of the products is shown in Table 6 (entries 3-7).

Next, we have turned our attention to the regioselective synthesis of 1,4-DHPs by following method B. A mixture of DMAD (**145**, 1 mmol), *n*-butylamine (**183b**, 1 mmol) and crotonaldehyde (**184a**, 1.2 mmol) was stirred following method B and the major product **185b** was obtained in 72% yield.

Encouraged by this result, the reaction of various other amines such as *iso*-butylamine, *iso*-propylamine, *n*-hexylamine, cyclohexylamine, furfurylamine and ethylamine were also studied with DMAD and crotonaldehyde under identical reaction conditions. The reaction time and percentage yield of the products **185c**-**h** are summarized in Table 6.

In case of cinnamaldehyde, both the method A and B did show almost a similar regioselectivity pattern giving good yields of products **185i** and **185j** as mentioned in Table 6. The ^{1}H NMR and ^{13}C NMR spectra of compound **185i** are given in the Experimental Section (Figure 3). All these products were characterized by IR, ^{1}H and ^{13}C NMR spectra and by their elemental analyses. The present method A and B were unsuccessful for the synthesis of substituted N-aryl dihydropyridines using aniline. This may be due to less nucleophilicity of aniline as compared to aliphatic amines.

A plausible mechanism for the formation of 1,4 and 1,6-DHPs is given in Scheme 48. Initially, the amine reacts with DMAD to form hydroamination product **A**. The intermediate **A** reacts with α,β-unsaturated aldehyde by either *path a* or *path b*. In *path a*, the intermediate **A** on reaction with α,β-unsaturated aldehyde leads to the formation of intermediate imine **B** which on electrocyclic cyclization gives 1,4-dihydropyridine derivative **185**. In *path b*, the intermediate **C** is formed from the intermediate **A** on reaction with α,β-unsaturated aldehyde *via* Michael addition reaction. Finally, 1,6-dihydropyridine derivative **186** is obtained through cyclization of **C** followed by dehydration. We believe that *path a*, is preferred over *path b* in the case of TfOH (pKa = -15) which is highly acidic as compared to TFA (pKa = 0.5), that favored the imine formation by protonation of carbonyl group as compared to Michael addition reaction.



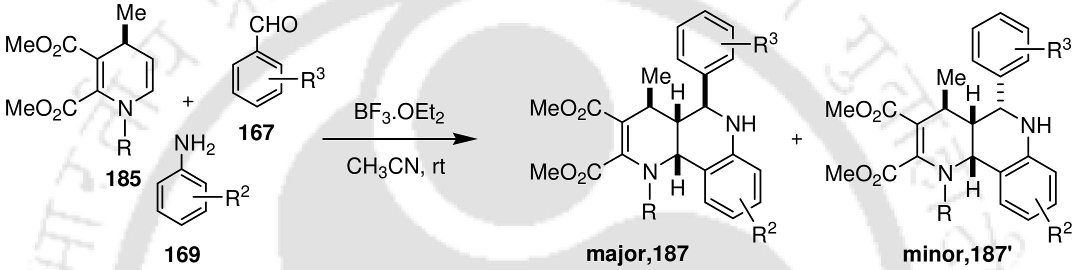
Scheme 48. *Proposed mechanism for amination reaction of DMAD promoting for cascade reaction*

The synthetic utility of 1,4- DHPs as a dienophile in imino-Diels-Alder reaction (Povarov reaction),[95] has been demonstrated for the synthesis of substituted naphthyridine derivatives for the creation of molecular diversity. The applications of 1,4-dihydropyridine as a dieneophile for Povarov reaction have also been reported by other chemists.[79,80] However, the newly designed 1,2,3,4-tetrasubstituted dihydropyridines having α and β amino acid functionality remained unexplored, which may offer a new platform for the synthesis of different substituted naphthyridine derivatives.

In view of these importance, a three component one-pot reaction was conducted with 1,4-DHP (**185a**), benzaldehyde and aniline using $BF_3.OEt_2$ (20 mol%) as a catalyst in acetonitrile. The cycloaddition reaction of the reactants afforded two diastereomers **187a** and **187a'** with ratio of 4:1. The major isomer **187a** was isolated in 65% yield. The disappearance of signals at δ 4.87 (dd, 1H, J = 5.6 Hz, J = 7.2 Hz, H-5), 5.75 (d, 1H, J = 7.2 Hz, H-6) for compound **185a** confirmed the formation of cycloadduct. The ^{1}H NMR spectroscopic data of compound **187a** is as follows: δ 1.09 (d, 3H, J = 6.8 Hz, C*H$_3$*), 1.92 (d, 1H, J = 10.8 Hz, H-4a), 2.36–2.43 (m, 1H, H-4), 3.65 (s, 3H, OC*H$_3$*), 3.78 (s, 3H, OC*H$_3$*), 4.14 (d, 1H, J = 16.8 Hz, NC*H*H), 4.17 (s, 1H, N*H*), 4.25 (d, 1H, J = 10.8 Hz, H-5), 4.29 (d, 1H, J = 16.8 Hz, NC*H*H), 4.42 (d, 1H, J = 2.8 Hz, H-10b), 6.47–6.51 (m, 2H, Ar*H*), 6.63 (d, 1H, J = 7.6 Hz, Ar*H*), 7.10 (t, 2H, J = 7.2 Hz, Ar*H*), 7.12–7.18 (m, 2H, Ar*H*), 7.23–7.28 (m, 2H, Ar*H*), 7.28–7.38 (m, 5H, Ar*H*). Similarly, the reaction of **185a** with aniline and various aromatic aldehydes tethered with Me, MeO, Cl, Br and NO_2

were also investigated. The reactions proceeded smoothly and various substituted naphthyridine derivatives **187b-f** were obtained in good yields. The ^{1}H NMR and ^{13}C NMR spectra compound **187c** is given in the Experimental Section (Figure 4). The reaction of aniline derivatives such as 4-methylaniline and 4-methoxyaniline were also studied under similar conditions and the results are summarized in Table 7. Finally, the reaction of 1,4-DHP **185b** with benzaldyhyde and aniline was performed to give major isomer **187i** in 59% yield.

Table 7. Synthesis of substituted naphthyridine derivatives **187**



Entry	R	R^3	R^2	Time (h)	Ratio^a (**187** : **187'**)	Yield^b (%)
1	Bn	H	H	6	4 : 1	**187a**, 65
2	Bn	Me	H	6	3 : 1	**187b**, 61
3	Bn	MeO	H	6	4 : 1	**187c**, 63
4	Bn	Cl	H	8	4 : 1	**187d**, 54
5	Bn	Br	H	8	4 : 1	**187e**, 62
6	Bn	NO$_2$	H	10	3 : 1	**187f**, 51
7	Bn	Cl	MeO	6	2 : 1	**187g**, 52 **187g'**, 21
8	Bn	Cl	Me	6	2 : 1	**187h-h'**, 76
9	*n*-C$_4$H$_9$	H	H	10	3 : 1	**187i**, 59

^{a}*Product ratio determined by crude ^{1}H NMR.* ^{b}*Isolated yield.*

The functionalized naphthyridine derivatives having four contiguous stereocenters, and gave only two diastereoisomers. A fairly good diastereoselectivity was observed in the above study. The structures of all the compounds were ascertained by usual spectroscopic studies as well as by comparison with literature precedent.[79,80] For example, the structure of compound **187i** was established by NMR (^{1}H, ^{13}C, COSY, NOESY). The major isomer with ^{1}H NMR peaks at δ values 4.42, 1.93 and 4.16 for H_{10b}, H_{4a} and H_5, having coupling constant values of the doublet, $J_{4a,10b}$ = 2.0 Hz and $J_{4a,5}$ = 10.8 Hz, represents *cis* arrangement of hydrogen between two ring fusions and the proton H_5 is *trans* with ring junction proton H_{4a}. In addition, H_{4a}, H_{10b} and Me are all in same plane, however H_4 and H_5 are in other plane depicted by NOE as shown in Figure 7. Finally, the observed structure and stereochemistry were fully supported by single crystal X-ray structures of compound **187b** (major isomer) and **187g'** (minor isomer) as shown in Figure 8.

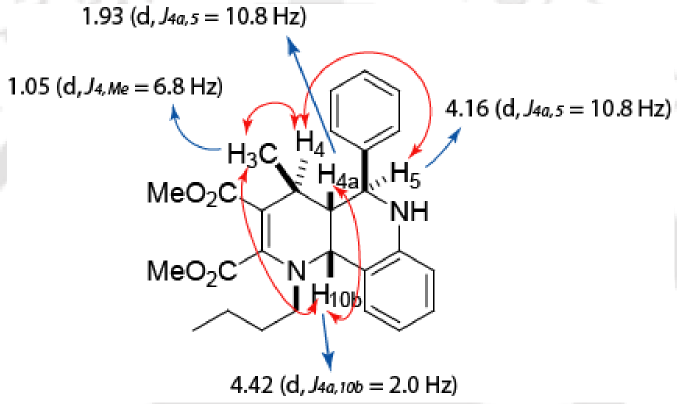
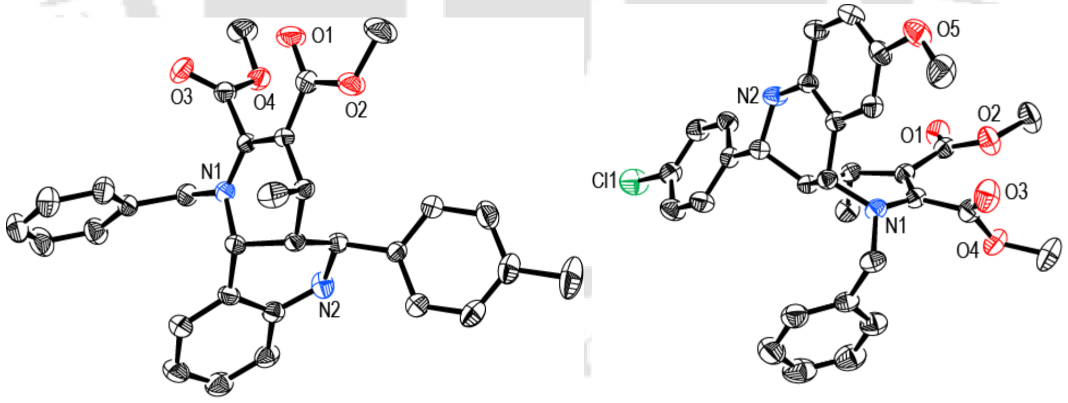


Figure 7. Diagnostic ^{1}H NMR and NOE of **187i**



187b (CCDC No. 810814) **187g'** (CCDC No. 810813)

Figure 8. *ORTEP molecular diagram with ellipsoid at 35% probability of* ***187b*** *and* ***187g'***

In conclusion, the Brønsted acid catalyzed synthesis of unsymmetrical tetrasubstituted 1,4- and 1,6-DHPs using one-pot three-component reactions of DMAD, aliphatic amines and α,β-unsaturated aldehydes have been accomplished. The regioselective synthesis of tetrasubstituted 1,4-DHPs have also been achieved. These 1,4-DHPs can be used as a new class of dien ophiles for imino-Diels-Alder reaction for the construction of highly substituted naphthyridine derivatives. The significant advantages of present protocol are simple experimental procedure, non toxic byproduct, high atom economy, good regioselectivity and diastereoselectivity. The new heterocyclic entities containing β-amino acid skeleton might exhibit interesting pharmacological activities.

Experimental

*General procedure for 1,4- and 1,6-dihydropyridines **185** and **186***

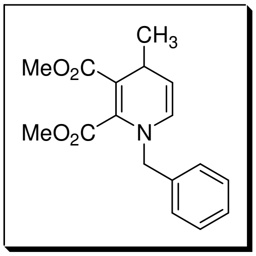
Method A: To a stirred solution of dimethyl acetylenedicarboxylate (DMAD, 1.0 mmol) in THF (2 mL) was added amine (1.0 mmol) at room temperature. After 10 min of stirring, α,β-unsaturated aldehyde (1.2 mmol) and trifluoroacetic acid (0.3 mmol) were added successively and it kept for stirring further. After completion of reaction (monitored by TLC), the reaction mixture was neutralized with $NaHCO_3$ solution and it was extracted with DCM (20 mL x 2). The organic phase was washed with water, brine solution and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the crude mixture was purified through silica gel chromatography using hexane/ethyl acetate/NEt_3 (92:7:1) and it afforded the products **185a-j** and **186a-j**, respectively in good yields.

Method B: the same procedure as Method A was followed except the catalyst triflic acid is used.

*General procedure for synthesis of substituted naphthyridine derivatives **187***

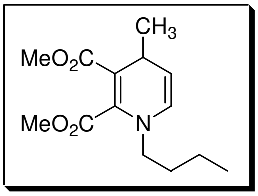
1,4-Dihydropyridine, **185a** (0.3 mmol) was added to a stirring solution of aromatic aldehydes (0.3 mmol) and aromatic amines (0.3 mmol) in acetonitrile (2 mL). Finally, catalyst $BF_3.OEt_2$ (20 mol%) was added to the reaction mixture and stirring was continued. After completion of reaction (monitored by TLC), the mixture was extracted with DCM (20 mL x 2). The organic phase was washed with saturated solution of $NaHCO_3$, brine solution and dried over Na_2SO_4. The crude products were purified by silica gel chromatography using hexane/ethyl acetate (85:15) to afford the products **187a-i** in good yields.

Dimethyl 1-benzyl-1,4-dihydro-4-methylpyridine-2,3-dicarboxylate (**185a**)



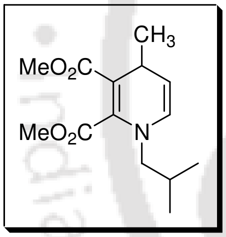
Yellow liquid; **IR** (KBr): 2951, 1739, 1695, 1575, 1434, 1269, 1216, 1187, 734 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.08 (d, 3H, J = 6.4 Hz, CH_3), 3.32–3.39 (m, 1H, H-4), 3.68 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.28 (d, 1H, J = 16.4 Hz, NC*H*H), 4.36 (d, 1H, J = 16.4 Hz, NCH*H*), 4.87 (dd, 1H, J = 5.6 Hz, J = 7.2 Hz, H-5), 5.75 (d, 1H, J = 7.2 Hz, H-6), 7.24–7.36 (m, 5H, Ar*H*); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 25.3, 27.1, 51.6, 52.9, 54.6, 101.2, 110.6, 127.3, 127.6, 128.0, 128.9, 137.0, 144.3, 166.1, 167.9; **Anal. Calcd** for $C_{17}H_{19}NO_4$ (301.34): C, 67.76; H, 6.36; N, 4.65. Found: C, 67.71; H, 6.32; N, 4.58.

Dimethyl 1-butyl-1,4-dihydro-4-methylpyridine-2,3-dicarboxylate (**185b**)



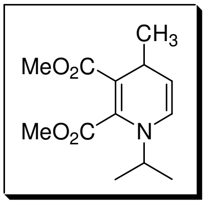
Yellow liquid; **IR** (KBr): 2955, 1742, 1694, 1573, 1419, 1269, 1216, 1190, 1089, 732 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.90 (t, 3H, J = 7.2 Hz, CH_3), 1.06 (d, 3H, J = 6.8 Hz, CH_3), 1.33–1.22 (m, 2H, CH_2), 1.56–1.51 (m, 2H, CH_2), 3.16–3.02 (m, 2H, NCH_2), 3.35–3.29 (m, 1H, H-4), 3.66 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.87 (dd, 1H, J = 5.6 Hz, J = 7.6 Hz, H-5), 5.77 (d, 1H, J = 7.6 Hz, H-6); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 13.9, 19.8, 25.2, 27.0, 32.3, 51.4, 52.9, 100.4, 110.1, 127.8, 144.3, 166.2, 168.0; **Anal. Calcd** for $C_{14}H_{21}NO_4$ (267.32): C, 62.90; H, 7.92; N, 5.24. Found: C, 62.81; H, 7.86; N, 5.15.

Dimethyl 1,4-dihydro-1-isobutyl-4-methylpyridine-2,3-dicarboxylate (**185c**)



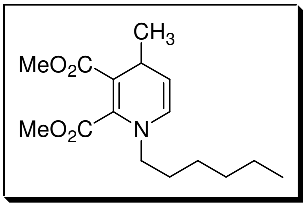
Dark yellow liquid; **IR** (KBr): 2956, 1742, 1695, 1572, 1418, 1268, 1231, 1210, 1191, 1091, 733 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 0.89 (t, 6H, J = 6.4 Hz, (CH_3)$_2$), 1.07 (d, 3H, J = 6.4 Hz, CH_3), 1.84–1.94 (m, 1H, CH(CH_3)$_2$), 2.84 (dd, 1H, J = 2.8 Hz, 7.2 Hz, CHH), 2.94 (dd, 1H, J = 3.6 Hz, 7.2 Hz, CHH), 3.30–3.36 (m, 1H, H-4), 3.68 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.87 (dd, 1H, J = 6.0 Hz, J = 7.6 Hz, H-5), 5.79 (d, 1H, J = 7.6 Hz, H-6); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 19.7, 19.9, 25.0, 26.9, 29.6, 51.4, 52.8, 59.0, 100.3, 109.4, 128.5, 144.4, 166.0, 167.8; **Anal. Calcd** for $C_{14}H_{21}NO_4$ (267.32): C, 62.90; H, 7.92; N, 5.24. Found: C, 62.84; H, 7.82; N, 5.13.

Dimethyl 1,4-dihydro-1-isopropyl-4-methylpyridine-2,3-dicarboxylate (**185d**)



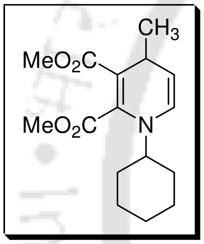
Yellow liquid; **IR** (KBr): 2953, 1742, 1694, 1568, 1422, 1268, 1249, 1190, 1115, 1074, 733 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.06 (d, 3H, J = 6.8 Hz, CH_3), 1.22 (d, 3H, J = 6.8 Hz, CH_3), 1.23 (d, 3H, J = 6.8 Hz, CH_3), 3.31–3.37 (m, 1H, H-4), 3.48–3.54 (m, 1H, NCH(CH_3)$_2$), 3.68 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.96 (dd, 1H, J = 5.6 Hz, J = 8.0 Hz, H-5), 5.97 (d, 1H, J = 8.0 Hz, H-6); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.2, 22.1, 25.0, 27.2, 51.1, 51.4, 52.9, 100.0, 110.9, 121.8, 144.5, 166.3, 167.9; **Anal. Calcd** for $C_{13}H_{19}NO_4$ (253.29): C, 61.64; H, 7.56; N, 5.53. Found: C, 61.55; H, 7.51; N, 5.41.

Dimethyl 1-hexyl-1,4-dihydro-4-methylpyridine-2,3-dicarboxylate (**185e**)



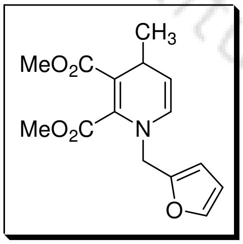
Yellow liquid; **IR** (KBr): 2953, 1742, 1695, 1571, 1419, 1268, 1190, 1091, 732 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, J = 7.2 Hz, CH_3), 1.07 (d, 3H, J = 6.8 Hz, CH_3), 1.18–1.34 (m, 6H, (CH_2)$_3$), 1.56–1.61 (m, 2H, CH_2), 3.03–3.16 (m, 2H, NCH_2), 3.30–3.37 (m, 1H, H-4), 3.68 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.88 (dd, 1H, J = 5.6 Hz, J = 7.6 Hz, H-5), 5.78 (d, 1H, J = 7.6 Hz, H-6); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.1, 22.6, 25.1, 26.2, 27.0, 30.1, 31.5, 51.4, 51.6, 52.8, 100.3, 110.0, 127.7, 144.3, 166.1, 167.9; **Anal. Calcd** for $C_{16}H_{25}NO_4$ (295.37): C, 65.06; H, 8.53; N, 4.74. Found: C, 65.01; H, 8.46; N, 4.64.

Dimethyl 1-cyclohexyl-1,4-dihydro-4-methylpyridine-2,3-dicarboxylate (**185f**)



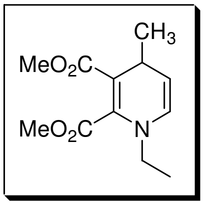
Yellow liquid; **IR** (KBr): 2935, 1741, 1696, 1570, 1421, 1262, 1234, 1185, 1111, 1097, 736 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.04 (d, 3H, J = 6.4 Hz, CH_3), 1.06–1.12 (m, 2H, CH_2), 1.15–1.31 (m, 2H, CH_2), 1.36–1.49 (m, 2H, CH_2), 1.78–1.87 (m, 4H), 2.98 (tt, 1H, J = 3.2 Hz, J = 11.6 Hz, NCH), 3.29–3.35 (m, 1H, H-4), 3.67 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.91 (dd, 1H, J = 5.6 Hz, J = 7.6 Hz, H-5), 5.99 (d, 1H, J = 8.0 Hz, H-6); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 24.9, 25.3, 25.9, 26.0, 27.2, 31.6, 32.7, 51.4, 52.9, 59.7, 99.9, 110.3, 122.9, 144.7, 166.4, 168.0; **Anal. Calcd** for $C_{16}H_{23}NO_4$ (293.36): C, 65.51; H, 7.90; N, 4.77. Found: C, 65.43; H, 7.83; N, 4.69.

Dimethyl 1-furfuryl-1,4-dihydro-4-methylpyridine-2,3-dicarboxylate (**185g**)



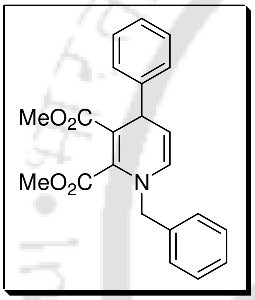
Yellow liquid; **IR** (KBr): 2953, 1739, 1695, 1575, 1434, 1417, 1288, 1270, 1188, 1114, 1099, 735 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.07 (d, 3H, J = 6.4 Hz, CH_3), 3.30–3.36 (m, 1H, H-4), 3.68 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.26 (d, 1H, J = 16.4 Hz, NCHH), 4.31 (d, 1H, J = 16.4 Hz, NCHH), 4.89 (dd, 1H, J = 5.2 Hz, J = 7.6 Hz, H-5), 5.87 (d, 1H, J = 7.6 Hz, H-6), 6.26 (dd, 1H, J = 0.8 Hz, J = 3.2 Hz, ArH), 6.33 (dd, 1H, J = 2.0 Hz, J = 3.2 Hz, ArH),7.37 (dd, 1H, J = 0.8 Hz, J = 2.0 Hz, ArH); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 25.2, 27.2, 47.6, 51.6, 53.0, 102.5, 108.7, 110.5, 110.7, 127.5, 142.9, 143.5, 150.3, 166.0, 167.8; **Anal. Calcd** for $C_{15}H_{17}NO_5$ (291.30): C, 61.85; H, 5.88; N, 4.81. Found: C, 61.80; H, 5.83; N, 4.73.

Dimethyl 1-ethyl-1,4-dihydro-4-methylpyridine-2,3-dicarboxylate (**185h**)



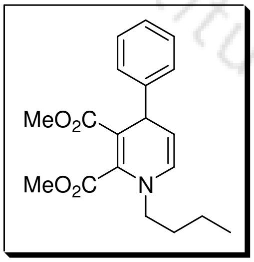
Yellow liquid; **IR** (KBr): 2953, 1742, 1694, 1574, 1418, 1269, 1242, 1209, 1191, 1078, 729 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): *δ* 1.08 (d, 3H, *J* = 6.4 Hz, C*H*$_3$), 1.19 (t, 3H, *J* = 7.2 Hz, C*H*$_3$), 3.10–3.24 (m, 2H, NC*H*$_2$), 3.31–3.38 (m, 1H, H-4), 3.68 (s, 3H, OC*H*$_3$), 3.90 (s, 3H, OC*H*$_3$), 4.90 (dd, 1H, *J* = 5.6 Hz, *J* = 7.6 Hz, H-5), 5.78 (d, 1H, *J* = 7.6 Hz, H-6); ^{13}**C NMR** (100 MHz, $CDCl_3$): *δ* 15.4, 25.3, 27.1, 44.8, 46.4, 51.5, 52.9, 100.6, 110.7, 127.1, 144.1, 166.2; **Anal. Calcd** for $C_{12}H_{17}NO_4$ (239.27): C, 60.24; H, 7.16; N, 5.85. Found: C, 60.16; H, 7.08; N, 5.73.

Dimethyl 1-benzyl-1,4-dihydro-4-phenylpyridine-2,3-dicarboxylate (**185i**)



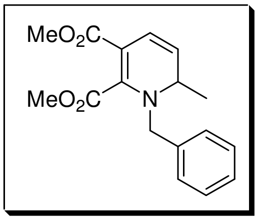
Yellow solid; M.p. 136-138 °C; **IR** (KBr): 2953, 1742, 1694, 1574, 1418, 1269, 1242, 1209, 1191, 729 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): *δ* 3.56 (s, 3H, OC*H*$_3$), 3.83 (s, 3H, OC*H*$_3$), 4.34 (d, 1H, *J* = 16.0 Hz, NC*H*H), 4.44 (d, 1H, *J* = 16.0 Hz, NCH*H*), 4.53 (d, 1H, *J* = 5.2 Hz, H-4), 4.97 (dd, 1H, *J* = 7.6 Hz, *J* = 5.2 Hz, H-5), 5.88 (d, 1H, *J* = 7.6 Hz, H-6), 7.17 (tt, 1H, *J* = 2.0 Hz, *J* = 6.8 Hz, Ar*H*), 7.22–7.27 (m, 4H, Ar*H*), 7.29–7.39 (m, 5H, Ar*H*); ^{13}**C NMR** (100 MHz, $CDCl_3$): *δ* 38.5, 51.5, 53.0, 54.8, 99.8, 109.5, 126.6, 127.2, 127.7, 128.1, 128.5, 128.9, 136.5, 144.1, 147.3, 165.9, 167.6; **Anal. Calcd** for $C_{22}H_{21}NO_4$ (363.41): C, 72.71; H, 5.82; N, 3.85. Found: C, 72.65; H, 5.76; N, 3.79.

Dimethyl 1-butyl-1,4-dihydro-4-phenylpyridine-2,3-dicarboxylate (**185j**)



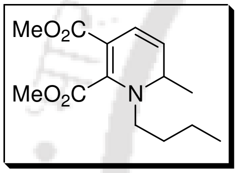
Yellow semi-solid; **IR** (KBr): 2927, 1741, 1693, 1566, 1424, 1261, 1192, 1079, 702 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): *δ* 0.93 (t, 3H, *J* = 7.6 Hz, C*H*$_3$), 1.28–1.37 (m, 2H, C*H*$_2$), 1.59–1.66 (m, 2H, C*H*$_2$), 3.08–3.25 (m, 2H, NC*H*$_2$), 3.54 (s, 3H, OC*H*$_3$), 3.91 (s, 3H, OC*H*$_3$), 4.51 (d, 1H, *J* = 5.2 Hz, H-4), 4.98 (dd, 1H, *J* = 5.6 Hz, *J* = 8.0 Hz, H-5), 5.69 (d, 1H, *J* = 8.0 Hz, H-6), 7.17–7.21 (m, 1H, Ar*H*), 7.25–7.32 (m, 4H, Ar*H*); ^{13}**C NMR** (100 MHz, $CDCl_3$): *δ* 13.8, 19.9, 32.2, 38.5, 51.4, 51.7, 53.0, 99.0, 109.1, 126.6, 127.3, 127.6, 128.6, 144.3, 147.8, 165.9, 167.7; **Anal. Calcd** for $C_{19}H_{23}NO_4$ (329.39): C, 69.28; H, 7.04; N, 4.25. Found: C, 69.21; H, 6.98; N, 4.14.

Dimethyl 1-benzyl-1,4-dihydro-6-methylpyridine-2,3-dicarboxylate (**186a**)



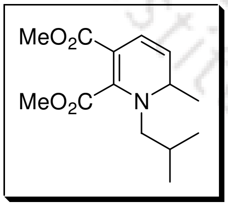
Yellow liquid; **IR** (KBr): 2950, 1739, 1693, 1542, 1434, 1297, 1230, 1125, 728 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.14 (d, 3H, J = 6.4 Hz, CH_3), 3.71 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.93–3.98 (m, 1H, H-6), 4.30 (d, 1H, J = 15.6 Hz, NC*H*H), 4.37 (d, 1H, J = 15.6 Hz, NCH*H*), 5.02 (dd, 1H, J = 5.2 Hz, J = 9.6 Hz, H-5), 6.41 (d, 1H, J = 9.6 Hz, H-4), 7.37–7.29 (m, 5H, Ar*H*); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 19.2, 51.3, 52.7, 53.1, 54.4, 97.8, 114.9, 121.3, 127.7, 128.2, 128.9, 136.4, 147.9, 166.0, 166.3; **Anal. Calcd** for $C_{17}H_{19}NO_4$ (301.34): C, 67.76; H, 6.36; N, 4.65. Found: C, 67.70; H, 6.31; N, 4.60.

Dimethyl 1-butyl-1,4-dihydro-6-methylpyridine-2,3-dicarboxylate (**186b**)



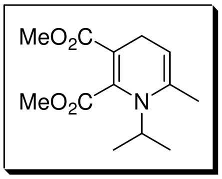
Yellow liquid; **IR** (KBr): 2957, 1742, 1693, 1540, 1435, 1294, 1227, 140, 729 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.91 (t, 3H, J = 7.6 Hz, CH_3), 1.14 (d, 3H, J = 6.0 Hz, CH_3), 1.26–1.35 (m, 2H, CH_2), 1.56–1.64 (m, 2H, CH_2), 3.06–3.19 (m, 2H, NCH_2), 3.68 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.00–4.07 (m, 1H, H-6), 5.08 (dd, 1H, J = 5.6 Hz, J = 9.2 Hz, H-5), 6.41 (d, 1H, J = 9.2 Hz, H-4); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 13.9, 19.7, 19.9, 31.4, 51.3, 53.0, 53.4, 97.5, 114.0, 121.7, 147.9, 166.0, 166.3; **Anal. Calcd** for $C_{14}H_{21}NO_4$ (267.32): C, 62.90; H, 7.92; N, 5.24. Found: C, 62.79; H, 7.84; N, 5.11.

Dimethyl 1,4-dihydro-1-isobutyl-6-methylpyridine-2,3-dicarboxylate (**186c**)



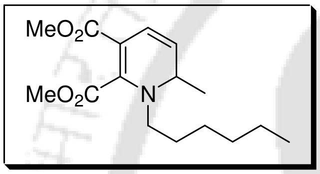
Dark yellow liquid; **IR** (KBr): 2958, 1742, 1693, 1538, 1435, 1295, 1235, 1143, 728 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.87 (d, 3H, J = 6.8 Hz, CH_3), 0.93 (d, 3H, J = 6.8 Hz, CH_3), 1.12 (d, 3H, J = 6.4 Hz, CH_3), 1.88–1.98 (m, 1H, C$H(CH_2)_2$), 2.88 (dd, 1H, J = 8.4 Hz, J = 14.4 Hz, NC*H*H), 3.01 (dd, 1H, J = 6.8 Hz, J = 14.4 Hz, NCH*H*), 3.68 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.95–4.01 (m, 1H, H-6), 5.11 (dd, 1H, J = 5.6 Hz, J = 9.2 Hz, H-5), 6.43 (d, 1H, J = 9.2 Hz, H-4); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 18.7, 19.7, 20.1, 28.3, 51.3, 52.9, 53.5, 58.6, 98.2, 114.0, 122.0, 147.9, 165.9, 166.3; **Anal. Calcd** for $C_{14}H_{21}NO_4$ (267.32): C, 62.90; H, 7.92; N, 5.24. Found: C, 62.83; H, 7.84; N, 5.12.

Dimethyl 1,4-dihydro-1-isopropyl-6-methylpyridine-2,3-dicarboxylate (**186d**)



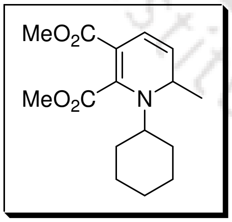
Yellow liquid; **IR** (KBr): 2978, 1739, 1690, 1532, 1435, 1241, 1182, 1123, 729 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.09 (d, 3H, J = 6.4 Hz, CH_3), 1.21 (d, 3H, J = 6.4 Hz, CH_3), 1.30 (d, 3H, J = 6.8 Hz, CH_3), 3.59–3. 65 (m, 1H, NCH), 3.69 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.07–4.13 (m, 1H, H-6), 5.14 (dd, 1H, J = 6.4 Hz, J = 9.2 Hz, H-5), 6.46 (d, 1H, J = 9.2 Hz, H-4); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 21.1, 22.4, 22.7, 46.5, 51.3, 53.1, 53.4, 99.8, 114.0, 122.2, 146.5, 166.5; **Anal. Calcd** for $C_{13}H_{19}NO_4$ (253.29): C, 61.64; H, 7.56; N, 5.53. Found: C, 61.57; H, 7.49; N, 5.44.

Dimethyl 1-hexyl-1,4-dihydro-6-methylpyridine-2,3-dicarboxylate (**186e**)



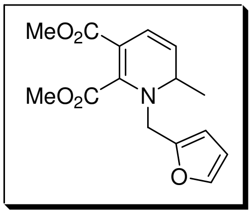
Yellow liquid; **IR** (KBr): 2955, 1742, 1693, 1540, 1435, 1294, 11243, 1188, 1140, 1097, 727 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.88 (t, 3H, J = 6.4 Hz, CH_3), 1.14 (d, 3H, J = 6.0 Hz, CH_3), 1.21–1. 34 (m, 6H, (CH_2)$_3$), 1.56–1.64 (m, 2H, CH_2), 3.05–3.18 (m, 2H, NCH_2), 3.68 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.00–4.07 (m, 1H, H-6), 5.08 (dd, 1H, J = 5.6 Hz, J = 9.6 Hz, H-5), 6.40 (d, 1H, J = 9.6 Hz, H-4); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.1, 19.7, 22.6, 26.3, 29.7, 31.5, 51.2, 51.5, 52.9, 53.4, 97.4, 114.0, 121.6, 147.8, 165.9, 166.2; **Anal. Calcd** for $C_{16}H_{25}NO_4$ (295.37): C, 65.06; H, 8.53; N, 4.74. Found: C, 64.98; H, 8.43; N, 4.62.

Dimethyl 1-cyclohexyl-1,4-dihydro-6-methylpyridine-2,3-dicarboxylate (**186f**)



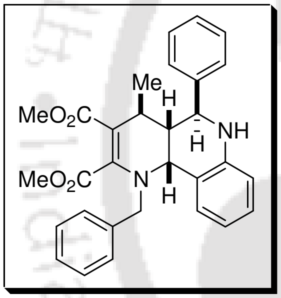
Yellow syrup; **IR** (KBr): 2936, 1740, 1693, 1531, 1435, 1231, 1121, 730 cm^{-1}; ^{1}**H NMR** (400 MHz, $CDCl_3$): δ 1.06 (d, 3H, J = 6.4 Hz, CH_3), 1.16–1.32 (m, 3H), 1.41–1.54 (m, 2H), 1.62–1.72 (m, 2H), 1.78–1.85 (m, 2H), 2.02–2.05 (m, 1H), 3.10 (tt, 1H, J = 3.6 Hz, J = 11.6 Hz, NCH), 3.69 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.06–4.13 (m, 1H, H-6), 5.13 (dd, 1H, J = 6.4 Hz, J = 9.2 Hz, H-5), 6.46 (d, 1H, J = 9.2 Hz, H-4); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 21.1, 25.3, 26.0, 26.1, 32.6, 33.3, 47.6, 51.2, 53.0, 62.1, 99.6, 113.9, 122.1, 146.6, 166.5; **Anal. Calcd** for $C_{16}H_{23}NO_4$ (293.36): C, 65.51; H, 7.90; N, 4.77. Found: C, 65.44; H, 7.86; N, 4.71.

Dimethyl 1-furfuryl-1,4-dihydro-6-methylpyridine-2,3-dicarboxylate (**186g**)



Yellow syrup; **IR** (KBr): 2953, 1738, 1694, 1435, 1297, 1151, 733 cm^{-1}; ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 1.09 (d, 3H, J = 6.0 Hz, CH_3), 3.69 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.05–4.11 (m, 1H, H-6), 4.25 (d, 1H, J = 16.0 Hz, NC*H*H), 4.35 (d, 1H, J = 16.4 Hz, NCH*H*), 5.08 (dd, 1H, J = 6.0 Hz, J = 9.2 Hz, H-5), 6.32–6.35 (m, 2H, Ar*H*), 6.38 (d, 1H, J = 9.2 Hz, H-4), 7.39–7.40 (m, 1H, Ar*H*); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 19.5, 47.6, 51.4, 53.2, 53.4, 98.7, 109.4, 110.8, 115.4, 121.1, 143.1, 147.0, 149.7, 165.9, 166.2; **Anal. Calcd** for $C_{15}H_{17}NO_5$ (291.30): C, 61.85; H, 5.88; N, 4.81. Found: C, 61.78; H, 5.84; N, 4.73.

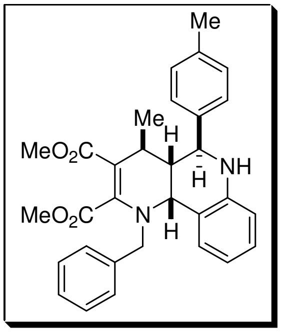
Dimethyl 1-benzyl-4-methyl-5-phenyl-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridine-2,3-dicarboxylate (**187a**)



White solid; M.p. 242–245 ºC; **IR** (KBr): 3413, 2955, 1744, 1683, 1573, 1498, 1224, 1142, 1088, 735 cm^{-1}; ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 1.09 (d, 3H, J = 6.8 Hz, CH_3), 1.92 (d, 1H, J = 10.8 Hz, H-4a), 2.36–2.43 (m, 1H, H-4), 3.65 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.14 (d, 1H, J = 16.8 Hz, NC*H*H), 4.17 (s, 1H, N*H*), 4.25 (d, 1H, J = 10.8 Hz, H-5), 4.29 (d, 1H, J = 16.8 Hz, NC*H*H), 4.42 (d, 1H, J = 2.8 Hz, H-10b), 6.47–6.51 (m, 2H, Ar*H*), 6.63 (d, 1H, J = 7.6 Hz, Ar*H*), 7.10 (t, 2H, J = 7.2 Hz, Ar*H*), 7.12–7.18 (m, 2H, Ar*H*), 7.23–7.28 (m, 2H, Ar*H*), 7.28–7.38 (m, 5H, Ar*H*); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 23.1, 26.9, 41.8, 51.2, 52.1, 52.8, 56.0, 98.3, 113.8, 115.6, 115.7, 127.1, 127.2, 128.0, 128.2, 128.6, 128.7, 130.2, 131.9, 137.6, 143.0, 144.3, 147.9, 166.9, 168.0; **Anal. Calcd** for $C_{30}H_{30}N_2O_4$ (482.57): C, 74.67; H, 6.27; N, 5.81. Found: C, 74.61; H, 6.14; N, 5.71.

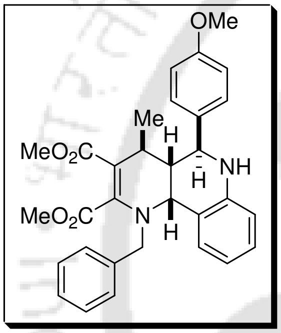
Dimethyl 1-benzyl-4-methyl-5-(4-methylphenyl)-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridine-2,3-dicarboxylate (**187b**)

White solid; M.p. 251–253 ºC; **IR** (KBr): 3416, 2952, 1741, 1685, 1571, 1498, 1224, 1142, 1088, 735 cm^{-1}; ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 1.09 (d, 3H, J = 6.8 Hz, CH_3), 1.90 (d, 1H, J = 10.4 Hz, H-4a), 2.36 (s, 3H, CH_3), 2.38–2.43 (m, 1H, H-4), 3.66 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.10 (s, 1H, N*H*), 4.15 (d, 1H, J = 17.2 Hz, NC*H*H), 4.21 (d, 1H, J = 10.8 Hz, H-5), 4.30 (d, 1H, J = 16.8 Hz, NCH*H*), 4.42 (br s, 1H, H-10b), 6.45 (d,



1H, *J* = 8.0 Hz, Ar*H*), 6.49 (d, 1H, *J* = 7.2 Hz, Ar*H*), 6.61 (d, 1H, *J* = 7.6 Hz, Ar*H*), 7.08 (t, 1H, *J* = 7.6 Hz, Ar*H*), 7.13–7.26 (m, 7H, Ar*H*), 7.32 (t, 2H, *J* = 7.6 Hz, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 21.4, 23.2, 27.1, 41.8, 51.3, 52.3, 52.9, 55.8, 98.3, 113.8, 115.6, 115.8, 127.3, 127.9, 128.6, 129.5, 130.2, 132.0, 137.7, 137.9, 140.0, 144.4, 148.0, 167.0, 168.1; **Anal. Calcd** for $C_{31}H_{32}N_2O_4$ (496.60): C, 74.98; H, 6.50; N, 5.64. Found: C, 74.89; H, 6.41; N, 5.52.

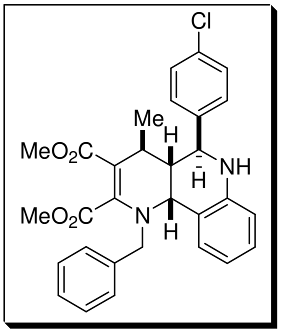
Dimethyl 1-benzyl-5-(4-methoxyphenyl)-4-methyl--1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridine-2,3-dicarboxylate (**187c**)



White solid; M.p. 232–234 ºC; **IR** (KBr): 3356, 2950, 1725, 1673, 1585, 1567, 1228, 1143, 1091, 734 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.09 (d, 3H, *J* = 6.8 Hz, C*H*$_3$), 1.89 (d, 1H, *J* = 11.2 Hz, H-4a), 2.36–2.43 (m, 1H, H-4), 3.66 (s, 3H, OC*H*$_3$), 3.78 (s, 3H, OC*H*$_3$), 3.82 (s, 3H, OC*H*$_3$), 4.10 (s, 1H, N*H*), 4.15 (d, 1H, *J* = 17.6 Hz, NC*H*H), 4.20 (d, 1H, *J* = 11.2 Hz, H-5), 4.30 (d, 1H, *J* = 17.2 Hz, NCH*H*), 4.41 (d, 1H, *J* = 2.8 Hz, H-10b), 6.46 (d, 1H, *J* = 8.4 Hz, Ar*H*), 6.49 (d, 1H, *J* = 7.2 Hz, Ar*H*), 6.62 (d, 1H, *J* = 7.6 Hz, Ar*H*), 6.87 (d, 2H, *J* = 8.8 Hz, Ar*H*), 7.08 (t, 1H, *J* = 8.0 Hz, Ar*H*), 7.16 (d, 2H, *J* = 7.6 Hz, Ar*H*), 7.22–7.26 (m, 3H, Ar*H*), 7.32 (t, 2H, *J* = 7.6 Hz, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 23.1, 27.0, 41.8, 51.3, 52.2, 52.8, 55.4, 98.2, 113.8, 114.1, 115.6, 115.8, 127.2, 128.6, 129.0, 130.2, 132.0, 134.9, 137.7, 144.4, 148.0, 159.6, 166.9, 168.0; **Anal. Calcd** for $C_{31}H_{32}N_2O_5$ (512.60): C, 72.64; H, 6.29; N, 5.47. Found: C, 72.53; H, 6.20; N, 5.36.

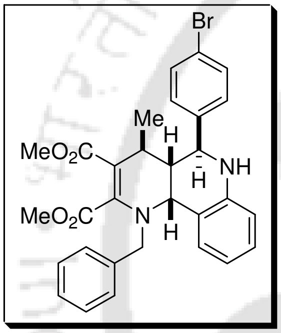
Dimethyl 1-benzyl-5-(4-chlorophenyl)-4-methyl--1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridine-2,3-dicarboxylate (**187d**)

White solid; M.p. 194–196 ºC; **IR** (KBr): 3358, 2948, 1719, 1686, 1573, 1494, 1225, 1142, 1090, 1013, 750 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): δ 1.10 (d, 3H, *J* = 6.8 Hz, C*H*$_3$), 1.87 (d, 1H, *J* = 10.0 Hz, H-4a), 2.27–2.37 (m, 1H, H-4), 3.67 (s, 3H, OC*H*$_3$), 3.78 (s, 3H, OC*H*$_3$), 4.12 (d, 1H, *J* = 17.6 Hz, NC*H*H), 4.17 (s, 1H, N*H*), 4.24 (d, 1H, *J* = 10.4 Hz, H-5), 4.27 (d, 1H, *J* = 17.2 Hz, NCH*H*), 4.41 (d, 1H, *J* = 2.8 Hz, H-10b), 6.49 (d,



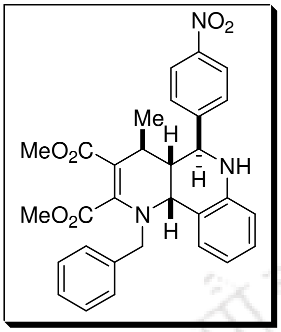
1H, J = 8.0 Hz, ArH), 6.52 (d, 1H, J = 7.6 Hz, ArH), 6.63 (d, 1H, J = 7.6 Hz, ArH), 7.10 (t, 1H, J = 8.0 Hz, ArH), 7.14 (d, 2H, J = 7.2 Hz, ArH), 7.24–7.34 (m, 7H, ArH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 23.0, 26.9, 41.6, 51.0, 51.3, 52.0, 52.9, 55.4, 98.1, 113.9, 115.6, 115.9, 127.1, 127.3, 128.7, 128.8, 129.4, 130.2, 132.0, 133.8, 137.5, 141.4, 144.2, 147.9, 166.9, 167.9; **Anal. Calcd** for $C_{30}H_{29}ClN_2O_4$ (517.02): C, 69.69; H, 5.65; N, 5.42. Found: C, 69.61; H, 5.59; N, 5.36.

Dimethyl 1-benzyl-5-(4-bromophenyl)-4-methyl--1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridine-2,3-dicarboxylate (**187e**)



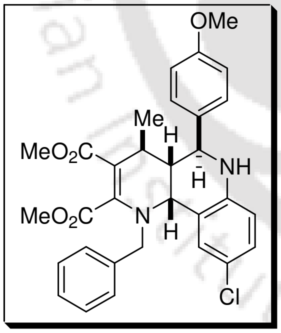
White solid; **IR** (KBr): 3356, 2947, 1716, 1684, 1572, 1492, 1223, 1141, 1088, 1011, 748 cm^{-1}; M.p. 188–189 ºC; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.10 (d, 3H, J = 6.8 Hz, CH_3), 1.86 (d, 1H, J = 10.4 Hz, H-4a), 2.35 (q, 1H, J = 6.8 Hz, CHCH$_3$), 3.67 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.12 (d, 1H, J = 17.2 Hz, NCHH), 4.14 (s, 1H, NH), 4.23 (d, 1H, J = 10.4 Hz, H-5), 4.28 (d, 1H, J = 17.2 Hz, NCHH), 4.40 (d, 1H, J = 2.4 Hz, H-10b), 6.48 (d, 1H, J = 8.0 Hz, ArH), 6.52 (d, 1H, J = 7.2 Hz, ArH), 6.63 (d, 1H, J = 7.6 Hz, ArH), 7.10 (t, 1H, J = 7.6 Hz, ArH), 7.14 (d, 2H, J = 7.6 Hz, ArH), 7.19 (d, 2H, J = 8.4 Hz, ArH), 7.24–7.27 (m, 1H, ArH), 7.32 (t, 2H, J = 7.6 Hz, ArH), 7.46 (d, 2H, J = 8.4 Hz, ArH); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 23.0, 27.0, 41.8, 51.0, 51.4, 52.2, 53.0, 55.5, 98.1, 113.9, 115.7, 116.0, 122.0, 127.2, 127.3, 128.7, 129.7, 130.3, 131.8, 137.5, 142.0, 144.1, 147.9, 166.9, 167.9; **Anal. Calcd** for $C_{30}H_{29}BrN_2O_4$ (561.47): C, 64.18; H, 5.21; N, 4.99. Found: C, 64.06; H, 5.10; N, 5.11.

Dimethyl 1-benzyl-4-methyl-5-(4-nitrophenyl)-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridine-2,3-dicarboxylate (**187f**)



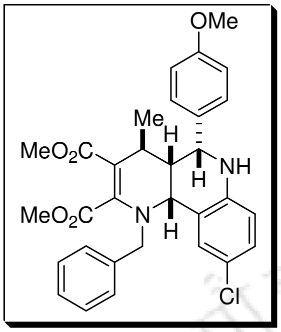
Yellow solid; M.p. 227–228 °C; **IR** (KBr): 3344, 2953, 1722, 1685, 1576, 1519, 1347, 1261, 1141, 1085, 756 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.11 (d, 3H, J = 6.8 Hz, C*H$_3$*), 1.91 (d, 1H, J = 10.4 Hz, H-4a), 2.31 (qd, 1H, J = 2.4 Hz, J = 6.8 Hz, C*H*CH$_3$), 3.68 (s, 3H, OC*H$_3$*), 3.80 (s, 3H, OC*H$_3$*), 4.13 (d, 1H, J = 17.2 Hz, NC*H*H), 4.19 (s, 1H), 4.31 (d, 1H, J = 17.2 Hz, NCH*H*), 4.40 (d, 2H, J = 10.0 Hz, N*H* and H-5), 6.53 (d, 1H, J = 8.0 Hz, Ar*H*), 6.57 (t, 1H, J = 7.6 Hz, Ar*H*), 6.64–6.68 (m, 1H, Ar*H*), 7.12–7. 15 (m, 3H, Ar*H*), 7.24–7.28 (m, 1H, Ar*H*), 7.32 (t, 2H, J = 7.2 Hz, Ar*H*), 7.50 (d, 2H, J = 8.4 Hz, Ar*H*), 8.19 (d, 2H, J = 8.8 Hz, Ar*H*); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 22.9, 27.1, 42.1, 50.9, 51.5, 52.4, 53.0, 55.7, 98.1, 114.2, 115.9, 116.6, 124.0, 127.2, 127.5, 128.7, 128.9, 130.4, 131.9, 137.2, 143.7, 148.0, 150.7, 166.8, 167.7; **Anal. Calcd** for $C_{30}H_{29}N_3O_6$ (527.57): C, 68.30; H, 5.54; N, 7.96. Found: C, 68.22; H, 5.41; N, 7.84.

Dimethyl 1-benzyl-5-(4-chlorophenyl)-9-methoxy-4-methyl-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridine-2,3-dicarboxylate (**187g**)



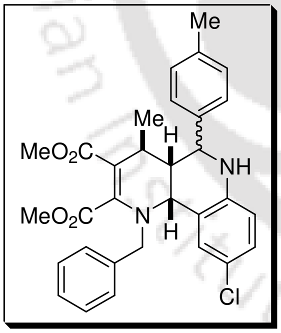
Light yellow solid; M.p 231–233 °C; **IR** (KBr): 3361, 2942, 1729, 1666, 1577, 1505, 1288, 1132, 1073, 703 cm^{-1}; **^{1}H NMR** (400 MHz, CDCl$_3$): δ 1.10 (d, 3H, J = 6.8 Hz, C*H$_3$*), 1.84 (d, 1H, J = 10.4 Hz, H-4a), 2.34 (qd, 1H, J = 2.8 Hz, J = 6.8 Hz, C*H*CH$_3$), 3.53 (s, 3H, OC*H$_3$*), 3.66 (s, 3H, OC*H$_3$*), 3.79 (s, 3H, OC*H$_3$*), 3.91 (br s, 1H, N*H*), 4.14 (d, 1H, J = 17.6 Hz, NC*H*H), 4.21 (d, 1H, J = 10.0 Hz, H-5), 4.32 (d, 1H, J = 17.2 Hz, NCH*H*), 4.36 (d, 1H, J = 2.4 Hz, H-10b), 6.18 (br s, 1H, Ar*H*), 6.46 (d, 1H, J = 8.4 Hz, Ar*H*), 6.75 (dd, 1H, J = 2.8 Hz, J = 8.8 Hz, Ar*H*), 7.17 (d, 2H, J = 7.2 Hz, Ar*H*), 7.23–7.38 (m, 7H, Ar*H*); **^{13}C NMR** (100 MHz, CDCl$_3$): δ 23.1, 27.1, 42.2, 51.2, 51.3, 52.5, 53.0, 55.7, 55.8, 98.4, 115.2, 115.7, 116.4, 117.9, 127.2, 127.4, 128.7, 128.9, 129.3, 133.8, 137.6, 138.3, 141.9, 147.9, 150.8, 166.9, 167.9; **Anal. Calcd** for $C_{31}H_{31}ClN_2O_5$ (547.04): C, 68.06; H, 5.71; N, 5.12. Found: C, 68.01; H, 5.63; N, 5.04.

Dimethyl 1-benzyl-5-(4-chlorophenyl)-9-methoxy-4-methyl-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridine-2,3-dicarboxylate (**187g'**)



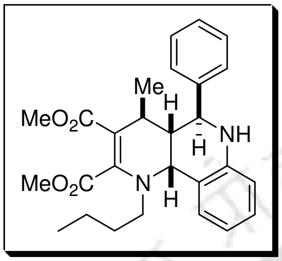
Light yellow solid; M.p. 253–255 ºC; **IR** (KBr): 3361, 2942, 1729, 1666, 1577, 1505, 1288, 1132, 1073, 703 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 0.54 (d, 3H, *J* = 6.4 Hz, C*H_3*), 1.84 (br s, 1H, H-4a), 2.70–2.74 (m, 1H, H-4), 3.56 (s, 3H, OC*H_3*), 3.69 (s, 3H, OC*H_3*), 3.77 (s, 1H), 3.82 (s, 3H, OC*H_3*), 4.26 (d, 1H, *J* = 15.6 Hz, NC*H*H), 4.47 (d, 1H, *J* = 15.6 Hz, NCH*H*), 4.55 (d, 1H, *J* = 4.8 Hz, H-5), 4.62 (d, 1H, *J* = 3.2 Hz, H-10b), 6.51 (d, 1H, *J* = 8.8 Hz, Ar*H*), 6.68 (dd, 1H, *J* = 2.8 Hz, 8.8 Hz, Ar*H*), 6.71 (br s, 1H, Ar*H*), 7.24–7.30 (m, 4H, Ar*H*), 7.33–7.40 (m, 5H, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 23.7, 25.2, 46.3, 51.2, 52.8, 55.7, 56.0, 56.3, 58.2, 108.2, 111.9, 115.8, 116.1, 119.6, 128.1, 128.2, 128.6, 129.0, 133.3, 137.6, 138.8, 139.8, 146.3, 152.6, 167.1, 167.4; **Anal. Calcd** for $C_{31}H_{31}ClN_2O_5$ (547.04): C, 68.06; H, 5.71; N, 5.12. Found: C, 68.01; H, 5.63; N, 5.04.

Dimethyl 1-benzyl-5-(4-chlorophenyl)-4,9-dimethyl-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridine-2,3-dicarboxylate (**187h-h'**)



Mixture of **187h** and **187h'** as light yellow solid; M.p 228–229 ºC; **IR** (KBr): 3352, 2947, 1724, 1690, 1665, 1575, 1285, 1228, 1144, 1087, 732 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 0.64 (d, 3H, *J* = 6.0 Hz, C*H_3*), 1.08 (d, 3H, *J* = 6.8 Hz, C*H_3*), 1.84–1.92 (m, 2H), 2.10 (s, 3H, C*H_3*), 2.17 (s, 3H, C*H_3*), 2.33 (qd, 1H, *J* = 2.0 Hz, *J* = 6.4 Hz, C*H*CH_3), 2.74–2.80 (m, 1H), 3.56 (s, 3H, OC*H_3*), 3.66 (s, 3H, OC*H_3*), 3.78 (s, 3H, OC*H_3*), 3.79 (s, 3H, OC*H_3*), 3.95 (br s, 1H, N*H*), 4.03 (br s, 1H, N*H*), 4.09 (d, 1H, *J* = 17.2 Hz, NC*H*H), 4.21 (d, 1H, *J* = 10.8 Hz, H-5), 4.22 (d, 1H, *J* = 15.2 Hz, NC*H*H), 4.29 (d, 1H, *J* = 17.2 Hz, NCH*H*), 4.35 (d, 1H, *J* = 2.8 Hz, H-5), 4.42 (d, 1H, *J* = 15.6 Hz, NCH*H*), 4.53 (d, 1H, *J* = 4.8 Hz, H-10b), 4.61(d, 1H, *J* = 3.2 Hz, H-10b), 6.34 (br s, 1H, Ar*H*), 6.42 (d, 1H, *J* = 8.0 Hz, Ar*H*), 6.49 (d, 1H, *J* = 8.0 Hz, Ar*H*), 6.78 (br s, 1H, Ar*H*), 7.40–7.23 (m, 16H, Ar*H*), 6.89 (d, 1H, *J* = 8.0 Hz, Ar*H*), 6.92 (d, 1H, *J* = 8.0 Hz, Ar*H*), 7.14 (d, 2H, *J* = 7.2 Hz, Ar*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* 20.3, 20.7, 23.1, 23.9, 25.6, 27.0, 42.0, 45.3, 51.0, 51.1, 51.3, 52.5, 52.7, 52.9, 55.3, 55.6, 57.9, 97.9, 105.8, 113.9, 114.4, 115.7, 118.1, 125.0, 127.2, 127.3, 127.4, 127.9, 128.3, 128.4, 128.6, 128.9, 129.3, 129.7, 130.9, 132.4, 133.2, 133.8, 137.6, 139.8, 141.7, 141.8, 142.5, 146.8, 148.0, 166.9, 167.4, 167.9.

Dimethyl 1-butyl-4-methyl-5-phenyl-1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridine-2,3-dicarboxylate (**187i**)



White solid; M.p. 172–174 ºC; **IR** (KBr): 3351, 2955, 1726, 1665, 1578, 1508, 1265, 1146, 1086, 736 cm^{-1}; ^{1}**H NMR** (400 MHz, CDCl$_3$): δ 0.78 (t, 3H, *J* = 7.6 Hz, C*H$_3$*), 1.05 (d, 3H, *J* = 6.8 Hz, C*H$_3$*), 1.05–1.29 (m, 1H), 1.30–1.40 (m, 1H), 1.60–1.66 (m, 2H), 1.93 (d, 1H, *J* = 10.8 Hz, H-4a), 2.31 (q, 1H, *J* = 6.4 Hz, H-4), 3.10–2.87 (m, 2H, NC*H$_2$*), 3.61 (s, 3H, OC*H$_3$*), 3.90 (s, 3H, OC*H$_3$*), 4.16 (d, 1H, *J* = 10.8 Hz, H-5), 4.18 (s, 1H, N*H*), 4.42 (d, 1H, *J* = 2.0 Hz, H-10b), 6.54 (d, 1H, *J* = 8.0 Hz, Ar*H*), 6.66 (t, 1H, *J* = 7.6 Hz, Ar*H*), 7.15 (d, 1H, *J* = 8.8 Hz, Ar*H*), 7.17 (d, 1H, *J* = 8.4 Hz, Ar*H*), 7.32 (br s, 5H, Ar*H*); ^{13}**C NMR** (100 MHz, CDCl$_3$): δ 13.7, 20.0, 23.2, 26.8, 30.9, 42.0, 48.5, 51.1, 51.4, 52.8, 55.9, 97.8, 113.9, 116.0, 116.5, 128.0, 128.2, 128.8, 130.2, 131.5, 143.0, 144.4, 147.6, 166.9, 168.1; **Anal. Calcd** for $C_{27}H_{32}N_2O_4$ (448.55): C, 72.30; H, 7.19; N, 6.25. Found: C, 72.22; H, 7.06; N, 6.14.

*XRD for Compounds **185i**, **187b** and **187g'***

Complete crystallographic data of **185i**, **187b** and **187g'** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 810812, 810814 and 810813 respectively. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

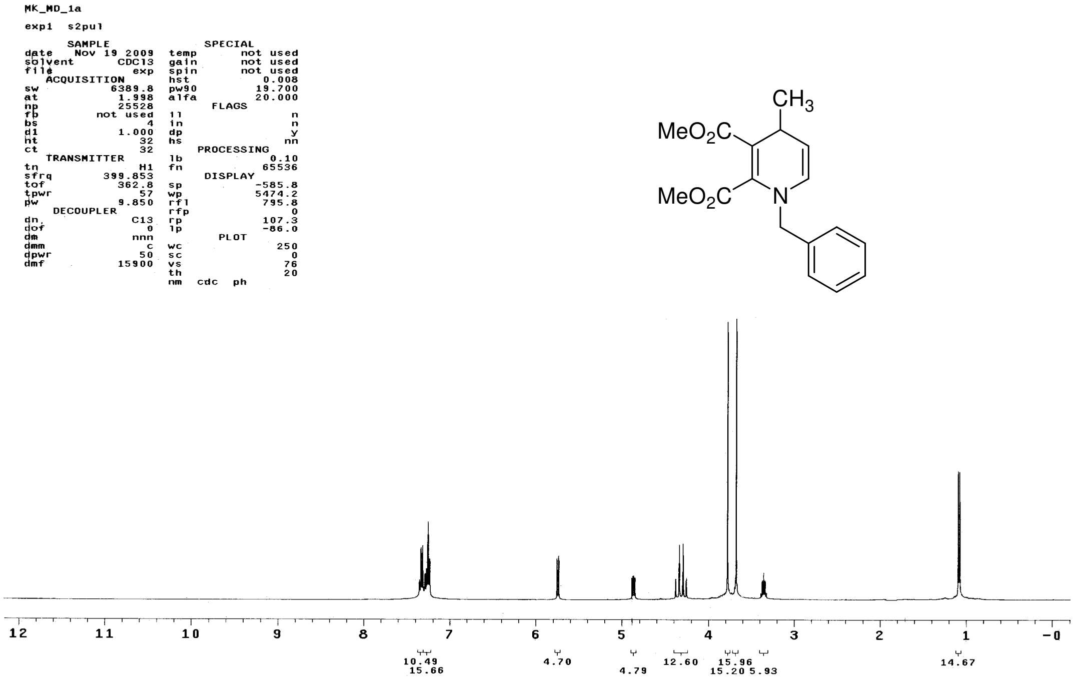
Table 9. Crystal data and structure refinement for **185i**, **187b** and **187g'** for atomic coordinates and equivalent isotropic displacement parameters and bond angles, please check the CIF.

Parameters	**Compound 185i**	**Compound 187b**	**Compound 187g'**
Empirical formula	$C_{22}H_{21}NO_4$	$C_{31}H_{32}N_2O_4$	$C_{31}H_{31}ClN_2O_5$
Formula weight	363.40	469.59	547.03
Temperature	298(2) K	296(2) K	298(2) K

Wavelength	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	Orthorhombic	Triclinic	Triclinic
Space group	P2(1)2(1)2(1)	P-1	P-1
Unit cell dimensions			
a	6.9470 (4) Å	9.6862 (12) Å	8.8160 (5) Å
b	14.9886 (9) Å	12.3439 (16) Å	12.6125 (7) Å
c	18.0309 (10) Å	12.7672 (4) Å	13.9715 (9) Å
α	90.00º	61.803º (7)	114.074 (3)º
β	90.00º	81.922º (8)	97.382 (3)º
γ	90.00º	79.378º (8)	94.268 (3)º
Volume	1877.48 (19) Å^3	1319.3 (3) Å^3	1392.77 (14) Å^3
Z	4	2	2
Density (calculated)	1.286 g/cm^3	1.250 g/cm^3	1.304 g/cm^3
Absorption coefficient	0.089 mm^{-1}	0.083 mm^{-1}	0.180 mm^{-1}
F(000)	768	528	576
Theta range for data collection	2.26 to 28.15º	1.81 to 28.30º	2.96 to 27.33º
Index ranges	-9 <= h <= 6, -19 <= k <= 16, -15 <= l <= 22	-12 <= h <= 12, -15 <= k <= 14, -16 <= l <= 16	-11 <= h <= 11, -16 <= k <= 16, -18 <= l <= 18
Reflections collected	8663	16856	15230
Independent reflections	4102 R_{int} = 0.0731	6545 R_{int} = 0.0591	6286 R_{int} = 0.0811
Completeness to θº	97.5% (θ = 28.15º)	100% (θ = 28.30º)	99% (θ = 27.33º)
Data / restraints / parameters	4102 / 0 / 246	6545 / 0 / 338	6286 / 0 / 358
Goodness-of-fit on F2	0.931	1.038	0.686

Final R indices [>2sigma(I)]	R_{obs} = 0.0467, wR_{obs} =0.1047	R_{obs} = 0.0427, wR_{obs} = 0.0754	R_{obs} = 0.0448,wR_{obs}=0.0785
R indices (all data)	R_{all} = 0.0796, wR_{all} = 0.1156	R_{all} = 0.0697, wR_{all} = 0.1096	R_{all}=0.0936, wR_{all} = 0.1296
Largest diff. peak and hole	0.148 and -0.170 e.Å^{-3}	0.151 and -0.160 e.Å^{-3}	0.224 and -0.338 e.Å^{-3}

^{1}H NMR (400 MHz, CDCl$_3$): *Dimethyl 1-benzyl-1,4-dihydro-4-methylpyridine-2,3-dicarboxylate* (**185a**)



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MK_MD_1a

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solvent      CDC13   gain        not used
file           exp   spin        not used
   ACQUISITION       hst            0.008
sw          6389.8   pw90          19.700
at           1.998   alfa          20.000
np           25528            FLAGS
fb        not used   il                 n
bs               4   in                 n
d1           1.000   dp                 y
nt              32   hs                nn
ct              32          PROCESSING
   TRANSMITTER       lb              0.10
tn              H1   fn             65536
sfrq       399.853           DISPLAY
tof          362.8   sp            -585.8
tpwr            57   wp            5474.2
pw           9.850   rfl            795.8
    DECOUPLER        rfp                0
dn             C13   rp             107.3
dof              0   lp             -86.0
dm             nnn             PLOT
dmm              c   wc               250
dpwr            50   sc                 0
dmf          15900   vs                76
                     th                20
                     nm   cdc   ph
```
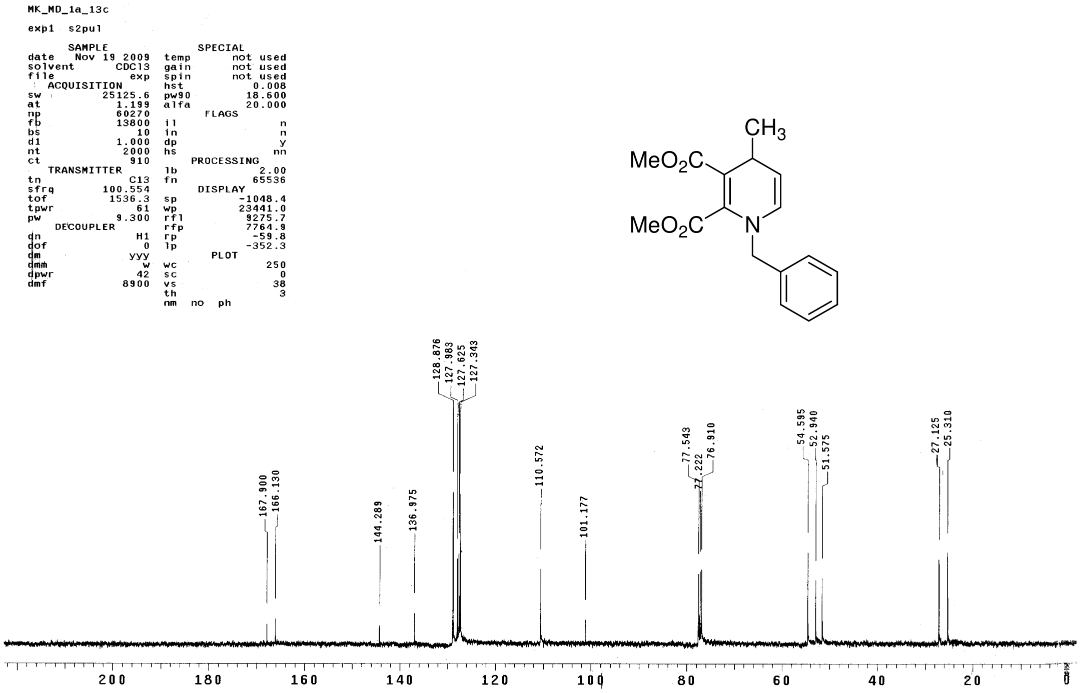
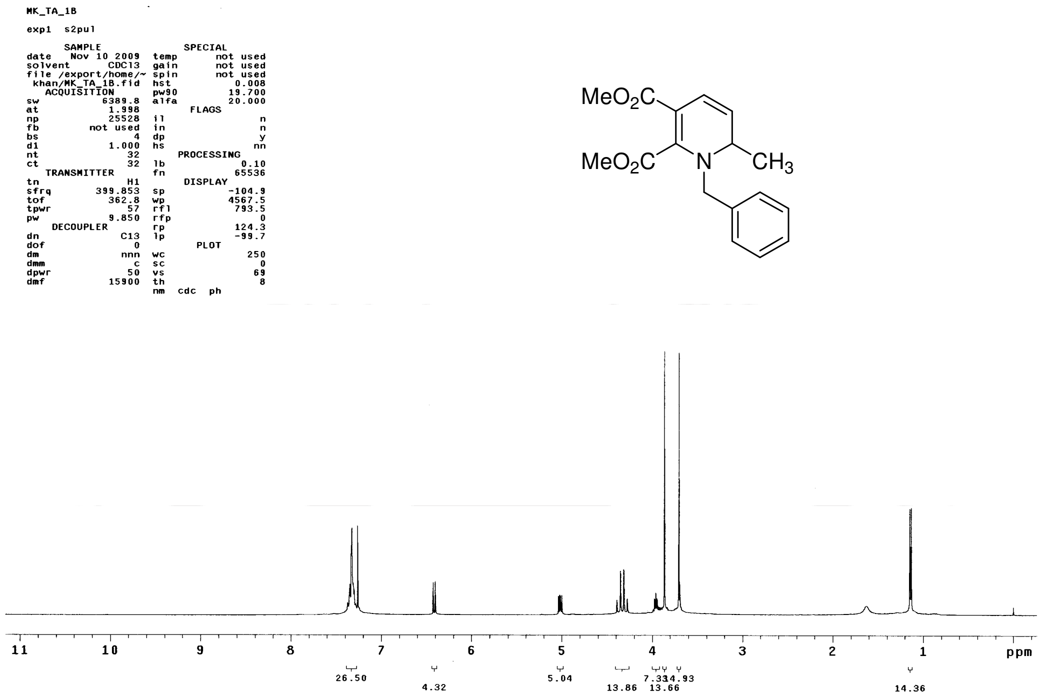

^{13}C NMR (100 MHz, CDCl$_3$): *Dimethyl 1-benzyl-1,4-dihydro-4-methylpyridine-2,3-dicarboxylate* (**185a**)



```
MK_MD_1a_13c

exp1  s2pul

      SAMPLE                SPECIAL
date   Nov 19 2009   temp        not used
solvent      CDC13   gain        not used
file           exp   spin        not used
   ACQUISITION       hst            0.008
sw         25125.6   pw90          18.600
at           1.199   alfa          20.000
np           60270            FLAGS
fb           13800   il                 n
bs              10   in                 n
d1           1.000   dp                 y
nt            2000   hs                nn
ct             910          PROCESSING
   TRANSMITTER       lb              2.00
tn             C13   fn             65536
sfrq       100.554           DISPLAY
tof         1536.3   sp           -1048.4
tpwr            61   wp           23441.0
pw           9.300   rfl           9275.7
    DECOUPLER        rfp           7764.9
dn              H1   rp             -59.8
dof              0   lp            -352.3
dm             yyy             PLOT
dmm              w   wc               250
dpwr            42   sc                 0
dmf           8900   vs                38
                     th                 3
                     nm   no   ph
```

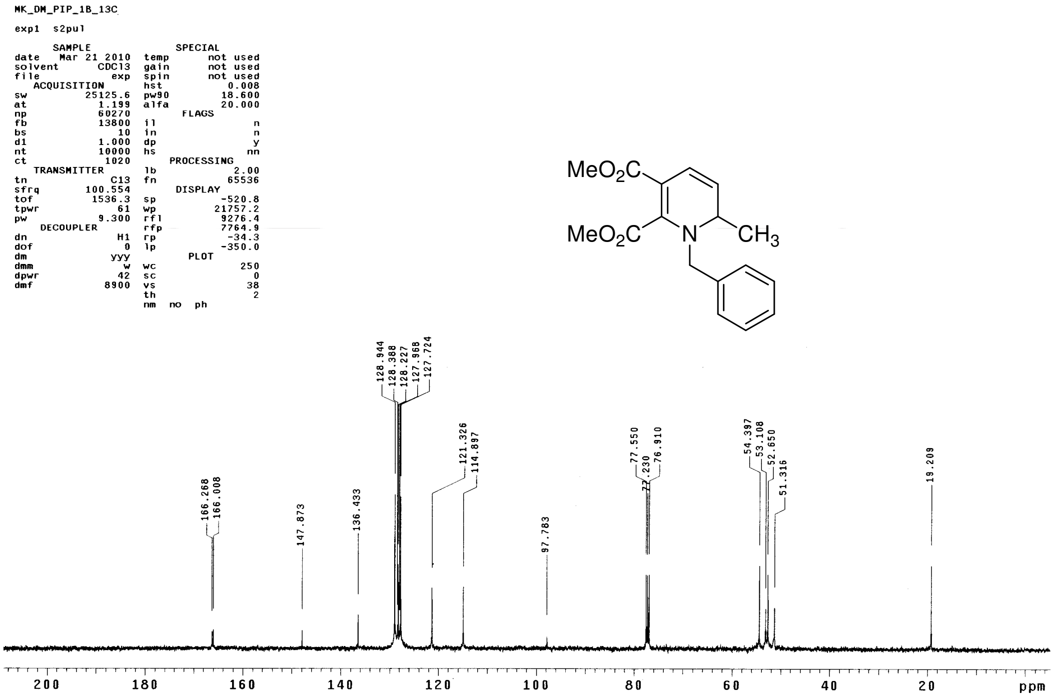
Figure 1

^{1}H NMR (400 MHz, CDCl$_3$): *Dimethyl 1-benzyl-1,4-dihydro-6-methylpyridine-2,3-dicarboxylate* (**186a**)



```
MK_TA_1B

exp1  s2pul

      SAMPLE                   SPECIAL
date   Nov 10 2009   temp       not used
solvent       CDC13   gain       not used
file /export/home/~  spin       not used
 khan/MK_TA_1B.fid   hst           0.008
   ACQUISITION       pw90         19.700
sw           6389.8  alfa         20.000
at            1.998        FLAGS
np            25528  il                n
fb         not used  in                n
bs                4  dp                y
d1            1.000  hs               nn
nt               32       PROCESSING
ct               32  lb             0.10
   TRANSMITTER       fn            65536
tn               H1         DISPLAY
sfrq        399.853  sp           -104.9
tof           362.8  wp           4567.5
tpwr             57  rfl           793.5
pw            9.850  rfp               0
    DECOUPLER        rp            124.3
dn              C13  lp            -99.7
dof               0          PLOT
dm              nnn  wc              250
dmm               c  sc                0
dpwr             50  vs               69
dmf           15900  th                8
                     nm   cdc   ph
```

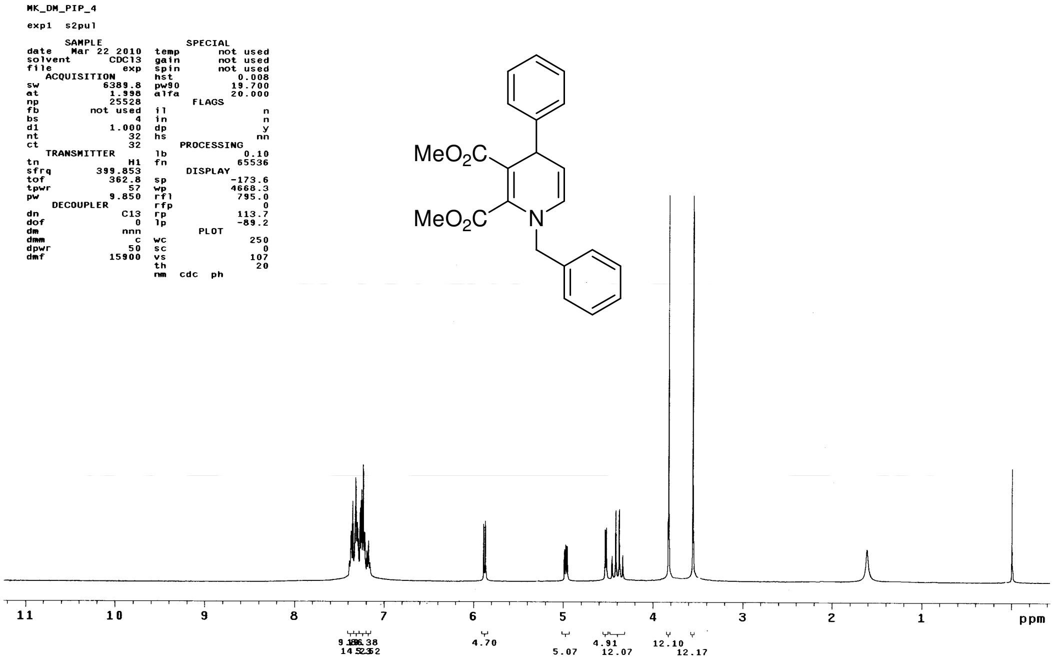
^{13}C NMR (100 MHz, CDCl$_3$): *Dimethyl 1-benzyl-1,4-dihydro-6-methylpyridine-2,3-dicarboxylate* (**186a**)



```
MK_DM_PIP_1B_13C

exp1  s2pul

      SAMPLE                   SPECIAL
date   Mar 21 2010   temp       not used
solvent       CDC13   gain       not used
file            exp  spin       not used
   ACQUISITION       hst           0.008
sw          25125.6  pw90         18.600
at            1.199  alfa         20.000
np            60270        FLAGS
fb            13800  il                n
bs               10  in                n
d1            1.000  dp                y
nt            10000  hs               nn
ct             1020       PROCESSING
   TRANSMITTER       lb             2.00
tn              C13  fn            65536
sfrq        100.554         DISPLAY
tof          1536.3  sp           -520.8
tpwr             61  wp          21757.2
pw            9.300  rfl          9276.4
    DECOUPLER        rfp          7764.9
dn               H1  rp            -34.3
dof               0  lp           -350.0
dm              yyy          PLOT
dmm               w  wc              250
dpwr             42  sc                0
dmf            8900  vs               38
                     th                2
                     nm   no   ph
```

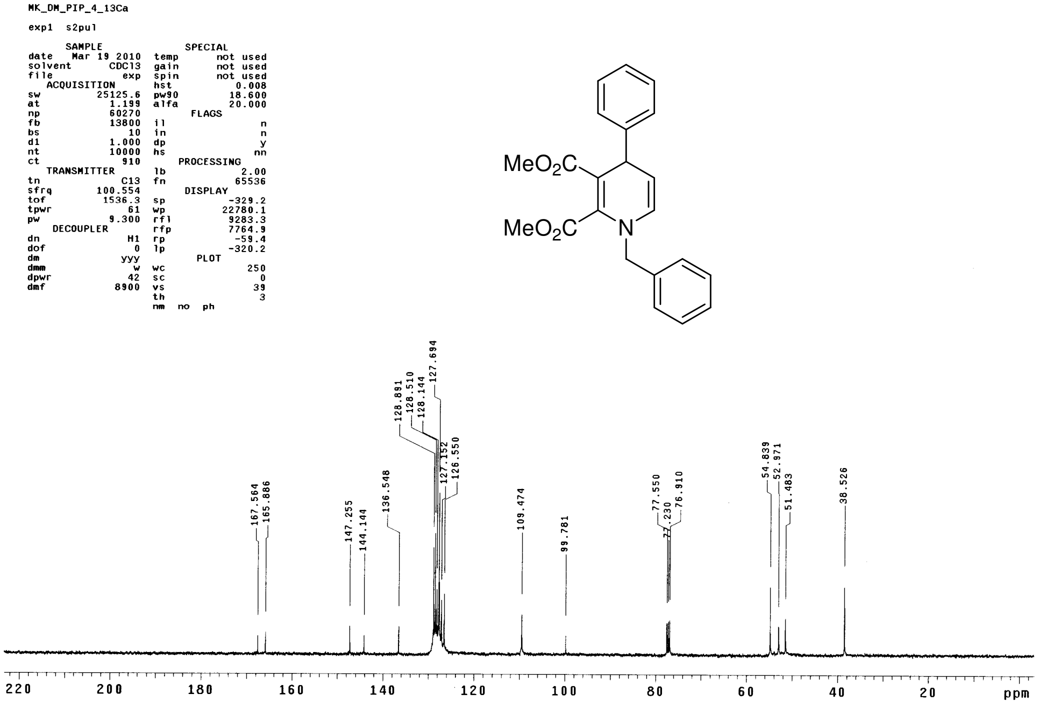
Figure 2

^{1}H NMR (400 MHz, CDCl$_3$): *Dimethyl 1-benzyl-1,4-dihydro-4-phenylpyridine-2,3-dicarboxylate* (**185i**)



```
MK_DM_PIP_4

exp1  s2pul

      SAMPLE                SPECIAL
date   Mar 22 2010  temp       not used
solvent      CDCl3  gain       not used
file           exp  spin       not used
   ACQUISITION      hst           0.008
sw          6389.8  pw90         19.700
at           1.998  alfa         20.000
np           25528          FLAGS
fb        not used  il                n
bs               4  in                n
d1           1.000  dp                y
nt              32  hs               nn
ct              32       PROCESSING
   TRANSMITTER      lb             0.10
tn              H1  fn            65536
sfrq       399.853          DISPLAY
tof          362.8  sp           -173.6
tpwr            57  wp           4668.3
pw           9.850  rfl           795.0
     DECOUPLER      rfp               0
dn             C13  rp            113.7
dof              0  lp            -89.2
dm             nnn           PLOT
dmm              c  wc              250
dpwr            50  sc                0
dmf          15900  vs              107
                    th               20
                    nm  cdc  ph
```

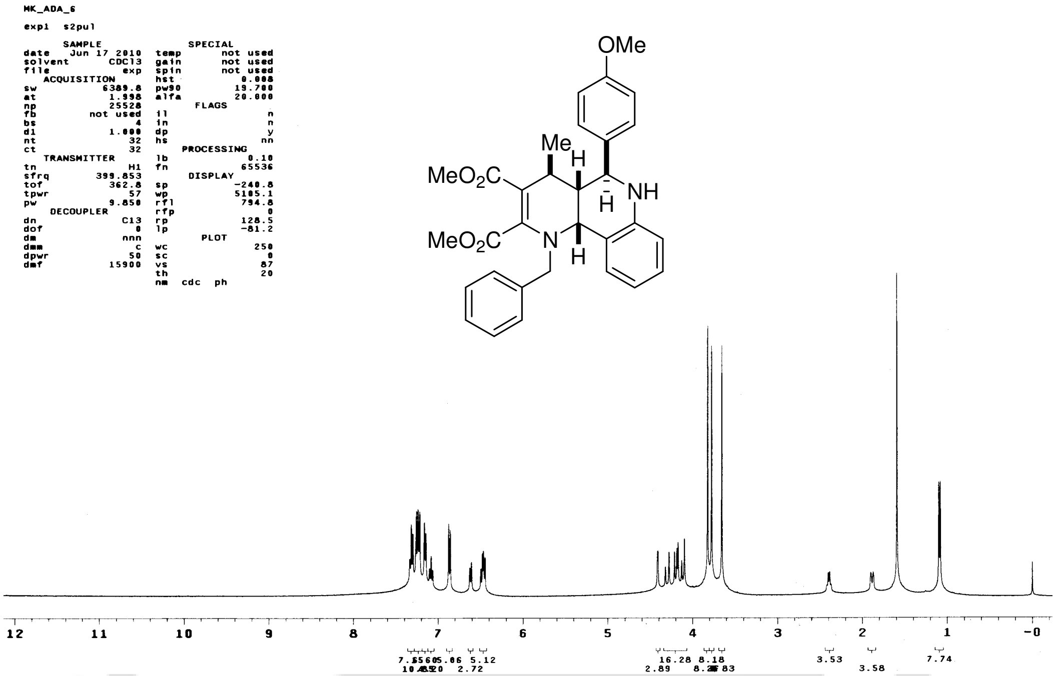
^{13}C NMR (100 MHz, CDCl$_3$): *Dimethyl 1-benzyl-1,4-dihydro-4-phenylpyridine-2,3-dicarboxylate* (**185i**)



```
MK_DM_PIP_4_13Ca

exp1  s2pul

      SAMPLE                SPECIAL
date   Mar 19 2010  temp       not used
solvent      CDCl3  gain       not used
file           exp  spin       not used
   ACQUISITION      hst           0.008
sw         25125.6  pw90         18.600
at           1.199  alfa         20.000
np           60270          FLAGS
fb           13800  il                n
bs              10  in                n
d1           1.000  dp                y
nt           10000  hs               nn
ct             910       PROCESSING
   TRANSMITTER      lb             2.00
tn             C13  fn            65536
sfrq       100.554          DISPLAY
tof         1536.3  sp           -329.2
tpwr            61  wp          22780.1
pw           9.300  rfl          9283.3
     DECOUPLER      rfp          7764.9
dn              H1  rp            -59.4
dof              0  lp           -320.2
dm             yyy           PLOT
dmm              w  wc              250
dpwr            42  sc                0
dmf           8900  vs               39
                    th                3
                    nm  no  ph
```

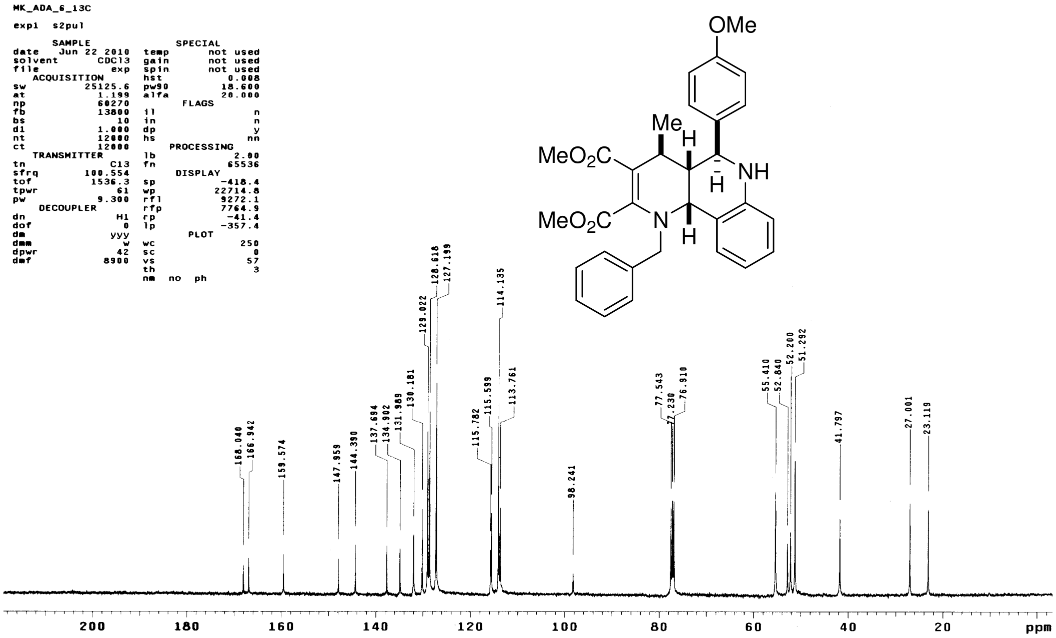
Figure 3

^{1}H NMR (400 MHz, CDCl$_3$): *Dimethyl 1-benzyl-5-(4-methoxyphenyl)-4-methyl--1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridine-2,3-dicarboxylate* (**187c**)



```
MK_ADA_6

expl  s2pul

      SAMPLE               SPECIAL
date   Jun 17 2010  temp       not used
solvent      CDCl3  gain       not used
file           exp  spin       not used
   ACQUISITION      hst           0.008
sw          6389.8  pw90         19.700
at           1.998  alfa         20.000
np           25528          FLAGS
fb        not used  il                n
bs               4  in                n
dl           1.000  dp                y
nt              32  hs               nn
ct              32       PROCESSING
   TRANSMITTER      lb             0.10
tn              H1  fn            65536
sfrq       399.853         DISPLAY
tof          362.8  sp           -240.8
tpwr            57  wp           5105.1
pw           9.850  rfl           794.8
    DECOUPLER       rfp               0
dn             C13  rp            128.5
dof              0  lp            -81.2
dm             nnn          PLOT
dmm              c  wc              250
dpwr            50  sc                0
dmf          15900  vs               87
                    th               20
                    nm  cdc  ph
```

^{13}C NMR (100 MHz, CDCl$_3$): *Dimethyl 1-benzyl-5-(4-methoxyphenyl)-4-methyl--1,4,4a,5,6,10b-hexahydrobenzo[h][1,6]naphthyridine-2,3-dicarboxylate* (**187c**)



```
MK_ADA_6_13C

expl  s2pul

      SAMPLE               SPECIAL
date   Jun 22 2010  temp       not used
solvent      CDCl3  gain       not used
file           exp  spin       not used
   ACQUISITION      hst           0.008
sw         25125.6  pw90         18.600
at           1.199  alfa         20.000
np           60270          FLAGS
fb           13800  il                n
bs              10  in                n
dl           1.000  dp                y
nt           12000  hs               nn
ct           12000       PROCESSING
   TRANSMITTER      lb             2.00
tn             C13  fn            65536
sfrq       100.554         DISPLAY
tof         1536.3  sp           -418.4
tpwr            61  wp          22714.8
pw           9.300  rfl          9272.1
    DECOUPLER       rfp          7764.9
dn              H1  rp            -41.4
dof              0  lp           -357.4
dm             yyy          PLOT
dmm              w  wc              250
dpwr            42  sc                0
dmf           8900  vs               57
                    th                3
                    nm  no  ph
```

Figure 4

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Part B (Chapter 1-3)

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CONCLUSION AND FUTURE PERSPECTIVES

The thesis describes new methodologies for diethyl- and dipropyl dithioacetal as well as *O*-isopropylidene derivatives of sugars using bromodimethylsulfonium bromide as catalyst. We have devised another method for *O*-isopropylidene derivatives of sugars catalyzed by TBATB. Moreover, we have developed cost effective methods for the synthesis of highly functionalized tetrahydropyridines using non-metallic, easily available and environmentally benign iodine. Finally, we have synthesized unsymmetrical highly substituted 1,4- and 1,6-dihydropyridines, regioselective and utility for the construction of more complex fused N-heterocycles.

In future, we believe that these carbohydrate based methodologies will be applicable in target-oriented synthesis as well as valuable additions in the modern synthetic organic synthesis. Further, we believe that the N-heterocyclic compounds prepared by these methods will be useful classes of compounds for further study for biological activities. From synthetic point of view the produced tetra- and dihydropyridines rings have various functionalities, which enable further modifications leading to molecular diversity. Finally, we are further extending the synthesis of 1,4- and 1,6-dihydropyridine and willing to regioselective controlled the both product especially, 1,6- DHPs which might be useful intermediate e.g. diene in Diels-Alder Reaction or others. Further studies are in progress in our laboratory.

LIST OF AUTHOR'S PUBLICATIONS AND COMMUNICATIONS

1. Selective and Effective Oxone-Catalysed α-Iodination of Ketones and 1,3-Dicarbonyl Compounds in the Solid state;
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6. Tetrabutylammonium Tribromide (TBATB): A Mild and Efficient Catalyst for *O*-Isopropylidenation of Carbohydrates;
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7. Sequential Three-Component Reactions: Synthesis, Regioselectivity and Application of Functionalized Dihydropyridines (DHPs) for the Creation of Fused Naphthyridines;

Abu T. Khan and **Md. Musawwer Khan** *Tetrahedron Lett.* **2011**, 0000 (*Accepted*).

8. Silica Supported Perchloric acid ($HClO_4$-SiO_2): An Efficient Catalyst for One-pot Synthesis of Tetrahydropyrimidine Derivatives;
   Abu T. Khan, **Md. Musawwer Khan** and Deb K. Das (*Communicated*).

9. Ferric Sulfate [$Fe_2(SO_4)_3.xH_2O$] Catalyzed Povarov reaction: An efficient and Useful Synthetic Protocol for the Synthesis of Tetrahydroquinoline Derivatives;
   Abu T. Khan, Deb K. Das and **Md. Musawwer Khan** (*Communicated*).

10. A Mild and Efficient Synthetic Protocol for Monoiodination of Organic Compounds Using a Combination of $VO(acac)_2/H_2O_2/NaI$;
    Abu T. Khan, Shahzad Ali and **Md. Musawwer Khan** (*Under preparation*).

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Bromodimethylsulfonium bromide (BDMS) mediated dithioacetalization of carbohydrates under solvent-free conditions

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ABSTRACT

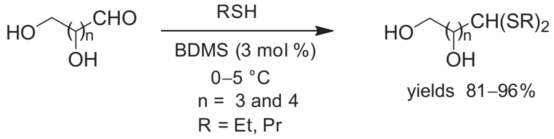
A variety of diethyl dithioacetals of sugars can be prepared in very good yields by the reaction of various monosaccharides with ethanethiol in the presence of 3 mol % bromodimethylsulfonium bromide (BDMS) at 0–5 °C. Similarly, dipropyl dithioacetal derivatives can also be obtained in good yields using propanethiol under identical reaction conditions. These dithioacetal derivatives were characterized by per-O-acetylation using silica gel-supported perchloric acid. The significant features of the present protocol are good-to-excellent yields, mild, clean, and solvent-free reaction conditions. This method is extremely suitable for the large-scale preparation of dithioacetal derivatives of various sugars.

1. Introduction

The dithioacetals obtained from reducing sugars, particularly diethyl dithioacetal derivatives, are valuable synthetic precursors in carbohydrate chemistry. Emil Fischer first demonstrated the preparation of diethyl dithioacetals of sugars in 1894, and today it is still one of the most useful and versatile synthetic methods to access open-chain sugars.[1] In fact, these dithioacetal derivatives are important synthetic precursors for aldehydo sugar derivatives through protection of the chain hydroxyl groups followed by subsequent deprotection of the dithioacetal group under neutral conditions with Hg(II) salts.[2] The acyclic aldehydo sugar derivatives are mainly used in the area of synthetic carbohydrate chemistry for the synthesis of *C*-disaccharides,[3] *C*-arylglycosides[4], and natural product synthesis.[5] For example, diethyl dithioacetals of D-arabinose and D-xylose have been used, respectively, for the synthesis of constanolactones A and B[6] and (+)-phorboxazole A, a potent cytostatic agent.[7] They are also used as key starting materials for the synthesis of azasugars[8] and carbasugars.[9,10] D-Galactose diethyl dithioacetal has been utilized as an acyclic glycosyl donor for furanoside synthesis.[11] As a matter of fact, the preparation of the dithioacetals of sugars provides ample opportunities for future applications of carbohydrates as precious renewable materials.

The diethyl dithioacetal derivatives of a free sugar are conventionally obtained from the reducing sugars with ethanethiol in the presence of an excess amount of concentrated HCl.[12–14] A few other methods are also known in the literature for the preparation of dithioacetal derivatives from free sugars using trifluoroacetic acid[15,16] and anhydrous zinc chloride.[17] The required excess amount of acid is one of the main drawbacks in the above methods. Therefore, there is a need to develop a milder set of reaction conditions that can replace the existing procedures using some other reagent as a catalyst. In continuation of our research objective to develop newer synthetic methodologies, we perceived that bromodimethylsulfonium bromide (BDMS) upon reaction with a thiol can generate dry HBr in the reaction medium, which might be a useful catalyst for dithioacetalization of sugars.

Bromodimethylsulfonium bromide (BDMS) has been explored by our research group[18–21] and by others[22–25] extensively as a useful brominating reagent as well as an efficient pre-catalyst for various organic transformations. The synthetic utility and its applications as an alternative brominating reagent and as a catalyst have been reviewed by us.[26] Recently, the catalytic efficacy of BDMS was reported for the preparation of *O*-isopropylidene derivatives.[27] In this paper, a practical and efficient method for the preparation of diethyl and dipropyl dithioacetals from reducing sugars



Scheme 1. Preparation of dithioacetal derivatives of sugar.

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Table 1
Optimization of reaction conditions with L-arabinose[a]

Entry	EtSH[b] (mL/mmol)	BDMS (mol %)	Solvent	Time (h)	Yield[c] (%)
1	1.9/25	5	DMF	1	51
2	1.9/25	10	DMF	1	59
3	1.9/25	5	DMSO	1	46
4	1.9/25	5	H_2O	1	23
5	1.9/25	5	–	1	63[d]
6	5.5/75	5	–	30	95
7	5.5/75	3	–	30	95

[a] Reactions were performed using 10 mmol of L-arabinose.
[b] Unreacted EtSH was recovered by short-path distillation.
[c] Isolated yields.
[d] Low yield due to improper mixing of sugar and EtSH.

using bromodimethylsulfonium bromide (BDMS) as a catalyst at 0–5 °C is reported (Scheme 1).

2. Results and discussion

For the present studies, the catalyst bromodimethylsulfonium bromide (BDMS) was prepared by following the literature procedure.[18] L-Arabinose (**1a**) was initially chosen as a model substrate. The reaction conditions for the dithioacetalization of sugars were optimized in terms of yield and reaction time. Several reactions were scrutinized using different amounts of catalyst with various solvents such as DMF, DMSO, and H_2O, and the results are summarized in Table 1.

It was noted that the best results were obtained by using 3 mol % of BDMS at 0–5 °C under solvent-free conditions. The product, L-arabinose diethyl dthioacetal (**1b**), was characterized by melting point and specific rotation. For further characterization **1b** was acetylated using silica gel-supported perchloric acid.[28] The acetylated product, 2,3,4,5-tetra-*O*-acetyl-L-arabinose diethyl dithioacetal (**1c**) was fully characterized by recording its melting point, IR, ^{1}H NMR, ^{1}H–^{1}H COSY, ^{13}C NMR, specific rotation, and by its elemental analysis.

After optimization of the reaction conditions, the reaction of D-glucose (**2a**) with ethanethiol was examined using the same mol % of catalyst under identical reaction conditions. The product, D-glucose diethyl dithioacetal (**2b**), was obtained in 91% yield (Table 2, entry 2). Encouraged by the above results, D-galactose (**3a**) was taken as a substrate under similar reaction conditions, and product **3b** was isolated in good yield (Table 2, entry 3). Likewise, other sugars such as D-mannose (**4a**), D-ribose (**5a**), D-xylose (**6a**), L-xylose (**7a**), L-rhamnose (**8a**), and L-fucose (**9a**) were converted into their corresponding diethyl dithioacetal derivatives **4b**–**9b**, upon reaction with ethanethiol in the presence of 3 mol % of BDMS in good-to-excellent yields (Table 2, entries 3–9).

The generality of the protocol was further examined with sugars such as L-arabinose (**1a**), D-glucose (**2a**), D-galactose (**3a**), and D-mannose (**4a**) and propanethiol under identical conditions. The corresponding dipropyl dithioacetals **10b**–**13b** were obtained in good yields (Table 2, entries 10–13).

All the dithioacetal derivatives **2b**–**13b** were per-O-acetylated to give the corresponding acetate derivatives **2c**–**13c** using $HClO_4$–SiO_2. They were fully characterized by recording their melting points, IR, ^{1}H, and ^{13}C NMR spectra and specific rotation as well as by elemental analyses. In addition, the structures of **1c** and **3c** (Fig. 1) were also confirmed by single-crystal X-ray data. For details see the Supplementary data.

Recently, it was reported[16] that the diethyl dithioacetal derivative of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**10a**) is an important starting material for the synthesis of valienamine, a compound that acts as α-glucosidase inhibitor.[29] To verify our protocol, substrate **10a** was reacted with ethanethiol in the presence of 3 mol % of catalyst under identical conditions, and it provided 2,3,4,6-*O*-benzyl-D-glucose diethyl dithioacetal (**14b**) in 84% yield (Table 2, entry 14). It is worth mentioning that the present protocol provides better yield and requires less reaction time than the method that uses trifluoroacetic acid.[16]

The formation of the product may be rationalized as follows. It has been shown that BDMS can generate HBr in the medium on reaction with methanol.[30] We believe that BDMS reacts with thiol to generate in situ dry HBr, which actually catalyzes the conversion of sugars into the corresponding dithioacetals (Scheme 2).

A one-pot dithioacetalization followed by a per-O-acetylation reaction can be accomplished by simply removing the excess ethanethiol without further recrystallization or purification of the product, which is generally not feasible with other methods. For example, per-O-acetylation of diethyl dithioacetal of L-xylose (**7b**) and L-fucose (**9b**) was carried out in the same reaction vessel after removing excess ethanethiol.

This method is highly efficient and should be very suitable for the large-scale preparation of dithioacetal derivatives without any difficulty by using only 2 mol % of the catalyst. For example, **1b** was obtained in quantitative yield when a mixture of L-arabinose (**1a**, 30 g, 200 mmol) and ethanethiol (100 mL) was treated with bromodimethylsulfonium bromide (0.888 g, 4.00 mmol) under similar reaction conditions. The efficacy and generality of the present method can be visualized at a glance from the comparison Table 3.

We have also performed a dithioacetalization reaction with aqueous HBr to verify the efficiency of our protocol. For this purpose, L-arabinose (10 mmol, 1.5 g) was treated with ethanethiol (10 mL) in the presence of a catalytic amount of aqueous HBr (0.1 mL) at ice-bath temperature. The desired product **1b** was obtained in 71% yield, which is lower than that of the BDMS-catalyzed reaction.

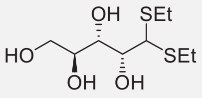
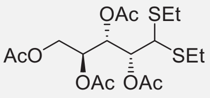
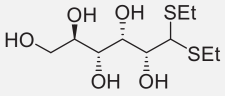
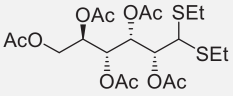
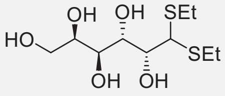
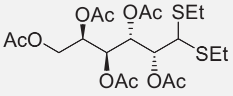
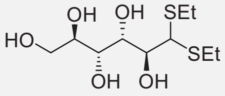
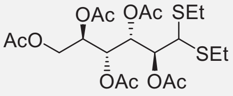
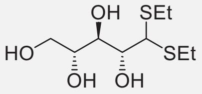
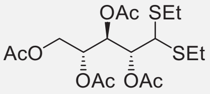
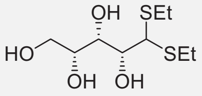
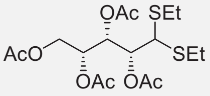
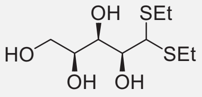
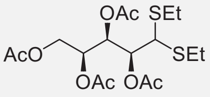
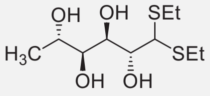
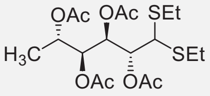
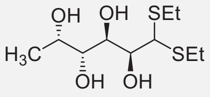
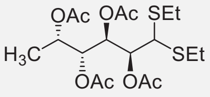
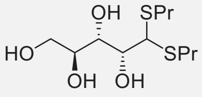
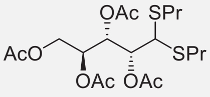
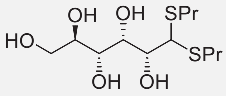
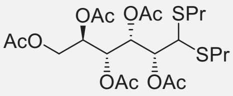
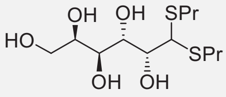
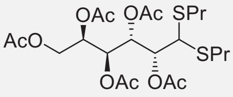
In conclusion, we have devised a simple, efficient, and practical synthetic protocol for the preparation of diethyl and dipropyl dithioacetal derivatives of sugars using a versatile catalyst, bromodimethylsulfonium bromide (BDMS). Mild and clean reaction conditions and good-to-excellent yields are some of the advantages of this method. In addition, this method may be a useful alternative for the large-scale preparation of dithioacetal derivatives of sugars.

3. Experimental

3.1. General

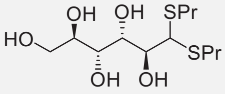
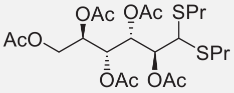
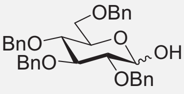
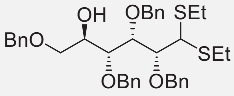
All sugars were purchased from Sigma–Aldrich Chemical Co. and Fluka. Thin-layer chromatography was performed on precoated TLC plates (0.2-mm layer thickness of Silica Gel 60 F-254). Zones were visualized by staining with either iodine vapor or MOSTAIN solution (by dissolving 20 g of ammonium heptamolybdate and 0.4 g cerium(IV) sulfate in 400 mL of 10% H_2SO_4 solution). Column chromatography was carried out using silica gel (60–120 mesh, E. Merck or Qualigen). Melting points were determined on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 243 polarimeter at 25 °C temperature. IR spectra were recorded on a Perkin–Elmer Spectrum One FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian (400 MHz) spectrometer using TMS as the internal reference. Chemical shifts reported in parts per million (ppm). ^{1}H NMR data are reported in the order of chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, and m = multiplet), number of protons and coupling constant in hertz. X-ray crystal data were collected with a Bruker Smart Apex-II CCD diffractometer using graphite monochromated Mo

Table 2
Dithioacetalization of various reducing sugars using BDMS as a catalyst[a]

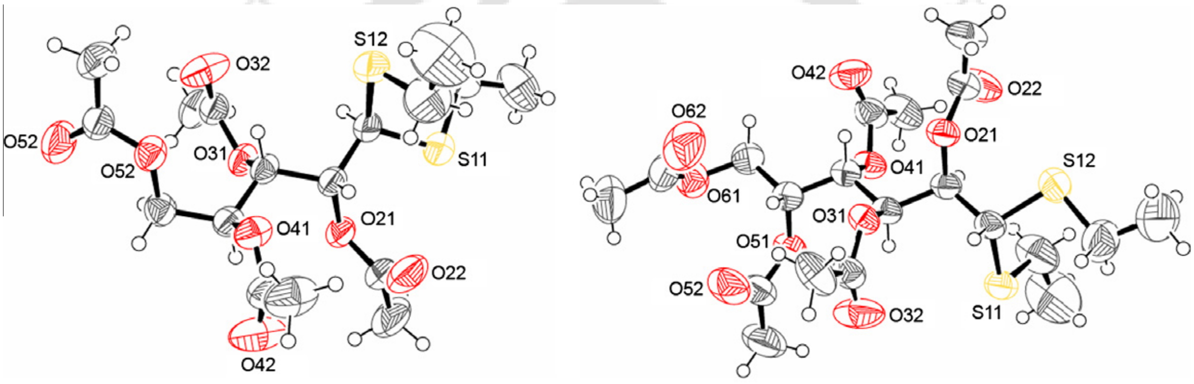
Entry	Substrate	Thiol	Product	Time (min)	Yield[b] (%)	Per-O-acetylated product[d]
1	L-Arabinose (**1a**)	EtSH	 (**1b**)	25	96	 (**1c**)
2	D-Glucose (**2a**)	EtSH	 (**2b**)	40	91	 (**2c**)
3	D-Galactose (**3a**)	EtSH	 (**3b**)	40	88	 (**3c**)
4	D-Mannose (**4a**)	EtSH	 (**4b**)	40	82	 (**4c**)
5	D-Ribose (**5a**)	EtSH	 (**5b**)	30	72	 (**5c**)
6	D-Xylose (**6a**)	EtSH	 (**6b**)	35	86	 (**6c**)
7	L-Xylose (**7a**)	EtSH	 (**7b**)	35	83[c]	 (**7c**)
8	L-Rhamnose (**8a**)	EtSH	 (**8b**)	45	86	 (**8c**)
9	L-Fucose (**9a**)	EtSH	 (**9b**)	45	89[c]	 (**9c**)
10	L-Arabinose (**1a**)	PrSH	 (**10b**)	40	91	 (**10c**)
11	D-Glucose (**2a**)	PrSH	 (**11b**)	60	88	 (**11c**)
12	D-Galactose (**3a**)	PrSH	 (**12b**)	55	83	 (**12c**)

(*continued on next page*)

Table 2 (*continued*)

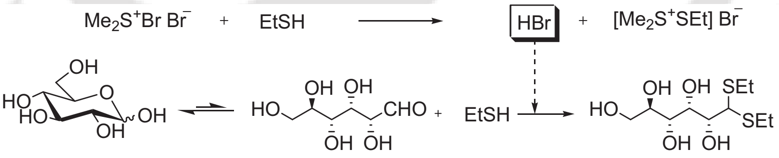
Entry	Substrate	Thiol	Product	Time (min)	Yield[b] (%)	Per-O-acetylated product[d]
13	D-Mannose (**4a**)	PrSH	 (**13b**)	60	81	 (**13c**)
14	 (**10a**)	EtSH	 (**14b**)	60	84[c]	–

[a] Sugar (20 mmol) was mixed with the thiol (10 mL) and the catalyst, BDMS (134 mg, 0.6 mmol) was added in two portions.
[b] Isolated yield.
[c] Reactions were carried out with 2 mmol of sugars.
[d] per-O-acetylations were performed with 2 mmol of dithioacetal derivatives of sugars using $HClO_4–SiO_2$.



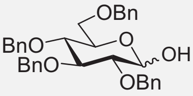
1c **3c**

Figure 1. Crystal structures of **1c** and **3c** (CCDC Nos.: 687605 and 687604).



Scheme 2. Plausible mechanism for the formation of D-glucose diethyl dithioacetal.

Table 3
Comparison of BDMS with other catalysts for the preparation of diethyl dithioacetal derivatives of sugars

Entry	Substrate	Catalyst	Catalyst (mol %)	Time (h)	Yield[a] (%)
1	L-Arabinose	Concd HCl	Excess	0.50	87[31]
		BDMS	3	0.50	96
2	D-Glucose	Concd HCl	Excess	0.50	63[32]
		BDMS	3	0.75	92
3	D-Galactose	Concd HCl	Excess	0.50	47[32]
		BDMS	3	0.75	88
4		TFA	Excess	12	77[16]
		BDMS	3	1	84

[a] Isolated yields.

Kα radiation (λ = 0.71073 Å) at 298 K, and elemental analyses were performed using a Perkin–Elmer CHNS/O 2400 Series II analyzer at the Indian Institute of Technology, Guwahati.

3.2. Preparation of bromodimethylsulfonium bromide (BDMS)

Methyl sulfide (Me_2S, 1.83 mL, 25 mmol) was dissolved in 5 mL of dry CH_2Cl_2 in a 150 mL standard joint conical flask. Br_2 (1.3 mL, 25 mmol) dissolved in 5 mL of dry CH_2Cl_2 was added slowly at ice-bath temperature over a period of 5 min. During the addition, light-orange crystals of bromodimethylsulfonium bromide began to separate out. After the addition of bromine was completed, the crystals of bromodimethylsulfonium bromide were collected by filtration. The solid material was then washed with dry hexane and dried under vacuum to give the crystalline product (4.3 g in 77%); mp 80 °C.

3.3. Typical experimental procedure for the preparation of L-arabinose diethyl dithioacetal (1b)

To an ice-cold stirring suspension of L-arabinose (**1a**, 3.02 g, 20.0 mmol) in EtSH (10 mL, 135 mmol), BDMS (0.134 g, 0.604 mmol) was added in two portions after an interval of 10 min. Stirring was continued, and after completion of the reaction, the excess EtSH (6.4 mL, 86 mmol) was removed by short-path distillation. *Note:* the recovered EtSH can be reused. The crude residue was dissolved in hot water (30 mL) and neutralized with solid $NaHCO_3$. After cooling, the solid product L-arabinose diethyl dithioacetal (**1b**) separated out and it was filtered off and dried to give 4.91 g of **1b** (96%) as a white solid: mp 124–126 °C, lit.[31] 127–128.7 °C; $[\alpha]_D^{25}$ −8.4 (*c* 1.0, H_2O).

3.4. Typical experimental protocol for 2,3,4,5-tetra-*O*-acetyl-L-arabinose diethyl dithioacetal (1c)[28]

A suspension of L-arabinose diethyl dithioacetal (**1b**, 0.512 g, 2.00 mmol) in Ac_2O (0.94 mL, 10.0 mmol) was placed in an ice bath and stirred. To the cold suspension of the reaction mixture was added $HClO_4$–SiO_2 (50 mg), and stirring was continued. After completion of the reaction (monitored by TLC), the reaction mixture was passed through a Celite pad and washed with toluene. The crude reaction mixture was further co-evaporated with toluene (2 × 10 mL) to remove traces of HOAc, and the crude product was purified by column chromatography on silica gel using 3:1 hexane–EtOAc to furnish 2,3,4,5-tetra-*O*-acetyl-L-arabinose diethyl dithioacetal (**1c**) as a colorless syrupy liquid, which was recrystallized from ethanol to give a colorless crystalline solid: mp 84 °C; $[\alpha]_D^{25}$ −34 (*c* 1.0, MeOH); IR (KBr): ν 1738, 1371, 1229 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ 5.72 (dd, 1H, *J* = 8.0, 2.8 Hz, H-3), 5.27 (dd, 1H, *J* = 8.0, 2.8 Hz, H-2), 5.13–5.09 (m, 1H, H-4), 4.26 (dd, 1H, *J* = 12.4, 2.8 Hz, H-5), 4.03 (dd, 1H, *J* = 12.4, 5.6 Hz, H-5′), 3.89 (d, 1H, *J* = 8.0 Hz, H-1), 2.76–2.58 (m, 4H, 2 × SCH_2CH_3), 2.11 (s, 3H, $COCH_3$), 2.10 (s, 3H, $COCH_3$), 2.04 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$), 1.23 (t, 3H, *J* = 7.6 Hz, SCH_2CH_3), 1.21 (t, 3H, *J* = 7.6 Hz, SCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$): δ 170.9, 170.2, 170.1, 169.7, 70.9, 69.7, 69.0, 62.3, 51.9, 25.0, 21.12, 21.06, 20.9, 14.5, 14.2. Anal. Calcd for $C_{17}H_{28}O_8S_2$ (424.54): C, 48.10; H, 6.65; S, 15.11. Found: C, 48.00; H, 6.44; S, 14.95.

3.5. D-Glucose diethyl dithioacetal (2b)

White solid: mp 125–126 °C (recrystallized from hot water), lit.[12] 127 °C, lit.[33] 123–124 °C; $[\alpha]_D^{25}$ −28 (*c* 1.0, H_2O).

3.6. 2,3,4,5,6-Penta-*O*-acetyl-D-glucose diethyl dithioacetal (2c)

White syrup: (lit.[28] 45–47 °C) $[\alpha]_D^{25}$ +13.6 (*c* 1.0, $CHCl_3$); IR (KBr): ν 1750, 1372, 1226 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ 5.73 (dd, 1H, *J* = 7.2, 2.8 Hz, H-3), 5.40 (dd, 1H, *J* = 8.4, 2.8 Hz, H-4), 5.26 (dd, 1H, *J* = 7.2, 4.0 Hz, H-2), 5.05–5.02 (m, 1H, H-5), 4.21 (dd, 1H, *J* = 12.4, 2.8 Hz, H-6), 4.10 (dd, 1H, *J* = 12.4, 4.8 Hz, H-6′), 4.04 (d, 1H, *J* = 4.0 Hz, H-1), 2.80–2.48 (m, 4H, 2 × SCH_2CH_3), 2.12 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 2.05 (s, 3H, $COCH_3$), 2.03 (s, 3H, $COCH_3$), 2.01 (s, 3H, $COCH_3$), 1.30 (t, 3H, *J* = 8.0 Hz, SCH_2CH_3), 1.20 (t, 3H, *J* = 7.6 Hz, SCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$): δ 170.5, 170.2, 169.9, 169.8, 169.6, 72.1, 70.0, 68.4, 68.3, 61.4, 50.6, 25.6, 24.8, 20.8, 20.7, 20.6, 20.5, 14.5, 14.3. Anal. Calcd for $C_{20}H_{32}O_{10}S_2$ (496.60): C, 48.37; H, 6.49; S, 12.91. Found: C, 48.29; H, 6.43; S, 12.82.

3.7. D-Galactose diethyl dithioacetal (3b)

White needles: mp 142–143 °C (recrystallized from MeOH), lit.[34] 138–140 °C; $[\alpha]_D^{25}$ −3.6 (*c* 1.0, H_2O).

3.8. 2,3,4,5,6-Penta-*O*-acetyl-D-galactose diethyl dithioacetal (3c)

Colorless solid: mp 78–80 °C (recrystallized from ethanol), lit.[14] 77.5–78.5 °C, lit.[33] 56–57 °C; $[\alpha]_D^{25}$ +11.6 (*c* 1.0, MeOH); IR (KBr): ν 1747, 1372, 1220 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ 5.75 (dd, 1H, *J* = 9.6, 1.6 Hz, H-3), 5.22 (dd, 1H, *J* = 9.6, 2.0 Hz, H-4), 5.19–5.16 (m, 1H, H-5), 5.14 (dd, 1H, *J* = 8.0, 1.6 Hz, H-2), 4.26 (dd, 1H, *J* = 12.0, 5.2 Hz, H-6), 3.83 (dd, 1H, *J* = 12.0, 7.2 Hz, H-6′), 3.80 (d, 1H, *J* = 6.8 Hz, H-1), 2.67–2.54 (m, 4H, 2 × SCH_2CH_3), 2.11 (s, 3H, $COCH_3$), 2.09 (s, 3H, $COCH_3$), 2.08 (s, 6H, 2 × $COCH_3$), 1.99 (s, 3H, $COCH_3$), 1.22 (t, 3 H, *J* = 7.2 Hz, SCH_2CH_3), 1.19 (t, 3H, *J* = 7.2 Hz, SCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$): δ 170.6, 170.5, 170.3, 169.9, 169.6, 70.5, 68.4, 68.1, 67.9, 62.3, 52.0, 28.9, 25.4, 25.1, 21.1, 20.9, 20.8, 14.4, 14.2. Anal. Calcd for $C_{20}H_{32}O_{10}S_2$ (496.60): C, 48.37; H, 6.49; S, 12.91. Found: C, 48.29; H, 6.41; S, 12.79.

3.9. D-Mannose diethyl dithioacetal (4b)

White solid: mp 135–136 °C (recrystallized from water); $[\alpha]_D^{25}$ +25.2 (*c* 1.0, H_2O).

3.10. 2,3,4,5,6-Penta-*O*-acetyl-D-mannose diethyl dithioacetal (4c)

White syrup: $[\alpha]_D^{25}$ +30 (*c* 0.35, MeOH); IR (KBr): ν 1749, 1371, 1218 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ 5.75 (dd, 1H, *J* = 7.2, 1.6 Hz, H-3), 5.50 (dd, 1H, *J* = 9.2, 2.0 Hz, H-4), 5.29 (dd, 1H, *J* = 7.2, 5.6 Hz, H-2), 5.09–5.06 (m, 1H, H-5), 4.22 (dd, 1H, *J* = 12.4, 2.8 Hz, H-6), 4.08 (dd, 1H, *J* = 12.4, 5.2 Hz, H-6′), 3.90 (d, 1H, *J* = 5.6 Hz, H-1), 2.76–2.60 (m, 4H, 2 × SCH_2CH_3), 2.10 (s, 3H, $COCH_3$), 2.09 (s, 6H, 2 × $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.06 (s, 3H, $COCH_3$), 1.28 (t, 3H, *J* = 7.2 Hz, SCH_2CH_3), 1.24 (t, 3H, *J* = 7.6 Hz, SCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$): δ 170.8, 170.7, 170.1, 169.9, 71.2, 69.2, 68.2, 67.4, 62.0, 51.5, 25.6, 25.3, 21.03, 21.0, 20.9, 14.4, 14.3. Anal. Calcd for $C_{20}H_{32}O_{10}S_2$ (496.60): C, 48.37; H, 6.49; S, 12.91. Found: C, 48.30; H, 6.41; S, 12.82.

3.11. D-Ribose diethyl dithioacetal (5b)

Cream-colored solid: mp 78–80 °C (recrystallized from water), lit.[33] 72–73 °C; $[\alpha]_D^{25}$ −38.2 (*c* 1.0, H_2O).

3.12. 2,3,4,5-Tetra-*O*-acetyl-D-ribose diethyl dithioacetal (5c)

Colorless solid: mp 47–48 °C (recrystallized from ethanol), lit.[33] 43–44 °C; $[\alpha]_D^{25}$ +29.6 (*c* 1.0, MeOH); IR (KBr): ν 1749, 1372, 1220 cm^{-1}; ^{1}H NMR (400 MHz; CDCl$_3$): δ 5.64 (dd, 1H, *J* = 6.0, 4.0 Hz, H-3), 5.40–5.37 (m, 1H, H-4), 5.32 (t, 1H, *J* = 6.0 Hz, H-2), 4.42 (dd, 1H, *J* = 12.0, 2.8 Hz, H-5), 4.13 (dd, 1H, *J* = 12.0, 7.6 Hz, H-5′), 3.95 (d, 1H, *J* = 6.0 Hz, H-1), 2.76–2.58 (m, 4H, 2 × SCH_2CH$_3$), 2.15 (s, 3H, COCH_3), 2.07 (s, 6H, 2 × COCH_3), 2.04 (s, 3H, COCH_3), 1.25 (t, 3H, *J* 7.2 Hz, SCH$_2$CH_3), 1.24 (t, 3H, *J* = 7.6 Hz, SCH$_2$CH_3); ^{13}C NMR (100 MHz; CDCl$_3$): δ 170.7, 169.9, 169.7, 169.3, 72.1, 71.2, 69.8, 62.2, 51.6, 25.13, 25.07, 20.9, 20.8, 20.7, 14.3, 14.1. Anal. Calcd for C$_{17}$H$_{28}$O$_8$S$_2$ (424.53): C, 48.10; H, 6.65; S, 15.11. Found: C, 48.03; H, 6.56; S, 14.92.

3.13. D-Xylose diethyl dithioacetal (6b)

White solid: mp 66–68 °C (recrystallized from toluene), lit.[10] 63–65 °C.

3.14. 2,3,4,5-Tetra-*O*-acetyl-D-xylose diethyl dithioacetal (6c)

Colorless solid: mp 48–49 °C (recrystallized from ethanol); $[\alpha]_D^{25}$ +9.9 (*c* 0.6, MeOH); IR (KBr): ν 1751, 1372, 1219 cm^{-1}; ^{1}H NMR (400 MHz; CDCl$_3$): δ 5.71 (dd, 1H, *J* = 6.0, 4.4 Hz, H-3), 5.33–5.31 (m, 1H, H-4), 5.30 (dd, 1H, *J* = 6.0, 5.2 Hz, H-2), 4.29 (dd, 1H, *J* = 12.0, 4.0 Hz, H-5), 4.00 (dd, 1H, *J* = 12.0, 6.8 Hz, H-5′),3.92 (d, 1H, *J* = 5.2 Hz, H-1), 2.54–2.73 (m, 4H, 2 × SCH_2CH$_3$), 2.10 (s, 3H, COCH_3), 2.09 (s, 3H, COCH_3), 2.07 (s, 3H, COCH_3), 2.04 (s, 3H, COCH_3), 1.26 (t, 3H, *J* = 7.2 Hz, SCH$_2$CH_3), 1.21 (t, 3H, *J* = 7.2 Hz, SCH$_2$CH_3); ^{13}C NMR (100 MHz; CDCl$_3$): δ 170.5, 170.4, 170.1, 169.7, 71.9, 70.5, 69.4, 62.2, 51.1, 25.4, 25.2, 20.8, 20.7, 14.3. Anal. Calcd for C$_{17}$H$_{28}$O$_8$S$_2$ (424.53): C, 48.10; H, 6.65; S, 15.11. Found: C, 48.00; H, 6.49; S, 14.88.

3.15. L-Xylose diethyl dithioacetal (7b)

White solid: mp 65–67 °C (recrystallized from toluene).

3.16. 2,3,4,5-Tetra-*O*-acetyl-L-xylose diethyl dithioacetal (7c)

Colorless solid; mp 48–50 °C (recrystallized from ethanol); $[\alpha]_D^{25}$ −9.8 (*c* 0.6 in CHCl$_3$); IR (KBr): 1751, 1373, 1221 cm^{-1}; ^{1}H and ^{13}C NMR are same as that of 2,3,4,5-tetra-*O*-acetyl-D-xylose diethyl dithioacetal (**6c**). Anal. Calcd for C$_{17}$H$_{28}$O$_8$S$_2$ (424.53): C, 48.10; H, 6.65; S, 15.11. Found: C, 47.98; H, 6.54; S, 14.98.

3.17. L-Rhamnose diethyl dithioacetal (8b)

White solid: mp 148–150 °C (recrystallized from ethanol) lit.[35] 137–138 °C; $[\alpha]_D^{25}$ −10.1 (*c* 1.0, MeOH).

3.18. 2,3,4,5-Tetra-*O*-acetyl-L-rhamnose diethyl dithioacetal (8c)

Syrup: $[\alpha]_D^{25}$ −44.6 (*c* 1.0, MeOH); IR (KBr): ν 1751, 1371, 1224 cm^{-1}; ^{1}H NMR (400 MHz; CDCl$_3$): δ 5.78 (dd, 1H, *J* = 7.6, 1.6 Hz, H-3), 5.28 (dd, 1H, *J* = 7.6, 4.4 Hz, H-2), 5.23 (dd, 1H, *J* = 8.4, 1.6 Hz, H-4), 4.92–4.85 (m, 1H, H-5), 3.83 (d, 1H, *J* = 4.4 Hz, H-1), 2.72–2.58 (m, 4H, 2 × SCH_2CH$_3$), 2.08 (s, 3H, COCH_3), 2.07 (s, 3H, COCH_3), 2.06 (s, 3H, COCH_3), 2.03 (s, 3H, COCH_3), 1.23 (t, 3H, *J* = 7.6 Hz, SCH$_2$CH_3), 1.22 (t, 3H, *J* = 7.2 Hz, SCH$_2$CH_3), 1.16 (d, 3H, *J* = 6.4 Hz, CH_3); ^{13}C NMR (100 MHz; CDCl$_3$): δ 170.4, 170.1, 169.9, 169.6, 71.1, 71.0, 69.0, 67.2, 51.5, 25.6, 25.3, 21.2, 21.0, 20.9, 16.5, 14.3, 14.1. Anal. Calcd for C$_{18}$H$_{30}$O$_8$S$_2$ (438.56): C, 49.30; H, 6.89; S, 14.62. Found: C, 49.21; H, 6.80; S, 14.49.

3.19. L-Fucose diethyl dithioacetal (9b)

White solid: mp 168–170 °C (recrystallized from ethanol) lit.[35] 167–168 °C.

3.20. 2,3,4,5-Tetra-*O*-acetyl-L-fucose diethyl dithioacetal (9c)

Colorless solid: mp 81–82 °C (recrystallized from ethanol); $[\alpha]_D^{25}$ +7.7 (*c* 0.39, MeOH); IR (KBr): ν 1748, 1372, 1212 cm^{-1}; ^{1}H NMR (400 MHz; CDCl$_3$): δ 5.80 (d, 1H, *J* = 9.6 Hz, H-3); 5.19 (dd, 1H, *J* = 8.4, 2.0 Hz, H-2), 5.07 (dd, 1H, *J* = 9.6, 2.0 Hz, H-4), 4.96–4.90 (m, 1H, H-5), 3.83 (d, 1H, *J* = 8.4 Hz, H-1), 2.76–2.52 (m, 4H, 2 × SCH_2CH$_3$), 2.12 (s, 6H, 2 × COCH_3), 2.10 (s, 3H, COCH_3), 2.09 (s, 3H, COCH_3), 1.24 (t, 3H, *J* = 7.6 Hz, SCH$_2$CH_3), 1.21 (t, 3H, *J* = 7.6 Hz, SCH$_2$CH_3), 1.14 (d, 3H, *J* = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz; CDCl$_3$): δ 170.7, 170.4, 169.6, 71.4, 70.8, 68.7, 67.5, 52.2, 25.4, 25.2, 21.3, 21.2, 20.9, 16.6, 14.5, 14.2. Anal. Calcd for C$_{18}$H$_{30}$O$_8$S$_2$ (438.56): C, 49.30; H, 6.89; S, 14.62. Found: C, 49.22; H, 6.71; S, 14.51.

3.21. L-Arabinose dipropyl dithioacetal (10b)

White needles: mp 138–139 °C (recrystallized from 3:1:1 H$_2$O–EtOH–EtOAc); $[\alpha]_D^{25}$ +13.3 (*c* 1.0, MeOH).

3.22. 2,3,4,5-Tetra-*O*-acetyl-L-arabinose dipropyl dithioacetal (10c)

Syrup: $[\alpha]_D^{25}$ −35 (*c* 1.0, MeOH); IR (KBr): ν 1749, 1372, 1217 cm^{-1}; ^{1}H NMR (400 MHz; CDCl$_3$): δ 5.74 (dd, 1H, *J* = 8.0, 2.8 Hz, H-3), 5.26 (dd, 1H, *J* = 8.4, 2.8 Hz, H-2), 5.13–5.10 (m, 1H, H-4), 4.27 (dd, 1H, *J* = 12.4, 3.2 Hz, H-5), 4.01 (dd, 1H, *J* = 12.4, 6.0 Hz, H-5′), 3.86 (d, 1H, *J* = 8.4 Hz, H-1), 2.74–2.50 (m, 4H, 2 × SCH_2CH$_2$), 2.12 (s, 3H, COCH_3), 2.11 (s, 3H, COCH_3), 2.06 (s, 3H, COCH_3), 2.05 (s, 3H, COCH_3), 1.63–1.56 (m, 4H, 2 × SCH$_2$CH_2), 1.01–0.96 (m, 6H, 2 × SCH$_2$CH$_2$CH_3); ^{13}C NMR (100 MHz; CDCl$_3$): δ 170.8, 170.2, 170.0, 169.7, 70.9, 69.6, 68.9, 62.3, 52.4, 33.0, 32.9, 22.7, 22.5, 21.1, 21.0, 20.9, 13.8, 13.6. Anal. Calcd for C$_{19}$H$_{32}$O$_8$S$_2$ (452.59): C, 50.42; H, 7.13; S, 14.17. Found: C, 50.31; H, 7.00; S, 14.06.

3.23. D-Glucose dipropyl dithioacetal (11b)

Light yellow solid: mp 148–150 °C (recrystallized from 3:1:1 H$_2$O–EtOH–EtOAc), lit.[36] 101–103 °C; $[\alpha]_D^{25}$ −6.4 (*c* 1.0, MeOH).

3.24. 2,3,4,5,6-Penta-*O*-acetyl-D-glucose dipropyl dithioacetal (11c)

Syrup: $[\alpha]_D^{25}$ −6.3 (*c* 1.0, MeOH); IR (KBr): ν 1747, 1369, 1215 cm^{-1}; ^{1}H NMR (400 MHz; CDCl$_3$): δ 5.74 (dd, 1H, *J* = 7.6, 2.8 Hz, H-3), 5.40 (dd, 1H, *J* = 8.4, 2.8 Hz, H-4), 5.25 (dd, 1H, *J* = 7.6, 4.0 Hz, H-2), 5.05–5.01 (m, 1H, H-5), 4.20 (dd, 1H, *J* = 12.4, 3.2 Hz, H-6), 4.11 (dd, 1 H, *J* = 12.4, 4.8 Hz, H-6′), 4.01 (d, 1H, *J* = 4.4 Hz, H-1), 2.82–2.74 (m, 1H, SCHH'CH$_2$), 2.66–2.58 (m, 1H, SCHH'CH$_2$), 2.56–2.50 (m, 1H, SCHH'CH$_2$), 2.78–2.40 (m, 1H, SCHH'CH$_2$), 2.12 (s, 3H, COCH_3), 2.07 (s, 3H, COCH_3), 2.06 (s, 3H, COCH_3), 2.04 (s, 3H, COCH_3), 2.02 (s, 3H, COCH_3), 1.69–1.51 (m, 4H, 2 × SCH$_2$CH_2), 1.02 (t, 3H, *J* = 7.6 Hz, SCH$_2$CH$_2$CH_3), 0.95 (t, 3H, *J* = 7.2 Hz, SCH$_2$CH$_2$CH_3); ^{13}C NMR (100 MHz; CDCl$_3$): δ 170.7, 170.4, 170.04, 170.03, 169.8, 72.3, 70.02, 68.5, 68.4, 61.6, 51.3, 33.8, 33.1, 22.7, 20.9, 20.89, 20.8, 20.7, 13.6. Anal. Calcd for C$_{22}$H$_{36}$O$_{10}$S$_2$ (524.65): C, 50.37; H, 6.92; S, 12.22. Found: C, 50.28; H, 6.81; S, 12.01.

3.25. D-Galactose dipropyl dithioacetal (12b)

White needles: mp 151–154 °C (recrystallized from 3:1:1 H_2O–EtOH–EtOAc); $[\alpha]_D^{25}$ +10.8 (*c* 1.0, MeOH).

3.26. 2,3,4,5,6-Penta-*O*-acetyl-D-galactose dipropyl dithioacetal (12c)

Syrup: $[\alpha]_D^{25}$ +6.6 (*c* 0.80, MeOH); IR (KBr): ν 1750, 1371, 1215 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ 5.79 (dd, 1H, *J* = 9.6, 2.0 Hz, H-3), 5.24 (d, 1H, *J* = 9.6, 2.0 Hz, H-4), 5.20–5.17 (m, 1H, H-5), 5.15 (dd, 1H, *J* = 8.4, 2.0 Hz, H-2), 4.28 (dd, 1H, *J* = 12.0, 5.2 Hz, H-6), 3.84 (dd, 1H, *J* = 12.0, 7.2 Hz, H-6′), 3.79 (d, 1H, *J* = 8.4 Hz, H-1), 2.70–2.60 (m, 4H, 2 × SCH_2CH_2), 2.13 (s, 3H, $COCH_3$), 2.11 (s, 6H, 2 × $COCH_3$), 2.10 (s, 3H, $COCH_3$), 2.02 (s, 3H, $COCH_3$), 1.64–1.52 (m, 4H, 2 × SCH_2CH_2), 0.99 (t, 3H, *J* = 7.6 Hz, $SCH_2CH_2CH_3$), 0.98 (t, 3H, *J* = 7.2 Hz, $SCH_2CH_2CH_3$); ^{13}C NMR (100 MHz; $CDCl_3$): δ 170.7, 170.6, 170.4, 170.1, 169.7, 70.7, 68.5, 68.2, 68.0, 62.4, 52.7, 33.6, 33.1, 22.7, 22.6, 21.2, 21.0, 20.9, 13.8, 13.7. Anal. Calcd for $C_{22}H_{36}O_{10}S_2$ (524.65): C, 50.37; H, 6.92; S, 12.22. Found: C, 50.26; H, 6.85; S, 12.13.

3.27. D-Mannose dipropyl dithioacetal (13b)

White reddish needles: mp 130–132 °C (recrystallized from 3:1:1 H_2O–EtOH–EtOAc); $[\alpha]_D^{25}$ +4.3 (*c* 1.0, MeOH).

3.28. 2,3,4,5,6-Penta-*O*-acetyl-D-mannose dipropyl dithioacetal (13c)

Syrup: $[\alpha]_D^{25}$ +26.1 (*c* 1.2, MeOH); IR (KBr): ν 1750, 1372, 1218 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ 5.74 (dd, 1H, *J* = 7.2, 1.6 Hz, H-3), 5.50 (dd, 1H, *J* = 9.2, 1.6 Hz, H-4), 5.28 (dd, 1H, *J* = 7.2, 6.0 Hz, H-2), 5.09–5.05 (m, 1H, H-5), 4.20 (dd, 1H, *J* = 12.8, 2.4 Hz, H-6), 4.08 (dd, 1H, *J* = 12.8, 5.2 Hz, H-6′), 3.87 (d, 1H, *J* = 6.0 Hz, H-1), 2.72–2.64 (m, 2H, SCH_2CH_2), 2.62–2.53 (m, 2H, SCH_2CH_2), 2.10 (s, 3H, $COCH_3$), 2.08 (s, 3H, $COCH_3$), 2.07 (s, 6H, 2 × $COCH_3$), 2.05 (s, 3H, $COCH_3$), 1.66–1.54 (m, 4H, 2 × SCH_2CH_2), 1.01 (t, 3H, *J* = 7.6, $SCH_2CH_2CH_3$), 0.98 (t, 3H, *J* = 7.6 Hz, $SCH_2CH_2CH_3$); ^{13}C NMR (100 MHz; $CDCl_3$): δ 170.8, 170.1, 169.9, 71.4, 69.2, 68.2, 67.4, 62.0, 52.1, 33.5, 33.2, 22.6, 22.5, 21.0, 20.9, 13.7. Anal. Calcd for $C_{22}H_{36}O_{10}S_2$ (524.65): C, 50.37; H, 6.92; S, 12.22. Found: C, 50.29; H, 6.80; S, 11.97.

3.29. 2,3,4,6-Tetra-*O*-benzyl-D-glucose diethyl dithioacetal (14b)

White syrup: $[\alpha]_D^{25}$ +27 (*c* 1.0, MeOH), lit.[16] $[\alpha]_D^{25}$ +20.0 (*c* 0.97, $CHCl_3$), lit.[37] $[\alpha]_D^{25}$ +19.5 (*c* 2.3, $CHCl_3$); IR (KBr): ν 3492, 1454, 1100 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$): δ 7.38–7.23 (m, 20H, ArH), 4.89 (d, 1H, *J* = 11.2 Hz, CHH), 4.80 (d, 1H, *J* = 11.2, CHH), 4.79 (d, 1H, *J* = 11.6, CHH), 4.67 (d, 1H, *J* = 11.6 Hz, CHH), 4.59–4.49 (m, 4H, 2 × CH_2), 4.27 (dd, 1H, *J* = 6.8, 3.6 Hz, H-3), 4.14 (dd, 1H, *J* = 6.8, 4.0 Hz, H-2), 4.15–4.03 (m, 1H, H-5), 3.93 (d, 1H, *J* = 4.0 Hz, H-1), 3.71 (dd, 1H, *J* = 6.8, 3.6 Hz, H-4), 3.66 (dd, 1H, *J* = 10.0, 4.0 Hz, H-6), 3.61 (dd, 1H, *J* = 10.0, 5.6 Hz, H-6′), 3.08 (d, 1H, *J* = 5.2 Hz, OH), 2.66 (q, 2H, *J* = 7.6 Hz, SCH_2CH_3), 2.60–2.50 (m, 2H, SCH_2CH_3), 1.18 (t, 3H, *J* = 7.2 Hz, SCH_2CH_3), 1.17 (t, 3H, *J* = 7.6 Hz, SCH_2CH_3); ^{13}C NMR (100 MHz; $CDCl_3$): δ 138.7, 138.4, 138.1, 128.6, 128.4, 128.3, 128.2, 128.03, 128.0, 127.96, 127.9, 127.6, 82.9, 80.3, 77.5, 75.5, 75.1, 73.7, 73.0, 71.6, 71.1, 54.0, 25.7, 25.5, 14.6. Anal. Calcd for $C_{38}H_{36}O_5S_2$ (646.28); C, 70.55; H, 7.17; S, 9.91. Found: C, 70.46; H, 7.03; S, 9.82.

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Supplementary data

Complete crystallographic data of **1c** and **3c** for the structural analyses have been deposited with the Cambridge Crystallographic Data Centre. The CCDC Nos. are 687605 and 687604, respectively, for **1c** and **3c**. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk). Supplementary data (CIF files, ^1H NMR, ^{13}C NMR) associated with this article can be found, in the online version, at doi:10.1016/j.carres.2010.07.044.

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Note

A simple and convenient synthetic protocol for O-isopropylidenation of sugars using bromodimethylsulfonium bromide (BDMS) as a catalyst

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ABSTRACT

Various *O*-isopropylidene derivatives of sugars and acyclic sugars were obtained in very good yields on reaction with acetone at room temperature with a catalytic amount of bromodimethylsulfonium bromide (BDMS). These *O*-isopropylidene derivatives can also be prepared in good yields on reaction with 2,2-dimethoxypropane (DMP) in acetonitrile using the same catalyst in shorter reaction times. Some of the advantages of this method are high effectiveness, a nonaqueous workup procedure, economic viability, and good yields.

The *O*-isopropylidene derivatives of sugars,[1] which are also known as acetonides of aldoses and ketoses, have been used extensively in carbohydrate chemistry to selectively protect the hydroxyl groups of different sugars.[2] They serve as valuable building blocks in carbohydrate chemistry, such as glycosyl acceptors[3] and glycosyl donors.[4] In addition, many of them have been used as key starting materials for natural product synthesis.[5,6] For example, 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol (**15**) has been used in the total synthesis of (+)-7-*epi*-goniofufurone[7] and other analogues. Similarly, 2,3:4,5-di-*O*-isopropylidene-D-xylose diethyl dithioacetal (**22**) has been utilized for the total synthesis of (+)-phorboxazole A, a potent cytostatic agent.[8] Moreover, these sugar derivatives are also important materials for structural and conformational studies.[9] Interestingly, some of them also exhibit important pharmacological properties. For example, 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**12**) is well known for its anti-inflammatory and antipyretic activities with a very low toxicity.[10] Therefore, there is a continued research interest to prepare these compounds in significant quantities.

The O-isopropylidenation of a carbohydrate molecule is usually performed by using anhydrous acetone in the presence of an acid catalyst such as concentrated H_2SO_4 or anhydrous $ZnCl_2$.[11] In addition, the same transformations are also possible by employing other acetonide-forming agents such as 2,2-dimethoxypropane (DMP) in *N*,*N*-dimethylformamide (DMF)[12] or 2-methoxypropene (MP) in the presence of a trace amount of acid catalyst.[13] Over the years, a wide variety of catalysts have been explored for the synthesis of *O*-isopropylidene derivative of sugars such as iodine,[14] and many Lewis acidic metal salts namely $CuSO_4$,[15] $FeCl_3$,[16] $AlCl_3$,[17] and ceric ammonium nitrate (CAN).[18] In addition, various heterogeneous catalysts have also been employed, such as Zeolite HY,[19] montmorillonite clay,[20] triphenylphosphine polymer-bound/iodine complex,[21] and sulfuric acid immobilized on silica gel[22] as well as vanadyl triflate ($VO(OTf)_2{\cdot}xH_2O$).[23] However, some of these methods have certain drawbacks such as low yields, harsh,[19,22] and inert atmospheric reaction conditions.[21,23] Hence, there is a need to devise a simple and practical synthetic methodology for the preparation of these valuable derivatives on a large scale.

The synthetic utility of bromodimethylsulfonium bromide (BDMS) has been explored by us[24,25] as well as by others[26–28] as a brominating reagent as well as an efficient catalyst in various organic transformations. Recently, Ye and co-workers have demonstrated the usefulness of BDMS as a promoter for glycosylation reactions.[29] Very recently its application in various organic transformations has also been reviewed by us.[30] Earlier we have reported the preparation of *O*,*O*-acetals of various carbonyl compounds with 1,2-ethanediol or 1,3-propanediol using bromodimethylsulfonium bromide (BDMS).[31] However, the acetalization reaction with carbohydrate molecules was not studied by using BDMS as a catalyst. As part of our ongoing research project to develop a new synthetic methodology, we wish to report here a practical and efficient method for the synthesis of O-isopropylidenation of sugars at room temperature with bromodimethylsulfonium bromide (BDMS) as a new catalyst for these processes (Scheme 1).

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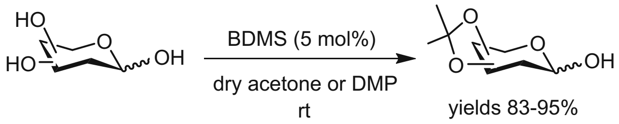
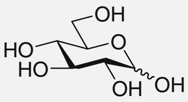
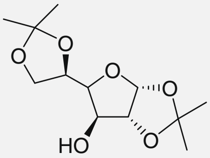
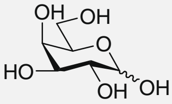
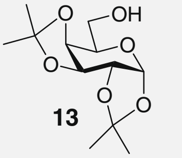
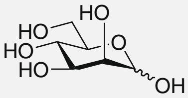
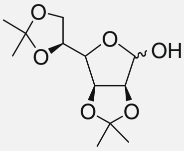
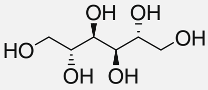
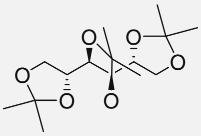
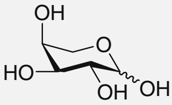
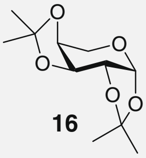
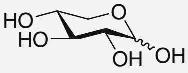
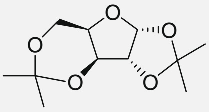


Scheme 1. O-Isopropylidenation of sugars.

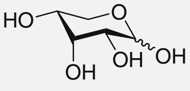
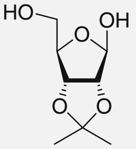
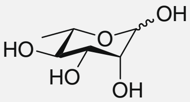
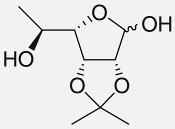
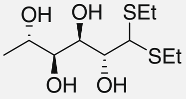
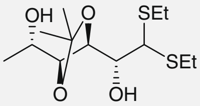
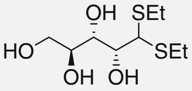
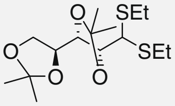
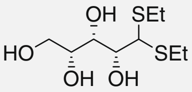
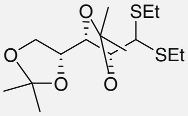
For our requirements, bromodimethylsulfonium bromide (BDMS) was prepared by following the literature procedure.[24] At the outset, we have tried to optimize the reaction conditions to obtain the desired *O*-isopropylidene derivatives. Using D-glucose (**1**) as a model substrate, after several trial reactions it was found that employing 5 mol % of BDMS provided the best results. Then a mixture of commercially available D-glucose (**1**, 2 mmol) in 10 mL of dry acetone was stirred in the presence of 5 mol % of the catalyst, and the product isolated from the reaction was 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**12**) in 84% yield. The product was characterized by its melting point, ^{1}H NMR, ^{13}C NMR spectra and specific rotation as well as by its elemental analysis. The spectral data were also compared with the earlier reported data.[21] Then the same reaction was carried out with 2,2-dimethoxypropane (DMP) in acetonitrile by employing the same amount of catalyst at room temperature. In this case we also obtained product **12** in 90% yield. The important feature of this modified reaction is that it took relatively much less reaction time as compared to that using dry acetone alone, which is shown in Table 1. From the outcome of the reactions, we conclude that only the thermodynamically controlled product was formed. Next, we have stud-

Table 1
Preparation of *O*-isopropylidene derivatives of sugars using bromodimethylsulfonium bromide (BDMS)

Entry	Substrate	Product	Time (h)	Method	Yield[a,b] (%)
1	 **1**	 **12**	10 4	A B	84 90
2	 **2**	 **13**	10 4	A B	85 91
3	 **3**	 **14**	2 1	A B	90 95
4	 **4**	 **15**	3 1	A B	86 89
5	 **5**	 **16**	10	A	86
6	 **6**	 **17**	2	A	91

(*continued on next page*)

Table 1 (*continued*)

Entry	Substrate	Product	Time (h)	Method	Yield[a,b] (%)
7	 **7**	 **18**	2	A	86
8	 **8**	 **19**	2	A	88
9	 **9**	 **20**	2	A	89
10	 **10**	 **21**	2	A	86
11	 **11**	 **22**	2	A	83

Method A: sugar (2 mmol) in dry acetone (10 mL) using BDMS (22 mg, 0.1 mmol).
Method B: sugar (2 mmol) in dry acetonitrile (10 mL) and 2,2-dimethoxypropane (1.0 mL, 8.14 mmol) using BDMS (22 mg, 0.1 mmol.)

[a] Isolated yield.

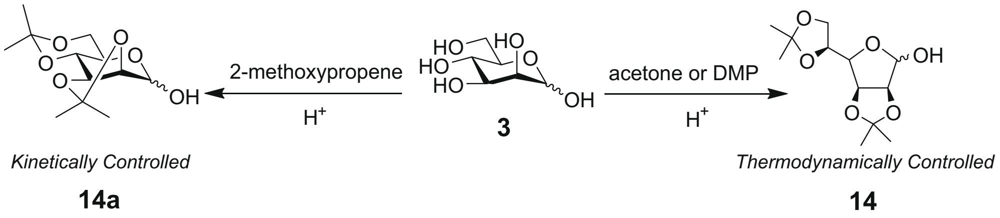
[b] All products were characterized by ^{1}H and ^{13}C NMR spectroscopy, optical rotation, and elemental analysis.

ied the reactions of D-galactose (**2**) with acetone as well as DMP using same mol % of the catalyst under identical reaction conditions. In both the cases, we obtained the thermodynamically controlled product, 1,2:3,4-di-*O*-isopropylidene-D-galactopyranose (**13**) in a yield of 85% and 91%, respectively. By encouraging results, D-mannose (**3**) was kept for isopropylidenation with acetone as well as with DMP individually under similar reaction conditions. The product was 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**14**) formed from both the reactions in good yields. The literature reveals[32] that the isopropylidenation of D-mannose (**3**) usually provides the thermodynamically controlled product **14** preferably on reaction with acetone or DMP in the presence of an acid catalyst instead of **14a** as shown in Scheme 2. However, recently, Rajput and Mukhopadhyay wrongly reported[22] the formation of 2,3:4,6-di-*O*-isopropylidene-D-mannopyranose (**14a**), a kinetically controlled product, using dry acetone in the presence of silica gel-supported sulfuric acid, although the spectral data closely matched with those of our compound.

To resolve the ambiguity of the structure, we have collected single crystal X-ray diffraction data of the product, and it was found that the structure of the product was that of 2,3:4,5-di-*O*-isopropylidene-D-mannofuranose (**14**) instead of kinetically controlled product **14a**, which is shown in Figure 1.

Likewise, D-mannitol (**4**) was converted into the corresponding 1,2:3,4:5,6-tri-*O*-isopropylidene-D-mannitol (**15**) in very good yields as shown in Table 1. Similarly, various sugars such as L-arabinose (**5**), D-xylose (**6**), D-ribose (**7**), and L-rhamnose (**8**) were converted to the corresponding *O*-isopropylidene derivatives **16–19** in good yields using dry acetone in the presence of 5 mol % of BDMS.

To show the generality of our protocol, a series of diethyl dithioacetal of sugars such as L-rhamnose (**9**), L-arabinose (**10**), and D-xylose (**11**) were further examined using identical conditions. The products **20**, **21**, and **22** were obtained in good yields from the corresponding dithioacetal derivatives. The results are summarized in Table 1. All these products were characterized by ^{1}H and ^{13}C NMR spectroscopy, as well as by elemental analysis. Interestingly, the diethyl dithioacetal group remains unaffected under these experimental conditions. Notably, we have also verified that the conversion of the various free sugars to the corresponding *O*-isopropylidene derivatives can be carried out in an even larger scale (100 mmol) without any difficulty by using 3 mol % of the catalyst



Scheme 2. Rationalization of acetonation product from D-mannose.

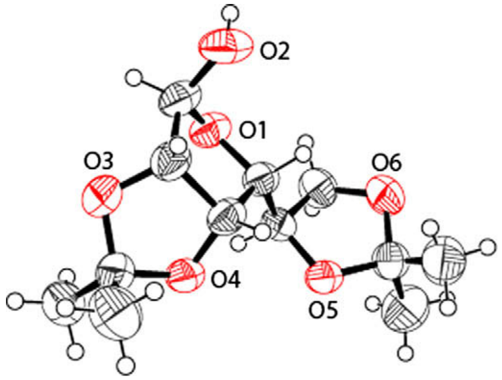


Figure 1. ORTEP plot of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**3b**) with atom numbering scheme.

instead of the heretofore required 5 mol %. For instance, when a mixture of D-mannitol (**4**) (18.22 g, 100 mmol) and dry acetone (400 mL) was treated with bromodimethylsulfonium bromide (0.670 g, 3 mmol), it was smoothly converted within 3 h to the *O*-isopropylidene derivative **15** in 92% yield. The following workup procedure was followed for the large-scale reaction. After completing the reaction, the reaction mixture was neutralized with solid $NaHCO_3$, and then it was passed through a Celite pad. Acetone was removed on a rotary evaporator, and the crude solid residue was recrystallized from ethanol to obtain the pure product. A total of 27.82 g of the pure product **15** was obtained from the above reaction. In this reaction, we have obtained a much better yield, and the reaction time is shorter than that with concentrated H_2SO_4.[7]

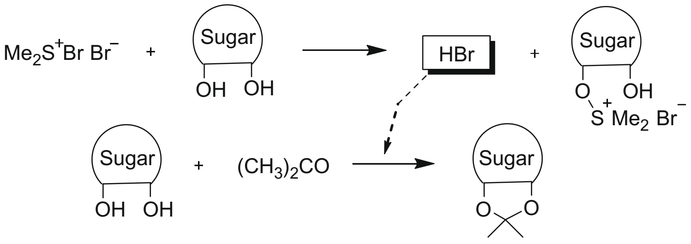
The formation of the *O*-isopropylidene products can be rationalized as follows: It has been proposed that bromodimethylsulfonium bromide may generate dry HBr in the medium upon reaction with the sugars. We believe that in situ-generated dry HBr catalyzes the O-isopropylidenation reaction of sugars or sugar derivatives into the corresponding *O*-isopropylidene derivatives (Scheme 3). It is also noted that the pH of the solution is ~2–3 during the reaction. The reaction of D-mannitol (**4**) and dry acetone was also examined with an equivalent amount of 48% aqueous HBr at room temperature. It was observed that under these conditions, not only provided a low yield (70%) of product, but also required much longer reaction time (5 h).

In summary, we have developed a simple, efficient, and catalytic method for the preparation of *O*-isopropylidene derivatives from free sugars as well as from other sugar derivatives by employing bromodimethylsulfonium bromide as a new catalyst for these processes. The notable advantages of the present protocol are good yields, clean reactions, and shorter reaction time. The reaction products can be obtained by direct recrystallization in case of solid products without going through tedious chromatographic separations. These processes involve nonaqueous workup procedures. Due to its operational simplicity, generality, and efficacy, this method is expected to have much wider applicability for the preparation of *O*-isopropylidene sugar derivatives on a large scale in the future.

1. Experimental

1.1. General methods

Starting material and reagents were purchased from commercial suppliers. Concentration under reduced pressure refers to the use of a rotary evaporator. Residual solvent was removed under high vacuum pressure. Analytical thin-layer chromatography was performed on precoated TLC plates (0.2 mm layer thickness of Silica Gel 60 F-254). Spots were visualized by staining with iodine vapor or MOSTAIN solution (by dissolving 20 g ammonium heptamolybdate and 0.4 g cerium(IV) sulfate in 400 mL of 10% H_2SO_4 solution). Column chromatography was carried out using silica gel (60–120 mesh, E. Merck or Qualigen). Melting points were determined on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 243 polarimeter at 25 °C. IR spectra were recorded on a Perkin–Elmer Spectrum One FTIR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian (400 MHz) spectrometer using TMS as internal reference. Chemical shifts are reported in parts per million (ppm) down field from TMS on the δ scale. ^1H NMR data are reported in the order of chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, and m = multiplet), number of protons, and coupling constant in hertz (Hz). Elemental analyses were performed by Perkin–Elmer CHNS/O-2400 analyzer.



Scheme 3. Proposed mechanism for O-isopropylidenation of carbohydrates using BDMS.

The X-ray diffraction data were collected on a Bruker Apex II smart diffractometer at 293 K.

Compounds **12**–**14**, **16**, and **18** have been reported previously,[21] and the spectral data are in good agreement with our data.

1.2. General procedures for the *O*-isopropylidenation

1.2.1. Method A: using anhydrous acetone

Bromodimethylsulfonium bromide (BDMS) (22 mg, 0.10 mmol) was added to a stirred solution of sugar (2 mmol) in dry acetone (10 mL) at room temperature. The reaction time was monitored by TLC as mentioned in Table 1. After completion of the reaction, the reaction mixture was concentrated in rotary evaporator. The crude residue was recrystallized in ethanol to obtain the desired product. However, in case of a liquid product or low-melting solid product, the crude residue was passed through a silica gel column to obtain the pure product.

1.2.2. Method B: using 2,2-dimethoxypropane

Into a mixture of sugar (2 mmol) in dry acetonitrile (10 mL) and 2,2-dimethoxypropane (1.0 mL, 8.14 mmol) was added bromodimethylsulfonium bromide (BDMS) (22 mg, 0.1 mmol) at room temperature. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated on a rotary evaporator. A similar procedure to that above (Section 1.2.1) was used to obtain the desired product in pure form.

1.2.3. 1,2:3,4:5,6-Tri-*O*-isopropylidene-D-mannitol (15)

White solid; mp 70–71 °C (lit[7] 68–70 °C); $[\alpha]_D^{25}$ +13.4 (*c* 1.0, MeOH); IR (KBr): 2983, 1371, 1256, 1064, 749 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.18–4.22 (m, 2H), 4.08 (dd, 2H, J = 6.4, 8.4 Hz), 3.99 (dd, 2H, J = 6.0, 8.4 Hz), 3.95 (dd, 2H, J = 2.0, 4.8 Hz), 1.43 (s, 6H, 2 × CH_3), 1.40 (s, 6H, 2 × CH_3), 1.36 (s, 6H, 2 × CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.4, 109.8, 79.6, 76.5, 66.5, 27.7, 26.7, 25.5. Anal. Calcd for $C_{15}H_{26}O_6$ (302.4): C, 59.58; H, 8.67. Found: C, 59.44; H, 8.58.

1.2.4. 1,2:3,5-Di-*O*-isopropylidene-D-xylofuranose (17)

White solid; mp 42–44 °C (lit[14] 44–46 °C); $[\alpha]_D^{25}$ +12.2 (*c* 1.5, H_2O) [lit[14] $[\alpha]_D^{25}$ +12.8 (*c* 2.6, H_2O)]; IR (KBr): 2990, 2938, 1375, 1200, 1165, 1081, 824 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.01 (d, 1H, J = 4.0 Hz, H-1), 4.53 (d, 1H, J = 4.0 Hz), 4.30 (d, 1H, J = 2.4 Hz), 4.08–4.10 (m, 2H), 4.03–4.04 (m, 1H), 1.50 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.39 (s, 3H, CH_3), 1.33 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 111.8, 105.3, 97.6, 84.8, 73.3, 71.7, 60.3, 29.0, 26.9, 26.3, 18.8. Anal. Calcd for $C_{11}H_{18}O_5$ (230.3): C, 57.38; H, 7.88. Found: C, 57.22; H, 7.78.

1.2.5. 2,3-*O*-Isopropylidene-L-rhamnofuranose (19)

Oil; $[\alpha]_D^{25}$ +16.2 (*c* 2.0, water) [lit[33] $[\alpha]_D^{25}$ +17.6 (*c* 2.8, H_2O)]; IR (Neat): 3434, 2923, 1489, 1071, 1021, 825 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.40 (d, 1H, J = 1.6 Hz, H-1), 4.87 (dd, 1H, J = 3.6, 6.0 Hz), 4.60 (d, 1H, J = 6.0 Hz), 4.05–4.00 (m, 1H), 3.93 (dd, 1H, J = 3.6, 7.2 Hz), 2.80 (br s, 1H, OH), 2.61 (d, 1H, J = 6.0 Hz, OH), 1.46 (s, 3H, CH_3), 1.32 (d, 3H, J = 6.0 Hz, CH_3), 1.31 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.9, 101.1, 85.6, 83.6, 80.3, 66.8, 26.1, 24.7, 20.6. Anal. Calcd for $C_9H_{16}O_5$ (204.22): C, 52.93; H, 7.90. Found: C, 52.81; H, 7.79.

1.2.6. 2,3-*O*-Isopropylidene-L-rhamnose diethyl dithioacetal (20)

Oil; $[\alpha]_D^{25}$ −30 (*c* 2.0, $CHCl_3$); IR (KBr): 3350, 2972, 2929, 1453, 1373, 1259, 1071, 873 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.19 (d, 1H, J = 2.0 Hz, H-1), 4.07 (dd, 1H, J = 7.2, 8.8 Hz, H-3), 3.84 (dd, 1H, J = 2.0, 8.8 Hz, H-2), 3.79 (dd, 1H, J = 6.4, 7.6 Hz), 3.71 (t, 1H, J = 7.6 Hz), 2.66–2.76 (m, 4H, 2 × SCH_2CH_3), 2.09 (s, 1H, OH), 1.38 (s, 6H, 2 × CH_3), 1.31 (d, 3H, J = 5.6 Hz, CH_3), 1.30 (t, 3H, J = 7.6 Hz, SCH_2CH_3), 1.29 (t, 3H, J = 7.2 Hz, SCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.2, 84.5, 80.0, 75.6, 69.3, 54.8, 27.0 (2C), 26.2, 25.9, 20.3, 14.9, 14.6. Anal. Calcd for $C_{13}H_{26}O_4S_2$ (312.5): C, 50.29; H, 8.44; S, 20.65. Found: C, 50.18; H, 8.36; S, 20.46.

1.2.7. 2,3:4,5-Di-*O*-isopropylidene-L-arabinose diethyl dithioacetal (21)

Oil; $[\alpha]_D^{25}$ −80.8 (*c* 1.0, MeOH) [lit[34] $[\alpha]_D^{25}$ −81 (*c* 1.0, MeOH)]; IR (KBr): 2986, 2931, 1455, 1372, 1219, 1064, 847 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.28–4.32 (m, 1H), 4.12–4.16 (m, 3H), 4.04 (d, 1H, J = 2.8 Hz, H-1), 3.97 (dd, 1H, J = 4.4, 8.4 Hz), 2.60–2.80 (m, 4H, 2 × SCH_2CH_3), 1.45 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.38 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.28 (t, 3H, J = 7.6 Hz, SCH_2CH_3), 1.26 (t, 3H, J = 7.6 Hz, SCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 110.2, 109.8, 84.6, 79.2, 77.2, 67.8, 52.4, 27.4, 27.2, 26.8, 25.3, 25.2, 25.0, 14.5, 14.4. Anal. Calcd for $C_{15}H_{28}O_4S_2$ (336.5): C, 53.54; H, 8.39; S, 19.06. Found: C, 53.41; H, 8.29; S, 18.88.

1.2.8. 2,3:4,5-Di-*O*-isopropylidene-D-xylose diethyl dithioacetal (22)

Oil; $[\alpha]_D^{25}$ −68.6 (*c* 2.0, Me_2CO) [lit[8] $[\alpha]_D^{25}$ −70.1 (*c* 2.6, Me_2CO)]; IR (KBr): 2981, 2935, 1453, 1370, 1229, 1063, 841 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 4.32–4.36 (m, 2H), 4.15 (dd, 1H, J = 3.2, 7.2 Hz), 4.06 (dd, 1H, J = 6.8, 8.0 Hz), 3.94 (t, 1H, J = 7.6 Hz), 3.91 (d, 1H, J = 5.6 Hz), 2.69–2.81 (m, 4H, 2 × SCH_2CH_3), 1.47 (s, 3H, CH_3), 1.44 (s, 6H, CH_3), 1.38 (s, 3H, CH_3), 1.28 (t, 3H, J = 7.6 Hz, SCH_2CH_3), 1.27 (t, 3H, J = 7.6 Hz, SCH_2CH_3); ^{13}C (100 MHz, $CDCl_3$): δ 110.3, 109.8, 80.3, 78.9, 75.5, 66.1, 53.3, 27.6, 27.4, 26.4, 25.8, 25.6, 25.2, 14.6, 14.5. Anal. Calcd for $C_{15}H_{28}O_4S_2$ (336.5): C, 53.54; H, 8.39; S, 19.06. Found: C, 53.28; H, 8.32; S, 19.22.

1.2.9. X-ray crystallographic data

2:3;5:6-Di-*O*-isopropylidene-D-mannofuranose (**14**): empirical formula $C_{12}H_{20}O_6$, colorless prismatic crystal, formula wt 260.28, orthorhombic, $P2(1)$, a = 6.6693(9), b = 10.8368(18), c = 18.904(3) Å, V = 1366.3(4) $Å^3$, Z = 4, $\mu(\lambda$ Mo Kα 0.71073 Å) = 0.101 mm^{-1}. F (0 0 0) = 560, GOF(S) = 0.986. Final indices $R1$ = 0.0418, $wR2$ = 0.0899 with $I > 2\sigma(I)$; $R1$ = 0.0857, $wR2$ = 0.1060 for all data.

Acknowledgments

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Supplementary data

Complete crystallographic data of **14** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 685637. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk). Supplementary data (CIF file, ^1H NMR, ^{13}C NMR) associated with this article can be found, in the online version, at doi:10.1016/j.carres.2009.09.017.

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Note

Tetrabutylammonium tribromide (TBATB): a mild and efficient catalyst for O-isopropylidenation of carbohydrates

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ABSTRACT

A wide range of *O*-isopropylidene derivatives can be prepared from the sugars and their derivatives on reaction with acetone at room temperature by employing 2 mol % of tetrabutylammonium tribromide (TBATB) as a catalyst. Good yields, low catalyst loading, mild reaction conditions, and a non-aqueous workup procedure are some major advantages of this protocol.

The *O*-isopropylidene acetal group is a common protecting group extensively used in carbohydrate chemistry for the preparation of valuable building blocks.[1,2] Especially, acetonation of an aldohexose results in the formation of an *O*-isopropylidene derivative with a selective unmasked hydroxyl group, depending upon the nature of the sugar. For example, D-mannose (**1**) on reaction with acetone in presence of a catalyst provides 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**15**) with an unprotected hydroxyl group at the anomeric position. However, D-glucose (**2**) gives 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**16**) on acetonation, leaving a free OH group at the C-3 position.[3] These compounds serve as glycosyl acceptors,[4] glycosyl donors[5] and valuable starting materials for the synthesis of various natural products.[6] For example, 2,3:4,5-di-*O*-isopropylidene-D-xylose diethyl dithioacetal (**24**) has been utilized for the total synthesis of (+)-phorboxazole A, a potent cytostatic agent.[7] Recently, the *O*-isopropylidene derivative of galactose, 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (**17**), has been used for conformational studies as well as in theoretical calculations.[8] In addition, some of these isopropylidene derivatives, namely 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**16**), exhibits antipyretic and anti-inflammatory activities with a low toxicity.[9] Therefore, there is a continuous research interest to prepare these important class of compounds in a large quantities.

Conventionally, the *O*-isopropylidene acetal derivatives of sugars are usually prepared from the corresponding sugar on reaction with anhydrous acetone in the presence of a catalytic amount of acid or Lewis acid, for example, concd H_2SO_4[10] or a combination of anhydrous $ZnCl_2$ and H_3PO_4.[11] Literature reports reveal that a number of catalysts have been utilized for acetonation, including anhydrous copper(II) sulfate,[12] $FeCl_3$,[13] pyridinium *p*-toluenesulfonate (PPTS),[14] iodine,[15] ceric ammonium nitrate (CAN),[16] Zeolite HY,[17] and montmorillonite clay.[18] Recently, some methods have also been reported using triphenylphosphine polymer-bound/iodine complex,[19] sulfuric acid immobilized on silica,[20] vanadyl triflate ($VO(OTf)_2{\cdot}xH_2O$)[21], or bromodimethylsulfonium bromide (BDMS).[22] However, many of these procedures have one or more drawbacks such as an excessive amount of catalyst,[18] harsh reaction conditions,[20] and inert atmospheric reaction conditions.[19,21] Although a large number of methods have been developed over the years, there is still a need to find better alternatives by exploring new reagents as catalysts for the preparation of *O*-isopropylidene derivatives.

A few years ago, Chaudhuri et al. reported[23] the environmentally benign synthesis of various organic ammonium tribromides and their application in bromination reactions. Later on, we have shown the efficacy of these solid organic ammonium tribromides for the deprotection of dithioacetals,[24] the interconversion of carbonyl compounds into 1,3-oxathiolanes and vice-versa,[25] as well as the synthesis of α-bromo enones[26] and various naturally occurring flavone derivatives.[27] A wide variety of organic transformations have also been developed by others involving tetrabutylammonium tribromide (TBATB).[28–33] Knowing the unique behavior, properties, and stabilities of these reagents, we conceived the idea that tetrabutylammonium tribromide (TBATB)

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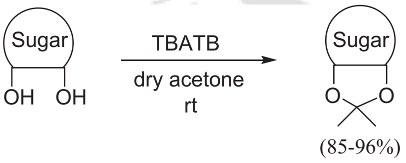
might be a useful catalyst for the preparation of various *O*-isopropylidene derivatives from sugars. In this paper, we report our successful results as depicted in Scheme 1.

For our present study, we prepared TBATB by following the standard literature procedure.[23] Initially, the reaction of D-mannose (**1**) was carried out in anhydrous acetone in presence of 0.5 mol % TBATB. The reaction was incomplete even after 8 h of stirring. Again, the same reaction was performed with 1, 2, and 5 mol % of catalyst, respectively. The best results (see Table 1) were obtained using 2 mol % catalyst with complete conversion within 2 h that furnished the product in 96% yield. The product was obtained as 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranose (**15**), a thermodynamically controlled product, which was characterized by the usual spectroscopic data, melting point, and specific rotation. These data closely matched with the reported data.[19] It is worthwhile to mention that the same transformation was also achieved within 1 h using 5 mol % catalyst.

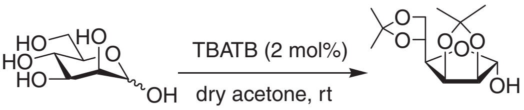
After optimizing the reaction conditions, other aldohexoses such as D-glucose (**2**) and D-galactose (**3**) were tried for isopropylidenation reaction and yielded the products **16** (88%) and **17** (89%) respectively. Next, a range of aldopentoses such as L-arabinose, D-xylose and D-ribose (entries 4–6, Table 2) were smoothly converted into the corresponding *O*-isopropylidene derivatives **18**–**20** in good yields.

To explore further the scope of this reaction, L-rhamnose (**7**) and D-mannitol (**8**) were transformed into the corresponding acetonides **21** and **22** under similar reaction conditions. It is important to mention here that a wide variety of diethyl dithioacetal derivatives of various sugars such as L-arabinose, D-xylose, and L-rhamnose (entries 9–11, Table 2) were also converted into the corresponding products **23**–**25** in good yields without any effect on the dithioacetal group. Further, we have extended our protocol for the O-isopropylidenation of methyl α-glucopyranoside (**12**) and uridine (**13**) and have provided the desired products **26** and **27** in good yields as shown in Table 2. Unfortunately, we did not get the desired product while the reaction was carried out with disaccharide derivative **14** in acetone using TBATB as catalyst under identical reaction reactions. However, we are trying to find out the suitable reaction conditions to obtain the desired *O*-isopropylidenation products from disaccharides, which will be reported in due course.



Scheme 1. O-Isopropylidenation of sugars.

Table 1
Screening of amount of TBATB for the O-isopropylidation of D-mannose at room temperature



Entry	Catalyst (mol %)	Time (h)	Conversion[a] (%)	Yield[b] (%)
1	No catalyst	12	0	0
2	0.5	8	50	75
3	1	5	70	80
4	2	2	100	96
5	5	1	100	94

[a] The reactions were performed with 2 mmol scale in 10 mL of dry acetone.
[b] Isolated yield based on starting material recovery.

Interestingly, we note that the conversion of the various free sugars to the respective *O*-isopropylidene derivatives can be achieved on a larger scale (100 mmol) without any difficulty by using only 1 mol % of the catalyst. For example, the reaction of the diethyl dithioacetal of L-arabinose (entry **9**, 25.6 g, 100 mmol) was investigated in dry acetone (400 mL) in the presence of TBATB (1 mmol). The reaction was complete within 2 h, and the desired product **23** was obtained in 91% yield. The above result indicates that a large-scale reaction is also feasible using a lesser amount of catalyst.

The formation of the product may be explained as follows: It was proposed earlier that benzyltrimethylammonium tribromide can react with alcohol to generate dry HBr in the medium.[34] We thus propose that dry HBr generated in situ catalyzes the O-isopropylidenation reaction of sugars or other sugar derivatives to the corresponding *O*-isopropylidene compounds. The reaction of D-mannose (**1**) and acetone was also examined with aqueous 48% HBr (5 μL) at room temperature. It was found that it requires a longer reaction time and provides a relatively low yield (64%) of product. Furthermore, the efficiency of TBATB in comparison with other catalysts is shown in Table 3. All products were fully characterized by IR, ^{1}H and ^{13}C NMR spectroscopy, specific rotation, and elemental analysis.

In summary, we have demonstrated a simple and efficient method for the preparation of *O*-isopropylidene derivatives from free sugars as well as from acyclic sugar derivatives by employing TBATB as catalyst. The notable advantages of the present protocol are the following: good yields, short reaction times, a stable and easy to handle catalyst, as well as a lower amount of catalyst loading. Due to its operational simplicity, generality, and efficacy, this method is expected to have wider applicability for the preparation of various *O*-isopropylidene derivatives of sugars.

1. Experimental

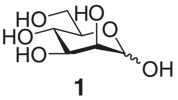
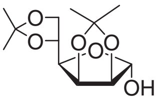
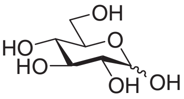
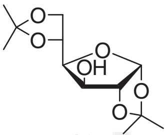
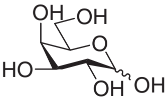
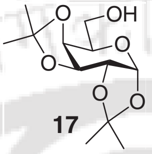
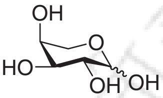
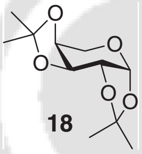
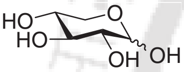
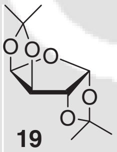
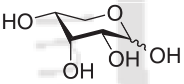
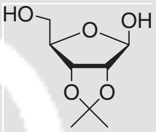
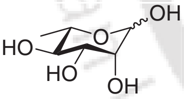
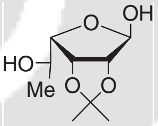
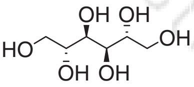
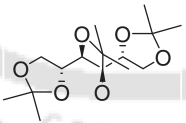
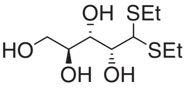
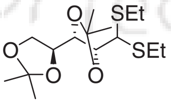
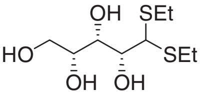
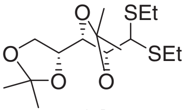
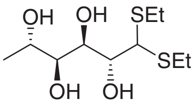
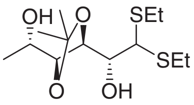
1.1. General methods

Starting materials and reagents used were of commercial grade. The progress of all reactions was monitored by TLC using plastic sheets precoated with Silica Gel 60 F_{254} to a thickness of 0.2 mm (E. Merck). Spots were detected by MOSTAIN solution (by dissolving 20 g ammonium heptamolybdate and 0.4 g cerium(IV) sulfate in 400 mL 10% H_2SO_4 solution). Column chromatography was carried out using silica gel (60–120 mesh, E. Merck, or Qualigen). Melting points were determined on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer 343 Polarimeter at 25 °C. IR spectra were recorded on a Perkin–Elmer IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian (400 MHz) spectrometer using TMS as the internal standard. Chemical shifts are expressed in parts per million (δ in ppm) in the order of multiplicity, coupling constant (in Hz), no. of protons and signal assignment. Elemental analysis was performed using a Perkin–Elmer CHNS/*O*-2400 Series II elemental analyzer.

1.2. General experimental procedure

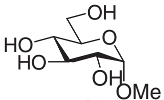
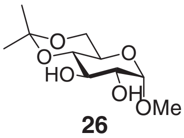
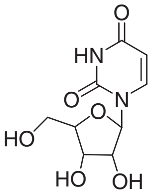
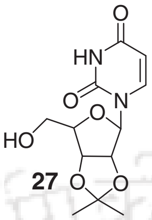
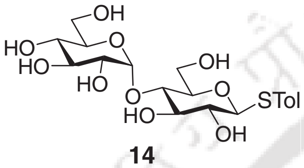
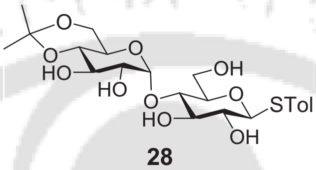
To a stirred solution of the sugar (2 mmol) in dry acetone (10 mL) tetrabutylammonium tribromide (TBATB) (19 mg, 0.04 mmol) was added at room temperature. The reaction was monitored by TLC as mentioned in Table 2. After completion of the reaction, one drop of NEt_3 was added to reaction mixture, and then acetone was removed on a rotary evaporator. Then the

Table 2
Results of the O-isopropylidenation of free sugars and their derivatives using TBATB as catalyst

Entry	Substrate	Product	Time (h)	Yield[a,b] (%)	Reference
1	 **1**	 **15**	2	96	19
2	 **2**	 **16**	8	88[c]	19
3	 **3**	 **17**	8	89[c]	19
4	 **4**	 **18**	5	86	19
5	 **5**	 **19**	3	89	22
6	 **6**	 **20**	1.5	86	19
7	 **7**	 **21**	1	88	22
8	 **8**	 **22**	2	94	22
9	 **9**	 **23**	1.5	91	22
10	 **10**	 **24**	1.5	85	22
11	 **11**	 **25**	1	87	22

(continued on next page)

Table 2 (*continued*)

Entry	Substrate	Product	Time (h)	Yield[a,b] (%)	Reference
12	 **12**	 **26**	10	72[c]	34
13	 **13**	 **27**	6	76	35
14	 **14**	 **28**	24	0.0	

[a] All products were characterized by ^{1}H NMR and ^{13}C NMR spectroscopy and by specific rotation and elemental analysis.
[b] The reaction was carried out with the sugar (2 mmol) in dry acetone (10 mL) using 2 mol % of catalyst TBATB.
[c] A trace amount of sugar remains undissolved.

Table 3
O-Isopropylidenation of D-glucose and D-mannose using various catalysts and their amount of loading

Entry	Substrate	Catalyst	Amount (mol %)	Time (h)	Yield[a] (%)
1	D-Glucose	FeCl$_3$	>10	6	83[13]
		Iodine	>10	4	80[15]
		)–Ph$_2$P–I$_2$	200	30 min	95[19]
		VO(OTf)$_2$	5	10	89[21]
		BDMS	5	10	84[22]
		TBATB	2	8	88 (in this work)
2	D-Mannose	FeCl$_3$	>10	1	90[13]
		Iodine	>10	25 min	85[15]
		)–Ph$_2$P–I$_2$	200	30 min	95[19]
		VO(OTf)$_2$	5	3	92[21]
		BDMS	5	2	90[22]
		TBATB	2	2	96 (in this work)

[a] Isolated yields.

crude residue was passed through a silica gel column to obtain the desired product in pure form. Compounds **15**, **16**, and **22** were isolated from the crude mixture by direct recrystallization after removing excess acetone. The spectral data of the compounds **15**–**18** and **20** have previously been reported,[19] and the spectral data are in good agreement with our data. Similarly, the spectral data of the compounds **19** and **21**–**25** have recently been reported.[22]

1.2.1. Methyl 4,6-*O*-isopropylidene-α-D-glucopyranoside (26)

White solid: mp 112–114 °C (lit.[34] 116 °C); $[\alpha]_D^{25}$ +108.6 (*c* 1.0, H_2O) [lit.[34] $[\alpha]_D^{25}$ +111 (*c* 1.0, H_2O)]; IR (KBr): 3436, 2975, 2948, 1371, 1228, 1201, 1068, 974, 835 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 2.59 (d, J = 2.0 Hz, 1H, OH), 3.41 (s, 3H, CH_3), 3.52 (q, J = 9.6 Hz, 1H, H-5), 3.54–3.64 (m, 2H, H-2, and H-4), 3.73 (t, J = 10.8 Hz, 1H, H-6′), 3.77 (t, J = 10.0 Hz, 1H, H-3), 3.86 (dd, J = 10.8 Hz, J = 5.6 Hz, 1H, H-6), 4.74 (d, J = 3.6 Hz, 1H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 29.3, 55.6, 62.5, 63.5, 72.1, 73.2, 73.7, 99.9, 100.0; Anal. Calcd for $C_{10}H_{18}O_6$ (234.25): C, 51.27; H, 7.75. Found: C, 51.16; H, 7.58.

1.2.2. 2′,3′-*O*-Isopropylideneuridine (27)

White solid: mp 145–146 °C (lit.[35] 146–1147 °C); IR (KBr): 3430, 3316, 2984, 1691, 1586, 1375, 1221, 1031, 847 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.99 (br s, 1H, NH), 3.81 (br d, J = 11.6 Hz, 1H, H-5′), 3.92 (br d, J = 11.6 Hz, 1H, H-5′), 4.30 (d, J = 3.2 Hz, 1H, H-4′), 4.96 (dd, J = 3.6, 6.4 Hz, 1H, H-2′), 5.04 (dd, J = 2.8, 6.4 Hz, 1H, H-3′), 5.59 (d, J = 1.6 Hz, 1H, H-1′), 5.74 (d, J = 8.0 Hz, 1H, H-5), 7.39 (d, J = 8.0 Hz, 1H, H-6), 9.11 (br s, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3, 27.2, 62.1, 80.6, 84.4, 86.9, 94.2, 102.3, 114.4, 142.4, 150.7, 164.3; Anal. Calcd for $C_{12}H_{16}N_2O_6$ (284.27): C, 50.70; H, 5.67; N, 9.85. Found: C, 50.53; H, 5.51, N, 9.96.

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Iodine catalyzed one-pot five-component reactions for direct synthesis of densely functionalized piperidines

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ABSTRACT

A simple and convenient one-pot multicomponent reaction (MCR) has been developed for the synthesis of highly functionalized piperidines catalyzed by molecular iodine. This strategy demonstrated five-component reactions of 1,3-dicarbonyl compounds, amines and aromatic aldehydes in methanol using 10 mol % of iodine at room temperature. This methodology provides an alternative approach for easy access of highly and fully substituted piperidines in moderate to good yields using three readily available starting materials. Notably, this method is mild, cheap, straight forward, applicable to broad range of substrates and environmentally friendly as compared to the existing methods. Synthetic and mechanistic studies are presented here.

1. Introduction

The piperidine and its analogues are widely distributed in many natural products, biologically active molecules and organic fine chemicals.[1] Some of them also act as therapeutic agents.[2] Compounds containing piperidine structural motif exhibit anti-hypertensive,[3] anti-bacterial,[4] anti-convulsant and anti-inflammatory activities.[5] Recently, Tripathi et al. reported that some of the substituted piperidines also display antimalarial activity.[6] As a result, a considerable efforts have been made from all over the world towards the synthesis of this important class of compounds due to their medicinal properties.[7] Some of the synthetic strategies for their preparation are imino-Diels-Alder reactions,[8] aza-Prins-cyclizations,[9] intramolecular Michael reactions[10] and intramolecular Mannich reaction onto iminium ions.[11] An alternative strategy for the synthesis of functionalized piperidines is using multicomponent reactions (MCRs). Recently, MCRs have emerged as a powerful synthetic tool in organic synthesis due to their advantages over the conventional multi-step synthesis.[12,13] In addition, MCRs are eco-friendly, superior atom economic as well as they avoid costly purification processes and protection-deprotection steps with minimum synthetic effort and time.[14] Therefore, MCRs satisfy some of the tenets of ‘Green Chemistry’. Literature reveals only a few methods to synthesis highly functionalized piperidine derivatives via MCRs using catalysts, such as a combination of L-proline/TFA,[6] bromodimethylsulfonium bromide (BDMS),[15a] tetrabutylammonium tribromide (TBATB)[15b] and $InCl_3$.[16] The aforesaid methods have some of the disadvantages such as use of expensive and excess amount of catalysts and failure in some of the cases to obtain the desired product. Therefore, there is a need for simple and greener methods, which are applicable to a broad range of substrates to access these compounds.

Molecular iodine has emerged as an inexpensive, non-toxic, non-metallic, readily available and environmentally benign catalyst for various organic transformations, which has been reviewed recently.[17] The current literature reveals that molecular iodine can be used as an efficient catalyst for a diverse range of multicomponent reactions[18a–d] as well as synthesis of various heterocycles.[18e–h] We conceived that molecular iodine is to be an ideal Lewis acid for one-pot synthesis of highly substituted piperidine derivatives from aromatic aldehydes, amines and β-keto esters. Herein, we disclose the synthesis and mechanistic aspects of densely functionalized piperidine derivatives (**1**) using MCRs (Scheme 1).

2. Results and discussion

Initially, the mixture of 4-methylbenzaldehyde (1 mmol), aniline (1 mmol) and methyl acetoacetate (1 mmol) in acetonitrile (5 mL) was treated with 10 mol % of iodine at room temperature. We obtained a highly functionalized piperidine **1a** in 36% yield

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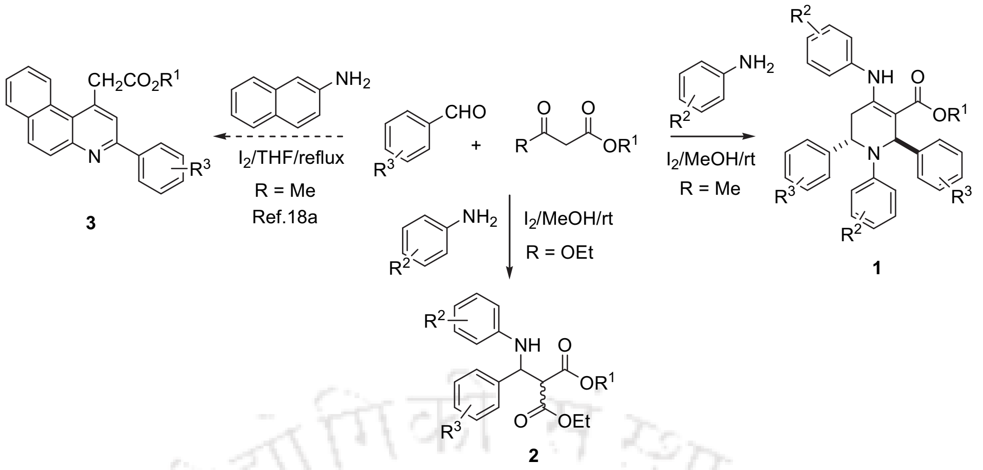


Scheme 1. Direction of product formation in iodine catalyzed MCRs.

along with unreacted methyl acetoacetate and the product was characterized from ^{1}H NMR, ^{13}C NMR spectra, HRMS and by elemental analysis. It is quite clear that the product **1a** was obtained via five-component reactions.

For optimization of the amount of catalyst and choosing the suitable solvent, various trial reactions were investigated with a combination of 4-methylbenzaldehyde, aniline and methyl acetoacetate to obtain the best yield of **1a**, which is summarized in Table 1. We have noted that 10 mol % of the catalyst gives the best result for the formation of product. It has also been observed that methanol is the best solvents for the present reaction among various other solvents, such as acetonitrile, dichloromethane, ethanol and ethyl acetate. For this transformation, ethanol can be a second choice of solvent. Under solvent-free conditions, the product was obtained in a moderate yield (48%) that may be due to lack of effective interaction of reactants with the catalyst in the absence of solvent.

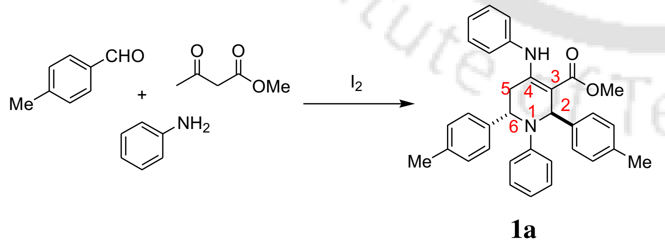
Having established the optimal reaction conditions, the mixture of 4-methylbenzaldehyde, aniline and ethyl acetoacetate in methanol was treated with 10 mol % iodine to obtain the desired piperidine derivative **1b** as shown in Table 2. Similarly, various other β-keto esters like *tert*-butyl acetoacetate and allyl acetoacetate also provided the corresponding piperidine derivatives **1c** and **1d** in good yields (Table 2, entries 3 and 4). From these observations, we may conclude that the alkoxy (–OR) moiety present in the β-keto ester does not have any significant role in determining the course of the reaction. However, in case of diethylmalonate (Table 2, entry 5), yielded the corresponding β-amino carbonyl compound (**2**) under identical reaction conditions. This can be attributed to the lack of enolizable alkyl group in the β-position.

In addition, the effect of an alkyl group was also studied by varying the substitutents at the β-position of the β-keto esters. The reaction of ethyl propionylacetate with 4-chlorobenzaldehyde and aniline afforded fully substituted piperidine **1e** in 42% yield in the presence of 10 mol % molecular iodine (Table 2, entry 6). Similarly, the reaction of ethyl butyrylacetate with 4-chlorobenzaldehyde and aniline also provided the desired piperidine **1f** in 36% yield under similar reaction conditions (Table 2, entry 7). The fully substituted piperidine derivatives were derivatives not reported earlier.[6,15a,16] From these observations, it is clear that methyl and ethyl group can be introduced easily at the 5-position of the piperidine ring by choosing a suitable β-keto ester. Next, we wanted to incorporate a phenyl group at the 5-position in the piperidine ring. For this purpose, the required β-keto ester (ethyl 3-oxo-4-phenylbutanoate) was prepared by following the literature procedure.[19] Then it was subjected with 4-chlorobenzaldehyde and aniline in presence of 10 mol % catalyst under identical reaction conditions (Table 2, entry 8). Unfortunately, we did not get the desired piperidine derivative after 48 h of stirring. These investigations suggest that not only methyl group but any enolizable alkyl group present in the β position of β-keto esters, is a necessary and sufficient condition for the formation of highly substituted piperidines using MCRs (Table 2).

We proceeded further to investigate the reaction of various aromatic aldehydes having substituents, such as OMe, Cl, Br, F and NO$_2$ with aniline and methyl acetoacetate under the same reaction conditions (Table 3, entries 1–8). The reaction time and yield of the products **1g**–**n** are shown in Table 3. The low yields obtained in case of entries **7** and **8** is caused by: (i) formation of more stable imine due to extra conjugation in the presence of nitro group, which is less reactive and (ii) partial or less solubility in methanol. Unfortunately, some of the aldehydes, such as β-naphthaldehyde and *n*-butanal, did not give the corresponding functionalized piperidines.

We have noted, in some cases, such as benzaldehyde, 4-chlorobenzaldehyde and 4-nitrobenzaldehyde, a small quantity of

Table 1
Optimization of reaction conditions for the synthesis of functionalized piperidine **1a**[a]



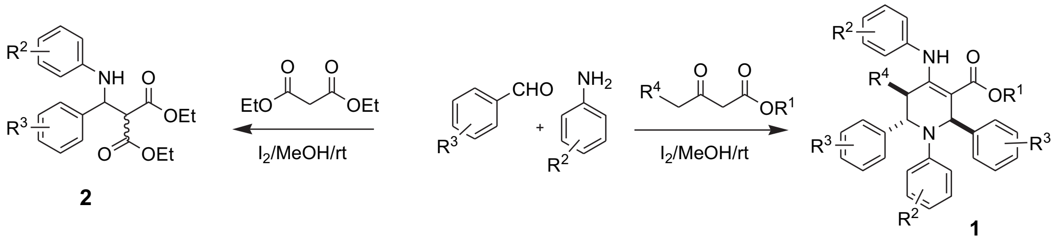
Entry	Solvent	Catalyst (mol %)	Time (h)	Yield[b] (%)
1	CH_3CN	No catalyst	12	0
2	CH_3CN	5	12	52
3	CH_3CN	10	12	72
4	CH_3CN	20	12	69
5	CH_2Cl_2	10	12	60
6	C_2H_5OH	10	10	78
7	CH_3OH	10	8	84
8	EtOAc	10	12	62
9	Neat	10	12	48

[a] Reaction conditions: 4-Methylbenzaldehyde, aniline and methyl acetoacetate were taken in 2:2:1 ratio at rt.

[b] Isolated yields.

Table 2

Scope of β-keto esters in the formation of product with aromatic aldehydes and amines using iodine as catalyst[a]



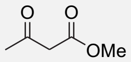
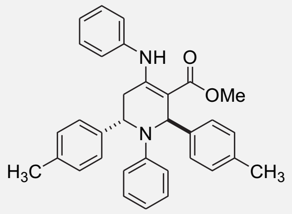
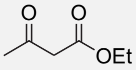
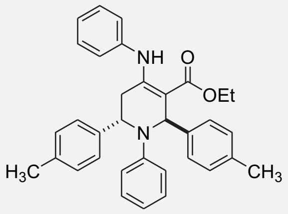
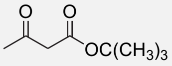
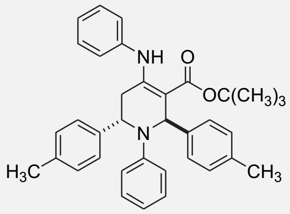
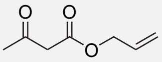
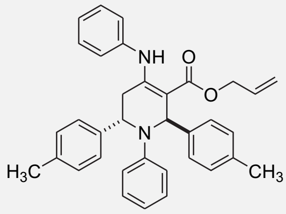
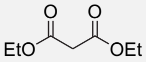
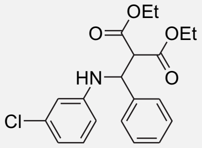
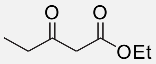
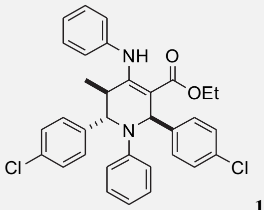
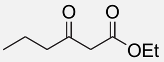
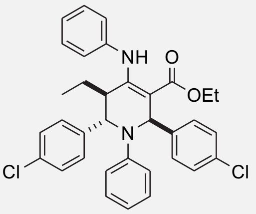
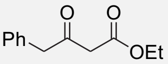
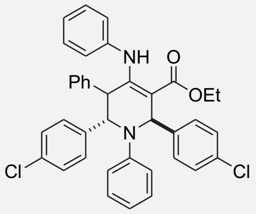
Entry	β-Keto esters	Time (h)	Product	Yield[b] (%)
1		8	 **1a**	84
2		8	 **1b**	78
3		10	 **1c**	68
4		10	 **1d**	66
5		8	 **2**	88[c]
6		48	 **1e**	42

Table 2 (*continued*)

Entry	β-Keto esters	Time (h)	Product	Yield[b] (%)
7		48	 **1f**	36
8		48		00[d]

[a] Reactions were performed in the ratio of 2:2:1 (aldehydes: amines: β-keto esters) in presence of 10 mol % iodine in 5 mL methanol at rt.

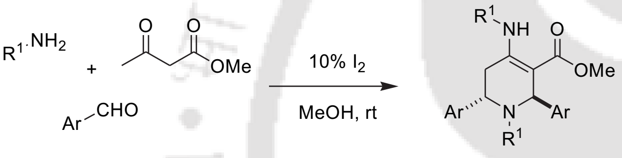
[b] Isolated yields.

[c] Unreacted imine (0.150 g) was recovered from the reaction.

[d] Determined by crude ^{1}H NMR.

Table 3

Scope for one-pot five-component reactions of methyl acetoacetate with aromatic aldehydes and amines[a]



1g-1u

Entry	Ar	R^1	Time (h)	Product	Yield[b] (%)
1	Ph	Ph	8	**1g**	81[c]
2	4-$CH_3OC_6H_4$	Ph	8	**1h**	74
3	3,4,5-$(CH_3O)_3C_6H_2$	Ph	18	**1i**	68
4	4-ClC_6H_4	Ph	6	**1j**	85[c]
5	4-BrC_6H_4	Ph	6	**1k**	81
6	4-FC_6H_4	Ph	8	**1l**	74
7	3-$NO_2C_6H_4$	Ph	6	**1m**	36
8	4-$NO_2C_6H_4$	Ph	6	**1n**	38[c]
9	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	8	**1o**	68
10	4-$CH_3C_6H_4$	4-$C_2H_5C_6H_4$	10	**1p**	65
11	4-$CH_3C_6H_4$	4-$CH_3OC_6H_4$	8	**1q**	74
12	4-$CH_3C_6H_4$	4-BrC_6H_4	8	**1r**	68
13	4-$CH_3C_6H_4$	4-$NO_2C_6H_4$	38	**1s**	57
14	4-$CH_3C_6H_4$	*n*-C_4H_9	48	**1t**	48
15	4-$CH_3C_6H_4$	$C_6H_5CH_2$	48	**1u**	55

[a] Aldehyde, amine and methyl acetoacetate were taken in 2:2:1 ratio in presence of 10 mol % iodine at rt.

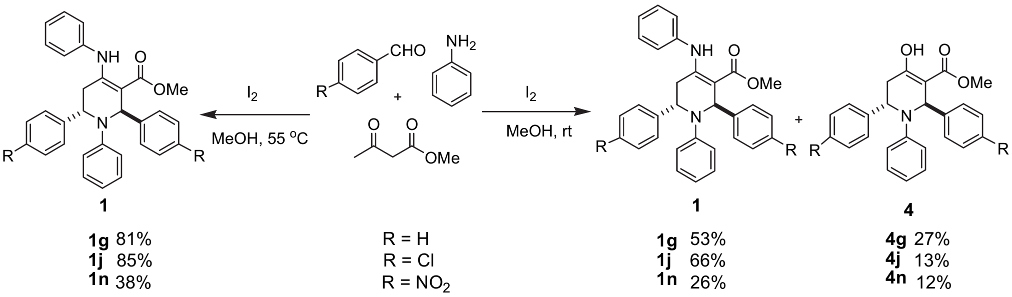
[b] Isolated yields.

[c] Reaction was carried out at 55 °C.

enol-piperidines were formed along with the desired piperidines as shown in Scheme 2. For example, the reaction of benzaldehyde with aniline and methyl acetoacetate in presence of iodine at room temperature provided, a mixture of desired piperidine **1g** and enol-piperidine **4g** in 53% and 27%, respectively.

It is speculated that the formation of **4** may be due to either hydrolysis of the enamine-piperidines **1** or through a four-component reaction. If the product **4** is forming from hydrolysis of **1**, then we expected the enol-piperidine derivative **4** should have obtained in more quantities at elevated temperature. To investigate this, the reaction was carried out at 55 °C and surprisingly, we isolated the piperidine **1g** exclusively in 81% yield not enol-piperidine after 5 h. Further, we did not obtain the hydrolysed product **4g** from **1g** even upon hydrolysis under both acidic and basic reaction conditions. From these observations, we may conclude that the enol-piperidine **4g** is obtained exclusively through a four-component reaction rather from hydrolysis of **1**.

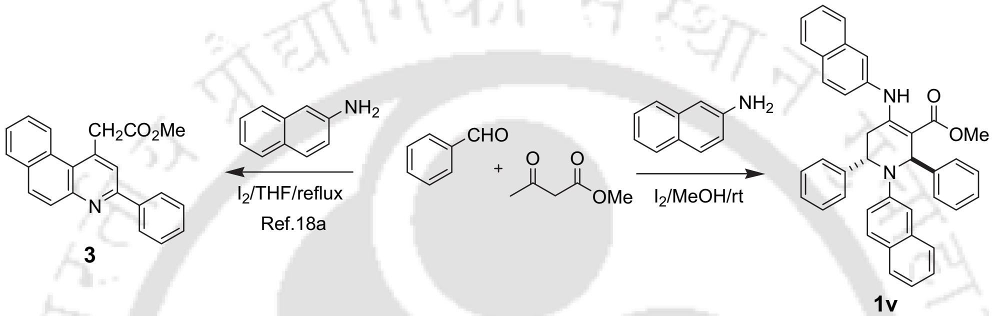
To find the generality and scope of this MCR, various amines were also examined. A wide variety of anilines tethered with substituents, such as Me, Et, OMe, Br, NO_2 were treated with 4-methylbenzaldehyde and methyl acetoacetate under similar reaction conditions. All the reactions underwent smoothly to provide the corresponding piperidine derivative **1o**–**s**, in moderate to good yields (Table 3, entries 9–13). Likewise, aliphatic amines viz. *n*-butylamine and benzylamine also afforded the corresponding piperidines **1t** and **1u**, respectively, in moderate yields. It is worthwhile to mention that



Scheme 2. Formation of product at different reaction conditions.

4-nitroaniline and aliphatic amines did not give the corresponding piperidine derivatives by using InCl$_3$.[15]

It is interesting to point out here, in our experimental conditions when 2-naphthylamine was treated with methyl acetoacetate and aldehydes, such as benzaldehyde and 4-methylbenzaldehyde to give the desired piperidine derivatives **1v** and **1w** in 53% and 51%, respectively. However, Wang et al. recently reported[18a] that same combination of 2-naphthylamine and benzaldehyde with methyl acetoacetate catalyzed by molecular iodine in THF at reflux temperature provided 3-aryl-1-substituted benzo[*f*]quinoline derivative **3** in good yield (Scheme 3). Unfortunately, 1-naphthylamine did not give the expected piperidine derivative under similar reaction conditions. This may be due to the steric hindrance of the bulky naphthyl group.



Scheme 3. Role of reaction condition towards different product formation.

The products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectra, HRMS and by elemental analysis. The assignment of the piperidine ring protons and carbons were made by using ^{1}H–^{1}H-COSY and ^{1}H–^{13}C-COSY spectra. And finally, the structures as well as the relative stereochemistry of piperidine **1f** (Fig. 1) and **1k** (Fig. S1) were confirmed by X-ray crystallographic analysis. From the structures, it was found that the piperidine ring adopted a boat conformation in case of compound **1f** in which flag pole positions 2 and 5 of the piperidine ring, as well as the CO group of the ester and the –NH are on the same side of the plane and having intramolecular hydrogen bonding, as shown in Figure 1.

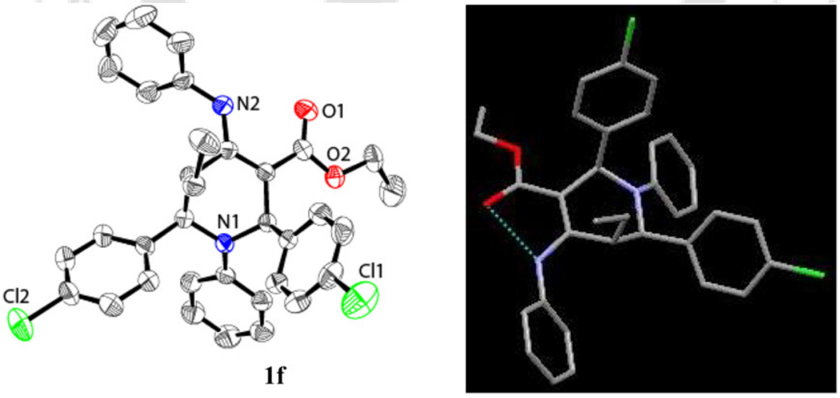
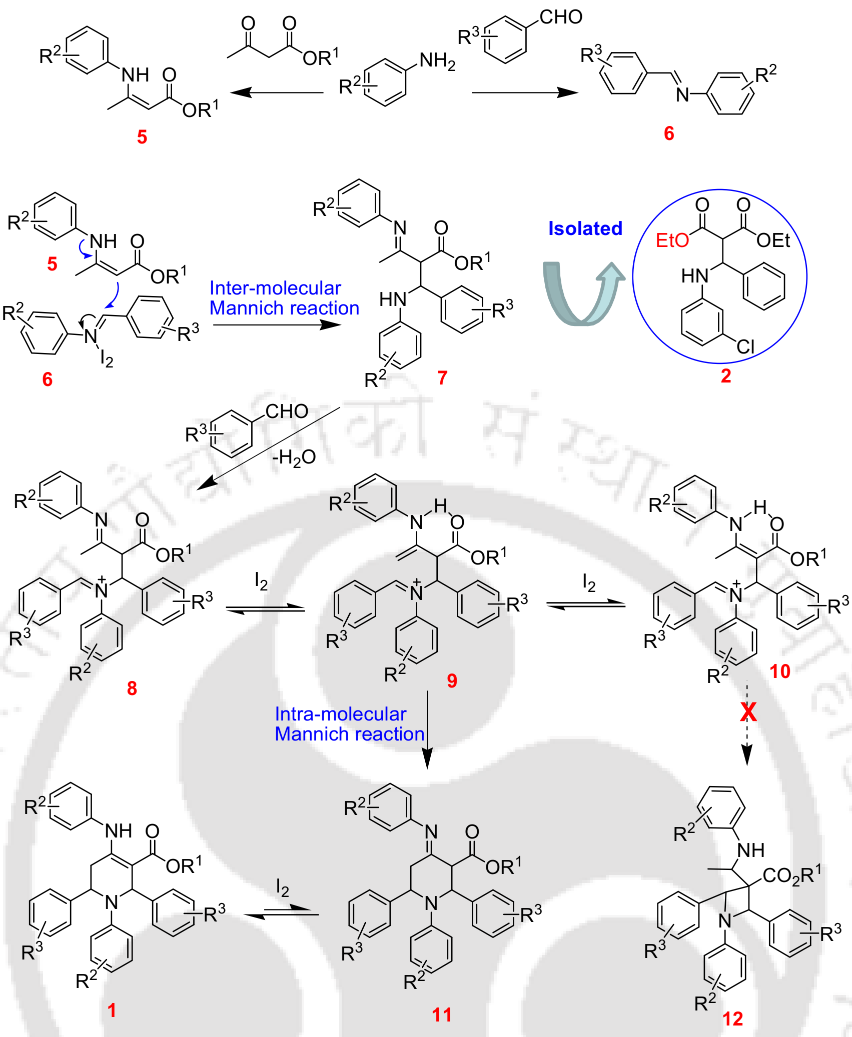


Figure 1. Crystal structures of **1f** (CCDC no. 756203).

Finally, we turned our attention towards mechanistic studies for this transformation. Earlier, reported papers[6,15a,16] proposed that the formation of piperidine is going through [4+2] aza-Diels-Alder reaction. It was expected that β-keto ester reacts with amine to give enamine **5** and it reacts with aldehyde to provide Knoevenagel type product, which acts as the reactive diene. Finally, it undergoes Diels-Alder reaction with imine **6** to give the desired product. To prove this mechanism, we had tried to trap the intermediate diene with other reactive dienophiles such as maleic anhydride, dihydropyran and dimethyl acetylenedicarboxylate. Unfortunately, we did not get any desired cycloaddition products. However, in the case of diethylmalonate on reaction with imine **6** furnished the Mannich-type product **2** (Table 2, entry 5). Therefore, we would like to propose an alternate plausible mechanism in which the product formed via double Mannich-type reactions. The enamine **4** and imine **5** were formed initially in the presence of iodine (Scheme 4). It is well known that enamine **5** would be a better nucleophile as compared to diethylmalonate. So, it is quite obvious that the nucleophilic attack by enamine **5** will take place preferentially on the iodine-activated imine **6** to give Mannich-type intermediate **7** like diethylmalonate. Then the intermediate **7** reacts with aldehyde to give **8** by elimination of water molecule. Further, there will be a spontaneous tendency in the presence of iodine for tautomerization to give the intramolecular hydrogen bonded species either **9** or **10**. However, the tautomer **9** immediately undergoes intramolecular Mannich-type reaction to form intermediate **11**. The tautomer **10** would have given a four-membered ring product **12**, which is unfavourable. Finally, the intermediate **11** tautomerizes to give the final piperidine derivative **1** due to conjugation with the ester group. However, the exact explanation is not yet clear and under investigation.

The formation of four-component product in a few cases discussed earlier (Scheme 3) may be explained as follows: the enol form of methyl acetoacetate reacts with imine **6** instead of enamine **5** to form a Mannich-type intermediate, which is analogue to **7**. The remaining steps may be similar as depicted in Scheme 4.



Scheme 4. A plausible mechanism for the formation of highly substituted piperidine in the presence of iodine.

3. Conclusions

In summary, a general methodology is reported for the formation of highly as well as fully functionalized piperidines in presence of iodine as catalyst via one-pot five-component reaction from common available starting materials. The salient features of this protocol are good yields, mild reaction conditions, environmentally benign, superior atom economy, the readily accessibility of the catalyst and its cost effectiveness. In addition, we propose the possibility for the formation of piperidines via double Mannich-type intermediates and mechanism is under investigation.

4. Experimental section

4.1. General

Melting points were determined on a Büchi melting point apparatus and are uncorrected. IR spectra were recorded on Perkin–Elmer 281 IR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian 400 spectrometer TMS as an internal reference; chemical shifts (δ scale) are reported in parts per million (ppm). ^{1}H NMR Spectra are reported in the order: no of protons, multiplicity and coupling constant (J value) in hertz (Hz); signals were characterized as s (singlet), d (doublet), t (triplet), m (multiplet), br s (broad singlet), dq (doublet of quartet) and ddt (doublet of doublet of triplet). HRMS spectra were recorded using WATERS MS system, Q-TOF premier and data analyzed using Mass Lynx 4.1. Elemental analyses were carried out using Perkin–Elmer 2400 Series II CHNS/O analyzer at the Department of Chemistry, Indian Institute of Technology, Guwahati. Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated Mo Kα radiation (λ=0.71073 Å) at 298 K.

4.2. General procedure for the synthesis of highly functionalized piperidines 1

To a solution of amine (2 mmol) and methyl acetoacetate (1 mmol) in 5 mL of methanol was added iodine (0.1 mmol) and stirred at room temperature. After 20 min, aromatic aldehyde (2 mmol) was added to the reaction mixture and stirring was continued for completion. The reaction time of individual cases is indicated in Tables 2 and 3. The thick precipitate was filtered off and washed with ethanol to give pure products.

*4.2.1. Methyl 2,6-bis(4-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1a**).* White solid (0.410 g, 84%); [found: C, 80.96; H, 6.55; N, 5.80. $C_{33}H_{32}N_2O_2$ requires C, 81.12; H, 6.60; N, 5.73%]; mp 215–217 °C; R_f (5% ethyl acetate/hexane) 0.46; ν_{max} (KBr) 1657 (C=O), 1591 (C=C) cm^{-1}; δ_H (400 MHz, CDCl$_3$) 10.25 (1H, s, NH), 7.19 (2H, d, J 8.0 Hz, ArH), 7.10–7.02 (11H, m, ArH), 6.59 (1H, t, J 7.2 Hz, ArH), 6.52 (2H, d, J 8.0 Hz, ArH), 6.39 (1H, s, H-2), 6.30 (2H, d, J 8.0 Hz, ArH), 5.11 (1H, d, *J* 3.2 Hz, H-6), 3.92 (3H, s, OMe), 2.86 (1H, dd, *J* 15.2, 5.6 Hz, H-5′), 2.75 (1H, dd, *J* 15.2, 2.4 Hz, H-5″), 2.33 (3H, s, Me), 2.32 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 168.8 (C=O), 156.5 (C-4), 147.2, 141.1, 139.8, 138.1, 136.8, 136.0, 129.4, 129.1, 129.0, 128.9, 126.7, 126.5, 126.0, 125.8, 116.1, 113.0, 98.2 (C-3), 58.1 (C-6), 55.0 (C-2), 51.2, 33.8 (C-5), 21.3, 21.2; HRMS (ESI): MH^+, found 489.2556. $C_{33}H_{32}N_2O_2$ requires 489.2542.

*4.2.2. Ethyl 2,6-bis(4-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1b**).* White solid (0.392 g, 78%); [found C, 81.13; H, 6.76; N, 5.69. $C_{34}H_{34}N_2O_2$ requires C, 81.24; H, 6.82; N, 5.57%]; mp 228–231 °C; R_f (5% ethyl acetate/hexane) 0.48; ν_{max} (KBr) 1649 (C=O), 1592 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.29 (1H, s, NH), 7.22 (2H, d, *J* 8.0 Hz, ArH), 7.10–7.02 (11H, m, ArH), 6.59 (1H, t, *J* 7.2 Hz, ArH), 6.53 (2H, d, *J* 8.8 Hz, ArH), 6.40 (1H, s, H-2), 6.30 (2H, d, *J* 7.6 Hz, ArH), 5.11 (1H, d, *J* 2.4 Hz, H-6), 4.51–4.40 (1H, m, OCH_aH_b), 4.36–4.26 (1H, m, OCH_aH_b), 2.86 (1H, dd, *J* 15.2, 5.6 Hz, H-5′), 2.76 (1H, dd, *J* 15.2, 2.4 Hz, H-5″), 2.33 (3H, s, Me), 2.32 (3H, s, Me), 1.46 (3H, t, *J* 7.2 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 168.4 (C=O), 156.2 (C-4), 147.2, 141.2, 139.9, 138.2, 136.8, 135.9, 129.4, 129.1, 129.0, 128.9, 126.7, 126.5, 125.9, 125.7, 116.1, 113.1, 98.5 (C-3), 59.8, 58.1 (C-6), 55.0 (C-2), 33.8 (C-5), 21.3, 21.2, 15.0; HRMS (ESI): MH^+, found: 503.2683. $C_{34}H_{34}N_2O_2$ requires 503.2699.

*4.2.3. tert-Butyl 2,6-bis(4-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1c**).* Light yellow solid (0.361 g, 68%); [found C, 81.32; H, 7.31; N, 5.37. $C_{36}H_{38}N_2O_2$ requires C, 81.47; H, 7.22; N, 5.28%]; mp 171–173 °C; R_f (5% ethyl acetate/hexane) 0.64; ν_{max} (KBr) 3447 (N–H), 1648 (C=O), 1592 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.25 (1H, s, NH), 7.23 (2H, d, *J* 8.0 Hz, ArH), 7.09–7.03 (11H, m, ArH), 6.58 (1H, t, *J* 7.2 Hz, ArH), 6.51 (2H, d, *J* 8.4 Hz, ArH), 6.35 (1H, s, H-2), 6.29 (2H, d, *J* 7.2 Hz, ArH), 5.08 (1H, d, *J* 3.2 Hz, H-6), 2.82 (1H, dd, *J* 15.2, 5.6 Hz, H-5′), 2.74 (1H, dd, *J* 15.2, 2.8 Hz, H-5″), 1.64 (9H, s, CMe_3), 2.31 (3H, s, Me), 2.33 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 168.4 (C=O), 155.3 (C-4), 147.4, 141.5, 140.0, 138.5, 136.7, 135.8, 129.4, 129.1, 128.9, 126.7, 126.6, 125.7, 125.4, 116.1, 113.1, 100.2 (C-3), 80.1, 58.2 (C-6), 55.4 (C-2), 33.8 (C-5), 29.0, 21.3, 21.2; HRMS (ESI): MH^+, found: 531.3013. $C_{36}H_{38}N_2O_2$ requires 531.3012.

*4.2.4. Allyl 2,6-bis(4-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1d**).* Light yellow solid (0.339 g, 66%); [found C, 81.56; H, 6.57; N, 5.51. $C_{35}H_{34}N_2O_2$ requires C, 81.68; H, 6.66; N, 5.44%]; mp 186–188 °C; R_f (5% ethyl acetate/hexane) 0.49; ν_{max} (KBr) 3242 (N–H), 1658 (C=O), 1591 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.26 (1H, s, NH), 7.21 (2H, d, *J* 8.0 Hz, ArH), 7.15–7.02 (11H, m, ArH), 6.58 (1H, t, *J* 7.2 Hz, ArH), 6.52 (2H, d, *J* 8.4 Hz, ArH), 6.43 (1H, s, H-2), 6.30 (2H, dd, *J* 8.0, 2.4 Hz, ArH), 6.15–6.06 (1H, m, =CH), 5.45 (1H, dq, *J* 17.2, 1.2 Hz, $=CH_aH_b$), 5.31 (1H, dq, *J* 10.4, 1.2 Hz, $=CH_aH_b$), 5.10 (1H, d, *J* 3.6 Hz, H-6), 4.87 (1H, ddt, *J* 13.6, 5.6, 1.6 Hz, CH_aH_b), 4.80 (1H, ddt, *J* 13.6, 5.5, 1.6 Hz, CH_aH_b), 2.86 (1H, dd, *J* 15.2, 5.6 Hz, H-5′), 2.76 (1H, dd, *J* 15.2, 2.4 Hz, H-5″), 2.32 (3H, s, Me), 2.31 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 168.0 (C=O), 156.8 (C-4), 147.2, 141.2, 139.8, 138.1, 136.8, 136.0, 133.3, 129.4, 129.1, 129.04, 128.98, 126.8, 126.5, 126.0, 125.8, 117.8, 116.2, 113.1, 98.2 (C-3), 64.5, 58.1 (C-6), 55.1 (C-2), 33.9 (C-5), 21.3, 21.2; HRMS (ESI): MH^+, found: 515.2697. $C_{35}H_{34}N_2O_2$ requires 515.2699.

*4.2.5. Ethyl 2,6-bis(4-chlorophenyl)-5-methyl-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1e**).* White solid (0.234 g, 42%); [found: C, 71.01; H, 5.33; N, 5.12. $C_{33}H_{30}N_2O_2Cl_2$ requires C, 71.09; H, 5.42; N, 5.02%]; mp 198–199 °C; R_f (5% ethyl acetate/hexane) 0.45; ν_{max} (KBr) 1651 (C=O), 1594 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.38 (1H, s, NH), 7.27–7.18 (9H, m, ArH), 7.09 (2H, t, *J* 7.6 Hz, ArH), 7.00 (2H, d, *J* 8.4 Hz, ArH), 6.68 (1H, t, *J* 7.2 Hz, ArH), 6.57 (2H, d, *J* 8.4 Hz, ArH), 6.52–6.50 (2H, m, ArH), 6.20 (1H, s, H-2), 4.87 (1H, s, H-6), 4.43–4.35 (1H, m, CH_aH_b), 4.32–4.24 (1H, m, CH_aH_b), 3.01 (1H, dq, *J* 7.2 Hz, 1.6 Hz, H-5), 1.37 (3H, t, *J* 7.2 Hz, Me), 1.04 (3H, d, *J* 7.2 Hz, Me); δ_C (100 MHz, $CDCl_3$) 169.0 (C=O), 159.8 (C-4), 147.4, 142.8, 141.8, 138.2, 132.8, 132.2, 129.4, 129.3, 129.0, 128.7, 128.8, 128.1, 127.1, 126.7, 117.9, 115.5, 96.1 (C-3), 64.0 (C-6), 60.1 (C-2), 55.7, 38.7 (C-5), 19.2, 14.8.

*4.2.6. Ethyl 2,6-bis(4-chlorophenyl)-5-ethyl-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1f**).* White solid (0.206 g, 36%); [found: C, 71.34; H, 5.53; N, 5.02. $C_{34}H_{32}N_2O_2Cl_2$ requires C, 71.45; H, 5.64; N, 4.90%]; mp 239–241 °C; R_f (5% ethyl acetate/hexane) 0.47; ν_{max} (KBr) 1655 (C=O), 1594 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.78 (1H, s, NH), 7.43–7.38 (4H, m, ArH), 7.34 (2H, d, *J* 8.4 Hz, ArH), 7.25–7.12 (10H, m, ArH), 6.78 (2H, d, *J* 8.0 Hz, ArH), 5.99 (1H, s, H-2), 4.86 (1H, d, *J* 4.0 Hz, H-6), 4.33–4.25 (1H, m, CH_aH_b), 4.15–4.07 (1H, m, CH_aH_b), 3.05–3.04 (1H, m, H-5), 1.22 (3H, t, *J* 7.2 Hz, Me), 0.85–0.77 (1H, m, CH_aH_b), 0.76–0.67 (1H, m, CH_aH_b), 0.18 (3H, t, *J* 7.2 Hz, Me); δ_C (100 MHz, $CDCl_3$) 169.2 (C=O), 161.8 (C-4), 151.2, 145.8, 139.9, 139.1, 132.7, 132.4, 129.6, 129.0, 128.9, 128.5, 128.4, 126.6, 126.3, 119.2, 116.8, 95.6 (C-3), 63.8 (C-6), 61.7 (C-2), 60.0, 43.1 (C-5), 22.2, 14.6, 12.1.

*4.2.7. Methyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1g**).* To a solution of amine (2 mmol) and methyl acetoacetate (1 mmol) in 5 mL of methanol was added iodine (0.1 mmol) and stirred at 55 °C. After 10 min, benzaldehyde (2 mmol) was added to the reaction mixture and stirring was continued for completion at the same temperature. The reaction mixture was cooled to room temperature. The thick precipitate was filtered off and washed with ethanol to give pure products as white solid (0.373 g, 81%); [found: C, 80.72; H, 6.07; N, 6.09. $C_{31}H_{28}N_2O_2$ requires C, 80.84; H, 6.13; N, 6.08%]; mp 185–186 °C; R_f (5% ethyl acetate/hexane) 0.38; ν_{max} (KBr) 3444 (N–H), 1661 (C=O), 1591 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.24 (1H, s, NH), 7.32–7.24 (8H, m, ArH), 7.16 (2H, d, *J* 8.0 Hz, ArH), 7.10–7.03 (5H, m, ArH), 6.59 (1H, t, *J* 7.2 Hz, ArH), 6.51 (2H, d, *J* 8.8 Hz, ArH), 6.44 (1H, s, H-2), 6.27 (2H, d, *J* 8.0 Hz, ArH), 5.14 (1H, d, *J* 4.4 Hz, H-6), 3.93 (3H, s, Me), 2.86 (1H, dd, *J* 15.2, 5.6 Hz, H-5′), 2.75 (1H, dd, *J* 15.2, 2.4 Hz, H-5″), δ_C (100 MHz, $CDCl_3$) 168.7 (C=O), 156.4 (C-4), 147.1, 144.0, 142.9, 137.9, 129.0, 128.9, 128.8, 128.4, 127.3, 126.8, 126.5, 126.0, 125.9, 116.3, 113.0, 98.0 (C-3), 58.3 (C-6), 55.2 (C-2), 51.2, 33.8 (C-5); HRMS (ESI): MH^+, found: 461.2256. $C_{31}H_{28}N_2O_2$ requires 461.2229.

*4.2.8. Methyl 2,6-bis(4-methoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1h**).* White solid (0.385 g, 74%); [found C, 76.01; H, 6.11; N, 5.49. $C_{33}H_{32}N_2O_4$ requires C, 76.13; H, 6.20; N, 5.38%]; mp 186–188 °C; R_f (5% ethyl acetate/hexane) 0.16; ν_{max} (KBr) 1654 (C=O), 1593 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.27 (1H, s, NH), 7.21 (2H, d, *J* 8.8 Hz, ArH), 7.11 (2H, d, *J* 7.2 Hz, ArH), 7.07 (1H, t, *J* 7.2 Hz, ArH), 7.06 (2H, d, *J* 8.8 Hz, ArH), 7.05 (2H, d, *J* 8.4 Hz, ArH), 6.81 (4H, d, *J* 8.8 Hz, ArH), 6.60 (1H, t, *J* 7.2 Hz, ArH), 6.52 (2H, d, *J* 8.0 Hz, ArH), 6.38–6.34 (3H, m, ArH and H-2), 5.07 (1H, d, *J* 3.2 Hz, H-6), 3.92 (3H, s, OMe), 3.79 (3H, s, OMe), 3.78 (3H, s, OMe), 2.85 (1H, dd, *J* 15.2, 5.6 Hz, H-5′), 2.75 (1H, dd, *J* 15.2, 2.4 Hz, H-5″); δ_C (100 MHz, $CDCl_3$) 168.8 (C=O), 158.8, 158.2, 156.5 (C-4), 147.1, 138.1, 136.0, 134.8, 129.0, 127.8, 127.6, 125.9, 125.8, 116.2, 114.1, 113.7, 113.1, 98.2 (C-3), 57.7 (C-6), 55.4, 54.7 (C-2), 51.2, 33.9 (C-5); HRMS (ESI): MH^+, found: 521.2449. $C_{33}H_{32}N_2O_4$ requires 521.2440.

*4.2.9. Methyl 2,6-bis(3,4,5-trimethoxyphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1i**).* Light yellow solid (0.435 g, 68%); [found: C, 69.28; H, 6.24; N, 4.46. $C_{37}H_{40}N_2O_8$ requires C, 69.36; H, 6.29; N, 4.37%]; mp 197–199 °C; R_f (30% ethyl acetate/hexane) 0.22; ν_{max} (KBr) 1655 (C=O), 1594 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.26 (1H, s, NH), 7.15 (2H, d, *J* 7.6 Hz, ArH), 7.12 (1H, t, *J* 7.2 Hz, ArH), 7.09 (2H, d, *J* 8.0 Hz, ArH), 6.65 (1H, t, *J* 7.6 Hz, ArH), 6.57 (2H, d, *J* 8.0 Hz, ArH), 6.53 (2H, s, ArH), 6.39 (2H, d, *J* 7.7 Hz, ArH), 6.35 (2H, s, ArH), 6.34(1H, s, H-2), 5.03 (1H, d, *J* 3.2 Hz, H-6), 3.90 (3H, s, OMe), 3.85 (3H, s, OMe), 3.84 (3H, s, OMe), 3.74

(6H, s, 2×OMe), 3.70 (6H, s, 2×OMe), 2.95 (1H, dd, *J* 15.2, 5.6 Hz, H-5′), 2.77 (1H, dd, *J* 15.2, 2.4 Hz, H-5″); δ_C (100 MHz, $CDCl_3$) 168.5 (C=O), 157.0 (C-4), 153.4, 153.1, 147.0, 139.7, 138.5, 137.8, 137.0, 136.5, 128.9, 126.3, 126.2, 116.6, 113.1, 103.9, 103.2, 97.3 (C-3), 61.0, 58.3 (C-6), 56.0, 55.6 (C-2), 51.1, 33.8 (C-5); HRMS (ESI): MH^+, found: 641.2800. $C_{37}H_{40}N_2O_8$ requires 641.2863.

*4.2.10. Methyl 2,6-bis(4-chlorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1j**).* To a solution of amine (2 mmol) and methyl acetoacetate (1 mmol) in 5 mL of methanol was added iodine (0.1 mmol) and stirred at 55 °C. After 10 min, 4-chlorobenzaldehyde (2 mmol) was added to the reaction mixture and stirring was continued for completion at the same temperature. The reaction mixture was cooled to room temperature. The thick precipitate was filtered off and washed with ethanol to give pure products as white solid **1i** (0.450 g, 85%) as white solid; [found: C, 70.29; H, 4.83; N, 5.34. $C_{31}H_{26}Cl_2N_2O_2$ requires C, 70.32; H, 4.95; N, 5.29%]; mp 225–227 °C; R_f (5% ethyl acetate/hexane) 0.27; ν_{max} (KBr) 1660 (C=O), 1591 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.25 (1H, s, NH), 7.36–7.24 (5H, m, ArH), 7.15 (2H, d, *J* 7.2 Hz, ArH), 7.10 (2H, t, *J* 7.6 Hz, ArH), 7.07 (2H, d, *J* 8.4 Hz, ArH), 7.05 (2H, d, *J* 8.0 Hz, ArH), 6.64 (1H, t, *J* 7.2 Hz, ArH), 6.45 (2H, d, *J* 8.0 Hz, ArH), 6.40 (2H, d, *J* 8.0 Hz, ArH), 6.35 (1H, s, H-2), 5.09 (1H, d, *J* 2.4 Hz, H-6), 3.92 (3H, s, OMe), 2.82 (1H, dd, *J* 15.2, 5.6 Hz, H-5′), 2.74 (1H, dd, *J* 15.2, 2.4 Hz, H-5″); δ_C (100 MHz, $CDCl_3$) 168.4 (C=O), 156.2 (C-4), 146.6, 142.5, 141.0, 137.7, 133.0, 132.3, 129.2, 128.9, 128.6, 128.2, 127.9, 126.2, 125.9, 116.9, 113.1, 97.6 (C-3), 57.5 (C-6), 54.8 (C-2), 51.3, 33.8 (C-5); HRMS (ESI): MH^+, found: 529.1445. $C_{31}H_{26}N_2O_2Cl_2$ requires 529.1450.

*4.2.11. Methyl 2,6-bis(4-bromophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1k**).* Light yellow solid (0.500 g, 77%); [found: C, 60.45; H, 4.15; N, 4.97. $C_{31}H_{26}Br_2N_2O_2$ requires C, 60.21; H, 4.24; N, 4.53%]; mp 245–247 °C; R_f (5% ethyl acetate/hexane) 0.27; ν_{max} (KBr) 1661 (C=O), 1590 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.24 (1H, s, NH), 7.40 (2H, d, *J* 8.4 Hz, ArH), 7.39 (2H, d, *J* 8.4 Hz, ArH), 7.18 (2H, d, *J* 8.4 Hz, ArH), 7.16 (2H, d, *J* 8.0 Hz, ArH), 7.15 (1H, t, *J* 7.2 Hz, ArH), 7.08 (2H, t, *J* 7.2 Hz, ArH), 7.00 (2H, d, *J* 8.4 Hz, ArH), 6.65 (1H, t, *J* 7.2 Hz, ArH), 6.45 (2H, d, *J* 8.8 Hz, ArH), 6.40 (2H, d, *J* 7.6 Hz, ArH), 6.34 (1H, s, H-2), 5.08 (1H, d, *J* 3.6 Hz, H-6), 3.93 (3H, s, OMe), 2.82 (1H, dd, *J* 15.2, 5.6 Hz, H-5′), 2.74 (1H, dd, *J* 15.2, 2.4 Hz, H-5″); δ_C (100 MHz, $CDCl_3$) 168.4 (C=O), 156.1 (C-4), 146.5, 143.0, 141.6, 137.7, 131.9, 131.5, 129.2, 129.18, 128.6, 128.3, 126.2, 125.9, 121.1, 120.4, 116.9, 113.0, 97.6 (C-3), 57.5 (C-6), 54.9 (C-2), 51.3, 33.8 (C-5); HRMS (ESI): MH^+, found: 617.0433. $C_{31}H_{26}N_2O_2Br_2$ requires 617.0439.

*4.2.12. Methyl 2,6-bis(4-fluorophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1l**).* White solid (0.367 g, 74%); [found: C, 74.91; H, 5.11; N, 5.84. $C_{31}H_{26}F_2N_2O_2$ requires C, 74.98; H, 5.28; N, 5.64%]; mp 193–195 °C; R_f (5% ethyl acetate/hexane) 0.38; ν_{max} (KBr) 1657 (C=O), 1592 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.23 (1H, s, NH), 7.25 (2H, t, *J* 8.4 Hz, ArH), 7.17–7.06 (7H, m, ArH), 6.96 (4H, t, *J* 8.4 Hz, ArH), 6.64 (1H, t, *J* 7.2 Hz, ArH), 6.47 (2H, d, *J* 8.4 Hz, ArH), 6.39 (2H, d, *J* 8.0 Hz, ArH), 6.37 (1H, s, H-2), 5.11 (1H, d, *J* 2.8 Hz, H-6), 3.93 (3H, s, OMe), 2.83 (1H, dd, *J* 15.2, 5.6 Hz, H-5′), 2.75 (1H, dd, *J* 15.2, 2.4 Hz, H-5″); δ_C (100 MHz, $CDCl_3$) 168.6 (C=O), 163.4, 160.5, 156.3 (C-4), 146.7, 139.5, 138.2, 137.8, 129.2, 128.4, 128.3, 128.1, 128.0, 126.2, 125.9, 116.7, 115.8, 115.6, 115.3, 115.1, 113.1, 97.9 (C-3), 57.5 (C-6), 54.7 (C-2), 51.4, 33.9 (C-5); HRMS (ESI): MH^+, found: 497.2245. $C_{31}H_{26}N_2O_2F_2$ requires 497.2241.

*4.2.13. Methyl 2,6-bis(3-nitrophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1m**).* Yellow solid (0.198 g, 36%); [found C, 67.51; H, 4.68; N, 10.29. $C_{31}H_{26}N_4O_6$ requires C, 67.63; H, 4.76; N, 10.18%]; mp 182–183 °C; R_f (15% ethyl acetate/hexane) 0.21; ν_{max} (KBr) 3436 (N–H), 1655 (C=O), 1595 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.30 (1H, s, NH), 8.22 (1H, s, ArH), 8.15–8.10 (2H, m, ArH), 7.94 (s, 1H, ArH), 7.66 (1H, d, *J* 7.6 Hz, ArH), 7.50–7.45 (3H, m, ArH), 7.16–7.14 (3H, m, ArH), 7.10 (2H, t, *J* 7.2 Hz, ArH), 6.70 (1H, t, *J* 7.2 Hz, ArH), 6.48 (1H, s, H-2), 6.44 (2H, d, *J* 8.8 Hz, ArH), 6.41–6.38 (2H, m, ArH), 5.33 (1H, t, *J* 4.0 Hz, H-6), 3.99 (3H, s, OMe), 2.88 (2H, d, *J* 4.0 Hz, CH_2); δ_C (100 MHz, $CDCl_3$) 168.2 (C=O), 155.7 (C-4), 148.8, 148.7, 146.5, 145.9, 144.6, 137.3, 132.7, 129.8, 129.5, 129.3, 126.7, 125.8, 122.6, 122.0, 121.7, 121.5, 117.9, 113.2, 96.9 (C-3), 57.2 (C-6), 55.3 (C-2), 51.6, 33.9 (C-5).

*4.2.14. Methyl 2,6-bis(4-nitrophenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1n**).* The reaction was carried out at 55 °C, after completion, the reaction was cool to room temperature. The thick precipitate was filtered off and washed with ethanol to give pure products **1n** (0.209 g, 38%) as light yellow solid; [found C, 67.51; H, 4.69; N, 10.31. $C_{31}H_{26}N_4O_6$ requires C, 67.63; H, 4.76; N, 10.18%]; mp 239–241 °C; R_f (15% ethyl acetate/hexane) 0.21; ν_{max} (KBr) 3356 (N–H), 1660 (C=O), 1593 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.26 (1H, br s, NH), 8.14 (2H, d, *J* 8.8 Hz, ArH), 8.12 (2H, d, *J* 8.8 Hz, ArH), 7.48 (2H, d, *J* 8.4 Hz, ArH), 7.27 (2H, d, *J* 8.8 Hz, ArH), 7.17–7.13 (3H, m, ArH), 7.09 (1H, d, *J* 7.2 Hz, ArH), 7.07 (1H, d, *J* 7.2 Hz, ArH), 6.68 (1H, t, *J* 7.2 Hz, ArH), 6.46 (1H, s, H-2), 6.42–6.37 (4H, m, ArH), 5.25–5.24 (1H, m, H-6), 3.95 (3H, s, OMe), 2.85 (2H, d, *J* 4.0 Hz, CH_2); δ_C (100 MHz, $CDCl_3$) 168.1 (C=O), 155.7 (C-4), 151.8, 149.9, 147.5, 146.9, 145.9, 137.3, 129.5, 129.4, 127.6, 127.5, 126.6, 125.7, 124.1, 123.9, 117.8, 113.1, 96.8 (C-3), 57.5 (C-6), 55.4 (C-2), 51.6, 33.7 (C-5).

*4.2.15. Methyl 2,6-bis(4-methylphenyl)-1-(4-methylphenyl)-4-(4-methylphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1o**).* Light yellow solid (0.351 g, 68%); [found: C, 81.24; H, 7.01; N, 5.53. $C_{35}H_{36}N_2O_2$ requires C, 81.36; H, 7.02; N, 5.42%]; mp 206–208 °C; R_f (5% ethyl acetate/hexane) 0.48; ν_{max} (KBr) 3249 (N–H), 1655 (C=O), 1594 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.17 (1H, s, NH), 7.20 (2H, d, *J* 8.0 Hz, ArH), 7.09–7.03 (6H, m, ArH), 6.89 (2H, d, *J* 8.0 Hz, ArH), 6.87 (2H, d, *J* 8.8 Hz, ArH), 6.43 (2H, d, *J* 8.0 Hz, ArH), 6.35 (1H, s, H-2), 6.18 (2H, d, *J* 8.0 Hz, ArH), 5.07 (1H, d, *J* 4.0 Hz, H-6), 3.91 (3H, s, OMe), 2.82 (1H, dd, *J* 15.2, 5.6 Hz, H-5′), 2.72 (1H, dd, *J* 15.2, 2.4 Hz, H-5″), 2.34 (3H, s, Me), 2.32 (3H, s, Me), 2.27 (3H, s, Me), 2.15 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 168.8 (C=O), 156.8 (C-4), 145.1, 141.4, 140.1, 136.6, 135.8, 135.6, 135.4, 129.5, 129.4, 129.0, 126.7, 126.5, 126.1, 125.0, 113.0, 97.7 (C-3), 58.0 (C-6), 55.1 (C-2), 51.0, 33.7 (C-5), 21.3, 21.2, 21.0, 20.3; HRMS (ESI): MH^+, found: 517.2847. $C_{35}H_{36}N_2O_2$ requires 517.2855.

*4.2.16. Methyl 2,6-bis(4-methylphenyl)-1-(4-ethylphenyl)-4-(4-ethylphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1p**).* Light yellow solid (0.354 g, 65%); [found: C, 81.49; H, 7.07; N, 5.24. $C_{37}H_{40}N_2O_2$ requires C, 81.58; H, 7.40; N, 5.14%]; mp 177–178 °C; R_f (5% ethyl acetate/hexane) 0.48; ν_{max} (KBr) 3264 (N–H), 1653 (C=O), 1593 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.17 (1H, s, NH), 7.19 (2H, d, *J* 8.4 Hz, ArH), 7.09–7.03 (6H, m, ArH), 6.91 (2H, d, *J* 8.4 Hz, ArH), 6.88 (2H, d, *J* 8.8 Hz, ArH), 6.44 (2H, d, *J* 8.8 Hz, ArH), 6.35 (1H, s, H-2), 6.19 (2H, d, *J* 8.4 Hz, ArH), 5.07 (1H, d, *J* 3.6 Hz, H-6), 3.90 (3H, s, OMe), 2.82 (1H, dd, *J* 15.2, 5.6 Hz, H-5′), 2.73 (1H, dd, *J* 15.2, 2.4 Hz, H-5″), 2.56 (2H, q, *J* 7.6 Hz, CH_2CH_3), 2.45 (2H, q, *J* 7.6 Hz, CH_2CH_3), 2.31(3H, s, Me), 2.34 (3H, s, Me), 1.18 (3H, t, *J* 7.6 Hz, Me), 1.11 (3H, t, *J* 7.6 Hz, Me); δ_C (100 MHz, $CDCl_3$) 168.8 (C=O), 156.8 (C-4), 145.3, 142.0, 141.5, 140.2, 136.7, 135.8, 135.6, 131.5, 129.4, 129.1, 128.3, 126.8, 126.6, 126.2, 113.0, 97.8 (C-3), 58.2 (C-6), 55.2 (C-2), 51.1, 33.8 (C-5), 28.4, 27.8, 21.3, 21.2, 15.9, 15.7; HRMS (ESI): MH^+, found: 545.3151. $C_{37}H_{40}N_2O_2$ requires 545.3168.

*4.2.17. Methyl 2,6-bis(4-methylphenyl)-1-(4-methoxyphenyl)-4-(4-methoxyphenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1q**).* White solid (0.406 g, 74%); [found: C, 76.56; H, 6.55; N, 5.26.

$C_{35}H_{36}N_2O_4$ requires C, 76.62; H, 6.61; N, 5.11%]; mp 230–231 °C; R_f (5% ethyl acetate/hexane) 0.20; ν_{max} (KBr) 3442 (N–H), 1657 (C=O), 1611 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.08 (1H, s, NH), 7.16 (2H, d, *J* 8.0 Hz, ArH), 7.09–7.02 (6H, m, ArH), 6.64 (2H, d, *J* 9.2 Hz, ArH), 6.60 (2H, d, *J* 9.2 Hz, ArH), 6.43 (2H, d, *J* 9.2 Hz, ArH), 6.26 (1H, s, H-2), 6.21 (2H, d, *J* 9.2 Hz, ArH), 5.00 (1H, d, *J* 2.8 Hz, H-6), 3.89 (3H, s, OMe), 3.74 (3H, s, OMe), 3.65 (3H, s, OMe), 2.77 (1H, dd, *J* 15.2, 5.6 Hz, H-5′), 2.62 (1H, dd, *J* 15.2, 2.8 Hz, H-5″), 2.33 (3H, s, Me), 2.31 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 168.9 (C=O), 157.9, 157.2, 151.0 (C-4), 141.9, 141.5, 140.4, 136.7, 135.9, 131.0, 129.4, 129.0, 128.0, 126.9, 126.6, 114.7, 114.3, 114.2, 114.1, 97.3 (C-3), 58.1 (C-6), 55.8 (C-2), 55.7, 55.6, 51.0, 33.8 (C-5), 21.3, 21.2; HRMS (ESI): MH$^+$, found: 549.2753. $C_{35}H_{36}N_2O_4$ requires 549.2753.

*4.2.18. Methyl 2,6-bis(4-methylphenyl)-1-(4-bromophenyl)-4-(4-bromophenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1r**).* Light yellow solid (0.440 g, 68%); [found C, 61.23; H, 4.57; N, 4.46. $C_{33}H_{30}Br_2N_2O_2$ requires C, 61.32; H, 4.68; N, 4.33%]; mp 230–232 °C; R_f (5% ethyl acetate/hexane) 0.42; ν_{max} (KBr) 3446 (N–H), 1650 (C=O), 1605 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.17 (1H, s, NH), 7.20 (2H, d, *J* 8.4 Hz, ArH), 7.15–7.07 (8H, m, ArH), 7.02 (2H, d, *J* 8.0 Hz, ArH), 6.38 (2H, d, *J* 9.2 Hz, ArH), 6.31 (1H, s, H-2), 6.13 (2H, d, *J* 8.4 Hz, ArH), 5.06 (1H, d, *J* 3.6 Hz, H-6), 3.93 (3H, s, OMe), 2.84 (1H, dd, *J* 15.2, 5.6 Hz, H-5′), 2.70 (1H, dd, *J* 15.2, 2.4 Hz, H-5″), 2.34 (3H, s, Me), 2.32 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 168.6 (C=O), 155.6 (C-4), 146.1, 140.2, 139.2, 137.2, 137.1, 136.3, 132.1, 131.7, 129.6, 129.2, 127.4, 126.6, 126.4, 119.2, 114.7, 108.4, 98.9 (C-3), 58.1 (C-6), 55.2 (C-2), 51.3, 33.6 (C-5), 21.3, 21.2; HRMS (ESI): MH$^+$, found: 645.0753. $C_{33}H_{30}N_2O_2Br_2$ requires 645.0752.

*4.2.19. Methyl 2,6-bis(4-methylphenyl)-1-(4-nitrophenyl)-4-(4-nitrophenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1s**).* Yellow solid (0.330 g, 57%); [found: C, 68.39; H, 5.14; N, 9.88. $C_{33}H_{30}N_4O_6$ requires C, 68.50; H, 5.23; N, 9.68%]; mp 253–255 °C; R_f (15% ethyl acetate/hexane) 0.20; ν_{max} (KBr) 1658 (C=O), 1587 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.55 (1H, s, NH), 8.00 (2H, d, *J* 9.2 Hz, ArH), 7.97 (2H, d, *J* 9.6 Hz, ArH), 7.13 (6H, s, ArH), 7.02 (2H, d, *J* 8.0 Hz, ArH), 6.54 (2H, d, *J* 9.6 Hz, ArH), 6.48 (1H, s, H-2), 6.43 (2H, d, *J* 9.2 Hz, ArH), 5.27 (1H, d, *J* 3.2 Hz, H-6), 3.99 (3H, s, OMe), 3.06 (1H, dd, *J* 15.2, 5.6 Hz, H-5′), 2.94 (1H, dd, *J* 15.2, 2.4 Hz, H-5″), 2.34 (6H, s, 2×Me); δ_C (100 MHz, $CDCl_3$) 168.3 (C=O), 153.3 (C-4), 151.9, 144.1, 138.3, 138.1, 137.9, 137.5, 137.2, 130.0, 129.7, 126.2, 126.1, 125.9, 125.1, 123.1, 112.3, 102.0 (C-3), 58.5 (C-6), 55.8 (C-2), 52.0, 33.8 (C-5), 21.3, 21.2; HRMS (ESI): MH$^+$, found: 579.2244. $C_{33}H_{30}N_4O_6$ requires 579.2244.

*4.2.20. Methyl 2,6-bis(4-methylphenyl)-1-butyl-4-(butylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1t**).* Light yellow solid (0.215 g, 48%); [found C, 77.51; H, 8.91; N, 6.37. $C_{29}H_{40}N_2O_2$ requires C, 77.64; H, 8.99; N, 6.24%]; mp 158–160 °C; R_f (5% ethyl acetate/hexane) 0.46; ν_{max} (KBr) 3428 (N–H), 1649 (C=O), 1597 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.22 (1H, t, *J* 4.8 Hz, NH), 7.31 (2H, d, *J* 8.0 Hz, ArH), 7.17 (2H, *J* 8.0 Hz, ArH), 7.08 (4H, t, *J* 7.6 Hz, ArH), 4.92 (1H, s, H-2), 3.85 (1H, dd, *J* 11.6, 5.2 Hz, H-6), 3.55 (3H, s, OMe), 3.38–3.24 (2H, m, CH_2), 2.60 (1H, dd, *J* 17.2, 11.2 Hz, H-5′), 2.51 (1H, dd, *J* 17.2, 5.2 Hz, H-5″), 2.32 (3H, s, Me), 2.30 (3H, s, Me), 2.15–2.08 (2H, m, CH_2), 1.68–1.60 (2H, m, CH_2), 1.52–1.43 (2H, m, CH_2), 1.36–1.26 (2H, m, CH_2), 1.23–1.10 (2H, m, CH_2), 0.98 (3H, t, *J* 7.2 Hz, CH_3), 0.79 (3H, t, *J* 7.2 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 171.4 (C=O), 159.7 (C-4), 142.4, 139.3, 136.4, 135.6, 128.9, 128.8, 128.4, 127.3, 87.9 (C-3), 58.6 (C-6), 52.5 (C-2), 50.6, 44.7, 42.1, 32.5 (C-5), 31.1, 25.6, 21.3, 20.6, 20.5, 14.3, 14.1; HRMS (ESI): MH$^+$, found: 449.3160. $C_{29}H_{40}N_2O_2$ requires 449.3168.

*4.2.21. Methyl 2,6-bis(4-methylphenyl)-1-benzyl-4-(benzylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1u**).* Light yellow solid (0.284 g, 55%); [found C, 81.22; H, 7.07; N, 5.57. $C_{35}H_{36}N_2O_2$ requires C, 81.36; H, 7.02; N, 5.42%]; mp 172–173 °C; R_f (5% ethyl acetate/hexane) 0.32; ν_{max} (KBr) 3272 (N–H), 1650 (C=O), 1594 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 9.67 (1H, t, *J* 6.0 Hz, NH), 7.40–7.37 (6H, m, ArH), 7.32 (4H, t, *J* 8.0 Hz, ArH), 7.24 (2H, d, *J* 8.4 Hz, ArH), 7.20 (2H, d, *J* 8.4 Hz, ArH), 7.08 (4H, t, *J* 8.0 Hz, ArH), 4.73 (1H, s, H-2), 4.63 (1H, dd, *J* 15.6, 6.4 Hz, H-6), 4.57 (1H, dd, *J* 15.6, 6.0 Hz, $CH_a\mathit{H}_b$), 4.02 (1H, dd, *J* 11.2, 5.2 Hz, $C\mathit{H}_aH_b$), 3.37 (1H, d, *J* 13.6 Hz, $CH_a\mathit{H}_b$), 3.46 (3H, s, OMe), 3.32 (1H, d, *J* 13.6 Hz, $C\mathit{H}_aH_b$), 2.73 (1H, dd, *J* 17.2, 11.6 Hz, H-5′), 2.62 (1H, dd, *J* 17.2, 5.2 Hz, H-5″), 2.28 (3H, s, Me), 2.30 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 171.3, 159.0 (C-4), 141.9, 140.5, 139.1, 138.7, 136.7, 135.8, 129.1, 129.0, 128.8, 128.4, 128.3, 127.6, 127.4, 127.0, 126.9, 89.3, 58.1, 52.2, 50.6, 49.7, 46.3, 25.5, 21.3; HRMS (ESI): MH$^+$, found: 517.2872. $C_{35}H_{36}N_2O_2$ requires 517.2855.

*4.2.22. Diethyl 2-(phenyl(3-chlorophenylamino)methyl)malonate (**2**).* White solid (0.295 g, 88%); [found: C, 63.73; H, 5.79; N, 3.63. $C_{20}H_{22}ClNO_4$ requires C, 63.91; H, 5.90; N, 3.73%]; mp 112–114 °C; R_f (5% ethyl acetate/hexane) 0.2; ν_{max} (KBr) 3369 (N–H), 1752 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.35–7.32 (5H, m, ArH), 6.99 (1H, t, *J* 8.0 Hz, ArH), 6.61 (1H, d, *J* 8.0 Hz, ArH), 6.58 (1H, s), 6.46 (1H, d, *J* 8.4 Hz, ArH), 5.49 (1H, d, *J* 6.0 Hz), 5.18 (1H, br s), 4.17–4.07 (4H, m), 3.88 (1H, d, *J* 5.2 Hz), 1.17 (3H, t, *J* 7.2 Hz), 1.13 (3H, t, *J* 7.2 Hz); δ_C (100 MHz, $CDCl_3$) 168.2, 167.3, 148.0, 139.3, 135.0, 130.3, 128.9, 128.0, 126.8, 117.9, 113.6, 112.1, 62.1, 61.8, 58.1, 57.0, 14.1, 14.0.

*4.2.23. Methyl 4-hydroxy-1,2,6-triphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (**4g**).* To a solution of amine (2 mmol) and methyl acetoacetate (1 mmol) in 5 mL of methanol was added iodine (0.1 mmol) and stirred at room temperature. After 20 min, benzaldehyde (2 mmol) was added to the reaction mixture and stirring was continued for completion. The thick precipitate was filtered off and washed with ethanol to give mixture of two products of R_f (5% ethyl acetate/hexane) 0.38 and 0.49, respectively. Products were purified by column chromatography using ethyl acetate/hexane (98:2) furnished **4g** (0.124 g, 29%) as white solid; [found: C, 77.78; H, 5.91; N, 3.45. $C_{25}H_{23}NO_3$ requires C, 77.90; H, 6.01; N, 3.63%]; mp 166–168 °C; R_f (5% ethyl acetate/hexane) 0.49; ν_{max} (KBr) 1658 (C=C), 1595 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 11.94 (1H, br s, OH), 7.28–7.16 (10H, m, ArH), 7.03 (2H, t, *J* 7.2 Hz, ArH), 6.67 (1H, t, *J* 7.6 Hz, ArH), 6.55 (2H, d, *J* 8.4 Hz, ArH), 5.99 (1H, s, H-2), 5.12 (1H, t, *J* 5.2 Hz, H-6), 3.87 (3H, s, OMe), 3.08 (1H, dd, *J* 16.2, 5.6 Hz, H-5′), 2.73 (1H, dd, *J* 16.4, 4.8 Hz, H-5″); δ_C (100 MHz, $CDCl_3$) 170.8, 170.5, 142.7, 142.3, 128.9, 128.8, 128.5, 127.3, 127.1, 127.0, 126.6, 118.3, 116.5, 102.2, 57.6, 56.9, 52.2, 36.8.

*4.2.24. Methyl 4-hydroxy-2,6-bis(4-nitrophenyl)-1-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (**4n**).* Purification was performed by column chromatography using ethyl acetate/hexane (95:5) to furnished **4n** (0.057 g, 12%) as light yellow solid; [found: C, 63.02; H, 4.31; N, 8.71. $C_{25}H_{21}N_3O_7$ requires C, 63.15; H, 4.45; N, 8.84%]; mp 173–175 °C; R_f (15% ethyl acetate/hexane) 0.26; ν_{max} (KBr) 1638 (C=O), 1595 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 11.99 (1H, br s, OH), 8.11 (4H, t, *J* 7.2 Hz, ArH), 7.36 (2H, d, *J* 8.4 Hz, ArH), 7.33 (2H, d, *J* 8.4 Hz, ArH), 7.04 (2H, t, *J* 7.6 Hz, ArH), 6.76 (1H, t, *J* 7.2 Hz, ArH), 6.46 (2H, d, *J* 8.0 Hz, ArH), 5.95 (1H, s, H-2), 5.13 (1H, t, *J* 5.2 Hz, H-6), 3.85 (3H, s, OMe), 3.07 (1H, dd, *J* 17.2, 4.8 Hz, H-5′), 2.76 (1H, dd, *J* 17.2, 5.2 Hz, H-5″); δ_C (100 MHz, $CDCl_3$) 170.7, 149.4, 147.5, 129.3, 128.1, 127.8, 124.3, 123.9, 120.7, 118.2, 101.0, 58.4, 56.5, 52.4, 36.9.

*4.2.25. Methyl 1-(2-naphthyl)-4-(2-naphthylamino)-2,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carboxylate (**1v**).* Reaction was carried out with 2-naphthylamine (1 mmol), methyl acetoacetate (0.5 mmol) and benzaldehyde (1 mmol) in methanol (3 mL) in the presence of 10 mol % iodine at room temperature or at 55 °C. After completion of reaction, solid precipitate was filtered and washed with ethanol to give **1v** (0.297 g, 53%) as white solid; [found: C, 83.38; H, 5.63; N, 5.10. $C_{39}H_{32}N_2O_2$ requires C, 83.54; H, 5.75; N, 5.00%]; mp 196–198 °C; R_f (5% ethyl acetate/hexane) 0.30; ν_{max} (KBr) 3421 (N–H), 1657 (C=O), 1594 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.45 (1H, s, NH), 7.75 (1H, dd, *J* 8.0, 2.0 Hz, ArH), 7.59 (2H, t, *J* 8.4 Hz, ArH), 7.56–7.52 (2H, m, ArH), 7.47–7.41 (3H, m, ArH), 7.34–7.33 (4H, m, ArH), 7.31–7.20 (7H, m, ArH), 7.11 (1H, t, *J* 8.0 Hz, ArH), 6.97 (1H, dd, *J* 9.2, *J* 2.4 Hz, ArH), 6.77 (1H, d, *J* 2.4 Hz, ArH), 6.66 (1H, s, ArH), 6.59 (1H, s, H-2), 6.55 (1H, dd, *J* 8.8, 2.4 Hz, ArH), 5.30 (1H, br s, H-6), 3.99 (3H, s, OMe), 2.93 (2H, d, *J* 4.0 Hz, CH_2); δ_C (100 MHz, $CDCl_3$) 168.8 (C=O), 156.4 (C-4), 145.1, 144.0, 143.1, 135.5, 135.0, 133.5, 131.8, 129.1, 128.8, 128.5, 127.8, 127.7, 127.5, 127.4, 126.9, 126.7, 126.6, 126.5, 126.2, 125.9, 125.0, 123.3, 122.0, 116.2, 107.2, 98.4 (C-3), 58.6 (C-6), 55.4 (C-2), 51.4, 33.7 (C-5).

*4.2.26. Methyl 2,6-bis(4-methylphenyl)-1-(2-naphthyl)-4-(2-naphthylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (**1w**).* Reaction carried out with 2-naphthylamine (1 mmol), methyl acetoacetate (0.5 mmol) and methylbenzaldehyde (1 mmol) in methanol (3 mL) in the presence of 10 mol % iodine at room temperature. After completion, solid precipitate formed was filtered and washed with ethanol to give **1w** (0.300 g, 51%) as white solid; [found: C, 83.49; H, 5.91; N, 4.71. $C_{41}H_{36}N_2O_2$ requires C, 83.64; H, 6.16; N, 4.76%]; mp 220–222 °C; R_f (5% ethyl acetate/hexane) 0.33; ν_{max} (KBr) 3445 (N–H), 1656 (C=O), 1593 (C=C) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 10.45 (1H, s, NH), 7.75 (2H, d, *J* 7.2 Hz, ArH), 7.60 (2H, t, *J* 8.8 Hz, ArH), 7.54–7.50 (2H, m, ArH), 7.47–7.42 (3H, m, ArH), 7.25–7.23 (3H, m, ArH), 7.14 (4H, s, ArH), 7.09 (2H, t, *J* 8.0 Hz, ArH), 6.98 (1H, dd, *J* 9.2, 2.4 Hz, ArH), 6.77 (1H, d, *J* 2.0 Hz, ArH), 6.60 (1H, s, H-2), 6.59–6.57 (2H, m, ArH), 5.26 (1H, br s, H-6), 3.98 (3H, s, OMe), 2.91 (2H, d, *J* 4.0 Hz, CH_2), 2.39 (3H, s, Me), 2.32 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 168.9 (C=O), 156.4 (C-4), 145.2, 141.0, 140.1, 137.0, 136.1, 135.6, 135.0, 133.6, 131.5, 129.7, 129.2, 129.0, 128.7, 127.8, 127.6, 127.5, 126.8, 126.6, 126.5, 126.4, 126.1, 125.8, 125.0, 123.2, 121.9, 116.2, 107.1, 98.5 (C-3), 58.4 (C-6), 55.2 (C-2), 51.3, 33.7 (C-5), 21.4, 21.2.

4.2.27. Ethyl 3-oxo-4-phenylbutanoate. It was prepared according to the literature procedure[19] from phenylacetyl chloride. To a solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (1.44 g, 10 mmol) in CH_2Cl_2 (6 mL) at 0 °C in 100 mL round-bottomed flask equipped with a dropping funnel was added pyridine (2 mL) over 5 min. To this solution was then added a solution of phenylacetyl chloride (1.33 mL, 10 mmol) in CH_2Cl_2 (14 mL) over 10 min. This resulted in the formation of an orange solution. The reaction was stirred at 0 °C for 30 min and at rt for 1 h. CH_2Cl_2 (20 mL) was added and the solution was washed with water (30 mL×4). The organic phase was dried over $MgSO_4$ and the solvent was removed to give as an orange oil (2.2 g). This was dissolved in EtOH (30 mL) and heated at reflux for 3 h. Evaporation of the solvent afforded crude as an orange oil, which was purified by column chromatography using ethyl acetate/hexane (98:2) furnished (1.65 g, 80%) as a colourless oil; R_f (2% ethyl acetate/hexane) 0.4; ν_{max} (KBr) 1744 (C=O), 1716 (C=O) cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.36–7.28 (3H, m, ArH), 7.21 (2H, d, *J* 7.2 Hz, ArH), 4.17 (2H, q, *J* 7.2 Hz, OCH_2), 3.83 (3H, s, $PhCH_2$), 3.45 (2H, s, $COCH_2CO$), 1.26 (3H, t, *J* 7.2 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 200.6, 167.2, 133.4, 129.7, 129.0, 127.5, 61.5, 50.1, 48.4, 14.2.

4.3. Crystallographic description

Crystal data were collected with Bruker Smart Apex-II CCD diffractometer using graphite monochromated Mo Kα radiation (λ=0.71073 Å) at 298 K. Cell parameters were retrieved using SMART[20a] software and refined with SAINT[20a] on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS[20b]. The structure was solved by direct methods implemented in SHELX-97[20c] program and refined by full-matrix least-squares methods on F2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions. Compound **1f** empirical formula $C_{34}H_{32}Cl_2N_2O_2$, colourless prismatic crystal, formula wt 571.52, monoclinic, *P*2(1)/*n*, a=11.2764(3), b=12.9186(4), c=20.6225(6) Å, V=2976.78(15) Å^3, Z=4, F (0 0 0)=1200, GOF(S)=0.958. Final indices R_{obs}=0.0545, wR_{obs}=0.1747 with $I>2r(I)$; R_{all}=0.1118, wR_{all}=0.1924 for all data. Compound **1k** empirical formula $C_{31}H_{26}Br_2N_2O_2$, colourless prismatic crystal, formula wt 618.36, triclinic, *P*-1 a=10.1710(5), b=10.7901(5), c=13.9201(6) Å, V=1385.53(11) Å^3, Z=2, F (0 0 0)=624, GOF(S)=0.994. Final indices R_{obs}=0.0434, wR_{obs}=0.1026 with $I>2r(I)$; R_{all}=0.1047, wR_{all}=0.1289 for all data.

Complete crystallographic data of **1f** and **1k** for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, as supplementary publication CCDC no. are 756203 and 756204. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).

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Supplementary data

The general experimental procedures, X-ray crystallographic data (CIF file) of **1f** and **1k** as well as copies of ^1H and ^{13}C NMR and HRMS spectra of products. This information can be found in the online version, at doi:10.1016/j.tet.2010.07.075. These data include MOL files and InChIKeys of most important compounds described in this article.

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Sequential three-component reactions: synthesis, regioselectivity and application of functionalized dihydropyridines (DHPs) for the creation of fused naphthyridines

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ABSTRACT

Facile and efficient synthesis of tetrasubstituted 1,4- and 1,6-dihydropyridines (DHPs) has been achieved by employing three-component domino reaction using dimethyl acetylenedicarboxylate (DMAD), aliphatic amines, and α,β-unsaturated aldehyde in the presence of 30 mol % trifluoroacetic acid. Interestingly, regioselectivity for the synthesis of 1,4-dihydropyridines can be increased by using 30 mol % triflic acid. In addition, the synthesis of fused-naphthyridine derivatives has been accomplished involving imino-Diels–Alder reaction by employing 1,4-dihydropyridines, aromatic aldehydes, and aromatic amines.

Multi-component reactions (MCRs) have been proven to be an elegant and sophisticated approach to access complex structures in a single step from readily available synthetic precursors.[1] Superior atom economy, simpler procedures, lower costs, high variability, and high bond forming efficiency (BFE) are some important features of MCRs.[2]

Nitrogen containing heterocycles are widely distributed in natural products and pharmaceutically important small molecules. Among them, dihydropyridines (DHPs) represent an important class of the nitrogen-heterocycle. They exhibit a diverse range of biological activities[3] such as those for the treatment of cardiovascular disease and hypertension,[4] potent calcium channel antagonist, and agonist.[5] They also have potential application in other pharmacological activities.[6–10] In addition, they have been used as a hydride source for reductive amination[11] and used as synthetic intermediates.[12,13] After the first synthesis of dihydropyridines reported by Hantzsch,[14] many synthetic efforts have been made from all over the world to access these compounds due to their medicinal and synthetic usefulness.[15,16] In this Letter, we wish to report a three-component domino reaction for the synthesis of unsymmetrically substituted 1,4- and 1,6-DHPs, an improved method for regioselective synthesis of 1,4-DHPs and its application for the synthesis of naphthyridine derivatives using imino-Diels–Alder reaction.

With this objective, the reaction of dimethyl acetylenedicarboxylate (DMAD, **1**, 1 mmol), benzylamine (**2a**, 1 mmol), and crotonaldehyde (**3a**, 1 mmol) was carried out with 20 mol % of trifluoroacetic acid (TFA) in dicholoromethane and afforded two products **4a** and **5a** with overall 62% yield with the ratio of 56:44. The structures of compounds **4a** and **5a** were determined by IR, ^{1}H NMR, ^{13}C NMR spectra and from their elemental analysis. After obtaining the desired products, a suitable reaction condition was tried to find out both in terms of yield and selectivity of products. A series of experiments were performed with various catalysts such as TFA, acetic acid, pTSA, and triflic acid (TfOH) by varying the amounts of catalysts. Different solvents, such as DCM, DCE, MeOH, MeCN, THF, and toluene were also screened. The results and observations are summarized in Table SI-1, (Supplementary data). From these experiments, two optimized reaction conditions were obtained. Method A in which both the products **4a** and **5a** were obtained nearly in equal amounts with 82% overall yield from the reaction of **1**, **2a**, and **3a** using 30 mol % of TFA in THF. In method B a regioselective 1,2,3,4-tetrasubstituted dihydropyridine (**4a**) was obtained in 76% yield using TfOH acid (30 mol %) in THF.

After optimizing the reaction conditions, the reaction was performed with DMAD (**1**, 1 mmol), *n*-butylamine (**2b**, 1 mmol), and crotonaldehyde (**3a**, 1.2 mmol) by the following method A. Both the products **4b** and **5b** were obtained in the ratio of 55:45, respectively with 83% being the total yield. The scope of this protocol was further examined with various aliphatic amines, such as *iso*-butylamine, *iso*-propylamine, *n*-hexylamine, cyclohexylamine, and furfurylamine. The corresponding dihydropyridine derivatives **4c**–**g**

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and **5c**–**g** were obtained in good yields and the ratio of the products is shown in Table 1 (entries 3–7).

We turned our attention toward synthesis of regioselective 1,4-DHPs by the following method B. The mixture of DMAD (**1**, 1 mmol), *n*-butylamine (**2b**, 1 mmol) and crotonaldehyde (**3a**, 1.2 mmol) was stirred using method B and the major product **4b** was obtained in 72% yield.

Encouraged by this result, the reaction of various other amines, such as *iso*-butylamine, *iso*-propylamine, *n*-hexylamine, cyclohexylamine, furfurylamine, and ethylamine was also studied with DMAD and crotonaldehyde under identical reaction conditions. The reaction time and percentage yield of the products **4c**–**h** are summarized in Table 1.

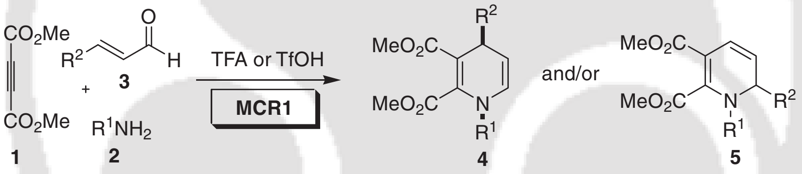
Cinnamaldehyde exhibits similar regioselectivity pattern in both protocols as mentioned in Table 1, however method B furnished good yields of products **4i** and **j**. All these products were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectra as well as elemental analysis. The structure of compound **4i** was confirmed by X-ray crystallographic analysis (Fig. SI1). The present methods were unsuccessful for the synthesis of substituted *N*-aryl dihydropyridines using aniline by following both the methods; this may be due to less nucleophilicity of aniline as compared to aliphatic amines.

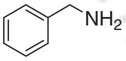
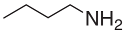
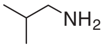
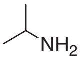
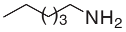
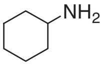
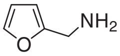
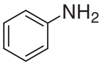
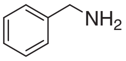
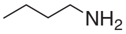
We propose a plausible mechanism for the formation of 1,4 and 1,6-DHPs. Initially, the amine reacts with DMAD to form hydroamination product **A**. The intermediate **A** reacts with α,β-unsaturated aldehyde in two ways either *path a* or *path b*. In *path a*, the intermediate **A** on reaction with α,β-unsaturated aldehyde leads to the formation of intermediate imine **B** which on electrocyclic cyclization gives the 1,4-dihydropyridine derivative **4**. In *path b*, the intermediate **C** is formed from the intermediate **A** on reaction with α,β-unsaturated aldehyde via Michael addition reaction. Finally, 1,6-dihydropyridine derivative **5** is obtained through cyclization from **C** followed by dehydration as shown in Scheme 1. We believe that *path a* is preferred to *path b* in the case of TfOH ($pK_a = -15$) which is highly acidic as compared to TFA ($pK_a = 0.5$), which favors imine formation by protonation of the carbonyl group as compared to Michael addition reaction.

The synthetic utility of 1,4-DHPs as a dienophile in imino-Diels–Alder reaction (Povarov reaction),[17] has been demonstrated for the synthesis of substituted naphthyridine derivatives for the creation of molecular diversity. The applications of 1,4-dihydropyridine as a dienophile have been described for Povarov reaction by others.[13] However, the newly designed 1,2,3,4-tetrasubstituted dihydropyridines having α and β amino acid functionality have remained unexplored, which may offer a new platform for the synthesis of different substituted naphthyridine derivatives.

With this idea in mind, a three component one-pot reaction was conducted with 1,4-DHP (**4a**), benzaldehyde, and aniline catalyzed by 20 mol % of $BF_3{\cdot}OEt_2$ in acetonitrile. The cycloaddition reaction

Table 1
Synthesis of various 1,2,3,4- and/or 1,2,3,6-tetrasubstituted dihydropyridines **4** and **5**[19]



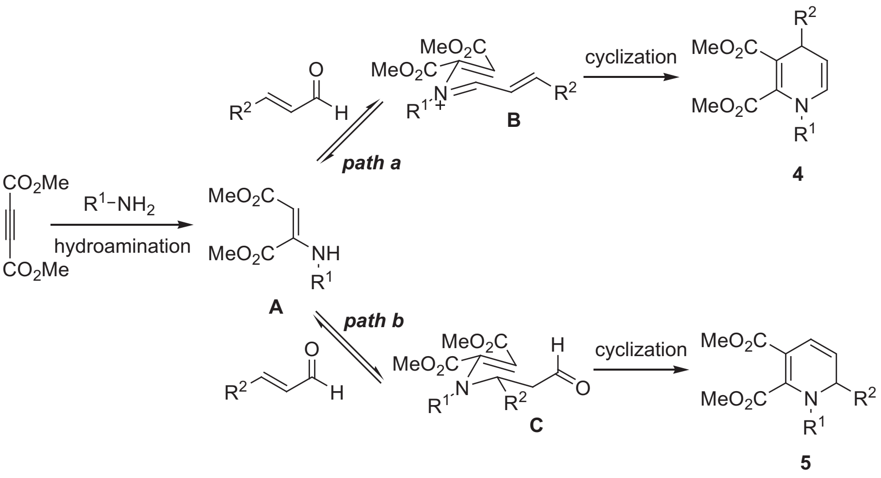
Entry	R^1NH_2	R^2	Method A		Method B	
			Ratio[a] (**4**:**5**)	Yield[b](%)	Ratio[a] (**4**:**5**)	Yield[c] (%)
1		Me	51:49	82	88:12	**4a**, 76
2		Me	55:45	83	86:14	**4b**, 72
3		Me	58:42	83	87:13	**4c**, 75
4		Me	60:40	82	83:17	**4d**, 69
5		Me	55:45	82	86:14	**4e**, 72
6		Me	54:46	81	88:12	**4f**, 73
7		Me	48:52	83	86:14	**4g**, 72
8		Me			78:22	**4h**, 57
9		Me	No reaction	–	–	No reaction
10		Ph	80:20	59	82:18	**4i**, 62
11		Ph	75:25	56	80:20	**4j**, 58

Method A: DMAD (1 mmol), Amines (1 mmol), enals (1.2 mmol) and TFAA (0.3 mmol) in THF at rt.
Method B: DMAD (1 mmol), Amines (1 mmol), enals (1.2 mmol) and TfOH (0.3 mmol) in THF at rt.

[a] Product ratio determined by crude ^{1}H NMR.

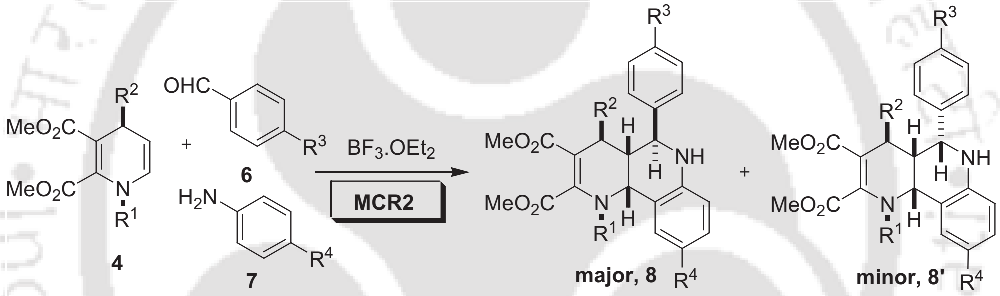
[b] Combined yields of **4** and **5**.

[c] Isolated yields.



Scheme 1. Proposed mechanism for amination reaction of DMAD promoting for cascade reaction.

Table 2
Synthesis of substituted naphthyridine derivatives **8**[20]



Entry	R^1	R^3	R^4	Time (h)	Ratio[a]	Yield[b] (%)
1	Bn	H	H	6	4:1	**8a**, 65
2	Bn	Me	H	6	3:1	**8b**, 61
3	Bn	MeO	H	6	4:1	**8c**, 63
4	Bn	Cl	H	8	4:1	**8d**, 54
5	Bn	Br	H	8	4:1	**8e**, 62
6	Bn	NO_2	H	10	3:1	**8f**, 51
7	Bn	Cl	MeO	6	2:1	**8g**, 52 **8g′**, 21
8	Bn	Cl	Me	6	2:1	**8h–h′**, 76
9	*n*-C_4H_9	H	H	10	3:1	**8i**, 59

[a] Ratio determined by crude ^{1}H NMR.
[b] Isolated yield.

afforded two diastereomers **8a** and **8a′** with a ratio of 4:1. The major isomer **8a** was isolated in 65% yield. Likewise, the reaction of **4a** with aniline and other aromatic aldehydes substituted with Me, MeO, Cl, Br, and NO_2 at position 4 was also investigated. The reactions proceeded smoothly and various substituted naphthyridine derivatives **8b**–**f** were obtained in good yields. The reaction of aniline derivatives such as 4-methylaniline and 4-methoxyaniline was also studied under similar conditions and the results are summarized in Table 2. Similar diastereoselectivity was observed by others[18] for imino-Diels–Alder reaction with an electron rich dienophile. However, we have obtained relatively lower diastereoselectivity in the case of 4-methyl aniline and 4-methoxyaniline due to steric repulsion between the benzyl group and a methyl or methoxy group present at the 4th-position. Finally, the reaction of 1,4-DHP **4b** with benzaldehyde and aniline was performed and gave major isomer **8i** in 59% yield.

The functionalized naphthyridine derivatives have four contiguous stereocenters, and gave only two diastereoisomers. A fairly good diastereoselectivity was observed in the above study. The structures of all the compounds were ascertained by usual spectroscopic studies as well as the literature precedent.[13] For example, the structure of compound **8i** was established by NMR (^{1}H, ^{13}C, COSY, NOESY). This isomer shows ^{1}H NMR peaks with δ values 4.42, 1.93, and 4.16 for H_1, H_2, and H_4, all having doublets with coupling constants $J_{1,2} = 2.0$ Hz and $J_{2,4} = 10.8$ Hz, representing *cis* arrangement of hydrogen between two ring fusions. The proton H_4 is *trans* with ring junction proton H_2. In addition, H_1, H_2, and Me are all in same plane, however, H_3 and H_4 are in other planes depicted by NOE as shown in Figure 1. Finally, the observed structure and stereochemistry were fully supported by single crystal X-ray structure determination of compound **8b** (major isomer) and **8g′** (minor isomer) as shown in Figure 2.[21]

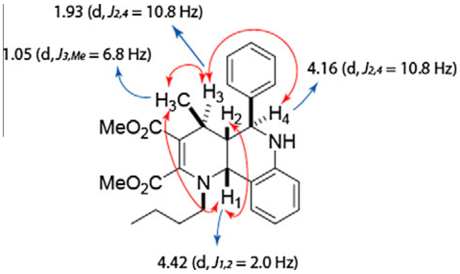
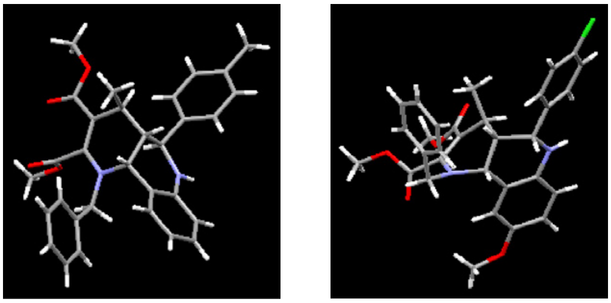


Figure 1. Diagnostic ^{1}H NMR and NOE of **8i**.



8b (CCDC no. 810814) **8g′** (CCDC no. 810813)

Figure 2. X-ray crystal structures of **8b** and **8g′**.

In conclusion, the Brønsted acid catalyzed synthesis of unsymmetrical tetrasubstituted 1,4- and 1,6-DHPs using one-pot three-component reactions of DMAD, aliphatic amines, and α,β-unsaturated aldehydes have been accomplished. The regioselective synthesis of tetrasubstituted 1,4-DHPs were also achieved in good yields. These 1,4-DHPs can be used for a new class of dienophiles for imino-Diels–Alder reaction for the construction of highly substituted naphthyridine derivatives. The significant advantages of present protocol are simple experimental procedure, nontoxic byproduct, high atom economy, good regioselectivity, and diastereoselectivity. The new heterocyclic entities containing β-amino acid skeleton might exhibit interesting pharmacological activities. Further studies on regioselectivity and applications of these DHPs are going on in our laboratory which will be reported in due course of time.

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Supplementary data

Supplementary data (optimization table, X-ray crystallographic data (CIF file) of **4i**, **8b** and **8g′**, spectral data of all compounds and copies of ^{1}H and ^{13}C NMR spectra of products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.098.

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19. *General procedure for 1,4- and 1,6-dihydropyridines **4** and **5***: Method A: To a stirred solution of dimethyl acetylenedicarboxylate **1** (DMAD, 1.0 mmol) in THF (2 mL) was added amine **2** (1.0 mmol) at room temperature. After 10 min of stirring, α,β-unsaturated aldehyde **3** (1.2 mmol) and trifluoroacetic acid (0.3 mmol) were added successively and kept for further stirring. After completion of reaction (monitored by TLC), the reaction mixture was neutralized with $NaHCO_3$ solution and it was extracted with DCM (20 mL × 2). The organic phase was washed with water, brine solution, and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the crude mixture was purified through silica gel chromatography using hexane/ethyl acetate/NEt_3 (92:7:1) and it afforded the products **4a–j** and **5a–j**, respectively in good yields. For Method B, the same procedure was followed except that the catalyst triflic acid (30 mol %) is used in place of TFA. *Compound* **4a**: yellow liquid (126 mg, 42%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.24 (m, 5 H), 5.75 (d, 1H, J = 7.2 Hz), 4.87 (dd, 1H, J = 7.2 Hz, J = 5.6 Hz), 4.36 (d, 1H, J = 16.4 Hz), 4.28 (d, 1H, J = 16.4 Hz), 3.78 (s, 3H), 3.68 (s, 3H), 3.39–3.32 (m, 1H), 1.08 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 166.1, 144.3, 137.0, 128.9, 128.0, 127.6, 127.3, 110.6, 101.2, 54.6, 52.9, 51.6, 27.1, 25.3; IR ν_{max} (KBr): cm^{-1} 2951, 1739, 1695, 1575, 1434, 1269, 1216, 1187, 734. Anal Calcd for $C_{17}H_{19}NO_4$ (301.34): C, 67.76; H, 6.36; N, 4.65; found: C, 67.71; H, 6.32; N, 4.58. *Compound* **5a**: yellow liquid (121 mg, 40%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.29 (m, 5H), 6.41 (d, 1H, J = 9.6 Hz), 5.02 (dd, 1H, J = 9.6 Hz, J = 5.2 Hz), 4.37 (d, 1H, J = 15.6 Hz), 4.30 (d, 1H, J = 15.6 Hz), 3.98–3.93 (m, 1H), 3.87 (s, 3H), 3.71 (s, 3H), 1.14 (d, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 166.0, 147.9, 136.4, 128.9, 128.2, 127.7, 121.3, 114.9, 97.8, 54.4, 53.1, 52.7, 51.3, 19.2; IR ν_{max} (KBr): cm^{-1} 2950, 1739, 1693, 1542, 1434, 1297, 1230, 1125, 728. Anal Calcd for $C_{17}H_{19}NO_4$ (301.34): C, 67.76; H, 6.36; N, 4.65; found: C, 67.70; H, 6.31; N, 4.60.
20. *General procedure for synthesis of substituted tetrahydroquinoline derivatives* **8**: 1,4-DHP **4a** (0.3 mmol) was added to a stirring solution of aromatic aldehyde (0.3 mmol) and aromatic amine (0.3 mmol) in acetonitrile (2 mL). Finally, catalyst $BF_3{\cdot}OEt_2$ (20 mol %) was added to the reaction mixture and stirring was continued. After completion of the reaction (monitored by TLC), the mixture was extracted with DCM (20 mL × 2). The organic phase was washed with saturated solution of $NaHCO_3$, brine solution, and dried over Na_2SO_4. The

crude products were purified by silica gel chromatography (hexane/ethyl acetate, 85:15) to afford the products **8a–i** in good yields. *Compound* **8a**: White solid (94 mg, 65%); mp 242–245 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.28 (m, 5H), 7.28–7.23 (m, 2H), 7.18–7.12 (m, 2H), 7.10 (t, 2H, J = 7.2 Hz), 6.63 (d, 1H, J = 7.6 Hz), 6.51–6.47 (m, 2H), 4.42 (d, 1H, J = 2.8 Hz), 4.29 (d, 1H, J = 16.8 Hz), 4.25 (d, 1H, J = 10.8 Hz), 4.17 (s, 1H), 4.14 (d, 1H, J = 16.8 Hz), 3.78 (s, 3H), 3.65 (s, 3H), 2.43–2.36 (m, 1H), 1.92 (d, 1H, J = 10.8 Hz), 1.09 (d, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 166.9, 147.9, 144.3, 143.0, 137.6, 131.9, 130.2, 128.7, 128.6, 128.2, 128.0, 127.2, 127.1, 115.7, 115.6, 113.8, 98.3, 56.0, 52.8, 52.1, 51.2, 41.8, 26.9, 23.1; IR ν_{max} (KBr): cm^{-1} 3413, 2955, 1744, 1683, 1573, 1498, 1224, 1142, 1088, 735. Anal Calcd for $C_{30}H_{30}N_2O_4$ (482.57): C, 74.67; H, 6.27; N, 5.81; found: C, 74.61; H, 6.14; N, 5.71.

21. Complete crystallographic data of **4i**, **8b,** and **8g**′ for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC No. 810812, 810814 and 810813, respectively. Copies of this information may be obtained free of charge from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk or via: www.ccdc.cam.ac.uk).