

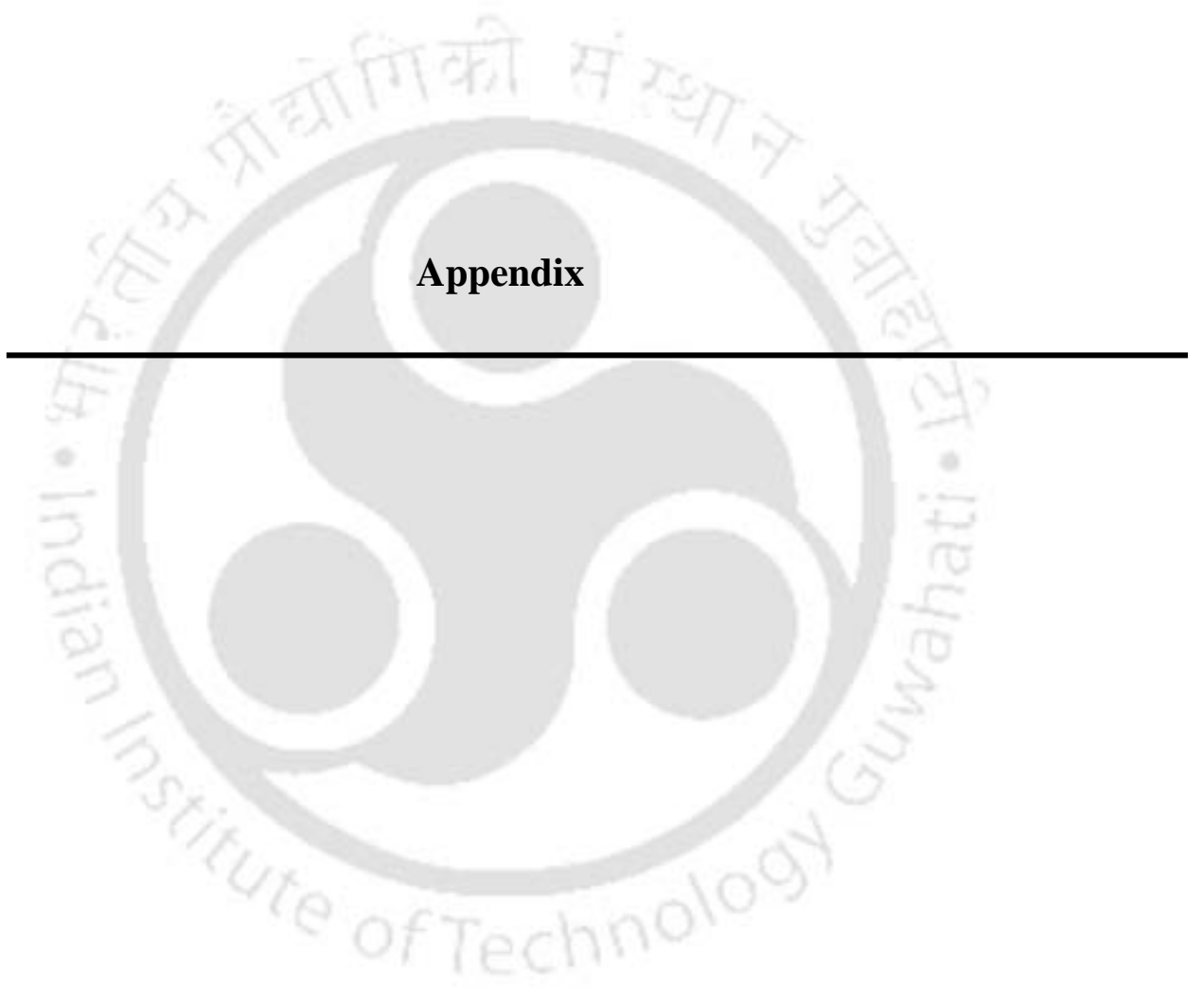
**INVESTIGATION OF BROMINATION REACTIONS USING ORGANIC
AMMONIUM TRIBROMIDE AND THEIR APPLICATIONS TOWARDS
BIOACTIVE NATURAL PRODUCTS SYNTHESIS**

*A Thesis Submitted
in Partial Fulfillment of the Requirements
for the Degree of*
DOCTOR OF PHILOSOPHY



by
GOPAL BOSE

to the
**DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY - GUWAHATI
North Guwahati, Guwahati -781 039
March, 2002**



Conclusion and Future Scope

In summary, we have developed a new synthetic protocol for the preparation of α -bromo-enones from their corresponding enones, synthesis of various naturally as well as non-naturally occurring highly substituted flavones and aurones from 2'-acetoxychalcones, and synthesis of 7-bromoaurones from 2'-hydroxychalcones.

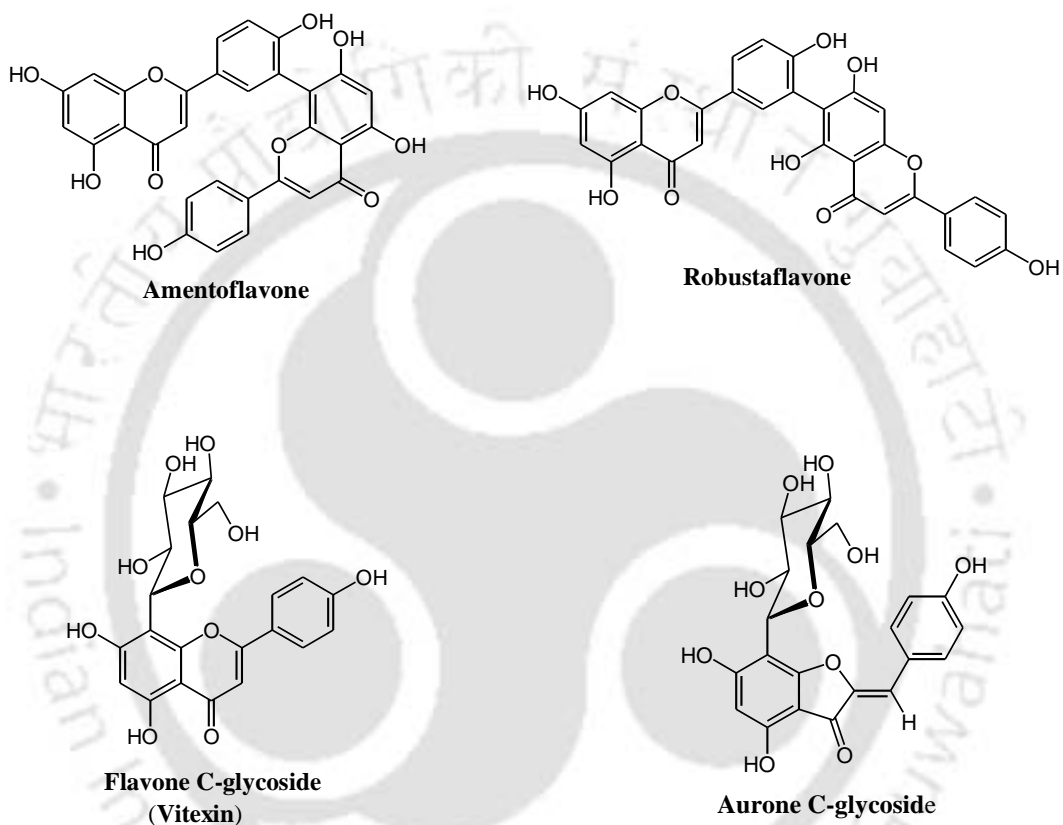
In all these methods, we have used solid organic ammonium tribromide particularly cetyltrimethylammonium tribromide (CetTMATB) and *n*-tetrabutylammonium tribromide (TBATB) instead of molecular bromine. In our protocols there are several advantages such as highly efficient and chemoselective, non-hazardous, easy to maintain stoichiometric ratio while performing the reaction.

In addition, we have demonstrated an unambiguous synthesis of flavones by tuning the cyclisation step using 0.1 M NaOMe solution in dry methanol. Mechanistically, we have shown that cyclisation is possible exclusively at the β -position of α -bromo-chalcones which are not reported earlier. We have also demonstrated unambiguous synthesis of aurones from 2'-acetoxychalcones by tuning the bromination and cyclisation steps which are very difficult till today. It is also important mechanistically that the cyclisation of the brominated products of 2'-acetoxychalcones are possible exclusively at the α -position. In addition, we have also accomplished the synthesis of various substituted 7-bromoaurones from 2'-hydroxychalcones, which are valuable starting materials for aurone C-glycoside synthesis. However, the synthesis of 8-bromoflavones could not be overcome by the strategy, which is applied for flavone synthesis. Interestingly, we have realized that the synthesis of 8-bromoflavone can be achieved under different reaction conditions, which will be reported in due course.

The future scope of our ongoing research includes the comparative study of other organic tribromides e.g. benzyltrimethylammonium tribromide in the preparation of α -bromo-enones, bromination of 2'-acetoxychalcones as well as 2'-hydroxychalcones. We have to synthesize 8-bromoflavone derivatives in substantial amount so that the synthesis of bisflavonoids such as amentoflavone and flavone C-glycoside such as vitexin can be achieved. Till today, the synthesis of 6-bromoflavone is not reported in literature, which is a valuable starting material

Conslusion and Future Scope

for the synthesis of biologically potent molecule robustaflavone. Therefore, the tasks are left in our hand to accomplish 8-bromo and 6-bromoflavone derivatives and further used them to the other natural product synthesis. As the research work is a continuous process, the remaining part of the work will be continued in future.



LIST OF AUTHOR'S PUBLICATIONS AND COMMUNICATIONS

1. Regioselective Bromination of Organic Substrates by Tetrabutylammonium Bromide Promoted by V_2O_5 - H_2O_2 : An Environmentally Favorable Synthetic Protocol.
U. Bora, G. Bose, M. K. Chaudhuri, S. S. Dhar, R. Gopinath, A. T. Khan and B. K. Patel, *Org. Lett.* **2000**, 2, 247.
2. A Convenient and Useful Method of Preparation of α -Bromoenones from the Corresponding Enones Using Organic Ammonium Tribromide (OATB).
G. Bose, P. M. B. Barua, M. K. Chaudhuri, D. Kalita and A. T. Khan, *Chemistry Lett.* **2001**, 290.
3. An Expedient and Efficient Method for the Cleavage of Dithioacetals to the Corresponding Carbonyl Compounds Using Organic Ammonium Tribromide (OATB).
E. Mondal and G. Bose and A. T. Khan, *Synlett* **2001**, 785.
4. Oxidative Cleavage of Diethyldithioacetals by Ammonium Bromide Promoted by $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ - H_2O_2 : A Useful Synthetic Protocol for Regeneration of Carbonyl Compounds.
A. T. Khan, J. Boruwa, E. Mondal and G. Bose, *Indian J. Chem.* **2001**, 40B, 1039.
5. An Environmentally Benign Synthesis of Aurones and Flavones from 2'-Acetoxychalcones Using n-Tetrabutylammonium Tribromide.
G. Bose, E. Mondal, A. T. Khan and M. J. Bordoloi, *Tetrahedron Lett.* **2001**, 42, 8907.
6. A Useful and Environmentally Benign Synthetic Protocol for Dethiolization by Employing Vanadium Pentoxide Catalyzed Oxidation of Ammonium Bromide by Hydrogen Peroxide.
E. Mondal, G. Bose, P. R. Sahu and A. T. Khan, *Chemistry Lett.* **2001**, 1158.
7. A Mild and Environmentally Benign Synthetic Protocol for Catalytic Hydrolysis of Thioglycosides.
P. M. Bujar Barua, P. R. Sahu, E. Mondal, G. Bose and A. T. Khan, *Synlett* **2002**, 81.

Author's Publications

8. A Useful and Convenient Synthetic Procedure for Hydrolysis of Thioglycosides.
E. Mondal, P. M. Bujar Barua, G. Bose and A. T. Khan, *Chemistry Lett.* **2002**, 210.
9. An Exceptionally Simple and Catalytic Method for Regeneration of Carbonyl
Functionality from Their Corresponding 1,3-Oxathiolanes.
E. Mondal, P. R. Sahu, G. Bose and A. T. Khan, *J. Chem. Soc., Perkin Trans. I.* **2002**,
(in press).
10. A Useful and Convenient Synthetic Protocol for Interconversion of Carbonyl
Compounds to the Corresponding 1,3-Oxathiolanes and Vice-versa by Employing
Organic Ammonium Tribromide (OATB).
E. Mondal, P. R. Sahu, G. Bose and A. T. Khan *Tetrahedron Lett.* **2002**, 43, (in press).
11. A Short and Convenient Synthesis of 8-Bromoflavones and 7-Bromoaurones.
G. Bose and A. T. Khan, *Tetrahedron*. Submitted for Publication.

References

1. Auwers, v. K.; Muller, K. *Chem. Ber.* **1908**, *41*, 4233.
2. Auwers, K. von; Anschutz, L. *Dtsch. Chem. Ber.* **1921**, *54*, 1543.
3. Warriar, A. M.; Khanolkar, A. P.; Hutchins, W. A.; Wheeler, T. S. *Current Science* **1937**, *5*, 475.
4. Algar, J.; Flynn, J. P. *Proc. Roy. Irish Acad.* **1934**, *42B*, 1.
5. Oyamada, T. *J. Chem. Soc. Japan* **1934**, *55*, 1256.
6. Donnelly, J. A.; Fox, M. J.; Sharma, T.C. *tetrahedron* **1979**, *35*, 875.
7. Bien, S.; Ber, M.; Flohr, E. *Israel J. Chem.* **1967**, *5*, 51.
8. Donnelly, J. A.; Doran, H. J. *Tetrahedron* **1975**, *31*, 1791.
9. Varma, R. S.; Varma, M. *Tetrahedron Lett.* **1992**, *33*, 5937.
10. Shimokoriyama, M., In *The Chemistry of Flavonoid Compounds*; Eds.; T. A. Geissman, 1962; p. 305.
11. Orzalesi, H.; Castel, J.; Flandre, O.; Darmanaden, R.; Damon, M. *Ger. Offen.* 2,829,619 (*Chem. Abstr.* **1979**, *90*, 197859z).
12. (a) Roger, C. R. *Experientia* **1988**, *44*, 725. (b) Havsteen, B. *Biochem. Pharmacol.* **1983**, *32*, 1141. (c) Middleton, E. Jr.; Kandaswami, C. *Biochem. Pharmacol.* **1992**, *43*, 1167.
13. Edwards, J. M.; Raffauf, R. F.; Quesne, W. L. *J. Nat. Prod.* **1979**, *42*, 85.
14. Verma, A.; Johnson, J. A.; Gould, M. N.; Tanner, M. A. *Cancer Res.* **1988**, *48*, 5754.
15. Kandaswami, C.; Perkins, E.; Solonuk, D. S.; Drzewiecki, G. Middleton, E. Jr. *Cancer Letters* **1991**, *56*, 147.
16. Teo, C. C.; Kon, O. L.; Sim, K. Y.; Ng, S. C. *J. Med. Chem.* **1992**, *35*, 1330.
17. Markaverich, B. M.; Gregory, R.; Varma, R. S.; Varma, M.; Clerk, J.; Waldrep, J. C. *PCT Int. Appl.* WO 9117,749 (*Chem. Abstr.* **1992**, *116*, 120880x).
18. Kajigaeshi, S.; Kakinami, T.; Hirakawa, T. *Chem. Lett.* **1987**, 627.

19. Geissman, T. A.; Harborne, J. B. *J. Am. Chem. Soc.* **1956**, 78, 832.
20. Postema, M. H. D., Ed. *C-Glycoside synthesis*, CRC press: London, 1995; pp 297-300.
21. Muller, D.; Fleury, J. P. *Tetrahedron Lett.* **1991**, 32, 2229 and references therein.
22. Varshney, A. K.; Rahman, W.; Okigawa, M.; Kawano, N. *Experientia* **1973**, 29, 784.
23. Zembower, D. E.; Zhang, H. *J. Org. Chem.* **1998**, 63, 9300.
24. Postema, M. H. D. Ed. *C-Glycoside synthesis*; CRC press: London, 1995.
25. Chang, C. T.; Chen, T.S.; Chen, F. C. *J. Org. Chem.* **1961**, 26, 3142.



CHAPTER 3

REFERENCES

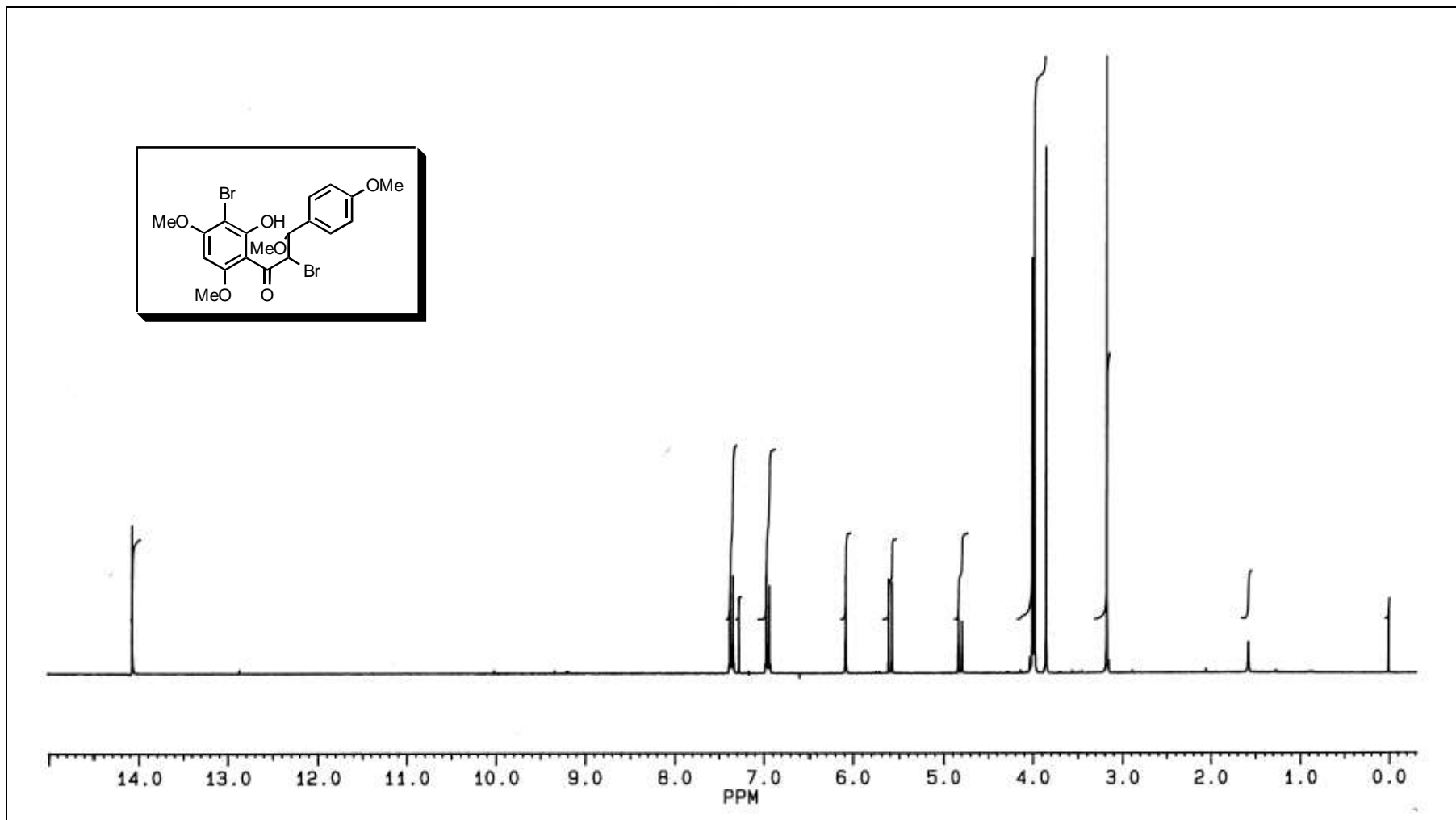


Figure 24: ¹H-NMR spectrum of 1-(3-Bromo-2-hydroxy-4,6-dimethoxyphenyl)-2-bromo-3-methoxy-3-(4-methoxyphenyl)propan-1-one (300 MHz, CDCl₃) (**27b**)

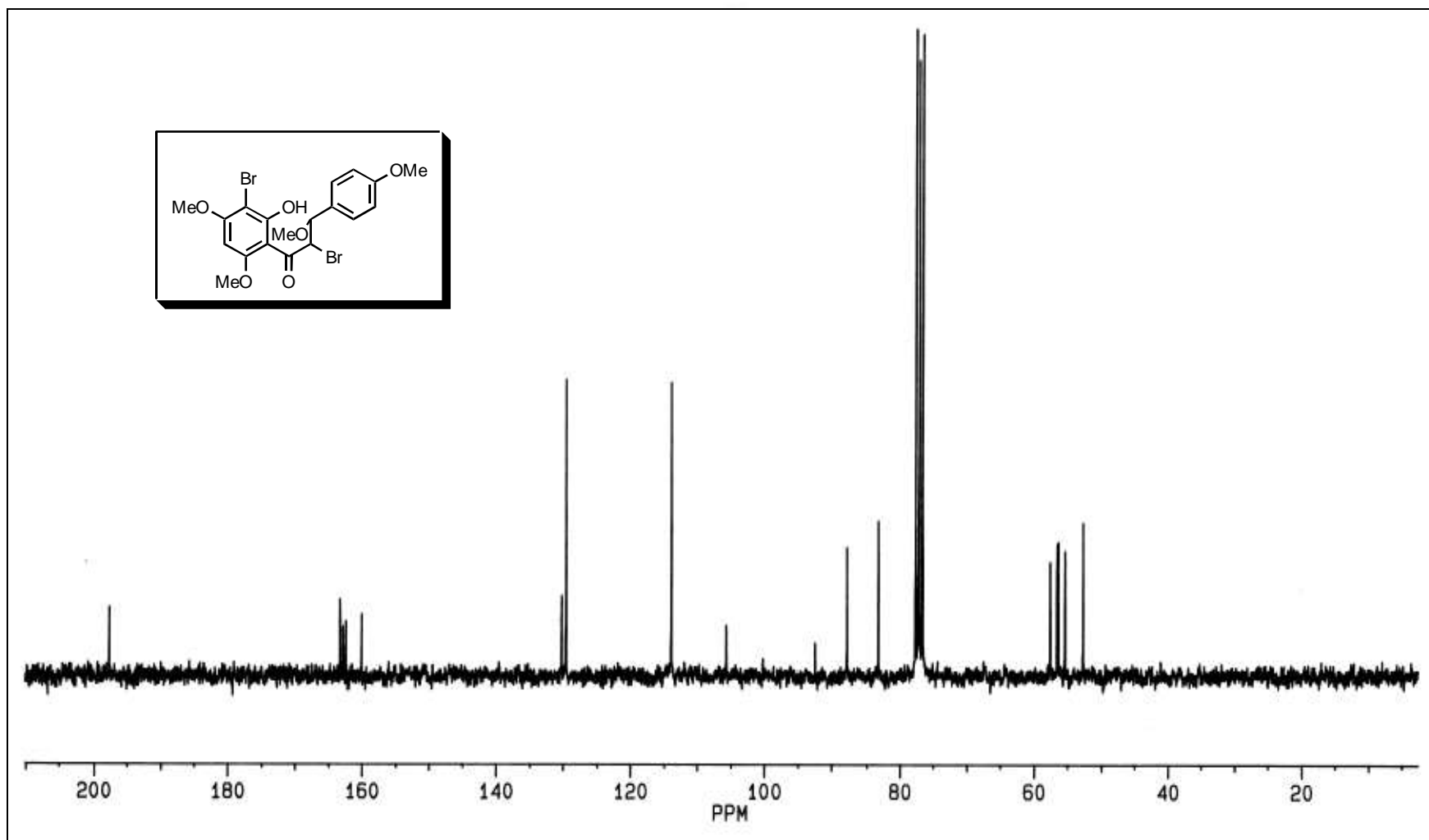


Figure 25: ¹³C-NMR spectrum of 1-(3-Bromo-2-hydroxy-4,6-dimethoxyphenyl)-2-bromo-3-methoxy-3-(4-methoxyphenyl)propan-1-one (75 MHz, CDCl₃) (**27b**)

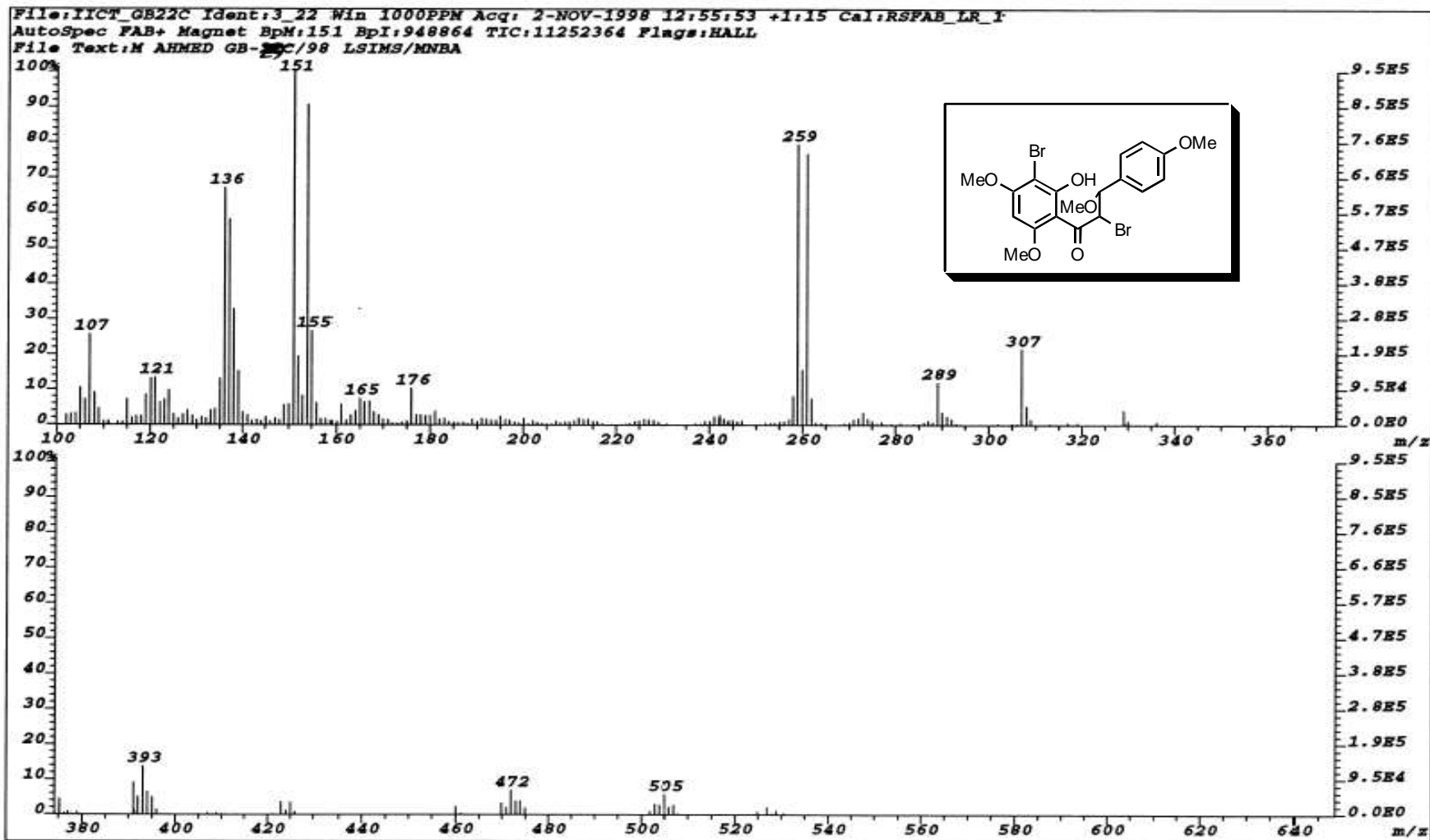


Figure 26: Mass spectrum of 1-(3-Bromo-2-hydroxy-4,6-dimethoxyphenyl)-2-bromo-3-methoxy-3-(4-methoxyphenyl)propan-1-one (27b)

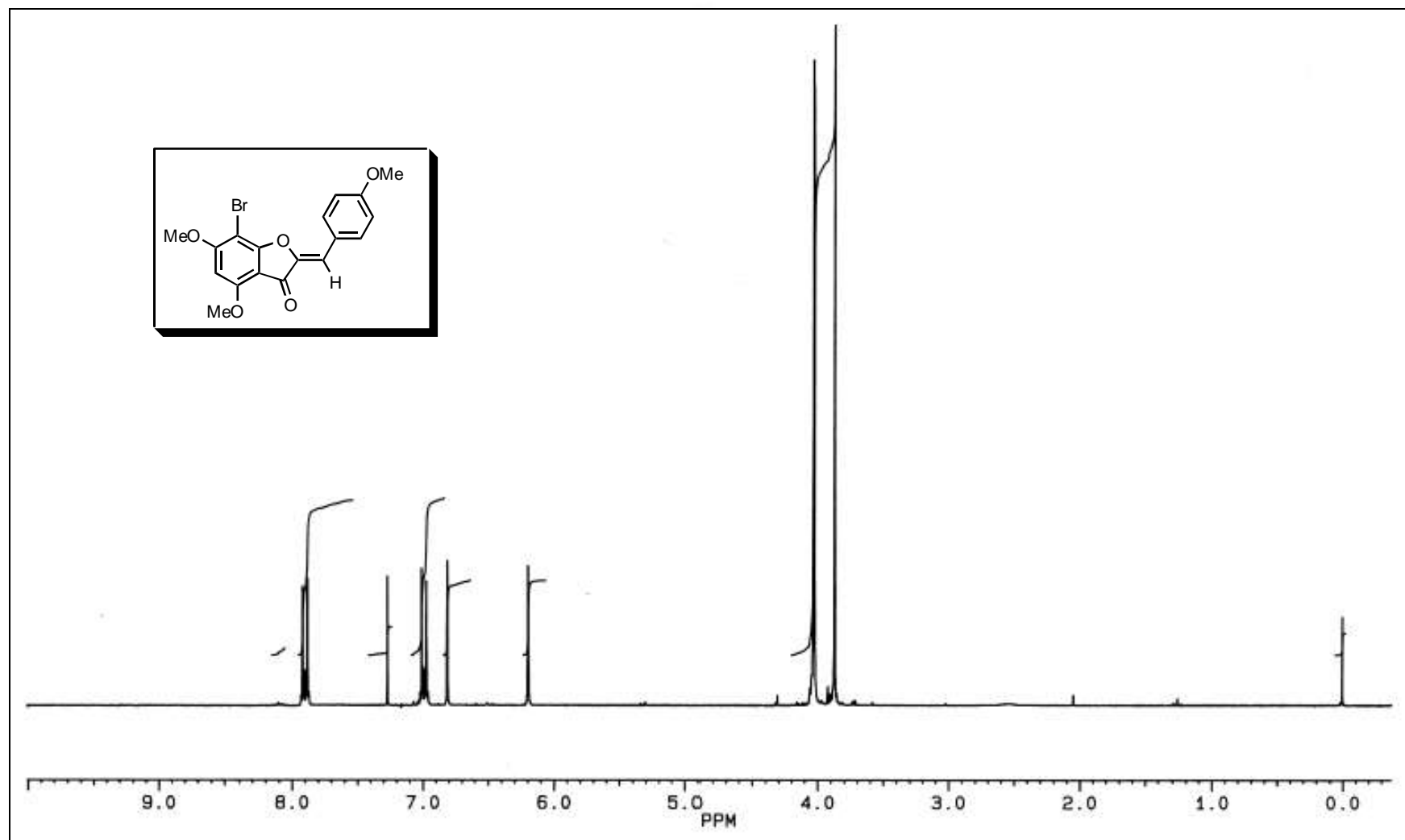


Figure 27: ¹H-NMR spectrum of 7-Bromo-4,6-dimethoxy-2-[(4-methoxyphenyl)methylene]-3(2H)-benzofuranone (300 MHz, CDCl₃) (**28b**)

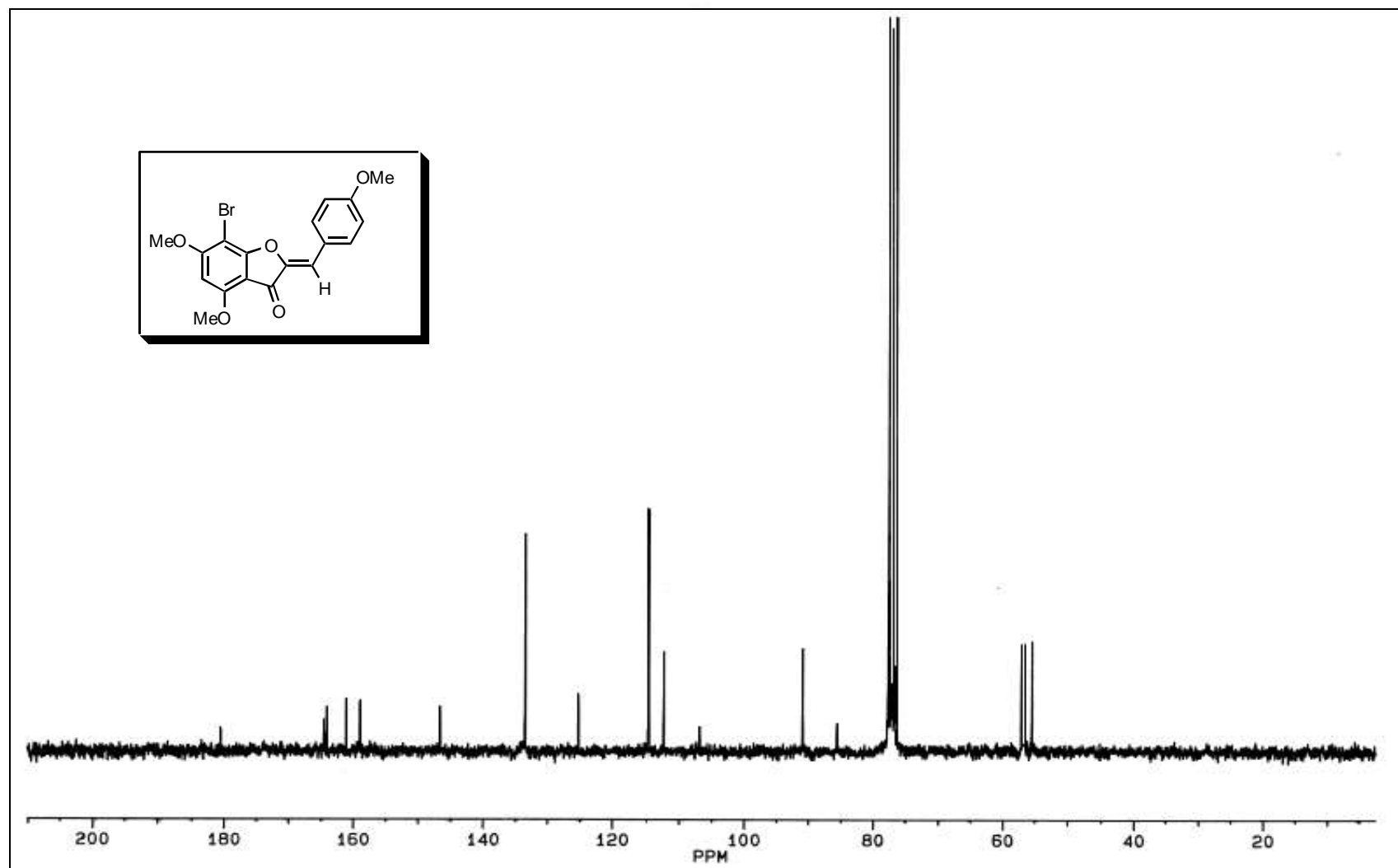


Figure 28: ¹³C-NMR spectrum of 7-Bromo-4,6-dimethoxy-2-[(4-methoxyphenyl)methylene]-3(2H)-benzofuranone (75 MHz, CDCl₃) (**28b**)

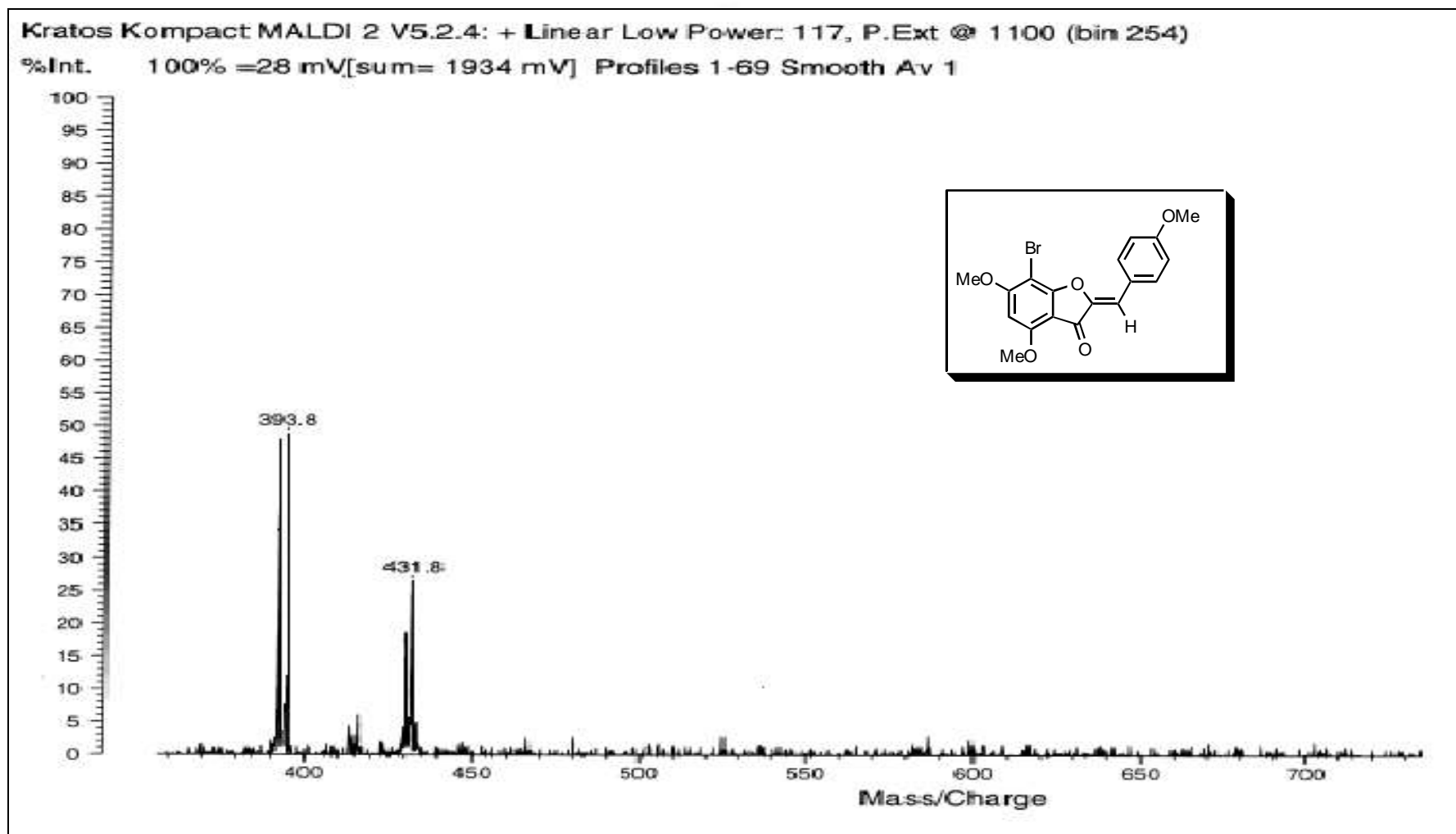


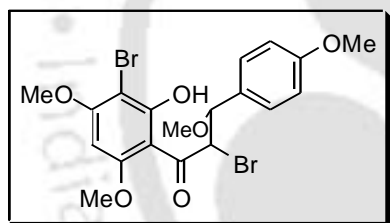
Figure 29: Mass spectrum of 7-Bromo-4,6-dimethoxy-2-[(4-methoxyphenyl)methylene]-3(2H)-benzofuranone (**28b**)

Experimental

General Procedure for Preparation of 2,3'-Dibromo-2'-hydroxy-3-methoxy chalcone:

To a well-stirred solution of 2'-hydroxychalcone **26b-f** (1 mmol) in CH₂Cl₂-MeOH mixture (5:2; 7 mL) at 0-5 °C is added TBATB (1.20 g, 2.5 mmol for **26b**, 1.44 g, 3.0 mmol for **26c-f**) in portion and stirring is continued at the same temperature for (40-50 min) as monitored by TLC. CH₂Cl₂ (15 mL) is added followed by a 5% solution of Na₂S₂O₇ (5 mL). The extracted organic part is washed with water (2 x 10 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude reaction mixture is purified by column chromatography using ethyl acetate-hexane as eluent to get the desired product **27b-f** as yellow or yellow-orange solid in 73-90% yield.

2-Bromo-1-(3-bromo-2-hydroxy-4,6-dimethoxyphenyl)-3-methoxy-3-(4-methoxyphenyl)propan-1-one (**27b**)



Reaction time: 45 min.

Yield: 73 %, yellow needles

Melting point: 161-162 °C

R_f: 0.33 (EtOAc/hexane 3:7)

UV (MeOH): λ_{\max}/nm 228.5 ($\epsilon = 65,958 \text{ M}^{-1}\text{cm}^{-1}$)

307.5 ($\epsilon = 17,152 \text{ M}^{-1}\text{cm}^{-1}$)

IR (KBr): cm^{-1} 1619, 1600, 1515, 1216.

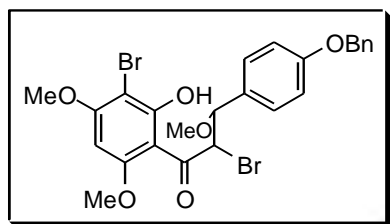
¹H NMR (250 MHz, CDCl₃/TMS): δ 3.16 (s, 3H, -OCH₃), 3.83 (s, 3H, -OCH₃), 3.96 (s, 3H, -OCH₃), 3.99 (s, 3H, -OCH₃), 4.79 [d, 1H, $J = 9.8 \text{ Hz}$, -CH(OMe)Ph-], 5.58 [d, 1H, $J = 9.8 \text{ Hz}$, -COCH(Br)-], 6.06 (s, 1H, ArH), 6.93 (d, 2H, $J = 8.7 \text{ Hz}$, ArH), 7.34 (d, 2H, $J = 8.7 \text{ Hz}$, ArH), 14.07 (s, 1H, -OH).

¹³C NMR (62.5 MHz, CDCl₃/TMS): δ 52.56, 55.24, 56.23, 56.43, 57.45, 83.10, 87.55, 92.25, 105.48, 113.72 (2C), 129.38 (2C), 130.03, 159.88, 162.23, 162.69, 163.13, 197.61.

Mass (m/z, EIMS): 505 (M⁺), 151 (base peak)

Elemental Analysis	Calculated	Found
M. F. C ₁₉ H ₂₀ Br ₂ O ₆	C 45.26	45.55
(504.17)	H 4.00	3.96

3-(4-Benzyloxyphenyl)-2-bromo-1-(3-bromo-2-hydroxy-4,6-dimethoxyphenyl)-3-methoxypropan-1-one (27c)



Reaction time: 50 min.

Yield: 74 %, yellow needles

Melting point: 164-165 °C

R_f: 0.35 (EtOAc/hexane 3:7)

UV (MeOH): λ_{max} /nm 229.0 nm ($\epsilon = 63,582 \text{ M}^{-1}\text{cm}^{-1}$)

307.5 nm ($\epsilon = 17,623 \text{ M}^{-1}\text{cm}^{-1}$)

IR (KBr): cm^{-1} 1625, 1598, 1557, 1225, 1174.

¹H NMR (250 MHz, CDCl₃/TMS): δ 3.16 (s, 3H, -OCH₃), 3.95 (s, 3H, -OCH₃), 3.98 (s, 3H, -OCH₃), 4.79 [d, 1H, $J = 9.8 \text{ Hz}$, -CH(OMe)Ph-], 5.08 (s, 2H, -OCH₂-), 5.58 [d, 1H, $J = 9.8 \text{ Hz}$, -COCH(Br)-], 6.06 (s, 1H, ArH), 7.01 (d, 2H, $J = 8.6 \text{ Hz}$, ArH), 7.32-7.57 (m, 7H, ArH), 14.02 (s, 1H, -OH).

¹³C NMR (62.5 MHz, CDCl₃/TMS): δ 51.58, 55.26, 55.43, 56.49, 69.14, 82.17, 86.64, 91.34, 104.56, 113.65 (2C), 126.51 (2C), 127.02, 127.61 (2C), 128.44 (2C), 129.40, 136.00, 158.21, 161.25, 161.73, 162.16, 196.63.

Elemental Analysis

M. F. C₂₅H₂₄Br₂O₆
(580.27)

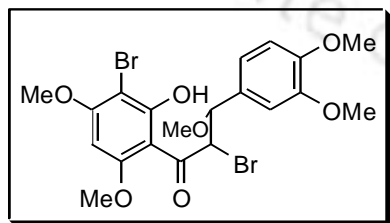
Calculated

C 51.74
H 4.17

Found

51.99
4.08

2-Bromo-1-(3-bromo-2-hydroxy-4,6-dimethoxyphenyl)-3-methoxy-3-(3,4-dimethoxyphenyl)propan-1-one (27d)



Reaction time: 45 min.

Yield: 75 %, yellow crystals

Melting point: 168-169 °C

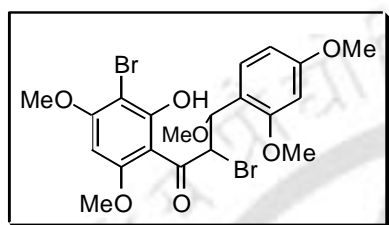
R_f: 0.35 (EtOAc/hexane 2:3)

IR (KBr): cm^{-1} 1623, 1589, 1221, 1155.

¹H NMR (300 MHz, CDCl₃/TMS): δ 3.19 (s, 3H, -OCH₃), 3.91 (s, 3H, -OCH₃), 3.92 (s, 3H, -OCH₃), 3.96 (s, 3H, -OCH₃), 3.99 (s, 3H, -OCH₃), 4.78 [d, 1H, $J = 9.7 \text{ Hz}$, -CH(OMe)Ph-], 5.57 [d, 1H, $J = 9.7 \text{ Hz}$, -COCH(Br)-], 6.07 (s, 1H, ArH), 6.88-7.00 (m, 3H, ArH), 14.02 (s, 1H, -OH).

Elemental Analysis	Calculated	Found
M. F. C ₂₀ H ₂₂ Br ₂ O ₇	C 44.96	45.53
(534.19)	H 4.15	3.98

2-Bromo-1-(3-bromo-2-hydroxy-4,6-dimethoxyphenyl)-3-methoxy-3-(2,4-dimethoxyphenyl) propan-1-one (27e)



Reaction time: 45 min.

Yield: 82 %, yellow needles

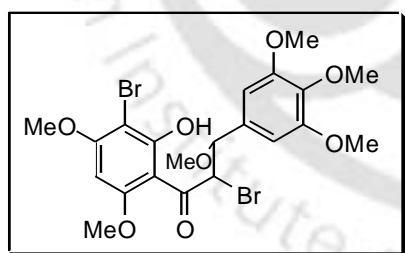
Melting point: 160-161 °C

R_f: 31 (EtOAc/hexane 3:7)

IR (Neat): cm⁻¹ 1619, 1585, 1298, 1217.

¹H NMR (400 MHz, CDCl₃/TMS): δ 3.19 (s, 3H, -OCH₃), 3.85 (s, 3H, -OCH₃), 3.93 (s, 3H, -OCH₃), 3.99 (s, 6H, -OCH₃), 5.22 [d, 1H, J = 9.6 Hz, -CH(OMe)Ph-], 5.81 [d, 1H, J = 9.2 Hz, -COCH(Br)-], 6.07 (s, 1H, ArH), 6.71 (m, 2H, ArH), 7.19 (d, 1H, J = 8.9 Hz, ArH), 14.05 (s, 1H, -OH).

2-Bromo-1-(3-bromo-2-hydroxy-4,6-dimethoxyphenyl)-3-methoxy-3-(3,4,5-trimethoxyphenyl)propan-1-one (27f)



Reaction time: 40 min.

Yield: 90 %

Melting point: 158-159 °C

R_f: 0.33 (EtOAc/hexane 2:3)

IR (Neat): cm⁻¹ 1629, 1593, 1285, 1132.

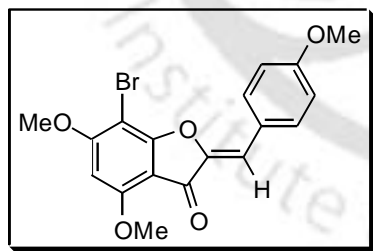
¹H NMR (400 MHz, CDCl₃/TMS): δ 3.18 (s, 3H, -OCH₃), 3.89 (s, 6H, -OCH₃), 3.91 (s, 6H, -OCH₃), 4.02 (s, 3H, -OCH₃), 5.58 [d, 1H, J = 9.5 Hz, -CH(OMe)Ph-], 6.12 (s, 1H, ArH), 6.25 [d, 1H, J = 9.5 Hz, -COCH(Br)-], 6.68 (s, 2H, ArH), 13.89 (s, 1H, -OH).

^{13}C NMR (100 MHz, CDCl_3/TMS): δ 50.94, 52.07, 56.20 (2C), 56.41, 56.53, 60.90, 83.61, 87.64, 92.48, 104.99, 105.55 (2C), 133.70, 138.63, 153.17 (2C), 162.10, 163.05, 163.36, 195.18.

General Procedure for the Preparation of 7-bromo aurones:

In a 25 mL of round bottom flask is taken the substrate 2,3'-Dibromo-2'-hydroxy-3-methoxychalcone **27b-f** (0.5 mmol) and dissolved in ethanol (5 mL) by mechanical stirring at room temperature. When the solution becomes clear, it is brought to ice bath temperature and 0.2 M KOH (0.056 g, 1 mmol) in ethanol-water mixture (3:2, 5 mL) is added dropwise with continuous stirring. The reaction is over within 1.0-1.5 hrs as monitored by TLC. Ethanol-water mixture is removed in rotavapor under reduced pressure. Dichloromethane (15 mL) is added and neutralized with 5% HCl solution (5 mL). The organic layer is washed with water (2 x 10 mL), dried over anhydrous Na_2SO_4 and finally concentrated *in vacuo*. The crude reaction mixture is purified by column chromatography using ethyl acetate-hexane as eluent to get the desired product **28b-f** as yellow or yellow-orange solid in 44-92% yield.

7-Bromo-4,6-dimethoxy-2-[(4-methoxyphenyl)methylene]-3(2H)-benzofuranone (28b)



Reaction time: 1.0 hr

Yield: 92 %, yellow needles

Melting point: 252-253 °C

R_f: 0.32 (EtOAc/hexane 1:1)

IR (KBr): cm^{-1} 1705, 1610, 1180

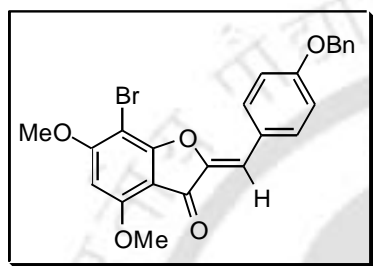
^1H NMR (250 MHz, CDCl_3/TMS): δ 3.86 (s, 3H, $-\text{OCH}_3$), 4.01 (s, 3H, $-\text{OCH}_3$), 4.02 (s, 3H, $-\text{OCH}_3$), 6.18 (s, 1H, Ar-H), 6.80 (s, 1H, $=\text{CHPh}$ -), 6.98 (d, 2H, $J = 8.9$ Hz, ArH), 7.89 (d, 2H, $J = 8.9$ Hz, ArH).

^{13}C NMR (62.5 MHz, CDCl_3/TMS): δ 55.33, 56.57, 56.96, 85.44, 90.69, 106.62, 112.22, 114.51 (2C), 125.01, 132.27 (2C), 146.41, 158.78, 160.90, 163.94, 164.35, 180.34.

Mass (m/z; EIMS): 392/390.

Elemental Analysis	Calculated	Found
M. F. C ₁₈ H ₁₅ BrO ₅ (391.21)	C 55.26 H 3.86	55.52 3.66

2-[(4-Benzyloxyphenyl)methylene]-7-bromo-4,6-dimethoxy-3(2H)-benzofuranone (28c)



Reaction time: 1.0 hr

Yield: 77 %, yellow needles

Melting point: 210-211 °C

R_f: 0.32 (EtOAc/hexane 1:1)

IR (KBr): cm⁻¹ 1705, 1620, 1190.

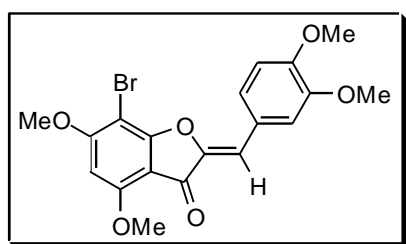
¹H NMR (250 MHz, CDCl₃/TMS): δ 3.99 (s, 3H, -OCH₃), 4.00 (s, 3H, -OCH₃), 5.11 (s, 2H, -OCH₂-), 6.16 (s, 1H, ArH), 6.78 (s, 1H, =CHPh-), 7.03 (d, 2H, *J* = 8.9 Hz, ArH), 7.36-7.42 (m, 5H, ArH), 7.86 (d, 2H, *J* = 8.8 Hz, ArH).

¹³C NMR (62.5 MHz, CDCl₃/TMS): δ 56.58, 56.98, 70.06, 85.41, 90.77, 112.02, 115.40 (2C), 125.25, 127.38 (2C), 127.44, 128.07, 128.60, 128.69, 133.25 (2C), 136.53, 146.44, 158.76, 160.06, 163.94, 164.30, 180.23.

Mass: (m/z; MALDI) 468.6/466.6

Elemental Analysis	Calculated	Found
M. F. C ₂₄ H ₁₉ BrO ₅ (467.31)	C 61.68 H 4.09	61.22 3.98

7-Bromo-4,6-dimethoxy-2-[(3,4-dimethoxyphenyl)methylene]-3(2H)-benzofuranone (28d)



Reaction time: 1.5 hrs

Yield: 72 %, yellow needles

Melting point: 219-220 °C

R_f: 0.34 (EtOAc/hexane 1:1)

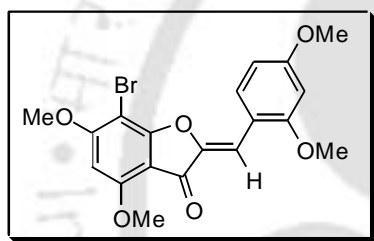
IR (KBr): ν_{\max} / cm^{-1} 1690, 1600, 1510, 1225, 1110.

^1H NMR (250 MHz, CDCl_3/TMS): δ 3.94 (s, 3H, $-\text{OCH}_3$), 4.02 (s, 3H, $-\text{OCH}_3$), 4.03 (s, 6H, $-\text{OCH}_3$), 6.15 (s, 1H, ArH), 6.81 (s, 1H, $=\text{CHPh}$ -), 6.92 (d, 1H, $J = 8.3$ Hz, ArH), 7.33 (dd, 1H, $J = 8.3$ Hz, 1.9 Hz, ArH), 7.83 (d, 1H, $J = 1.9$ Hz, ArH).

Mass (m/z; EIMS): 422/420

Elemental Analysis	Calculated	Found
M. F. $\text{C}_{19}\text{H}_{17}\text{BrO}_6$	C 54.17	54.28
(421.24)	H 4.06	4.01

7-Bromo-4,6-dimethoxy-2-[(2,4-dimethoxyphenyl)methylene]-3(2H)-benzofuranone (28e)



Reaction time: 1.0 hr

Yield: 68 %, yellow plates

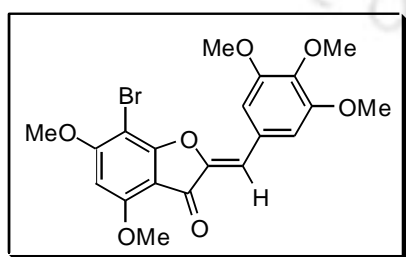
Melting point: 228-229 °C

R_f: 0.53 (EtOAc/hexane 3:2)

IR (KBr): cm^{-1} 1698, 1608, 1092.

^1H NMR (400 MHz, CDCl_3/TMS): δ 3.91 (s, 3H, $-\text{OCH}_3$), 3.95 (s, 3H, $-\text{OCH}_3$), 4.01 (s, 6H, $-\text{OCH}_3$), 6.18 (s, 1H, ArH), 6.45 (s, 1H, $=\text{CHPh}$), 6.94 (d, 1H, $J = 8.0$ Hz, ArH), 7.48 (d, 1H, $J = 1.8$ Hz, ArH), 7.51 (d, 1H, $J = 8.1$ Hz, ArH).

7-Bromo-4,6-dimethoxy-2-[(3,4,5-trimethoxyphenyl)methylene]-3(2H)benzofuranone (28f)



Reaction time: 1.5 hrs

Yield: 44 %, Yellow cryslline solid

Melting point: 234-235 °C

R_f: 0.28 (EtOAc/hexane 1:1)

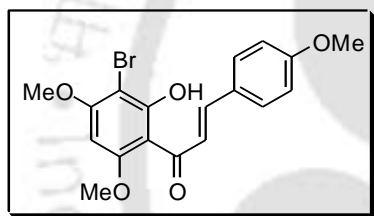
IR (KBr): cm^{-1} 1692, 1595, 1211, 1097.

$^1\text{H NMR}$ (400 MHz, CDCl_3/TMS): δ 3.91 (s, 3H, $-\text{OCH}_3$), 3.96 (s, 6H, $-\text{OCH}_3$), 4.01 (s, 3H, $-\text{OCH}_3$), 4.02 (s, 3H, $-\text{OCH}_3$), 6.17 (s, 1H, ArH), 6.74 (s, 1H, $=\text{CHPh}$), 7.23 (s, 2H, ArH).

$^{13}\text{C NMR}$ (100 MHz, CDCl_3/TMS): δ 56.06 (2C), 56.54, 56.98, 60.95, 85.25, 90.59, 106.28, 108.45 (2C), 112.15, 127.59, 139.50, 147.02, 153.16 (2C), 158.82, 164.08, 164.20, 180.2.

Elemental Analysis	Calculated	Found
M. F. $\text{C}_{20}\text{H}_{19}\text{BrO}_7$ (451.27)	C 53.23 H 4.24	53.08 4.01

Experimental Data of 1-(3-Bromo-2-hydroxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one (33)



Reaction time: 1 hr

Yield: 76 %, Yellow needles

Melting point: 192 °C

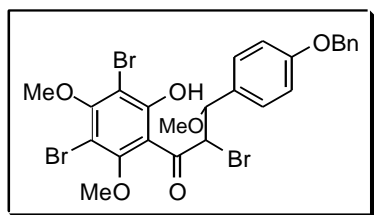
R_f: 0.37(EtOAc/hexane 3:7)

IR (Neat): cm^{-1} 1625, 1648, 1225, 1174.

$^1\text{H NMR}$ (300 MHz, CDCl_3/TMS): δ 3.86 (s, 3H, $-\text{OCH}_3$), 3.98 (s, 3H, $-\text{OCH}_3$), 3.99 (s, 3H, $-\text{OCH}_3$), 6.03 (s, 1H, ArH), 6.93 (d, 2H, $J = 9.0$ Hz, ArH), 7.56 (d, 2H, $J = 9.0$ Hz, ArH), 7.75 (d, 2H, $J = 15.6$ Hz, ArH), 7.83 (d, 2H, $J = 15.6$ Hz, ArH), 14.95 (s, 1H, $-\text{OH}$).

$^{13}\text{C NMR}$ (75 MHz, CDCl_3/TMS): 55.41, 56.08, 56.31, 87.17, 92.42, 114.40 (2C), 122.04, 124.47, 128.04, 130.27 (2C), 143.53, 161.58, 161.75, 162.17, 163.21, 192.65.

Experimental Data of 3-(4-Benzyloxyphenyl)-2-bromo-1-(3,5-dibromo-2-hydroxy-4,6-dimethoxyphenyl)-3-methoxypropan-1-one (35)



Reaction time: 20 min.

Yield: 39 %, yellow oil

R_f: 0.72 (EtOAc/hexane 3:7)

IR (Neat): cm^{-1} 1628, 1605, 1221, 1144.

^1H NMR (300 MHz, CDCl_3/TMS): δ 3.14 (s, 3H, $-\text{OCH}_3$), 3.97 (s, 3H, $-\text{OCH}_3$), 3.98 (s, 3H, $-\text{OCH}_3$), 4.74 [d, 1H, $J = 9.9$ Hz, $-\text{CH}(\text{OMe})\text{Ph}-$], 5.08 (s, 2H, $-\text{OCH}_2-$), 5.74 [d, 1H, $J = 9.9$ Hz, $-\text{COCH}(\text{Br})-$], 7.01 (d, 2H, $J = 8.5$ Hz, ArH), 7.33-7.46 (m, 7H, ArH), 12.65 (s, 1H, $-\text{OH}$).

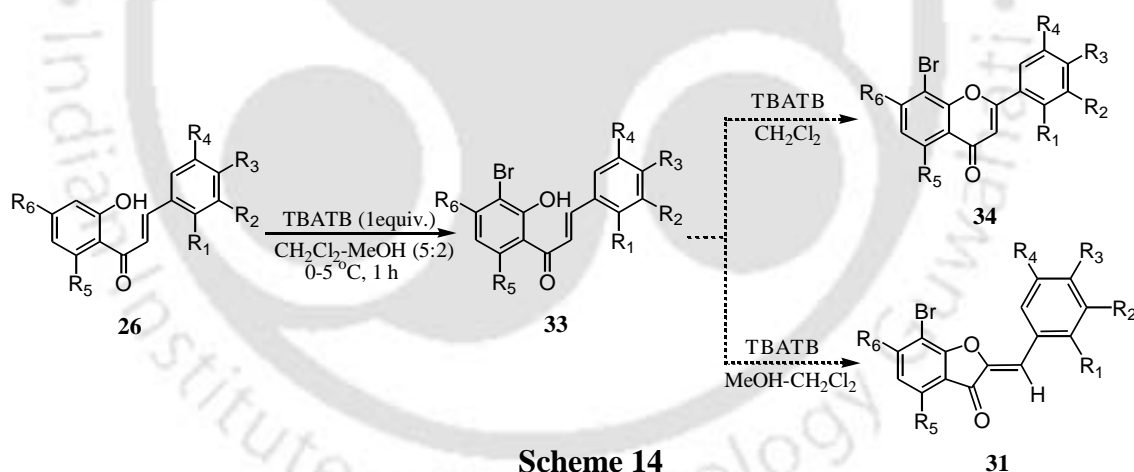


PRESENT WORK ON THE BROMINATION OF VARIOUS 2'-
HYDROXYCHALCONES USING *n*-TETRABUTYLAMMONIUM
TRIBROMIDE (TBATB) AND THEIR APPLICATIONS TOWARDS 7-
BROMOAUROONES SYNTHESIS

EXPERIMENTAL

Discussion

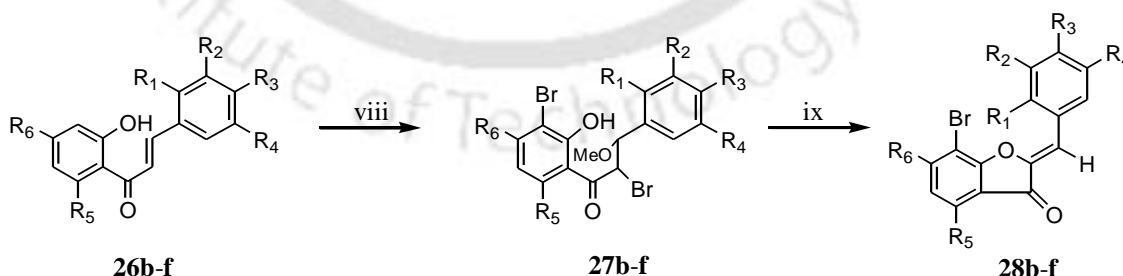
Naturally occurring aurones are usually found as *O*-glycosides¹⁹ such as leptosidin, aureusidine and sulfuretin. Similarly flavones are also found in nature as *O*-glycosides as well as *C*-glycosides such as vitexin.²⁰ In addition, some bisflavones such as amentoflavone²¹ and robustaflavone,²² which are biologically potent compounds, are well known in literature. Recently, the synthesis of amentoflavone has been achieved by using 8-bromoflavone.²¹ Similarly, the synthesis of robustaflavone is reported by using 6-iodoflavone.²³ In recent times, the synthesis of *C*-glycosides has gained considerable attention to the synthetic chemist.²⁴ We realize that the bromo derivative, particularly 7-bromoaurone and 8-bromoflavone could be utilized for *C*-glycoside synthesis. From the literature survey we have found that much work has not been done on the synthesis of 7-bromoaurone and 8-bromoflavone. Only one method is known for the synthesis of 8-bromoflavone.²⁵ Interestingly the structure of 8-bromoflavone was wrongly assigned. We have observed that 2'-hydroxychalcone on reaction with 1 equivalent amount of TBATB provided mononuclear ring brominated product as shown in scheme 14.



Therefore, we thought that the mononuclear ring brominated product can be assembled to the 7-bromoaurone or 8-bromoflavone by employing our previous protocols.

From the scheme 14 it seems that if the compound **26** is treated with excess amount of TBATB in CH₂Cl₂-MeOH instead of two step brominations (**26**→**33**→**31**), then 7-bromoaurone could be accessed by cyclisation with alkali. On the other hand, 8-bromoflavone **34** could be achieved easily by bromination of compound **33** using TBATB in CH₂Cl₂, followed by dehydrobromination and finally cyclisation by employing 0.1 M NaOMe solution as already discussed in chapter 2 in part II.

As per our assumption as well as optimization of reaction conditions through several trials, we have succeeded to transform the substrate 2'-hydroxychalcone **26b** to the dibromo product **27b** on treatment with 2.5 equivalent amount of TBATB in CH₂Cl₂-MeOH (5:2) in 73% yield. The product **27b** is characterized by IR, ¹H NMR, ¹³C NMR, mass spectra as well as elemental analysis. In IR spectrum, the stretching frequency for -OH and carbonyl group are not observed due to the strong intramolecular H-bonding between the carbonyl and ortho hydroxyl group. In ¹H NMR spectrum, the new signal for three-proton singlet at δ 3.16 indicates the incorporation of -OCH₃ group during bromination. The disappearance of olefinic hydrogen at δ 7.77 and appearing of two new signals as doublet at δ 4.79 and δ 5.58 with $J = 9.8$ Hz indicate the bromination of olefinic double bond (figure 24). The absence of characteristic proton signal at δ 5.93 indicates the mono nuclear ring bromination at 3'-position instead of 5'-position because of the presence of two -OMe groups nearby. In addition, the signal at δ 14.07 indicates the presence of hydroxyl group at 2'-position, which is not observed in IR spectrum. The ¹³C NMR spectrum is also in full agreement with our proposed structure (figure 25). Subsequently, various 2'-hydroxychalcones **26c-f** are converted to the corresponding brominated product **27c-f** under the identical reaction conditions. All the products are characterized by IR, ¹H NMR, ¹³C NMR, mass spectra and/or elemental analysis. The results are summarized in table 2. Unfortunately, the compound **26a** does not provide the expected brominated product **27a** on treatment with 2.5 equivalent amount of TBATB under similar reaction conditions. In this case we have obtained a mixture of products which we have not characterized.



Reagents and conditions: viii) TBATB (2.5-3.0 equiv.), CH₂Cl₂-MeOH (5:2), 40-50 min, 75-90 %. ix) 0.2 M KOH, EtOH-H₂O (4:1), 0-5 °C, 1-1.5 h, 44-92%.

Scheme 15

[N. B.: The numbering of the compounds **b-f** is same as that of the compounds (**b-f**) mentioned in **scheme 11** in *chapter 3 part II*].

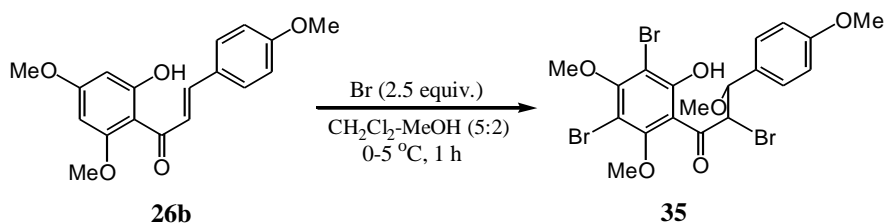
However, when the compound **26a** is treated with 1 equivalent of TBATB then α -bromo- β -methoxy dihydrochalcone **8** is obtained instead of the nuclear ring-brominated product. ring-brominated products.

Next, we cyclised the compound **27b** to the expected product **28b** on treatment with 0.2 KOH in aqueous ethanol in good yield as shown in scheme 15. The product **28b** is characterized by IR, ^1H NMR, ^{13}C NMR, mass spectra as well as elemental analysis. In IR spectrum, the band at 1705 cm^{-1} indicates the presence of carbonyl group. In ^1H NMR spectrum, the absence of signals at δ 3.16 and δ 14.07 indicate the disappearance of $-\text{OCH}_3$ and $-\text{OH}$ group. In addition, a new proton signal at δ 6.80 other than the aromatic protons indicates the methylene proton in aurone moiety (figure 27). The ^{13}C NMR spectrum is also in full support with our proposed structure (figure 28). Likewise, various brominated product **27c-f** are transformed to the corresponding 7-bromoaurones **28c-f** under the identical reaction conditions. All the products are characterized by IR, ^1H NMR, ^{13}C NMR, mass spectra and/or elemental analysis and results are summarized in table 2.

Table 2. Preparation of different substituted 7-bromo aurones

Entry (26)	Time (min.)	Dibromo product (27)	Yield (%)	Time (min)	Aurone (28)	Yield (%)
26b	45	27b	73	60	28b	92
26c	50	27c	74	60	28c	77
26d	45	27d	82	60	28d	68
26e	40	27e	90	90	28e	44
26f	45	27f	75	90	28f	72

In order to study the selectivity of the reagent, we performed the same reaction with molecular bromine under the similar experimental reaction conditions. Surprisingly we have observed that the substrate **26b** undergoes ring bromination at both 3'- and 5'-position to give compound **35** in low yield (shown in scheme 16). This further confirms the selectivity of the reagent TBATB.



Scheme 16



PRESENT WORK ON THE BROMINATION OF VARIOUS 2'-HYDROXYCHALCONES USING *n*-TETRABUTYLAMMONIUM TRIBROMIDE (TBATB) AND THEIR APPLICATIONS TOWARDS 7-BROMOAURONES SYNTHESIS

DISCUSSION

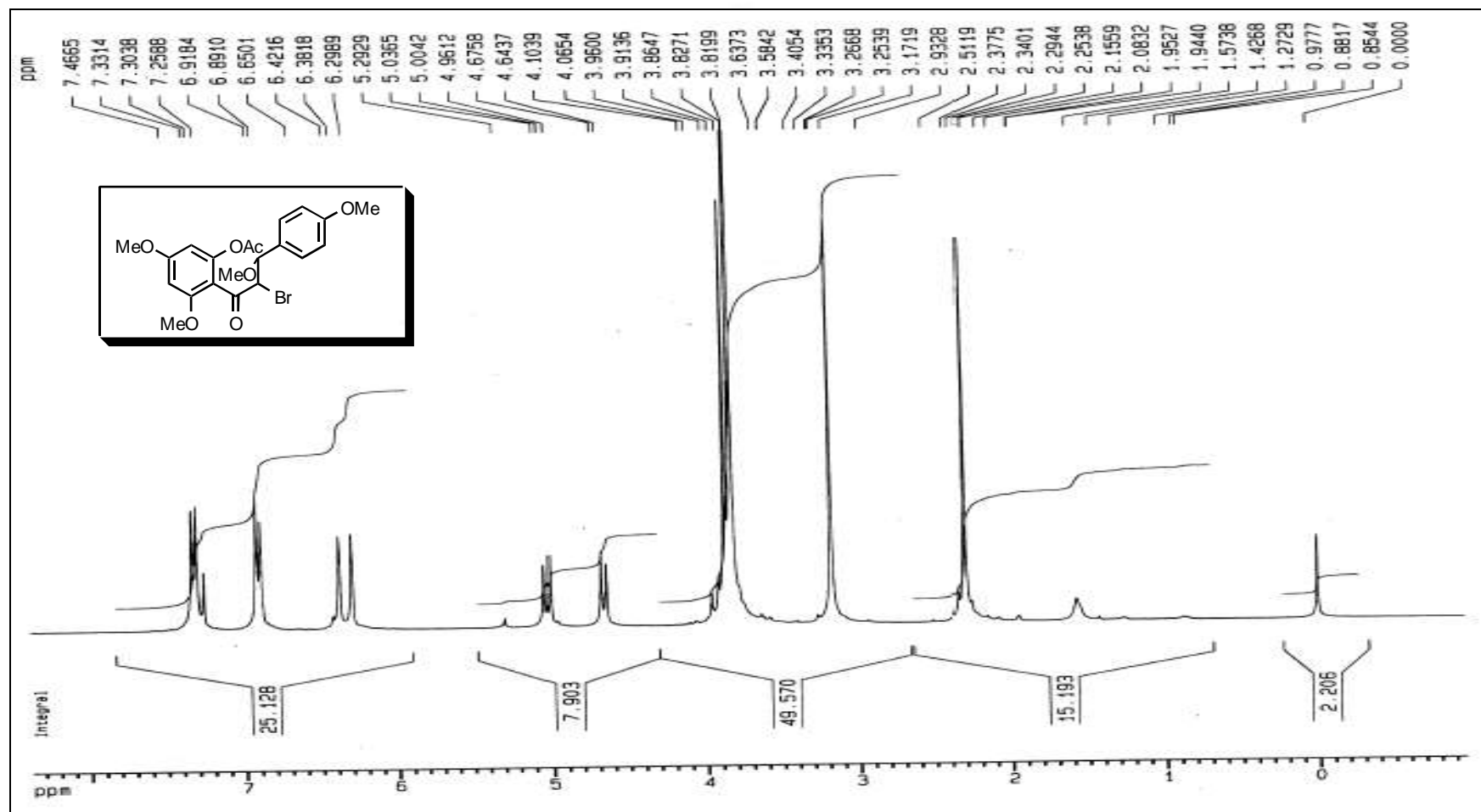


Figure 19: ¹H-NMR spectrum of 1-(2-Acetoxy-4,6-dimethoxyphenyl)-2-bromo-3-methoxy-3-(4-methoxyphenyl)propan-1-one (300 MHz, CDCl₃) (**30b**)

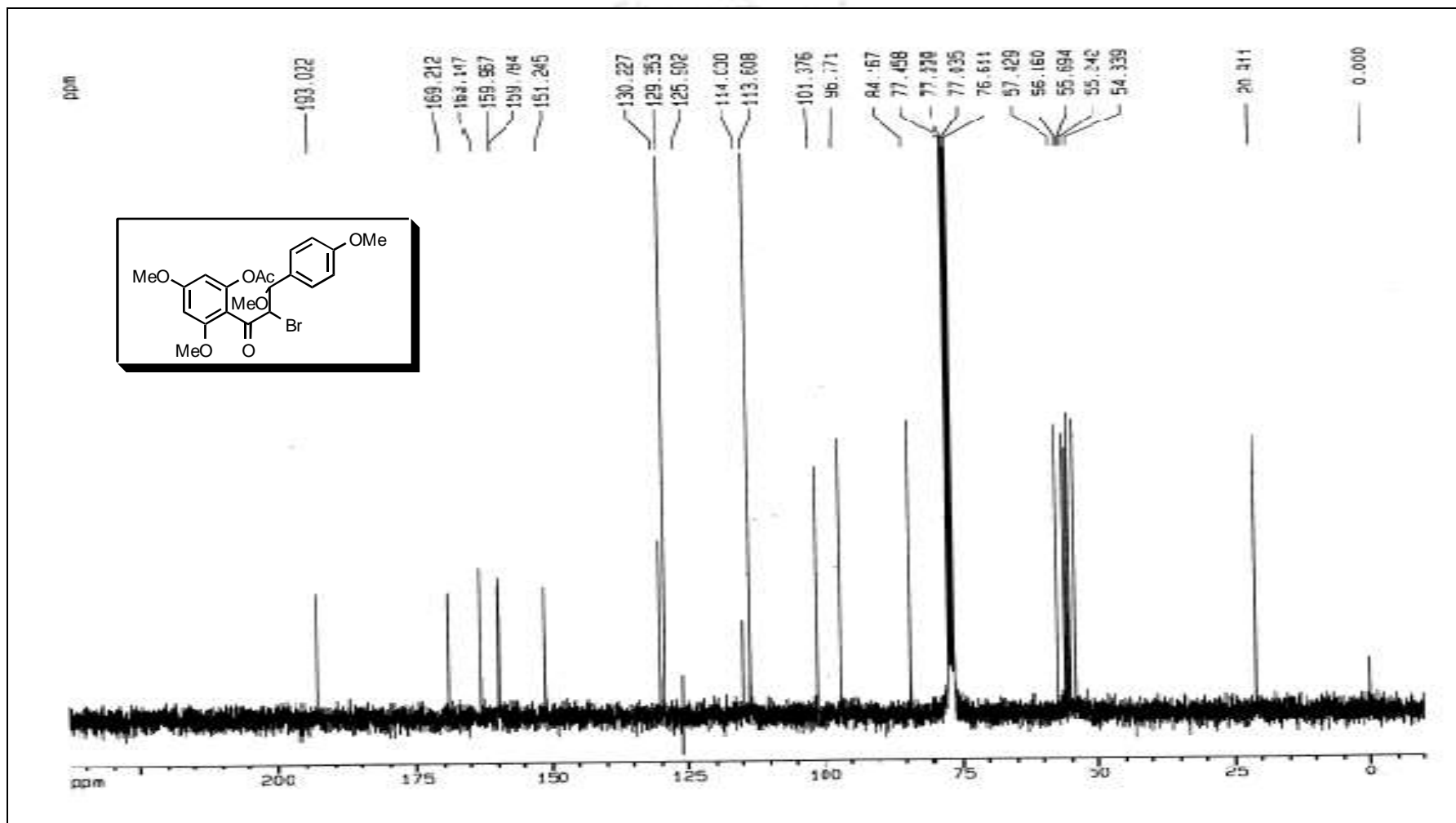


Figure 20: ¹³C-NMR spectrum of 1-(2-Acetoxy-4,6-dimethoxyphenyl)-2-bromo-3-methoxy-3-(4-methoxyphenyl)propan-1-one (75 MHz, CDCl₃) (**30b**)

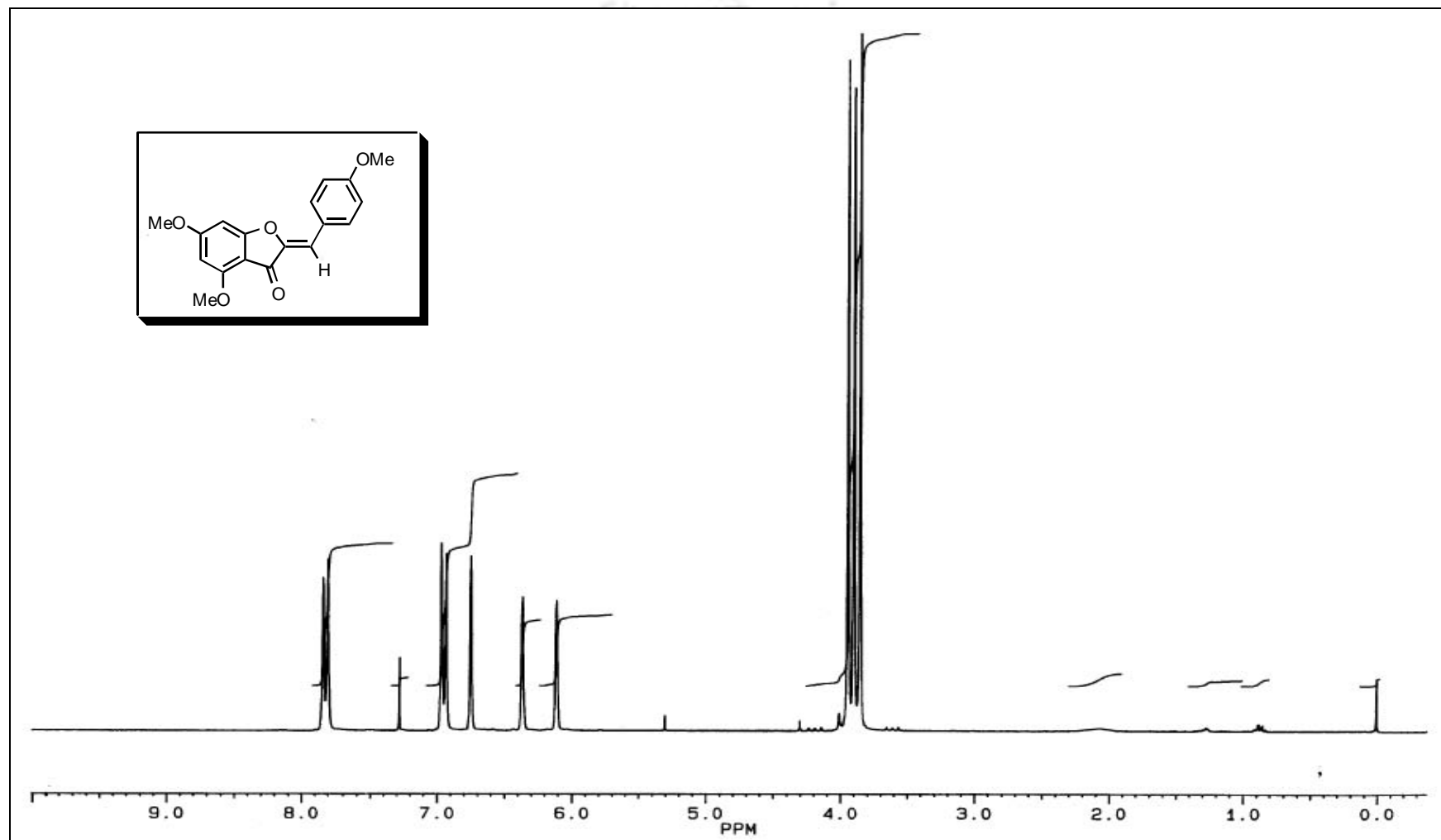


Figure 21: ¹H-NMR spectrum of 4,6-Dimethoxy-2-[(4-methoxyphenyl)methylene]-3(2H)-benzofuranone (300 MHz, CDCl₃) (**31b**)

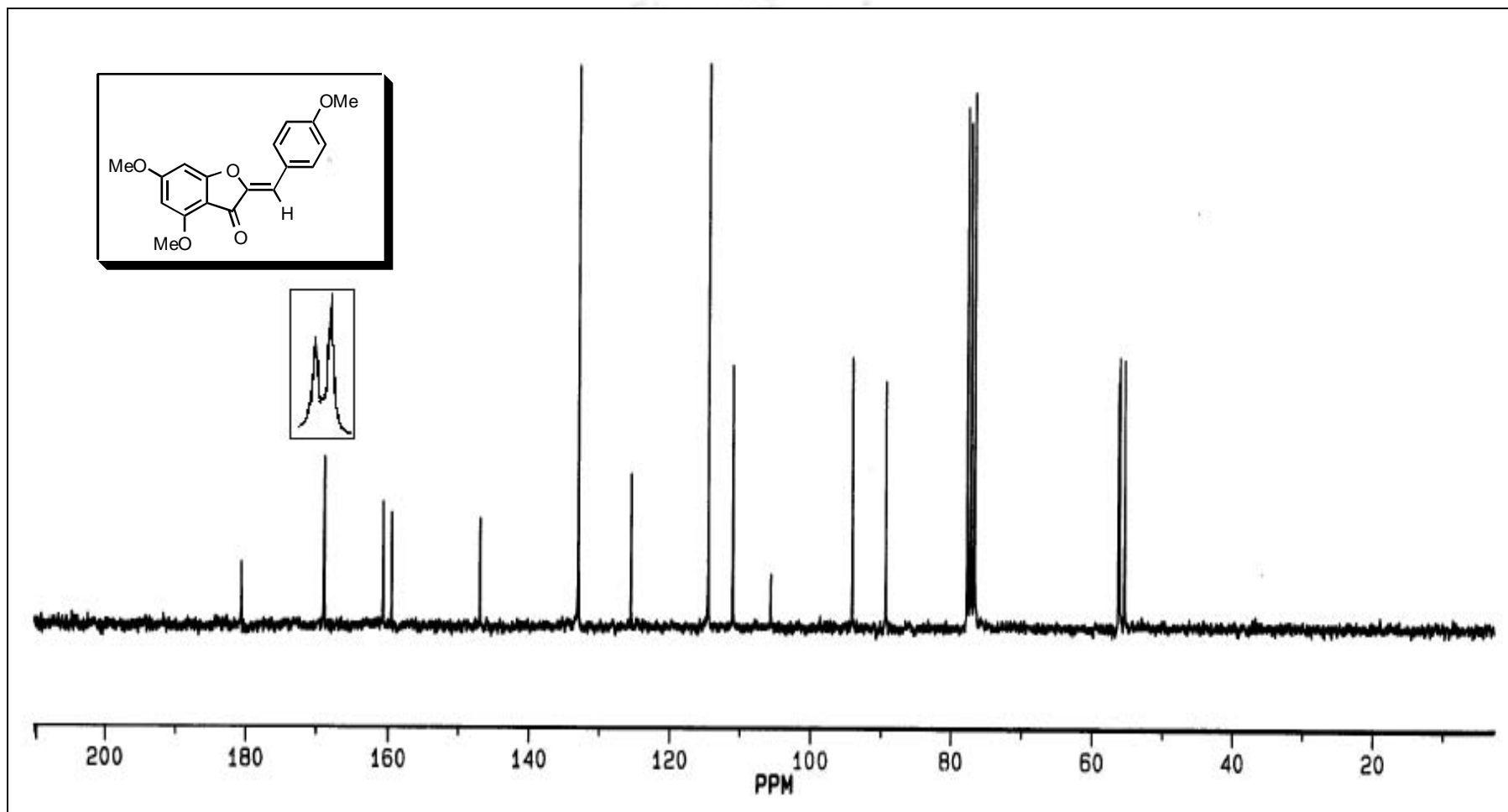


Figure 22: ¹³C-NMR spectrum of 4,6-Dimethoxy-2-[(4-methoxyphenyl)methylene]-3(2H)-benzofuranone (75 MHz, CDCl₃) (**31b**)

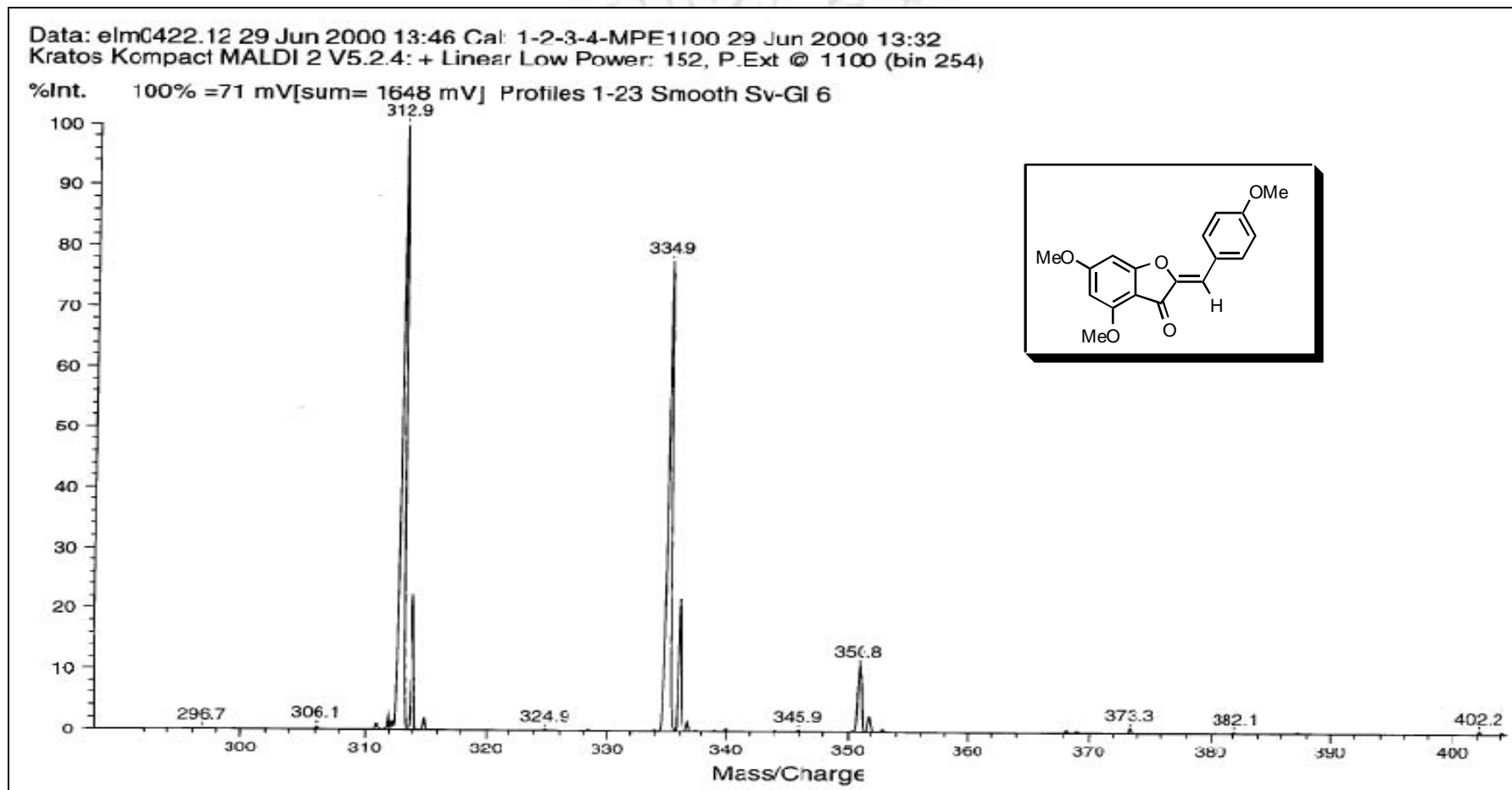


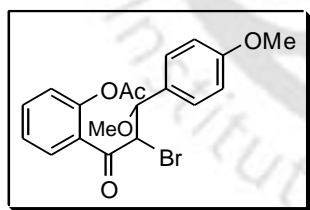
Figure 23: Mass spectrum of 4,6-Dimethoxy-2-[(4-methoxyphenyl)methylene]-3(2H)-benzofuranone (**31b**)

Experimental

General Procedure for the Preparation of 2'-Acetoxy-2-bromo-3-methoxychalcone:

To a well-stirred solution of 2'-Acetoxy chalcone **29a-f** (1 mmol.) in CH₂Cl₂-MeOH (5:2, 7mL) at ice bath temperature is added CaCO₃ (0.400 g, 4.0 mmol) followed by TBATB (0.578 gm, 1.2 mmol.) and stirring is continued for 0.5-2.0 hrs. The reaction is monitored by TLC. After completion of reaction, the reaction mixture is quenched by adding a 5% solution of Na₂S₂O₇ (1 mL). Extracted the organic part in CH₂Cl₂ (2 x 15 mL) and washed with water (2 x 15 mL). The collected organic part is then dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude products are finally purified by column chromatography using EtOAc- Hexane mixture as eluent. The products **30a-f** are obtained in 75-85%.

1-(2-Acetoxyphenyl)-2-bromo-3-methoxy-3-(4-methoxyphenyl)propan-1-one (**30a**)



Reaction time: 2.0 hrs

Yield: 80 %, yellow crystalline solid

Melting point: 119-120 °C

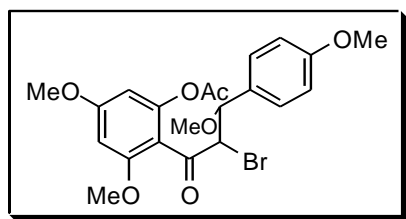
R_f: 0.41 (EtOAc/hexane 1:19)

IR (KBr): cm⁻¹ 1752, 1646, 1619, 1401, 1255.

¹H-NMR (400 MHz, CDCl₃/TMS): δ 2.37 (s, 3H, -COCH₃), 3.16 (s, 3H, -OCH₃), 3.83 (s, 3H, -OCH₃), 4.72 [d, 1H, *J* = 9.8 Hz, -CH(OMe)Ph-], 5.02 [d, 1H, *J* = 10.0 Hz, -COCH(Br)-], 6.94 (d, 2H, *J* = 8.5 Hz, ArH), 7.17 (d, 1H, *J* = 8.0 Hz, ArH), 7.33-7.37 (m, 3H, ArH), 7.55-7.59 (m, 1H, ArH), 7.84 (dd, 1H, *J* = 7.8 Hz, 1.68 Hz, ArH).

¹³C-NMR (100 MHz, CDCl₃/TMS): δ 21.20, 50.78, 55.19, 57.42, 83.39, 113.68 (2C), 123.99, 126.23, 129.20, 129.28 (2C), 129.49, 130.30, 133.59, 149.02, 159.89, 169.19, 194.01.

1-(2-Acetoxy-4,6-dimethoxyphenyl)-2-bromo-3-methoxy-3-(4-methoxyphenyl)propan-1-one (30b)



Reaction time: 1.0 hr

Yield: 80 %, pale yellow solid

Melting point: 123-124 °C

R_f: 0.37 (EtOAc/hexane 3:7)

IR (KBr): cm⁻¹ 1765, 1700, 1620, 1230, 1110.

¹H-NMR (300 MHz, CDCl₃/TMS): δ 2.29 (s, 3H, -COCH₃), 3.17 (s, 3H, -OCH₃), 3.82 (s, 3H, -OCH₃), 3.83 (s, 3H, -OCH₃), 3.86 (s, 3H, -OCH₃), 4.65 [d, 1H, *J* = 9.6 Hz, -CH(OMe)Ph-], 5.01 [d, 1H, *J* = 9.6 Hz, -COCH(Br)-], 6.29 (s, 1H, ArH), 6.38 (s, 1H, ArH), 6.90 (d, 2H, *J* = 8.2 Hz, ArH), 7.31 (d, 2H, *J* = 8.2 Hz, ArH).

¹³C-NMR (75 MHz, CDCl₃/TMS): δ 20.91, 54.33, 55.24, 55.69, 56.16, 57.42, 84.16, 96.77, 101.37, 113.60 (2C), 114.83, 129.35 (2C), 130.22, 151.24, 159.78, 159.96, 163.14, 169.21, 193.02.

Elemental Analysis

M. F. C₂₁H₂₃BrO₇
(467.312)

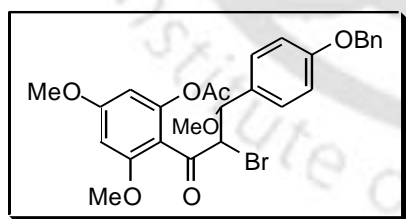
Calculated

C 53.97
H 4.96

Found

53.33
4.92

1-(2-Acetoxy-4,6-dimethoxyphenyl)-3-(4-benzyloxyphenyl)-2-bromo-3-methoxypropan-1-one (30c)



Reaction time: 1.0 hr

Yield: 75 %, white crystalline solid

Melting point: 138-139 °C

R_f: 0.34 (EtOAc/hexane 3:7)

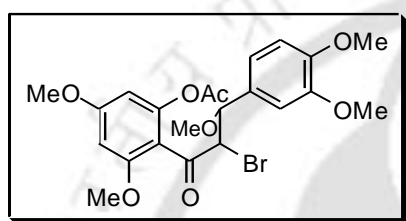
IR (KBr): cm⁻¹ 1752, 1685, 1595, 1138, 1085.

¹H-NMR (300 MHz, CDCl₃/TMS): δ 2.28 (s, 3H, -COCH₃), 3.17 (s, 3H, -OCH₃), 3.82 (s, 3H, -OCH₃), 3.85 (s, 3H, -OCH₃), 4.66 [d, 1H, *J* = 9.6 Hz, -CH(OMe)Ph-], 5.02 [d, 1H, *J* = 9.6 Hz, -COCH(Br)-], 5.06 (s, 2H, -OCH₂-), 6.29 (d, 1H, *J* = 2.1 Hz, ArH), 6.37 (d, 1H, *J* = 2.1 Hz, ArH), 6.98 (d, 2H, *J* = 8.6 Hz, ArH), 7.30-7.42 (m, 7H, ArH).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3/TMS): δ 20.93, 54.36, 55.71, 56.18, 57.49, 70.08, 84.17, 96.79, 101.40, 114.50 (2C), 114.85, 127.57 (2C), 128.05, 128.64 (2C), 129.41 (2C), 130.54, 136.98, 151.27, 159.08, 159.98, 163.17, 169.24, 193.01.

Elemental Analysis	Calculated	Found
M. F. $\text{C}_{27}\text{H}_{27}\text{BrO}_7$	C 59.67	59.83
(543.410)	H 5.00	4.88

1-(2-Acetoxy-4,6-dimethoxyphenyl)-2-bromo-3-methoxy-3-(3,4-dimethoxyphenyl)propan-1-one (30d)



Reaction time: 0.5 hr

Yield: 76 %, yellow solid

Melting point: 125-126 °C

R_f: 0.56 (EtOAc/hexane 2:3)

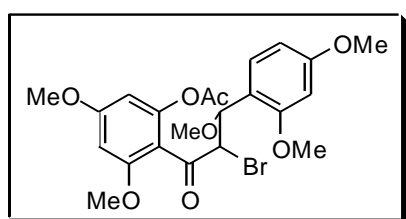
IR (KBr): cm^{-1} 1750, 1650, 1600, 1200, 1090.

$^1\text{H-NMR}$ (250 MHz, CDCl_3/TMS): δ 2.29 (s, 3H, $-\text{COCH}_3$), 3.17 (s, 3H, $-\text{OCH}_3$), 3.82 (s, 3H, $-\text{OCH}_3$), 3.85 (s, 3H, $-\text{OCH}_3$), 3.88 (s, 6H, $-\text{OCH}_3$), 4.63 [d, 1H, $J = 9.7$ Hz, $-\text{CH}(\text{OMe})\text{Ph-}$], 4.98 [d, 1H, $J = 9.7$ Hz, $-\text{COCH}(\text{Br})-$], 6.29 (d, 1H, $J = 2.2$ Hz, ArH), 6.38 (d, 1H, $J = 2.2$ Hz, ArH), 6.87-6.94 (m, 3H, ArH).

$^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3/TMS): δ 20.82, 54.32, 55.62, 55.81, 55.92, 56.07, 57.45, 84.59, 96.70, 101.42, 110.58, 110.69, 114.81, 121.05, 130.56, 148.88, 149.19, 151.18, 159.94, 163.13, 169.08, 192.98.

Elemental Analysis	Calculated	Found
M. F. $\text{C}_{22}\text{H}_{25}\text{BrO}_8$	C 53.13	52.81
(497.338)	H 5.06	4.83

1-(2-Acetoxy-4,6-dimethoxyphenyl)-2-bromo-3-methoxy-3-(2,4-dimethoxyphenyl)propan-1-one (30e)



Reaction time: 1.25 hrs

Yield: 85 %, yellow solid

Melting point: 165-167 °C

R_f: 0.58 (EtOAc/hexane 2:3)

IR (KBr): cm^{-1} 1755, 1675, 1605, 1210, 1150.

$^1\text{H-NMR}$ (400 MHz, CDCl_3/TMS): δ 2.30 (s, 3H, $-\text{COCH}_3$), 3.20 (s, 3H, $-\text{OCH}_3$), 3.80 (s, 3H, $-\text{OCH}_3$), 3.81 (s, 3H, $-\text{OCH}_3$), 3.82 (s, 3H, $-\text{OCH}_3$), 3.83 (s, 3H, $-\text{OCH}_3$), 5.08 [d, 1H, $J = 9.2$ Hz, $-\text{COCH}(\text{Br})-$], 5.37 [d, 1H, $J = 9.2$ Hz, $-\text{CH}(\text{Br})\text{OMe}-$], 6.27 (d, 1H, $J = 2.2$ Hz, ArH), 6.33 (d, 1H, $J = 2.2$ Hz, ArH), 6.47 (m, 2H, ArH), 7.19 (d, 1H, $J = 9.0$ Hz, ArH).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3/TMS): δ 20.82, 53.38, 55.19, 55.44, 55.56, 55.94, 57.54, 79.05, 96.48, 98.33, 101.09, 104.28, 114.78, 118.71, 129.45, 150.93, 159.19, 159.70, 160.75, 162.81, 169.22, 192.65

Elemental Analysis

M. F. $\text{C}_{22}\text{H}_{25}\text{BrO}_8$
(497.338)

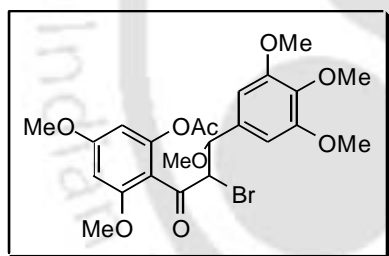
Calculated

C 53.13
H 5.06

Found

52.98
4.99

1-(2-Acetoxy-4,6-dimethoxyphenyl)-2-bromo-3-methoxy-3-(3,4,5-trimethoxyphenyl)propan-1-one (30f)



Reaction time: 1.0 hr

Yield: 84 %, yellow crystalline solid

Melting point: 166-167 °C

R_f: 0.63 (EtOAc/hexane 2:3)

UV (MeOH): $\lambda_{\text{max}}/\text{nm}$ 288.0 ($\epsilon = 26,587 \text{ M}^{-1}\text{cm}^{-1}$)

IR (KBr): cm^{-1} 1745, 1700, 1620, 1120.

$^1\text{H-NMR}$ (400 MHz, CDCl_3/TMS): δ 2.30 (s, 3H, $-\text{COCH}_3$), 3.21 (s, 3H, $-\text{OCH}_3$), 3.83 (s, 3H, $-\text{OCH}_3$), 3.86 (s, 6H, $-\text{OCH}_3$), 3.87 (s, 6H, $-\text{OCH}_3$), 4.62 [d, 1H, $J = 9.5$ Hz, $-\text{CH}(\text{OMe})\text{Ph}-$], 4.98 [d, 1H, $J = 9.5$ Hz, $-\text{COCH}(\text{Br})-$], 6.30 (d, 1H, $J = 1.7$ Hz, ArH), 6.38 (d, 1H, $J = 1.9$ Hz, ArH), 6.63 (s, 2H, ArH).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3/TMS): δ 20.90, 54.22, 55.71, 56.13 (3C), 57.78, 60.84, 85.21, 96.67, 101.45, 104.96 (2C), 114.68, 133.60, 137.85, 151.20, 152.96 (2C), 160.01, 163.25, 169.26, 193.11.

Elemental Analysis

M. F. $\text{C}_{23}\text{H}_{27}\text{BrO}_9$
(527.36)

Calculated

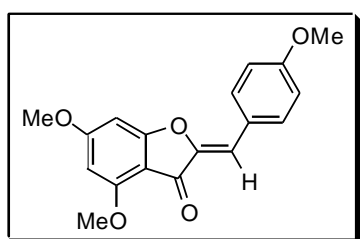
C 52.38
H 5.16

Found

52.15
5.01

General procedure for the preparation of Aurones:

In a 25 mL round bottom flask is taken 2-acetoxy-2-bromo-3-methoxy chalcone **30a-f** (0.5 mmol) in ethanol (5 mL) and kept for stirring at ice-bath temperature. Into it 0.2 M KOH (0.056 g, 1.0 mmol) solution in ethanol-water mixture (3:2, 5 mL) is added in portion over a period of 5 min. The stirring is continued at the same temperature for (1.00-3.25 hrs) as monitored by TLC. Ethanol-water mixture is removed in rotavapor and dichloromethane (15 mL) is added for extraction. The organic layer is washed with 5% HCl solution (5 mL), to neutralize the solution. Separate the organic part in a separatory funnel and washed with water (2 x 15 mL). The collected organic part is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product is purified by column chromatography using ethyl acetate-hexane mixture as eluent. The solid products **31a-f** are obtained in 85-95% yield.

2-[(4-Methoxyphenyl)methylene]-3(2H)-benzofuranone (31a)**Reaction time:** 3.25 hrs**Yield:** 87 %, white solid**Melting point:** 139-140 °C (lit. m.p. 139 °C)**R_f:** 0.48 (EtOAc/hexane 1:19)**IR (KBr):** cm^{-1} 1716, 1644, 1618, 1605, 1251.**¹H-NMR (400 MHz, CDCl₃/TMS):** δ 3.86 (s, 3H, -OCH₃), 6.88 (s, 1H, =CHPh-), 6.98 (d, 2H, $J = 8.8$ Hz, ArH), 7.20 (t, 1H, $J = 7.6$ Hz, ArH), 7.32 (dd, 1H, $J = 8.2$ Hz, 0.7 Hz, ArH), 7.63 (m, 1H, ArH), 7.80 (m, 1H, ArH), 7.89 (d, 2H, $J = 9.0$ Hz, ArH).**¹³C-NMR (100 MHz, CDCl₃/TMS):** δ 55.35, 112.83, 113.39, 114.46 (2C), 121.90, 123.23, 124.51, 125.01, 133.40 (2C), 136.49, 145.84, 161.04, 165.79, 184.52.**4,6-Dimethoxy-2-[(4-methoxyphenyl)methylene]-3(2H)-benzofuranone (31b)****Reaction time:** 1.0 hr**Yield:** 85 %, pale yellow solid**Melting point:** 167-168 °C**R_f:** 0.39 (EtOAc/hexane 1:1)

UV (MeOH): λ_{\max}/nm 389.0 ($\epsilon = 96,578 \text{ M}^{-1}\text{cm}^{-1}$)

326.5 ($\epsilon = 96,578 \text{ M}^{-1}\text{cm}^{-1}$)

IR (KBr): cm^{-1} 1700, 1620, 1600, 1255, 1100.

$^1\text{H-NMR}$ (300 MHz, CDCl_3/TMS): δ 3.84 (s, 3H, $-\text{OCH}_3$), 3.89 (s, 3H, $-\text{OCH}_3$), 3.94 (s, 3H, $-\text{OCH}_3$), 6.15 (d, 1H, $J = 1.6 \text{ Hz}$, Ar-H), 6.35 (d, 1H, $J = 1.6 \text{ Hz}$, Ar-H), 6.74 (s, 1H, $=\text{CHPh-}$), 6.95 (d, 2H, $J = 8.7 \text{ Hz}$, ArH), 7.82 (d, 2H, $J = 8.7 \text{ Hz}$, ArH).

$^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3/TMS): δ 55.27, 55.99, 56.12, 89.17, 93.90, 105.43, 110.85, 114.31 (2C), 125.31, 132.79 (2C), 146.77, 159.32, 160.55, 168.67, 168.76, 180.48.

Mass (m/z): 312

Elemental Analysis

M. F. $\text{C}_{18}\text{H}_{16}\text{O}_5$
(312.321)

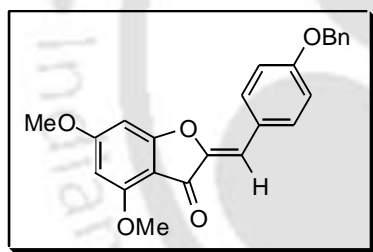
Calculated

C 69.22
H 5.16

Found

67.62
4.89

2-[(4-Benzyloxyphenyl)methylene]-4,6-Dimethoxy-3(2H)-benzofuranone (31c)



Reaction time: 1.5 hrs

Yield: 91 %, pale yellow solid

Melting point: 195-196 °C

R_f: 0.38 (EtOAc/hexane 1:1)

IR (KBr): cm^{-1} 1700, 1645, 1600, 1510, 1245, 1100.

$^1\text{H-NMR}$ (250 MHz, CDCl_3/TMS): δ 3.89 (s, 3H, $-\text{OCH}_3$), 3.94 (s, 3H, $-\text{OCH}_3$), 5.11 (s, 2H, $-\text{OCH}_2-$), 6.12 (d, 1H, $J = 1.7 \text{ Hz}$, ArH), 6.36 (d, 1H, $J = 1.7 \text{ Hz}$, ArH), 6.73 (s, 1H, $=\text{CHPh-}$), 7.02 (d, 2H, $J = 8.8 \text{ Hz}$, ArH), 7.32-7.44 (m, 5H, ArH), 7.81 (d, 2H, $J = 8.8 \text{ Hz}$, ArH).

$^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3/TMS): δ 56.40, 56.55, 70.59, 89.61, 94.36, 111.21, 115.66 (2C), 126.01, 127.79 (2C), 127.98, 128.46, 129.00 (2C), 133.22 (2C), 136.79, 147.26, 159.80, 160.15, 169.10, 169.22, 180.43.

Elemental Analysis

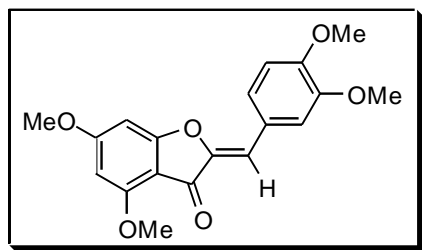
M. F. $\text{C}_{24}\text{H}_{20}\text{O}_5$ (388.419)

Calculated

C 74.21
H 5.19

Found

74.38
5.01

4,6-Dimethoxy-2-[(3,4-dimethoxyphenyl)methylene]-3(2H)-benzofuranone (31d)**Reaction time:** 1.0 hr**Yield:** 86 %, off white solid**Melting point:** 164-165 °C (lit. m.p. 169-170 °C)**R_f:** 0.32 (EtOAc/hexane 3:2)**UV (MeOH):** λ_{max} /nm 225.5, 278.0, 303.0.**IR (KBr):** cm^{-1} 1680, 1580, 1200, 1090.**¹H-NMR (250 MHz, CDCl₃/TMS):** δ 3.92 (s, 3H, -OCH₃), 3.93 (s, 3H, -OCH₃), 3.95 (s, 3H, -OCH₃), 3.96 (s, 3H, -OCH₃), 6.14 (d, 1H, $J = 1.8$ Hz, ArH), 6.35 (d, 1H, $J = 1.8$ Hz, ArH), 6.74 (s, 1H, =CHPh-), 6.92 (d, 1H, $J = 8.7$ Hz, ArH), 7.44 (m, 2H, ArH).**¹³C-NMR (62.5 MHz, CDCl₃/TMS):** δ 55.78, 55.80, 55.94, 56.01, 89.06, 93.80, 105.23, 110.94, 111.10, 113.50, 125.12, 125.42, 146.70, 148.86, 150.25, 159.19, 168.57 (2C), 180.27.**Mass (e/z):** 342.8**Elemental Analysis**M. F. C₁₉H₁₈O₆

(342.34)

Calculated

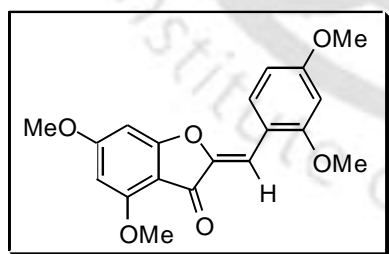
C 66.66

H 5.30

Found

66.53

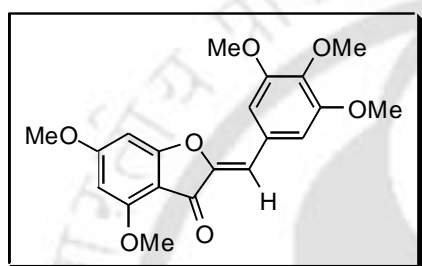
5.22

4,6-Dimethoxy-2-[(2,4-dimethoxyphenyl)methylene]-3(2H)-benzofuranone (31e)**Reaction time:** 0.75 hr**Yield:** 87 %, yellow solid**Melting point:** 178-179 °C**R_f:** 0.28 (EtOAc/hexane 3:2)**IR (KBr):** cm^{-1} 1692, 1645, 1600, 1520, 1102.**¹H-NMR (400 MHz, CDCl₃/TMS):** δ 3.90 (s, 3H, -OCH₃), 3.92 (s, 3H, -OCH₃), 3.94 (s, 3H, -OCH₃), 3.95 (s, 3H, -OCH₃), 6.11 (d, 1H, $J = 1.7$ Hz, ArH), 6.33 (d, 1H, $J = 1.7$ Hz, ArH), 6.72 (s, 1H, =CHPh-), 6.90 (d, 1H, $J = 8.0$ Hz, ArH), 7.43 (d, 1H, $J = 8.2$ Hz, ArH), 7.45 (s, 1H, ArH).

$^{13}\text{C-NMR}$ (62.5 MHz, CDCl_3/TMS): δ 55.94, 55.96, 56.12, 56.20, 89.18, 93.96, 105.43, 111.19, 111.23, 113.59, 125.29, 125.56, 146.84, 148.98, 150.37, 159.37, 168.74 (2C), 180.54.

Elemental Analysis	Calculated	Found
M. F. $\text{C}_{19}\text{H}_{18}\text{O}_6$	C 66.66	66.47
(342.34)	H 5.30	5.19

4,6-Dimethoxy-2-[(3,4,5-trimethoxyphenyl)methylene]-3(2H)-benzofuranone (31f)



Reaction time: 1.25 hrs

Yield: 95 %, pale yellow solid

Melting point: 208-209 °C

R_f: 0.31 (EtOAc/hexane 3:2)

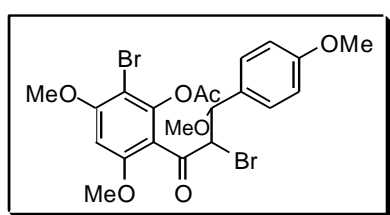
IR (KBr): cm^{-1} 1686, 1646, 1616, 1354, 1125.

$^1\text{H-NMR}$ (400 MHz, CDCl_3/TMS): δ 3.91 (s, 3H, $-\text{OCH}_3$), 3.93 (s, 3H, $-\text{OCH}_3$), 3.94 (s, 6H, $-\text{OCH}_3$), 3.96 (s, 3H, $-\text{OCH}_3$), 6.15 (d, 1H, $J = 1.7$ Hz, ArH), 6.34 (d, 1H, $J = 1.7$ Hz, ArH), 6.70 (s, 1H, $=\text{CHPh-}$), 7.13 (s, 2H, ArH).

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3/TMS): δ 56.14, 56.39 (2C), 56.46, 60.99, 89.27, 94.07, 108.55 (2C), 110.97, 112.26, 127.99, 147.35, 153.27 (2C), 159.44, 159.86, 168.84, 168.93, 180.47.

Elemental Analysis	Calculated	Found
M. F. $\text{C}_{20}\text{H}_{20}\text{O}_7$	C 64.51	64.38
(372.37)	H 5.41	5.36

Experimental Data of 1-(2-Acetoxy-3-bromo-4,6-dimethoxyphenyl)-2-bromo-3-methoxy-3-(4-methoxyphenyl)propan-1-one (32):



Reaction time: 0.75 hr

Yield: 47 %, off white solid

Melting point: 190-191 °C

R_f: 0.31 (EtOAc/hexane 3:7)

IR (KBr): cm^{-1} 1770, 1700, 1620, 1215, 1110.

$^1\text{H-NMR}$ (300 MHz, CDCl_3/TMS): δ 2.33 (s, 3H, $-\text{COCH}_3$), 3.27 (s, 3H, $-\text{OCH}_3$), 3.81 (s, 3H, $-\text{OCH}_3$), 3.91 (s, 6H, $-\text{OCH}_3$), 3.95 (s, 3H, $-\text{OCH}_3$), 4.64 [d, 1H, $J = 9.7$ Hz, $-\text{CH}(\text{OMe})\text{Ph}-$], 4.97 [d, 1H, $J = 9.6$ Hz, $-\text{COCH}(\text{Br})-$], 6.42 (s, 1H, ArH), 6.90 (d, 2H, $J = 8.2$ Hz, ArH), 7.31 (d, 2H, $J = 8.2$ Hz, ArH).





PRESENT WORK ON THE BROMINATION OF A WIDE VARIETY OF 2'-ACETOXYCHALCONES TO THE 2'-ACETOXY- α -BROMO- β -METHOXY-DIHYDROCHALCONES AND THEIR APPLICATIONS TOWARDS AURONE SYNTHESIS

EXPERIMENTAL

Discussion

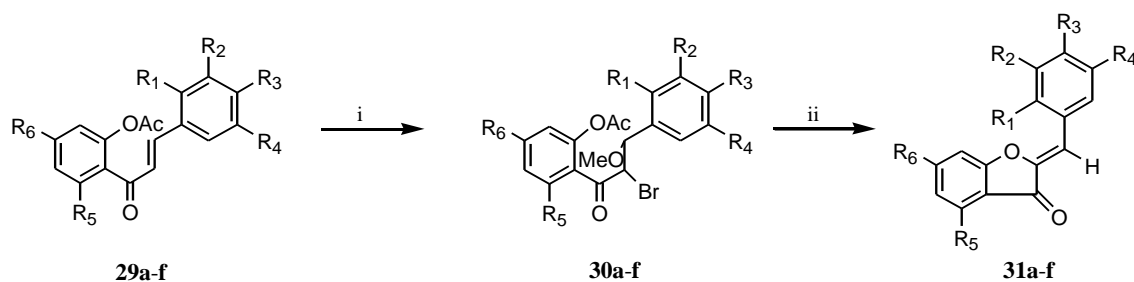
Aurones are structurally isomeric with flavones. They are important contributors to the pigmentation of flowers by virtue of their golden yellow colors that attracts insect. However, their occurrence in nature is not abundant in compare to flavones. Because of this limited occurrence in nature, they have received very little attention compared to the related and widely investigated flavones and isoflavones.¹⁰ For the same reason, their biological activity¹¹ has not been evaluated, in spite of the fact that their isomeric relations, flavonoids have displayed a wide spectrum of biological actions¹² including anti-proliferative activity.¹³⁻¹⁵ However, there is a recent report about the biological activity of aurones as a potent inhibitors.^{16,17} These results encourage us to search an alternative method for the synthesis of aurones.

From the observation³ of Wheeler it is evident that if the bromo group at the β -position of chalcone dihalide is substituted by a poor-leaving group such as an alkoxy group, then cyclisation might be possible exclusively at the α -position to get aurone. This route was not successful earlier due to difficulty in replacing the bromo group at the β -position by solvolysis.³

Therefore, Donnelly and his group tried to introduce an alkoxy group directly in substituted chalcone using NBS in methanol. However, they observed⁶ that with this reagent it undergoes nuclear ring bromination. So, it is obvious that substituted aurones cannot be obtained from substituted 2'-acetoxychalcones till today. As we have mentioned in chapter 2 in part II that TBATB has unique properties for bromination that does not give nuclear ring bromination while the reaction was performed with 2'-acetoxychalcones. Therefore, we thought that if we incorporate an alkoxy group at the β -position of 2'-acetoxychalcone by tuning the reaction conditions, then substituted aurones could be prepared exclusively. The results of our successful efforts are described below-

The compound 2'-acetoxychalcone **29b** is converted to the corresponding α -bromo- β -methoxy dihydrochalcone **30b** in 85 % yield on treatment with TBATB (1.2 equiv.) in presence of CaCO₃ in CH₂Cl₂-MeOH (5:2) as shown in scheme 11. The product **30b** is characterized by IR, ¹H NMR, ¹³C NMR and elemental analysis. In IR spectrum, the band at 1765 cm⁻¹ and 1700 cm⁻¹ indicate the presence of two carbonyl groups. In ¹H NMR spectrum, the signal as singlet at δ 2.29 shows the presence of -COCH₃ group and the signals as singlet at δ 3.17 clearly indicates the introduction of -OCH₃ groups in **29b** during bromination (figure 19). This also supports by getting an additional carbon signal at δ 54.33 for -OCH₃ carbon (figure 20) in ¹³C NMR. In addition, the disappearance of two signals at δ 6.86 and δ 7.38 ($J = 16.1$ Hz) and appearing of two new signals as doublet at δ 4.61 and δ 5.01 ($J = 11.6$ Hz) clearly indicates the addition of methoxy and bromo group at the olefinic double bond of the chalcone **29b**. Similarly, the compounds **29a** and **29c-f** are transformed into the corresponding brominated product **30a** and **30c-f**, on reaction with TBATB under identical reaction conditions. All the products are fully characterized by IR, ¹H NMR, ¹³C NMR and/or elemental analysis.

After getting the compounds α -bromo- β -methoxy dihydrochalcone **30a-f** in hand, our next goal is to cyclise them to the desired aurones. After several trial reactions, we have found that the compound **30b** is smoothly converted to the expected product **31b**, on treatment with aqueous KOH (0.2 M) in ethanol-water mixture (4:1). The final cyclised product **31b** is characterized by spectroscopic techniques like IR, ¹H NMR, ¹³C NMR and/or mass spectra as well as elemental analysis. In IR spectrum, the band at 1700 cm⁻¹ indicates the presence of one carbonyl group. In ¹H NMR spectrum, the disappearance of the signals at δ 2.29, δ 3.17, δ 4.61 and δ 5.01 indicates the deacetylation followed by cyclisation. In addition the new signal at δ 6.84 other than the aromatic proton indicate the presence of methylene proton (=CHPh-) in the aurone skeleton (figure 21). In ¹³C NMR spectrum, the signals at δ 110.85 (=CHPh-) and δ 146.77 (C-2) appears due to the formation of aurone over flavone, where the expected carbon signals would have been at δ 107.29 (=CHPh-) and δ 162.05 (C-2) (figure 22). Similarly, the brominated product **30a** and **30c-f** are cyclised to the corresponding aurones **31a** and **31c-f** under identical reaction conditions. The reaction conditions are mentioned in scheme 11 and the results are summarized in table 1.



- a:** $R_1 = R_2 = R_4 = R_5 = R_6 = \text{H}$, $R_3 = \text{OMe}$
b: $R_1 = R_2 = R_4 = \text{H}$, $R_3 = R_5 = R_6 = \text{OMe}$
c: $R_1 = R_2 = R_4 = \text{H}$, $R_3 = \text{OBn}$, $R_5 = R_6 = \text{OMe}$
d: $R_1 = R_4 = \text{H}$, $R_2 = R_3 = R_5 = R_6 = \text{OMe}$
e: $R_1 = R_3 = R_5 = R_6 = \text{OMe}$, $R_2 = R_4 = \text{H}$
f: $R_1 = \text{H}$, $R_2 = R_3 = R_4 = R_5 = R_6 = \text{OMe}$

Reagents and Conditions: i) TBATB (1.2-1.5 equiv.), CaCO_3 , CH_2Cl_2 -MeOH (5:2), 0-5 °C, 0.5-2 h, 75-85%; ii) 0.2 M KOH, EtOH-H₂O (4:1), 0-5 °C, 0.75-3.25 h, 85-95%.

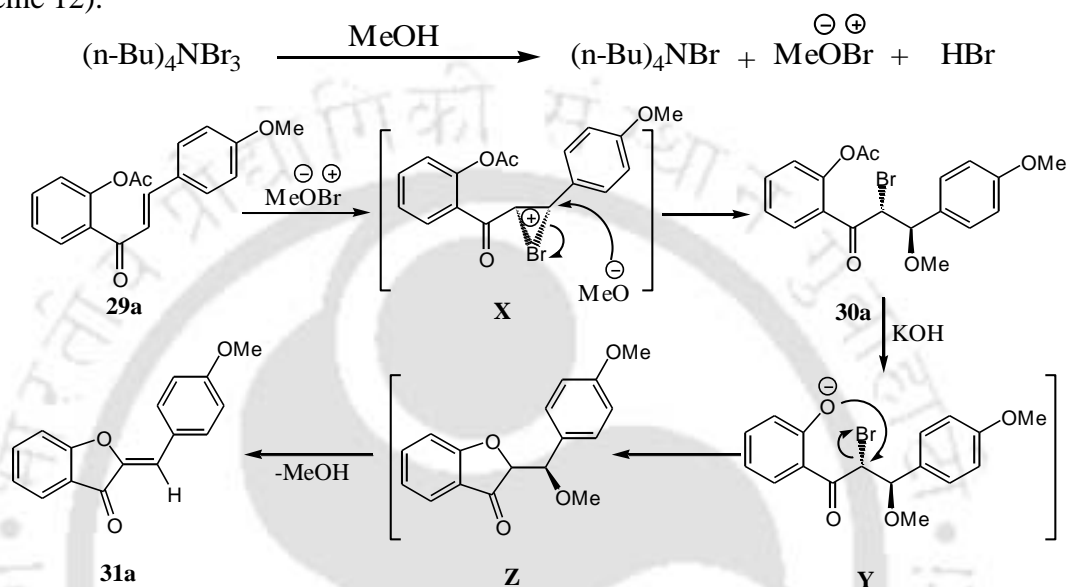
Scheme 11

Table 1. Preparation of different substituted aurones

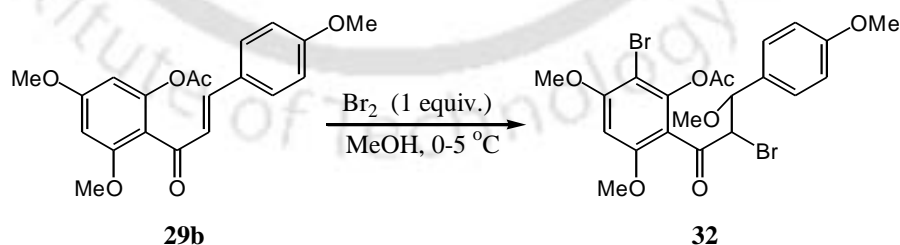
Entry (29)	Time (h)	α -bromo- β -methoxy dihydrochalcone (30)	Yield (%)	Time (h)	Aurones (31)	Yield (%)
29a	1.0	30a	80	1.0	31a	85
29b	1.0	30b	75	1.5	31b	91
29c	1.25	30c	85	0.75	31c	87
29d	1.0	30d	84	1.25	31d	95
29e	0.5	30e	76	1.0	31e	86
29f	2.0	30f	80	3.25	31f	87

The probable mechanism for the formation of the cyclized product aurones **31a-f** can be explained as follows. It has been shown that organic ammonium tribromide such as benzyltrimethylammonium tribromide generates HBr and MeOBr in methanol.¹⁸ We suggest that MeOBr is forming slowly, which reacts to the double bond in electrophilic manner to form cyclic bromonium ion intermediate (**X**), which is opened up by OMe ion to form the α -bromo- β -methoxy dihydrochalcone **30a**. The attack at the β -position is favored over α -position due to the *in situ* generated carbocation is benzylic in nature,

which is relatively stable than carbocation generated at the α -position. The formation of aurone can be explained that after deacetylation, the generated phenoxide anion at 2'-position preferably attacks at the α -position because Br is better leaving group in comparison to OMe, so the cyclisation takes exclusively at the α -position (shown in scheme 12).



Interestingly, the compound **29b** gives ring brominated product **32** on treatment with molecular bromine with methanol which was also observed by Donnelly *et al* on treatment with NBS in methanol (shown in scheme 13).⁶ This experiment further proves that TBATB is more versatile than the commonly used molecular bromine or NBS.



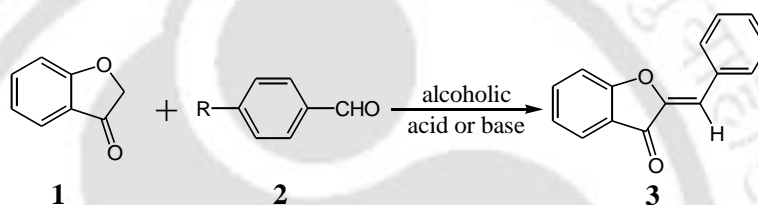
In conclusion, we have demonstrated that TBATB in methanol can be used for introduction of alkoxy group at the β -position of 2'-acetoxychalcone, which is a valuable synthon for the natural as well as non-natural aurone synthesis. We have also accomplished the synthesis of naturally occurring aurone derivative like aurosidine (**31e**).

PRESENT WORK ON THE BROMINATION OF A WIDE VARIETY OF 2'-ACETOXYCHALCONES TO THE 2'-ACETOXY- α -BROMO- β -METHOXY-DIHYDROCHALCONES AND THEIR APPLICATIONS TOWARDS AURONE SYNTHESIS

DISCUSSION

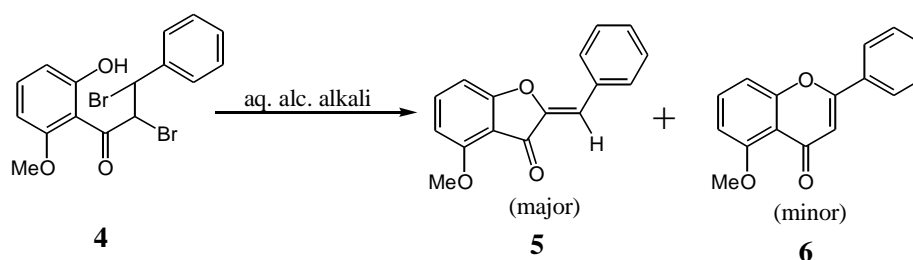
Introduction

von-Auwers and Mueller first reported¹ the preparation of aurone [2-benzylidenecoumaran-3-ones] (**3**) by condensation of coumaran-3-one (**1**) with an appropriate aromatic aldehyde **2** (R = H) in the presence of acid or alkali, as shown in scheme 1. However, this method has certain disadvantage for the preparation of ring-A substituted aurone because it is very difficult to prepare ring-A substituted coumaran-3-one (**1**).



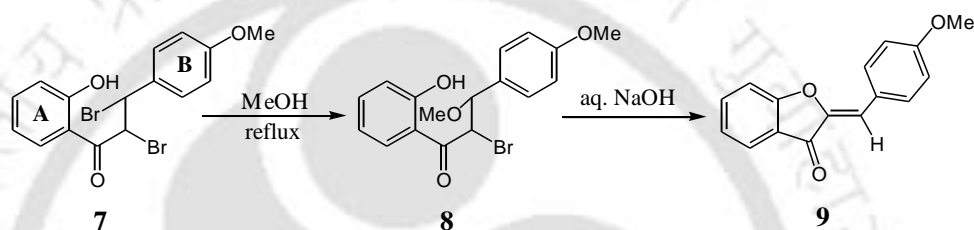
Scheme 1

Next, Auwers and Anschutz reported² an alternate procedure for the synthesis of ring-A substituted aurone **5** starting from chalcone dibromide **4** by cyclisation with aqueous ethanolic alkali as mentioned in scheme 2. This method has also some drawbacks that all types of chalcone dihalides do not provide aurones e.g. simple chalcone dihalide, because the *in situ* generated phenoxide anion at the 2'-position can attack either at α - or β -position of the chalcone dihalide. If it attacks at the α -position then we usually expect aurone, whereas flavone will be obtained if it attacks at the β -position. Therefore, there is always a chance to attack at α - or β -position, which is difficult to control under the reaction conditions.



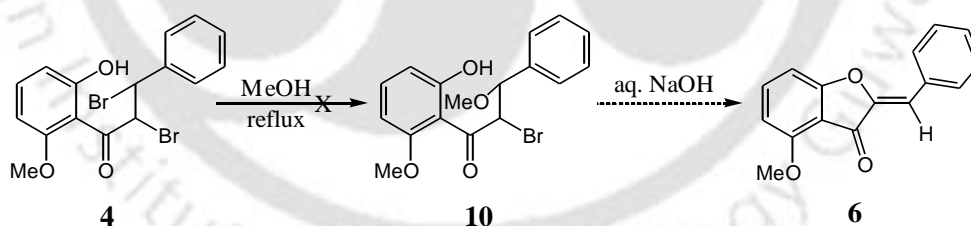
Scheme 2

Subsequently, Wheeler *et al* realized³ that in chalcone dibromides, if the bromo group at the β -position is replaced by a poor leaving group such as an alkoxy group, then the cyclisation might be possible exclusively at the α -position so that aurone will be the exclusive product. Keeping this idea in mind, Wheeler and his co-workers converted the respective chalcone dihalide into α -bromo-2'-hydroxy- β -methoxy dihydrochalcone (**8**), by solvolysis with methanol. The solvolized product α -bromo-2'-hydroxy- β -dihydrochalcone (**8**) is finally cyclized to the aurone **9** using aqueous NaOH solution, as shown in scheme 3.



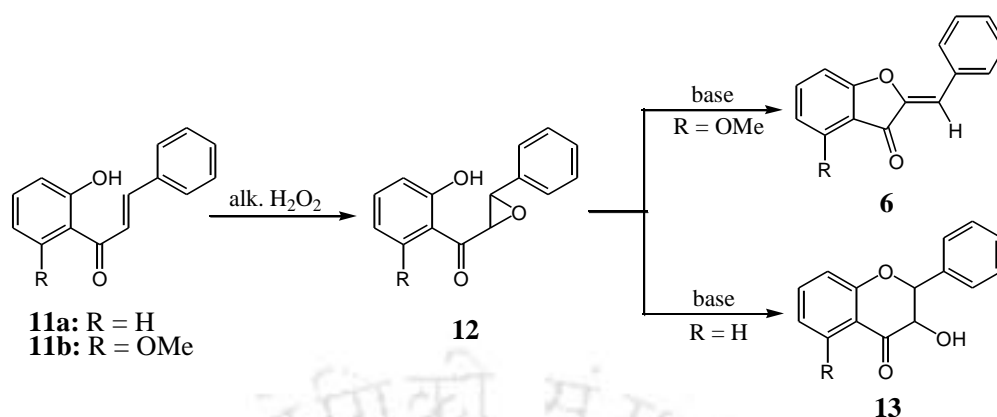
Scheme 3

However, they have observed that the solvolysis is favored only when there is an alkoxy substituent at the 2- or 4-position in the ring-B. Therefore, they have encountered difficulty to prepare aurones having no substituent in the ring B, as depicted in scheme 4.



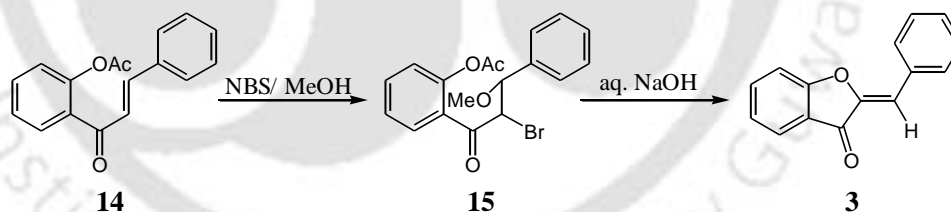
Scheme 4

In the mean time, Alger-Flynn⁴ and Oyamada⁵ reported one more approach for the synthesis of aurone **6** from 2'-hydroxychalcone **11b** with alkaline hydrogen peroxide, as shown in scheme 5. However, this method has also some drawbacks to access aurone with no substituent in ring-A. In that case they have obtained flavanol **13** instead of the expected aurone **6** from the simple chalcone **11a**.



Scheme 5

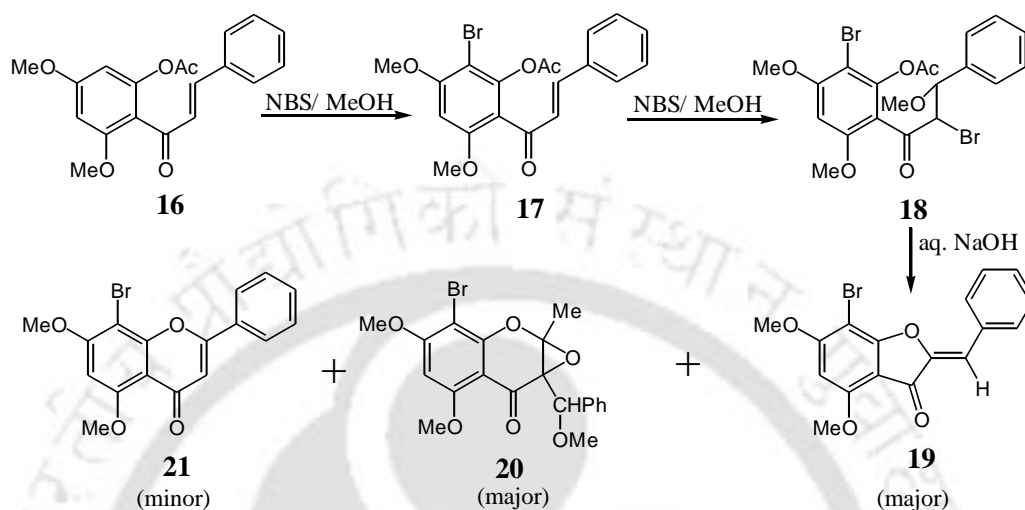
By the time Donnelly *et al* conceived⁶ that if the alkoxy group is incorporated at the β -position of the 2'-hydroxychalcone instead of chalcone dihalide (which is not accessible by Wheeler's method), then aurones could be obtained exclusively by cyclisation with alkali. By assuming this conception, Donnelly and his group tried to introduce an alkoxy group at the β -position by employing NBS in methanol. They had to choose 2'-acetoxychalcone instead of 2'-hydroxychalcone as the latter gives ring brominations under NBS in methanol reaction conditions, which was reported⁷ earlier by Bien and his group. Donnelly's approach is represented in scheme 6.



Scheme 6

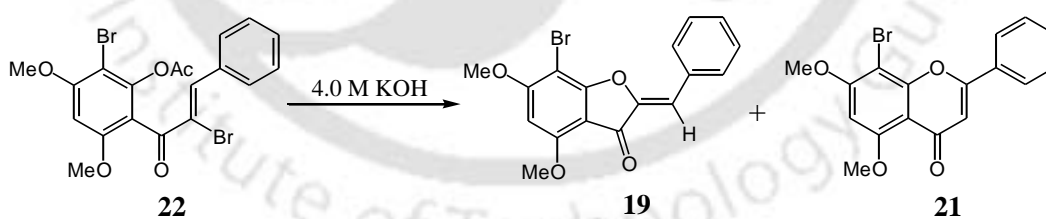
Then, Donnelly *et al* have attempted to synthesize 4,6-dimethoxyaurone, a naturally occurring aurone starting from 2'-acetoxy-4',6'-dimethoxychalcone (**16**) by following the identical reaction conditions. Under NBS in methanol reaction conditions, they have obtained nuclear ring brominated product (**17**), which on further reaction with methanolic NBS gave 2'-acetoxy-2,3'-dibromo-3,4',6'-trimethoxy dihydrochalcone (**18**). Interestingly, when the compound **18** was subjected to cyclisation in aqueous methanolic NaOH, it gave three major products viz. the two diastereomers of 8-bromo-5,7-dimethoxy-3-(α -methoxybenzyl)-2-methylchromone epoxide (**20**) and 7-bromo-4,6-dimethoxyaurone (**19**)

along with 8-bromo-5,7-dimethoxyflavone (**21**) as minor product (shown in scheme 7). Therefore, this route also suffers in the preparation of substituted aurones in ring A.



Scheme 7

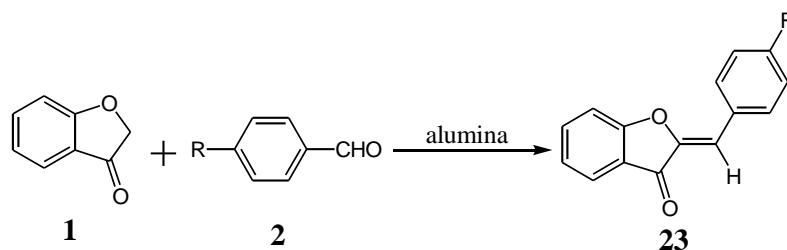
Donnelly and his group observed⁸ that α -bromo-chalcone **22** provided a mixture of 7-bromo-4,6-dimethoxyaurone (**19**) and 8-bromo-5,7-dimethoxyflavone (**21**) in almost equal amount in ratio on cyclisation with 4.0 M KOH as mentioned in scheme 8. From this observation, it is clear that of ring-A substituted 7-bromoaurone can not be prepared easily from 2'-acetoxy- α -bromo-chalcone.



Scheme 8

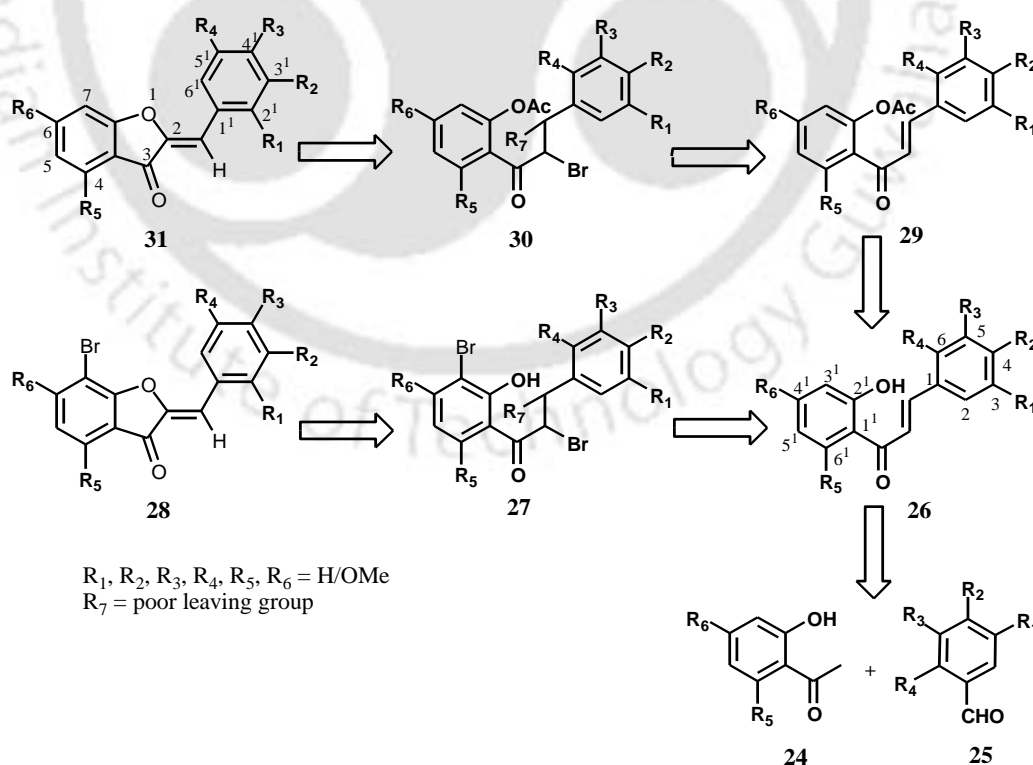
Recently, Verma *et al* reported⁹ a synthetic protocol for aurones starting from coumaran-3-one (**1**) and aromatic aldehydes **2** in presence of alumina surface as mentioned in scheme 9.

However, this method has also drawbacks for the preparation of ring-A substituted coumaran-3-one (**1**) as already mentioned in scheme 1.



Scheme 9

From the literature survey we have found that neither ring-A nor ring-B nor both ring substituted aurones and 7-bromoaurones were synthesized so far in elegant way. Knowing the unique behavior and properties of the reagent *n*-tetrabutylammonium tribromide (TBATB), we conceived the idea that TBATB might be further applied for the synthesis of highly substituted aurones from substituted 2'-acetoxychalcones by bromination, followed by cyclisation. Subsequently, 7-bromoaurones can also be synthesized from substituted 2'-hydroxychalcones in the similar way. The retrosynthetic analysis is represented in scheme 10. It seems that it is possible to make aurones and 7-bromoaurones in the shortest possible way by tuning the reaction conditions.



Scheme 1

A BRIEF REVIEW ON AURONES AND 7-BROMO AURONES

REVIEW OF LITERATURE

References

- (1) Gribble, G. W. *Chem. Soc. Rev.* **1999**, 28, 335
- (2) Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, 93, 1937.
- (3) Wittig, G.; Schoellkopt, U. *Chem. Ber.* **1954**, 87, 1318.
- (4) Grignard, V. *Compt. Rend.* **1900**, 130,1322.
- (5) Majumdar, K. C.; Khan, A. T.; Chattopadhyay, S. K. *Synthesis* **1988**, 552.
- (6) Dunn, G. L.; DiPasquo, V. J.; Hoover, R. E. *J. Org. Chem.* **1968**, 33, 1454.
- (7) Wender, P. A.; Hillemann, C. L.; Szymonifka, M. J. *Tetrahedron Lett.* **1980**, 21, 2205.
- (8) Isobe, M.; Nishikawa, T.; Pikul, S.; Goto, T. *Tetrahedron Lett.* **1987**, 28, 6485.
- (9) Smith III, A. B.; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, 47, 1855.
- (10) Han, X.; Corey, E. J. *Org. Lett.* **1999**, 1, 1871.
- (11) Guaciaro, M. A.; Wovkulich, P. M.; Smith III, A. B. *Tetrahedron Lett.* **1978**, 4661.
- (12) Janssen, C. G. M.; Simons, L. H. J.; Godefroi, E. F. *Synthesis* **1982**, 389.
- (13) Kowalski, C. J.; Weber, A. E.; Fields, K. W. *J. Org. Chem.* **1982**, 47, 5088.
- (14) Arai, S.; Nakayama, K.; Ishida, T.; Shioiri, T. *Tetrahedron Lett.* **1999**, 40, 4215.
- (15) Bordwell, F. G.; Wellman, K. M. *J. Org. Chem.* **1963**, 28, 2544.
- (16) Smith III, A. B.; Branca, S. J.; Guaciaro, M. A.; Wovkulich, P. M.; Korn, A. *Org. Synth. Coll. Vol.*; John Wiley: Singapore, 1990; Vol. VII, p. 271.
- (17) Ley, S. V.; Whittle, A. J. *Tetrahedron Lett.* **1981**, 22, 3301.
- (18) Righi, G.; Bovicelli, P.; Sperandio, A. *Tetrahedron Lett.* **1999**, 40, 5889.
- (19) Clark, J. H., Ed. *Chemistry of Waste Minimisation*, Chapman and Hall: London (1995).
- (20) Emilewicz, T.; Konstanecki, S. v. *Ber. Dtsch. Chem. Ges.* **1898**, 31, 696.
- (21) Emilewicz, T.; Konstanecki, S. v. *Ber. Dtsch. Chem. Ges.* **1899**, 32, 309.

- (22) Konstanecki, S. v.; Tambor, J. *Ber. Dtsch. Chem. Ges.* **1899**, 32, 2260.
- (23) Hutchins, W. A.; Wheeler, T. S. *J. Chem. Soc.* **1939**, 91.
- (24) Donnelly, D. J.; Donnelly, J. A.; Murphy, J. J.; Philbin, E. M.; Wheeler, T. S. *J. Chem. Soc. Chem. Comm.* **1966**, 351.
- (25) Auwers, K. v.; Anschutz, L. *Ber. Dtsch. Chem. Ges.* **1921**, 54, 1543.
- (26) Gowan, J. E.; Wheeler, T. S. Ed. *Name Index of Organic Reactions*, Longmans: London, 1960; p. 149.
- (27) Donnelly, D. J.; Donnelly, J. A.; Philbin, E. M. *Tetrahedron* **1972**, 28, 53.
- (28) Donnelly, D. J.; Donnelly, J. A.; Philbin, E. M. *Tetrahedron* **1972**, 28, 1867.
- (29) Konstanecki, S. v.; Ludwig, A. *Ber. Dtsch. Chem. Ges.* **1898**, 31, 2951.
- (30) Shah, N. M.; Parikh, S. R. *J. Indian Chem. Soc.* **1959**, 36, 726.
- (31) Donnelly, J. A.; Doran, H. J.; Murphy, J. J.; *Tetrahedron* **1973**, 29, 1037.
- (32) Pendse, H. K. *Rasayanam* **1956**, 2, 131.
- (33) Donnelly, J. A. *Tetrahedron* **1973**, 29, 2585.
- (34) Donnelly, J. A.; Doran, H. J. *Tetrahedron Lett.* **1974**, 4083.
- (35) Donnelly, J. A.; Doran, H. J. *Tetrahedron* **1975**, 31, 1565.
- (36) Donnelly, J. A.; Doran, H. J. *Tetrahedron* **1975**, 31, 1791.
- (37) Smith III, A. B. In *Strategies and Tactics in Organic Synthesis*; Eds.; Lindberg, T., Academic Press Inc.: San Diego, 1994; Vol. 1, pp. 239-243.
- (38) Gribble, G. W. In *Progress in the Chemistry of Organic Natural Products*; Eds.; Herz, W.; Kirby, G. W.; Moore, R. E.; Steglich, W.; Tamm, C., Springer-Verlag: Vienna, 1996; pp. 17-22 and references cited therein.
- (39) Larock, R. C. Ed. *Comprehensive Organic Transformations*, Wiley-VCH: New York, 1999; p. 638.
- (40) Chaudhuri, M. K.; Khan, A. T.; Patel, B. K.; Dey, D.; Kharmawopflang, W.; Lakshmiprabha, T. R.; Mandal, G. C. *Tetrahedron Lett.* **1998**, 39, 8163.
- (41) Bora, U.; Bose, G.; Chaudhuri, M. K.; Dhar, S. S.; Gopinath, R.; Khan, A. T.; Patel, B. K. *Org. Lett.* **2000**, 2, 247.

- (42) Fournier, M. J. L. In *Encyclopedia of Reagents for Organic Synthesis*; Eds.; Paquette, L. A., John Wiley & Sons: Singapore, 1995; Vol. 7, pp 4738-4740.
- (43) Buckles, R. E.; Popov, A. I.; Zelezny, W. F.; Smith, R. J. *J. Am. Chem. Soc.* **1951**, 73, 4525.
- (44) Vogel's In *Textbook of Practical Organic Chemistry*; Eds.; Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R., ELBS: Singapore, 1996; pp 1032-1035.
- (45) Vogel's In *Textbook of Practical Organic Chemistry* Eds.; Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R., ELBS: Singapore, 1996; p 1078.
- (46) Huang, Z.; Wu, L.; Zhu, L.; Huang, X. *Synth. Commun.* **1996**, 26, 677.
- (47) Davey, W.; Tivey, D. J. *J. Chem. Soc.* **1958**, 1230.
- (48) Bose, G.; Barua, P. M. B.; Chaudhuri, M. K.; Kalita, D.; Khan, A. T. *Chemistry Lett.* **2001**, 290.
- (49) Middleton, E., Jr. *Ann. Allergy* **1988**, 61, 53.
- (50) Forkmann, G.; Heller, W. In *Comprehensive Natural Products Chemistry*; Eds.; Barton, D.; Nakanishi, K.; Meth-Cohn, O. Pergamon press, Elsevier: New York, 1999; Vol.1, pp 713-748 and reference therein.
- (51) (a) Welton, A. F.; Tobias, L. D.; Fielter-Nazy, C.; Anderson, W.; Hope, W.; Meyers, K.; Coffey, J. W. In *Plant Flavonoids in Biology and Medicine*; Cody, V., Middleton, E., Jr., Harborne, J. B., Eds.; Alan R. Liss Inc.: New York, 1986; p 231.(b) Selway, J. W. T. In *Plant Flavonoids in Biology and Medicine*; Cody, V., Middleton, E., Jr., Harborne, J. B., Eds.; Alan R. Liss Inc.: New York, 1986; p 521.
- (52) *The Pharmacology of Benxopyran derivatives and related compounds*; Gaber, M., Eds.; Akademia Kiado: Budapest, 1988.
- (53) a) Inouye, Y.; Yamaguchi, K.; Take, Y.; Nakamura, S. *J. Antibiotics* **1989**, 62, 1523. b) Nakane, H.; Ono, K. *Biochemistry* **1990**, 29, 2841.
- (54) Geahlen, R. L.; Koonchanok, N. M.; McLaughlin, J. L.; Pratt, D. E. *J. Nat. Prod.* **1989**, 52, 982.

- (55) Hagiwara, M.; Inoue, S.; Tanaka, T.; Nunoki, K.; Ito, M.; Hidaka, H. *Biochem. Pharmacol.* **1988**, *37*, 2987.
- (56) Hirano, T.; Oka, K.; Akiba, M. *Res. Commun. Chem. Path. Pharmacol.* **1989**, *64*, 69.
- (57) Cassady, J. M.; Baird, W. H.; Chang, C. -J. *J. Nat. Prod.* **1990**, *53*, 22.
- (58) Ono, K.; Nakane, H. *J. Biochem.* **1990**, *108*, 609.
- (59) Ono, K.; Nakane, H.; Fukushima, M.; Chermann, J. C.; Barre-Sinoussi, F. *Eur. J. Biochem.* **1990**, *190*, 469.
- (60) Hu, C. Q.; Chen, K.; Shi, Q.; Kilkuskie, R.; Cheng, Y. C.; Lee, K. H. *J. Nat. Prod.* **1994**, *57*, 42.
- (61) (a) Gripenberg, J. In *The Chemistry of Flavonoid Compounds*; Geissman, T. A., Ed.; MacMillan: New York, 1962; p 409. (b) Wagner, H.; Farkas L. In *The Flavonoids*; Harborne, J. B., Mabry, T. J., Mabry, H., Eds.; Academic Press: New York, 1975, p 127. (c) Wang, L. *Zhongguo Yiyao Gongye ZaZhi* **1990**, *21*, 423.
- (62) Allan, J.; Robinson, R. *J. Chem. Soc.* **1924**, 2192.
- (63) (a) Baker, W. *J. Chem. Soc.* **1933**, 1381. (b) Mahal H. S.; Venkatraman, K. *J. Chem. Soc.* **1934**, 1767.
- (64) Inuma, M.; Iwashima, K.; Matsuura, S.; *Chem. Pharm. Bull.* **1984**, *32*, 4935.
- (65) Hoshino, Y.; Oohinata, T.; Takeno, N. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2351.
- (66) Doshi, A. G.; Soni, P. A.; Ghiya, B. *J. Indian J. Chem.* **1986**, *25B*, 759.
- (67) Imatuku, K.; Honda, M.; Mcomie, J. F. W. *Synthesis* **1987**, 199.
- (68) Makrandi, J. K.; Seema, J. *Chem. Ind. (London)* **1989**, 607.
- (69) Litkei, G.; Gulacsi, K.; Antus, S.; Blasko, G. *Leibigs Ann.* **1995**, 1711.
- (70) (a) LeFloc'h, Y.; LeFeuvre, M. *Tetrahedron Lett.* **1986**, *27*, 5503. (b) LeFloc'h, Y.; LeFeuvre, M. *Tetrahedron Lett.* **1986**, *27*, 2751.
- (71) Sankar, C. G.; Mallaiah, B. V.; Srimannarayana, G. *Synthesis* **1983**, 310 and references therein.
- (72) Mondal, E.; Bose, G.; Khan, A. T. *Synlett* **2001**, 785.
- (73) Mondal, E.; Sahu, P. R.; Bose, G.; Khan, A. T. *Tetrahedron Lett.* **2002**, *43*, in press and references therein.
- (74) Donnelly, J. A.; Fox, M. J.; Sharma, T. C. *Tetrahedron* **1979**, *35*, 875.

- (75) Hunt, G. M. *phytochemistry*, **1980**, *19*, 1415.
- (76) Johnson, F. R.; Robertson, A. *J. Chem. Soc.* **1930**, 25.
- (77) Tanaka, T.; Inuma, M.; Yoki, K.; Fuji, Y.; Mizuno, M. *Phytochemistry* **1992**, *31*, 993.
- (78) Nagarajan, G. R.; Pamer, V. S. *Phytochemistry* **1977**, *16*, 1317.
- (79) Jain, P. K.; Makrandi, J. K.; Grover, S. K. *Synthesis* **1982**, 221.
- (80) Narasimhachari, T. R.; Sheshadri, T. R. *Proc. Ind. Acad. Sci. (A)* **1949**, *30*, 151.
- (81) Fraser, A. W.; Lewis, J. R. *Phytochemistry* **1974**, *13*, 1561.
- (82) Nagar, A.; Guzral, V. K.; Guptam, S. R. *Phytochemistry* **1979**, *18*, 1245.
- (83) Chen, C. -C.; *Chem. Pharm. Bull.* **1984**, *32*, 166.



CHAPTER 1 & 2

REFERENCES

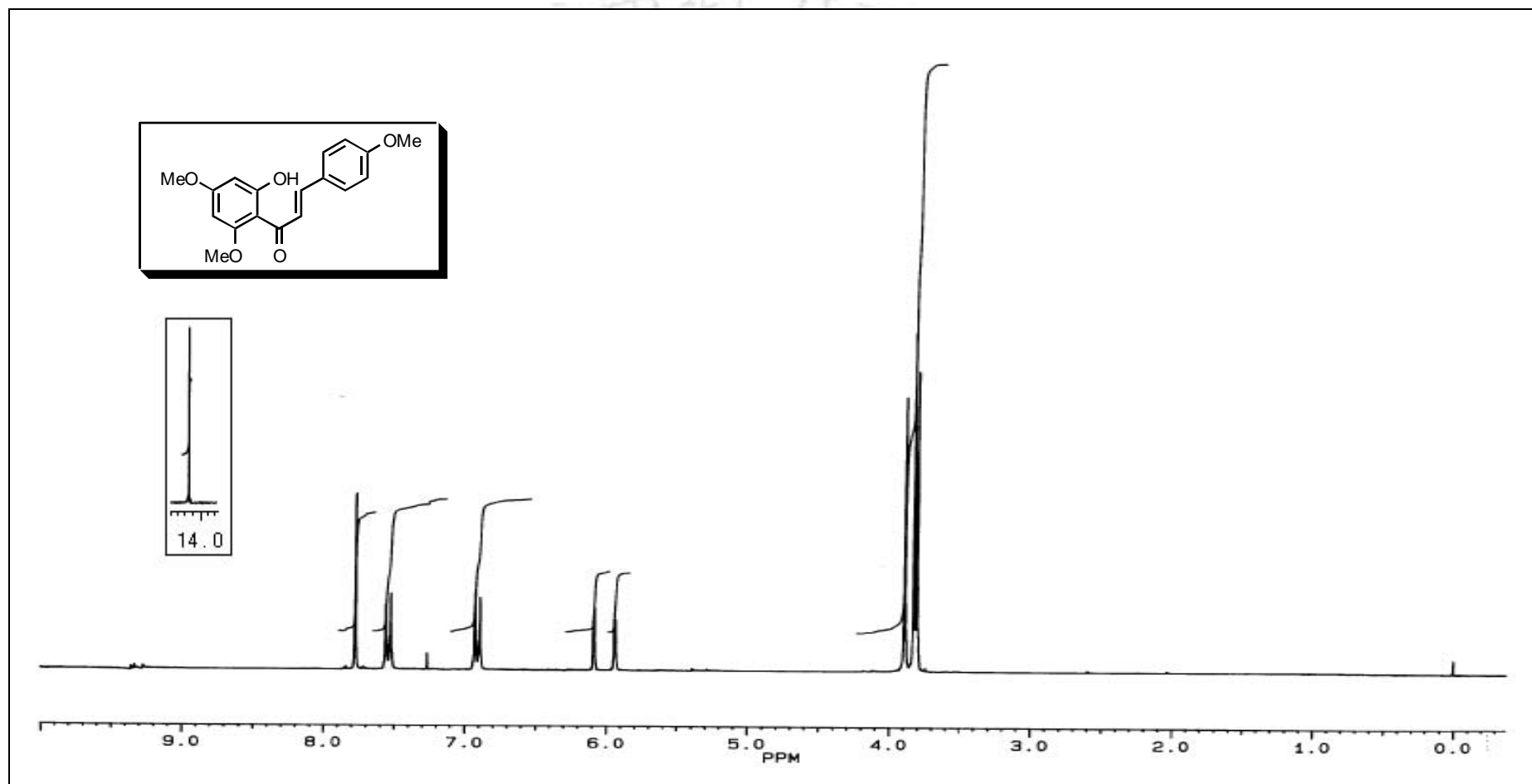


Figure 8: ¹H-NMR spectrum of 1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one (250 MHz, CDCl₃) (**84b**)

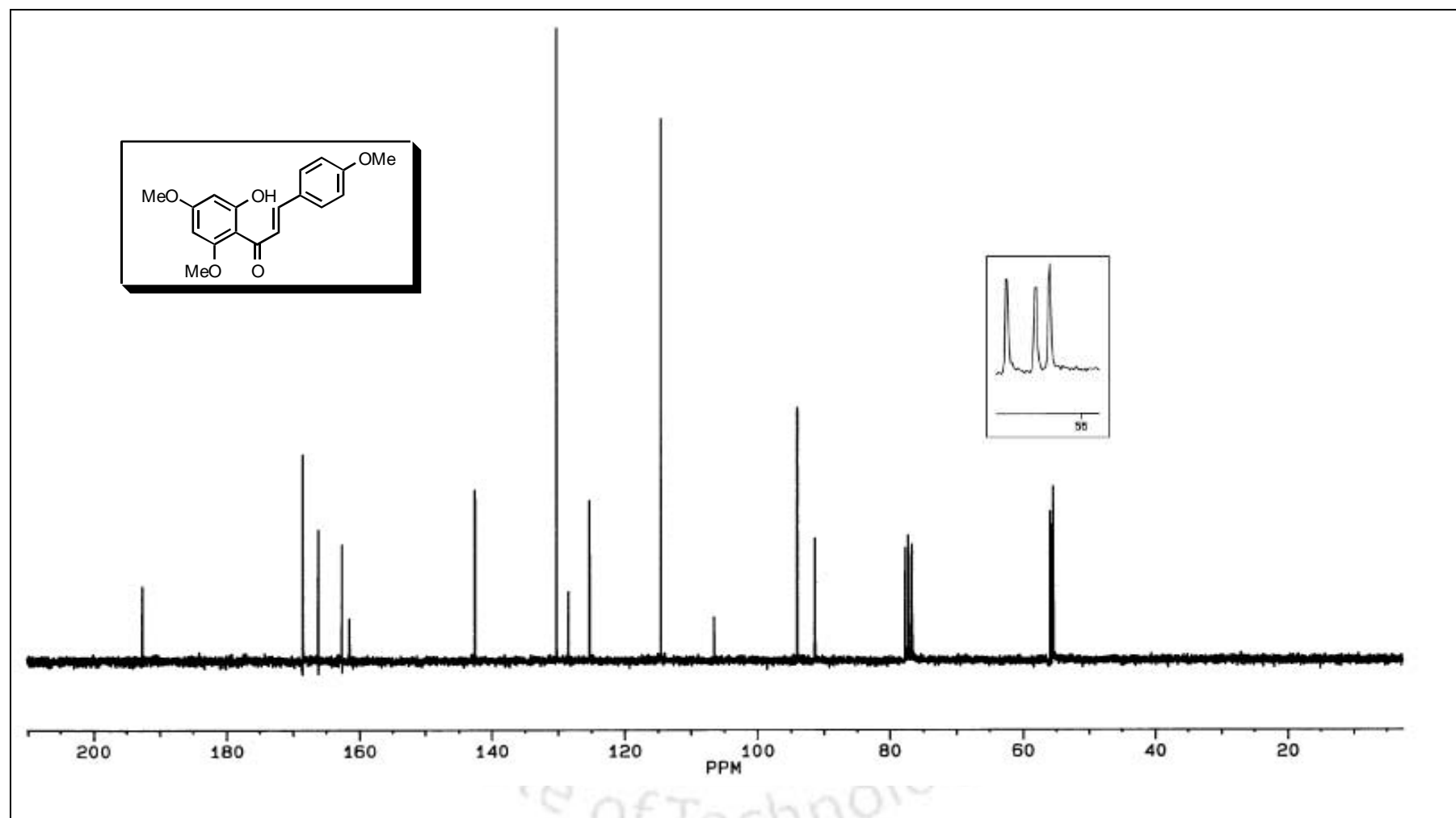


Figure 9: ^{13}C -NMR spectrum of 1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one (62.5 MHz, CDCl_3) (**84b**)

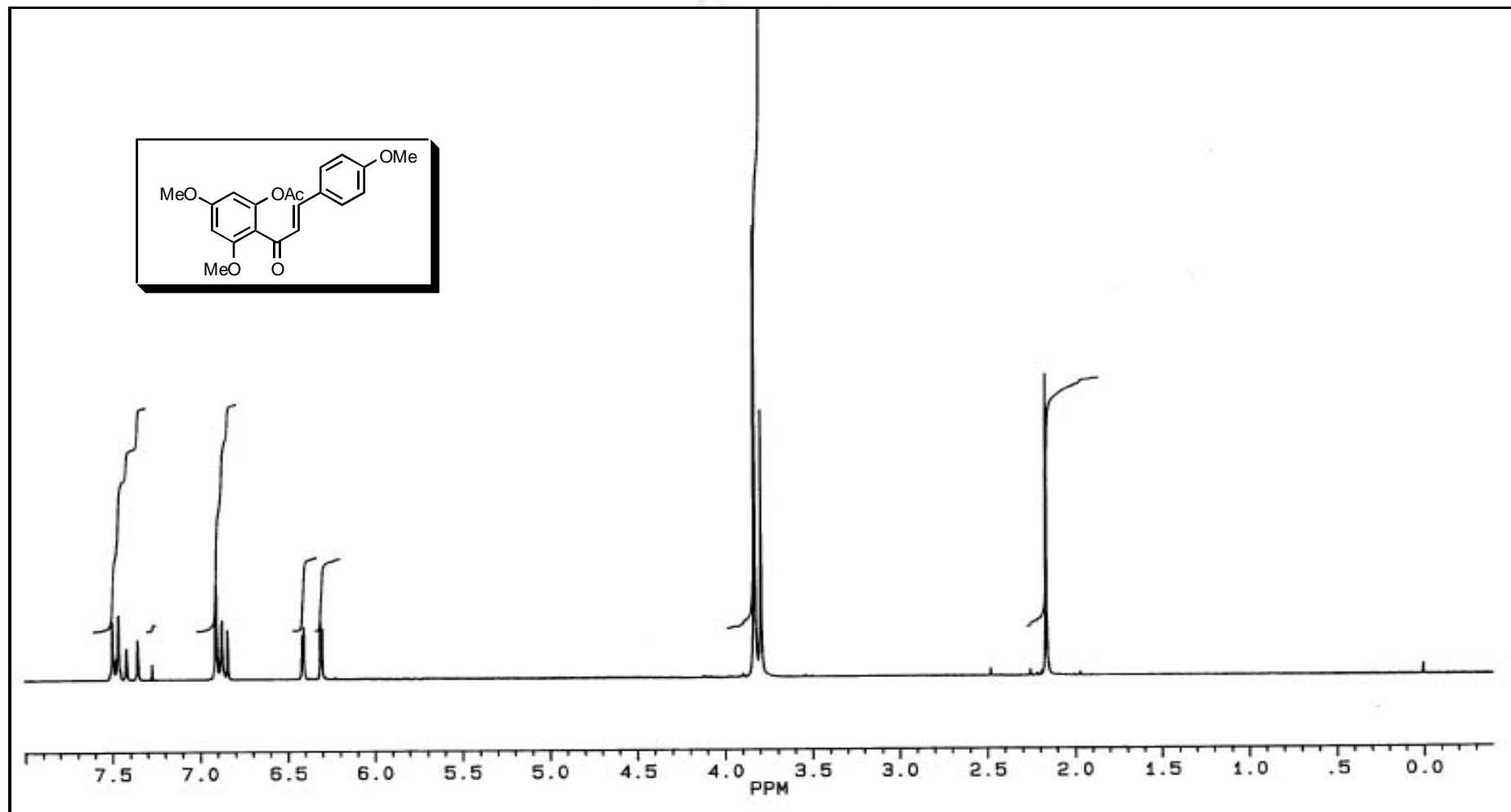


Figure 10: ¹H-NMR spectrum of 1-(2-Acetoxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one (250 MHz, CDCl₃) (**85b**)

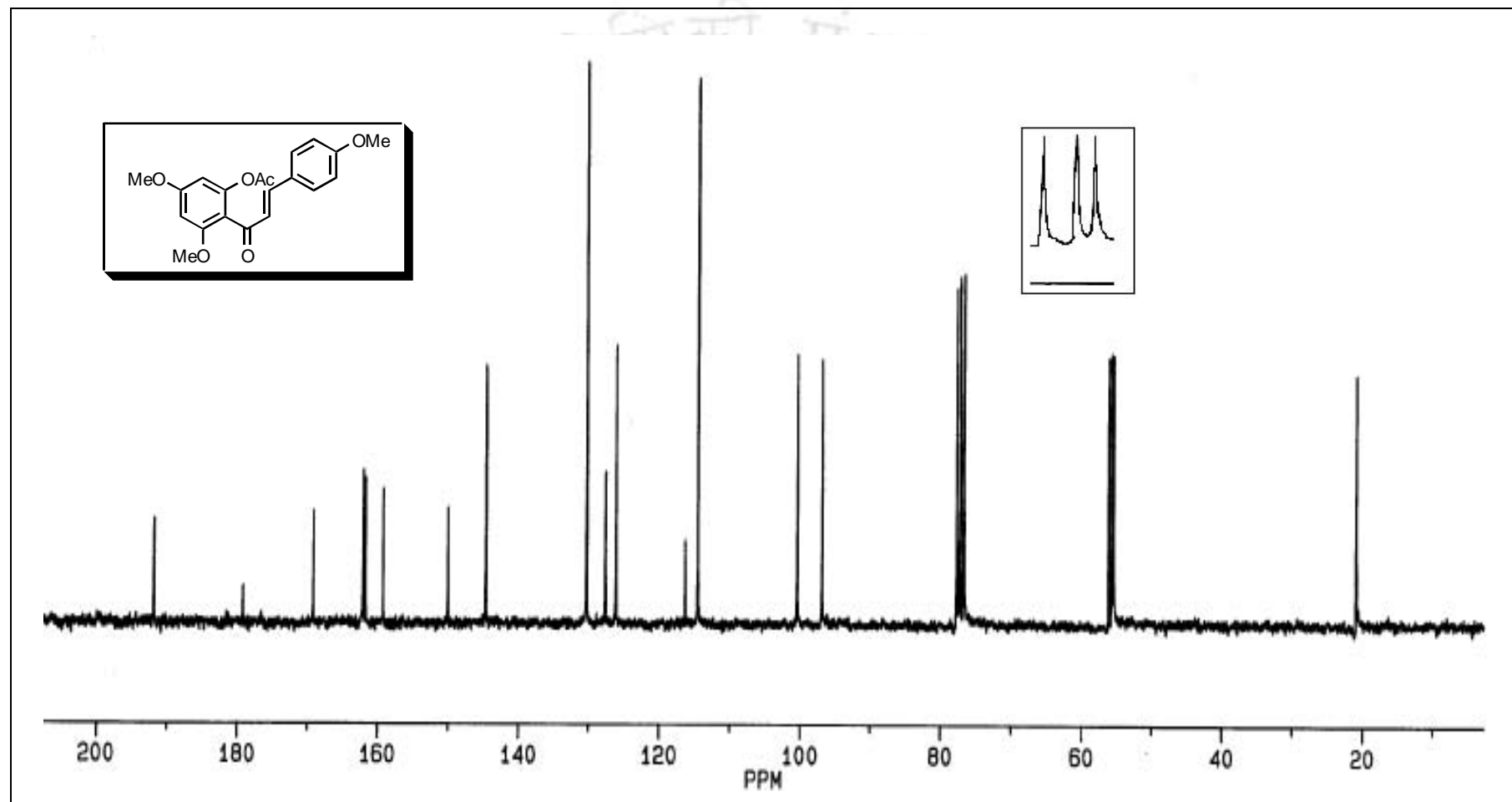


Figure 11: ^{13}C -NMR spectrum of 1-(2-Acetoxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one (62.5 MHz, CDCl_3) (**85b**)

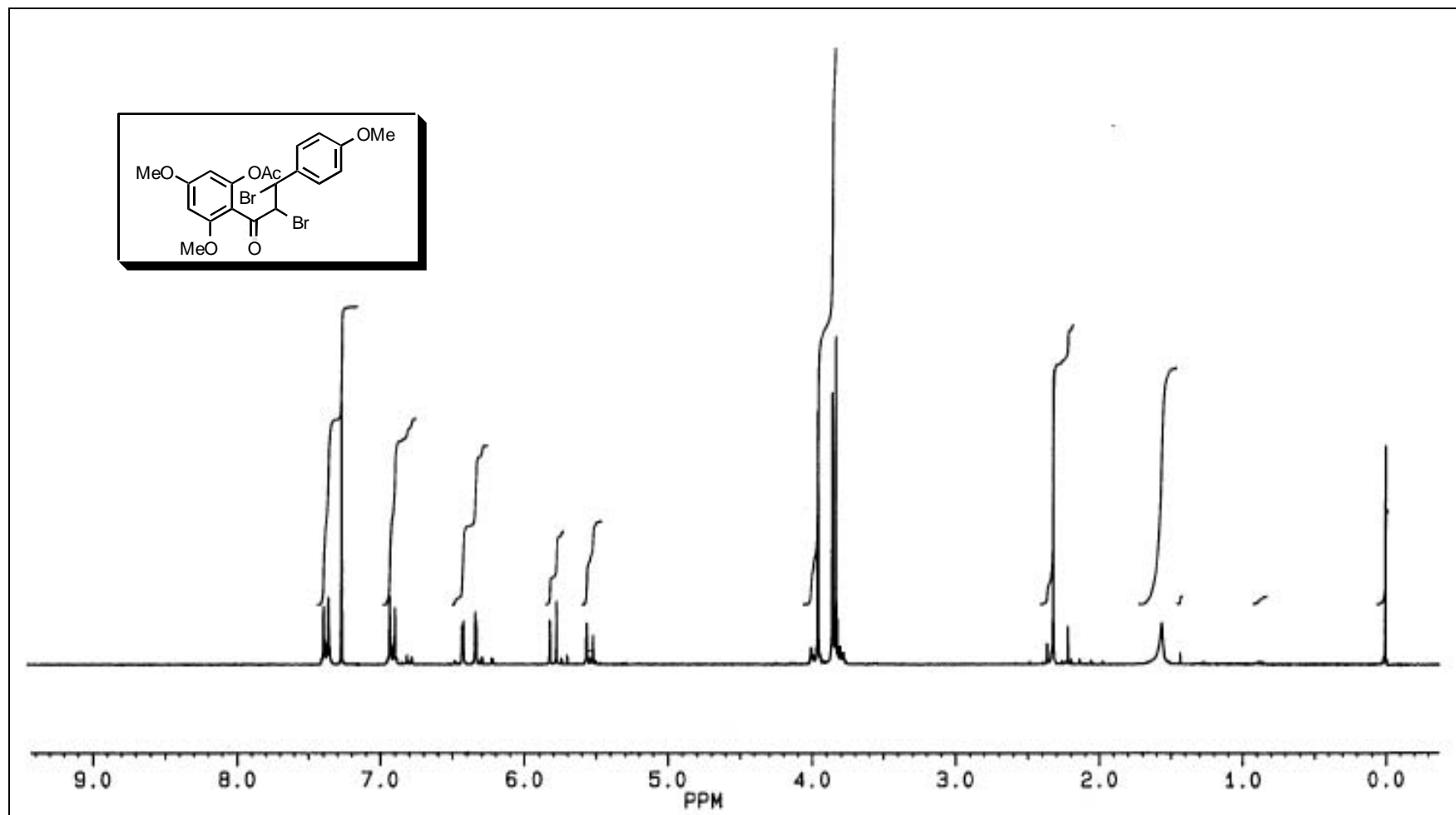


Figure 12: ¹H-NMR spectrum of 1-(2-Acetoxy-4,6-dimethoxyphenyl)-2-bromo-3-methoxy-3-(4-methoxyphenyl)propan-1-one (250 MHz, CDCl₃) (**86b**)

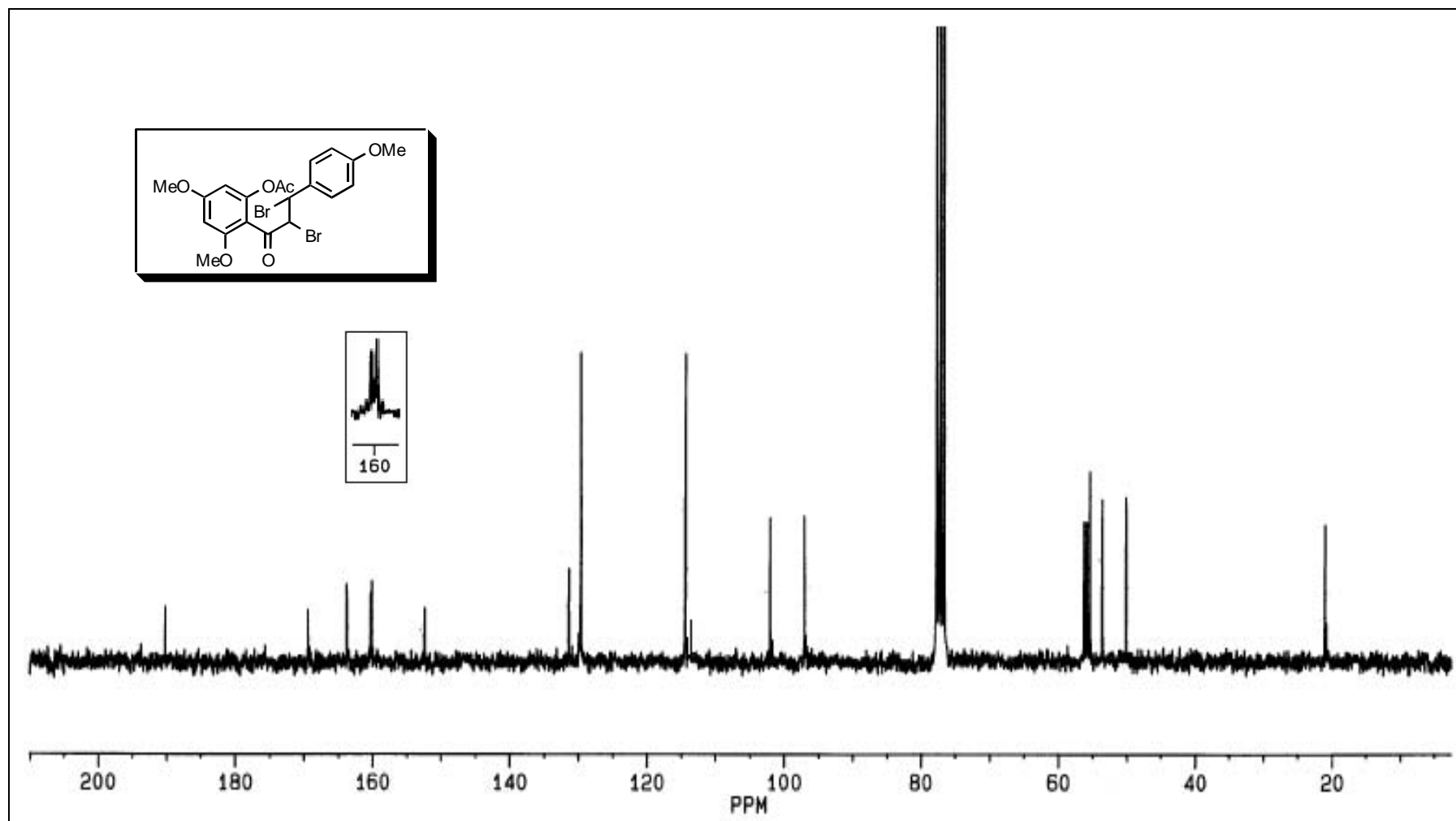


Figure 13: ^{13}C -NMR spectrum of 1-(2-Acetoxy-4,6-dimethoxyphenyl)-2-bromo-3-methoxy-3-(4-methoxyphenyl)propan-1-one (62.5 MHz, CDCl_3) (**86b**)

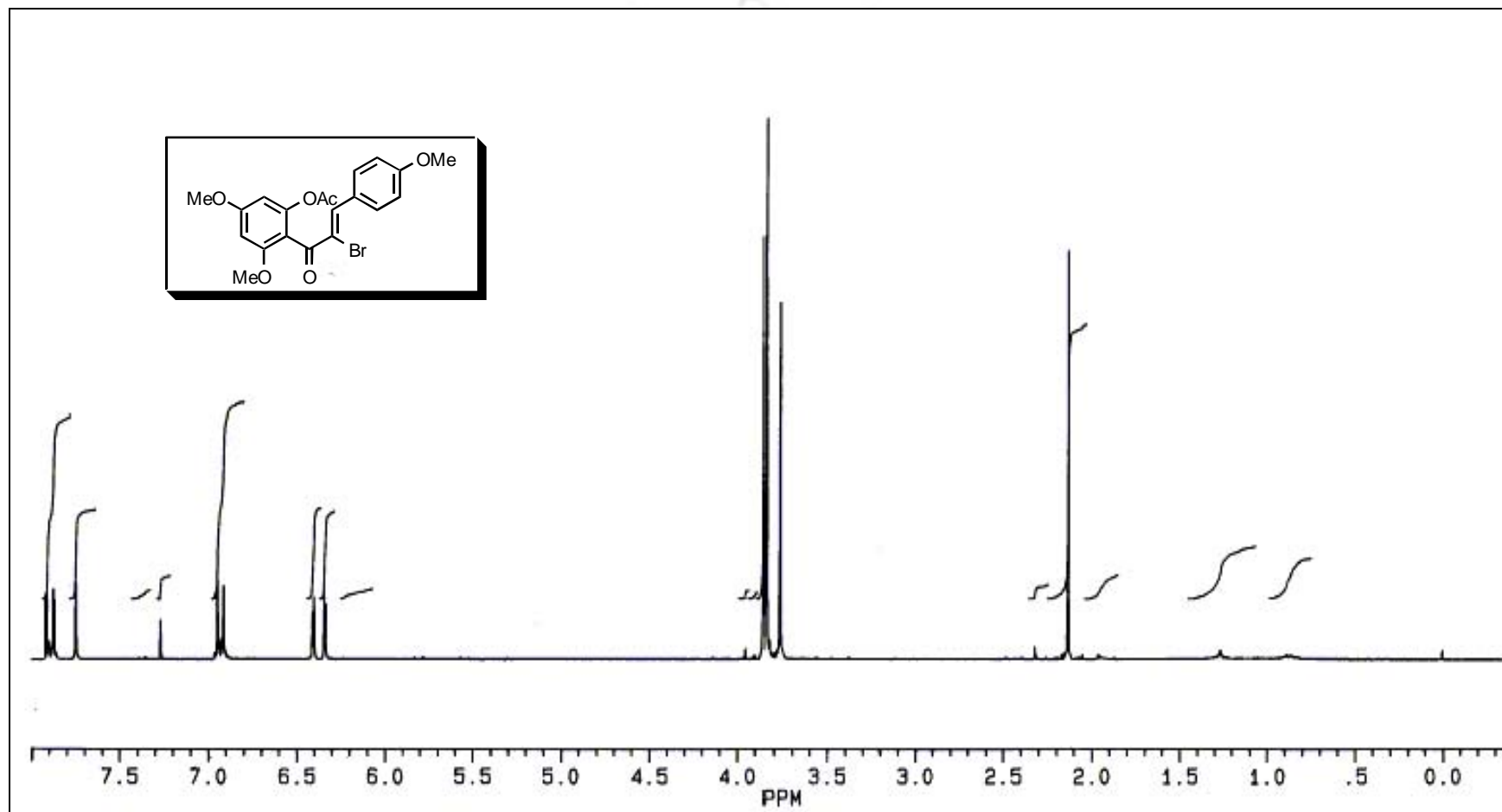


Figure 14: ¹H-NMR spectrum of 1-(2-Acetoxy-4,6-dimethoxyphenyl)-2-bromo-3-(4-methoxyphenyl)-2-propen-1-one (250 MHz, CDCl₃) (**87b**)

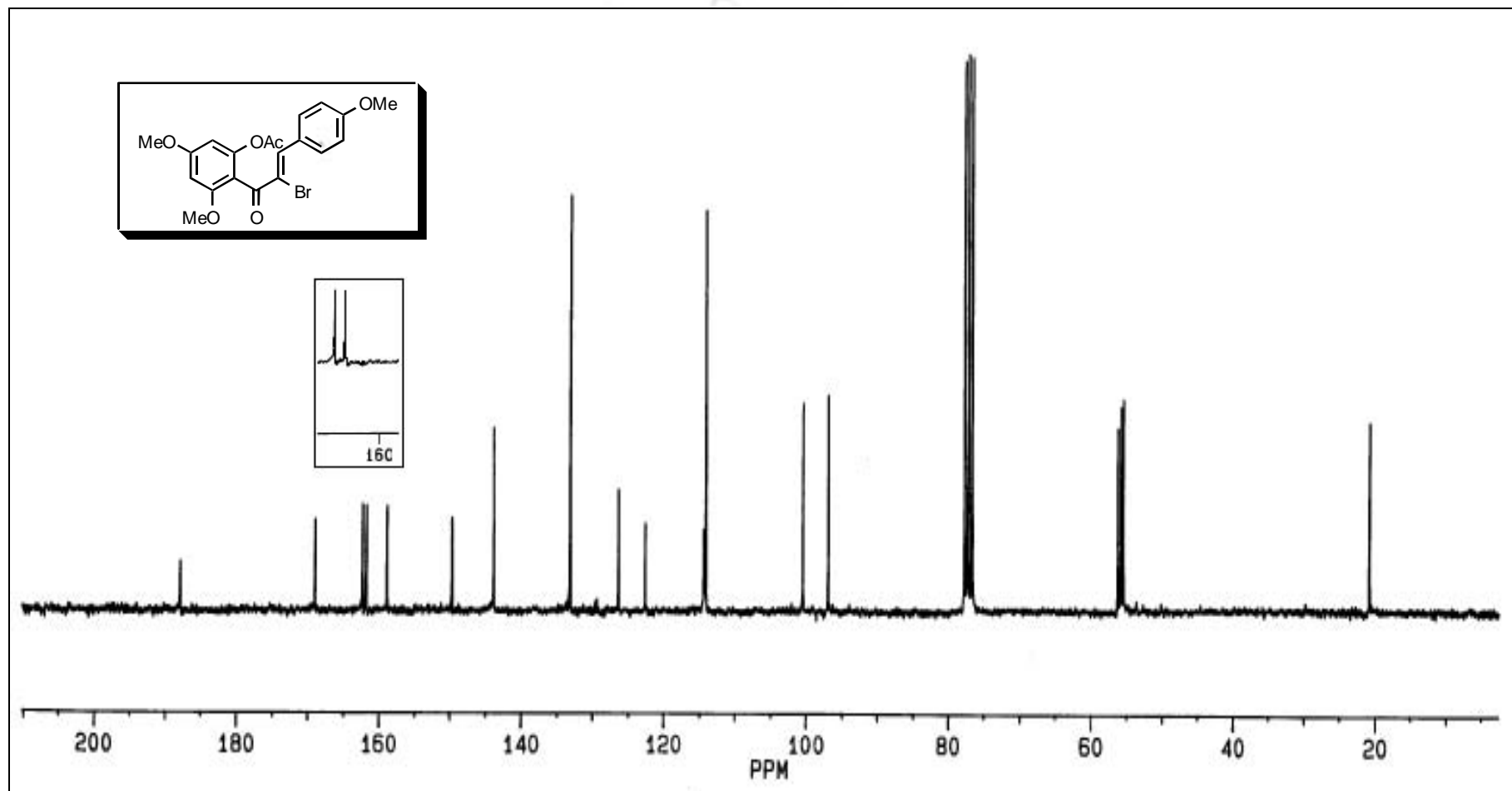


Figure 15: ¹³C-NMR spectrum of 1-(2-Acetoxy-4,6-dimethoxyphenyl)-2-bromo-3-(4-methoxyphenyl)-2-propen-1-one (62.5 MHz, CDCl₃) (**87b**)

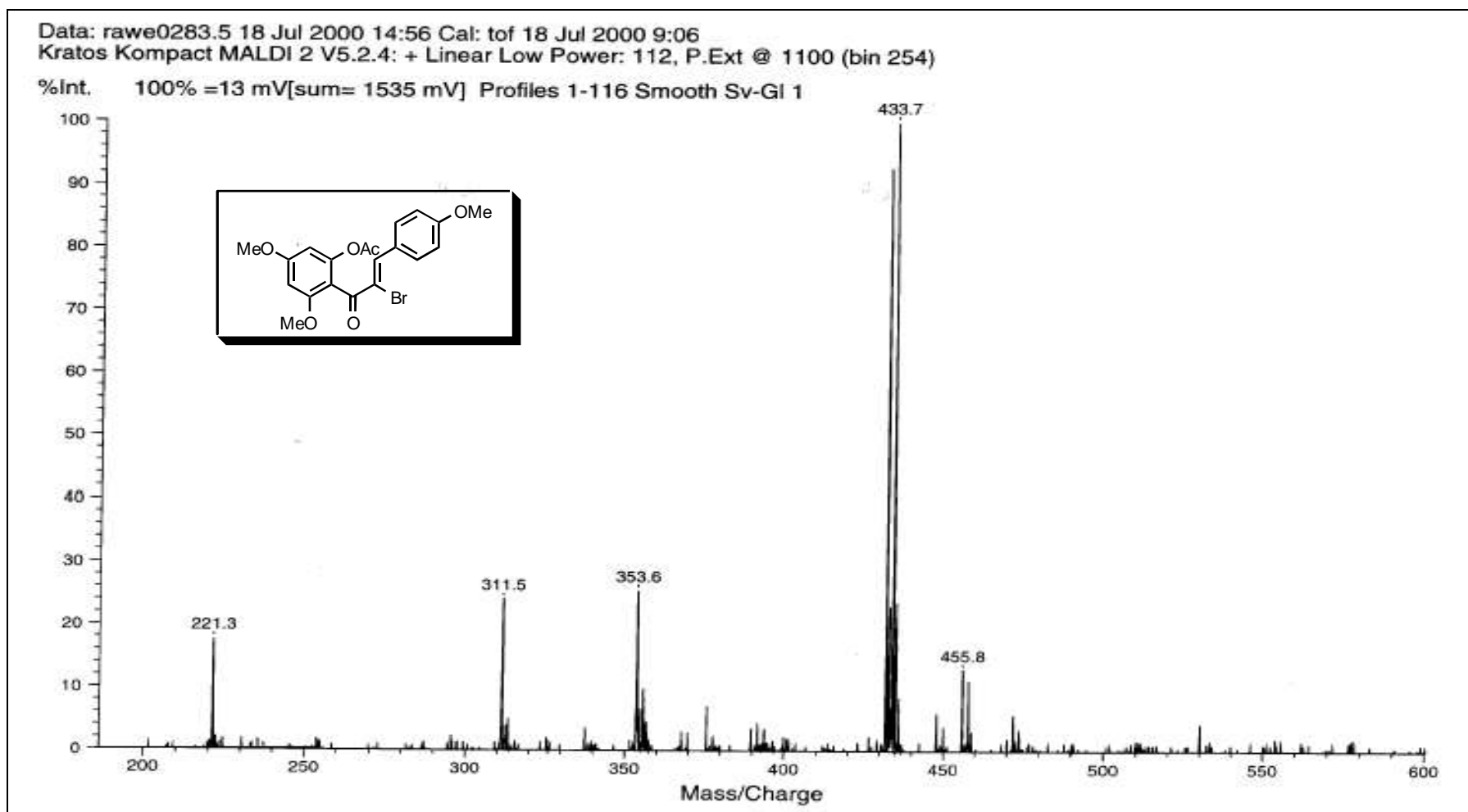


Figure 16: Mass spectrum of 1-(2-Acetoxy-4,6-dimethoxyphenyl)-2-bromo-3-(4-methoxyphenyl)-2-propen-1-one (**87b**)

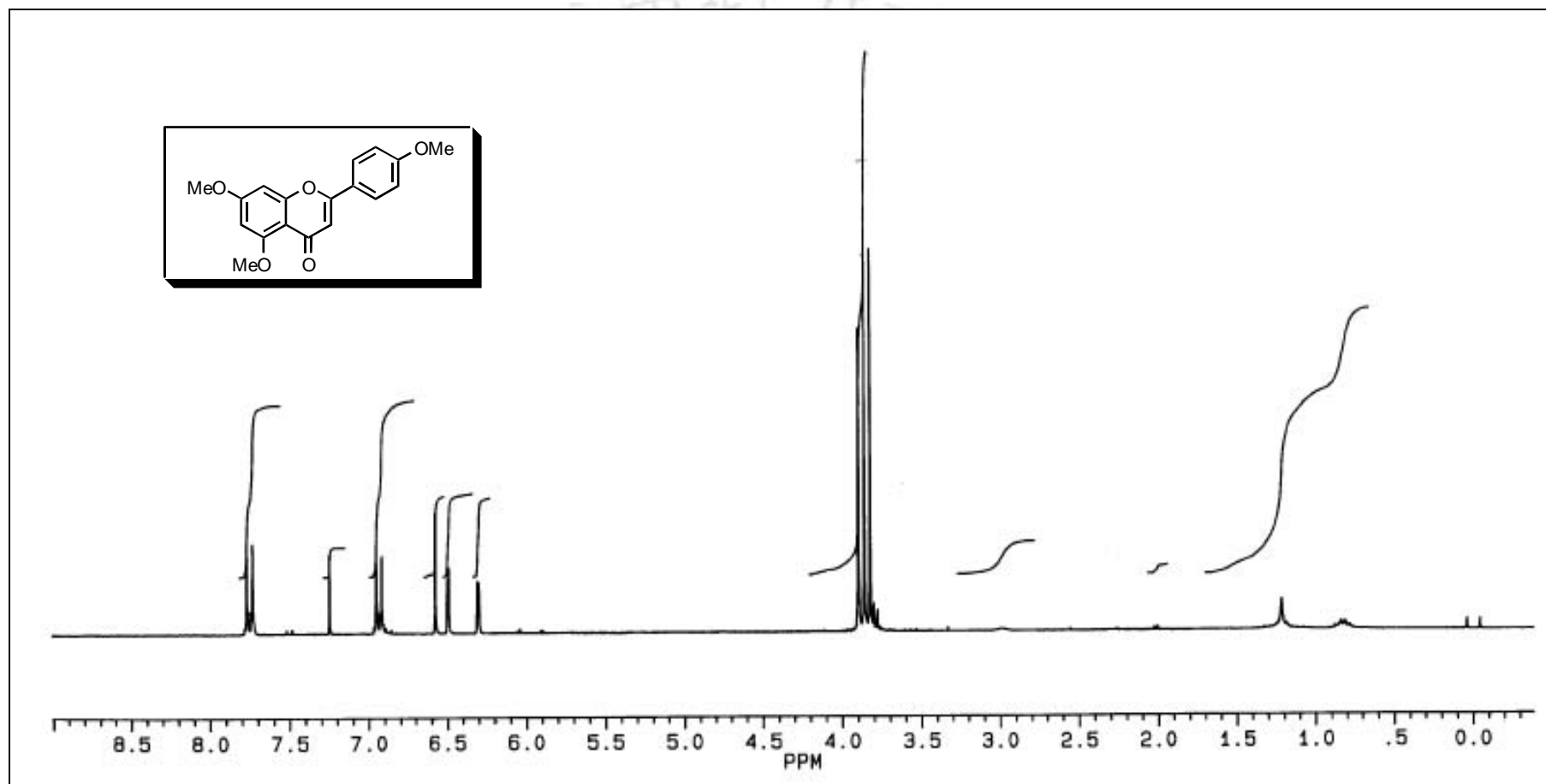


Figure 17: ¹H-NMR spectrum of 5,7-Dimethoxy-2-(4-methoxyphenyl)-4H-1-benzopyran-4-one (250 MHz, CDCl₃) (**88b**)

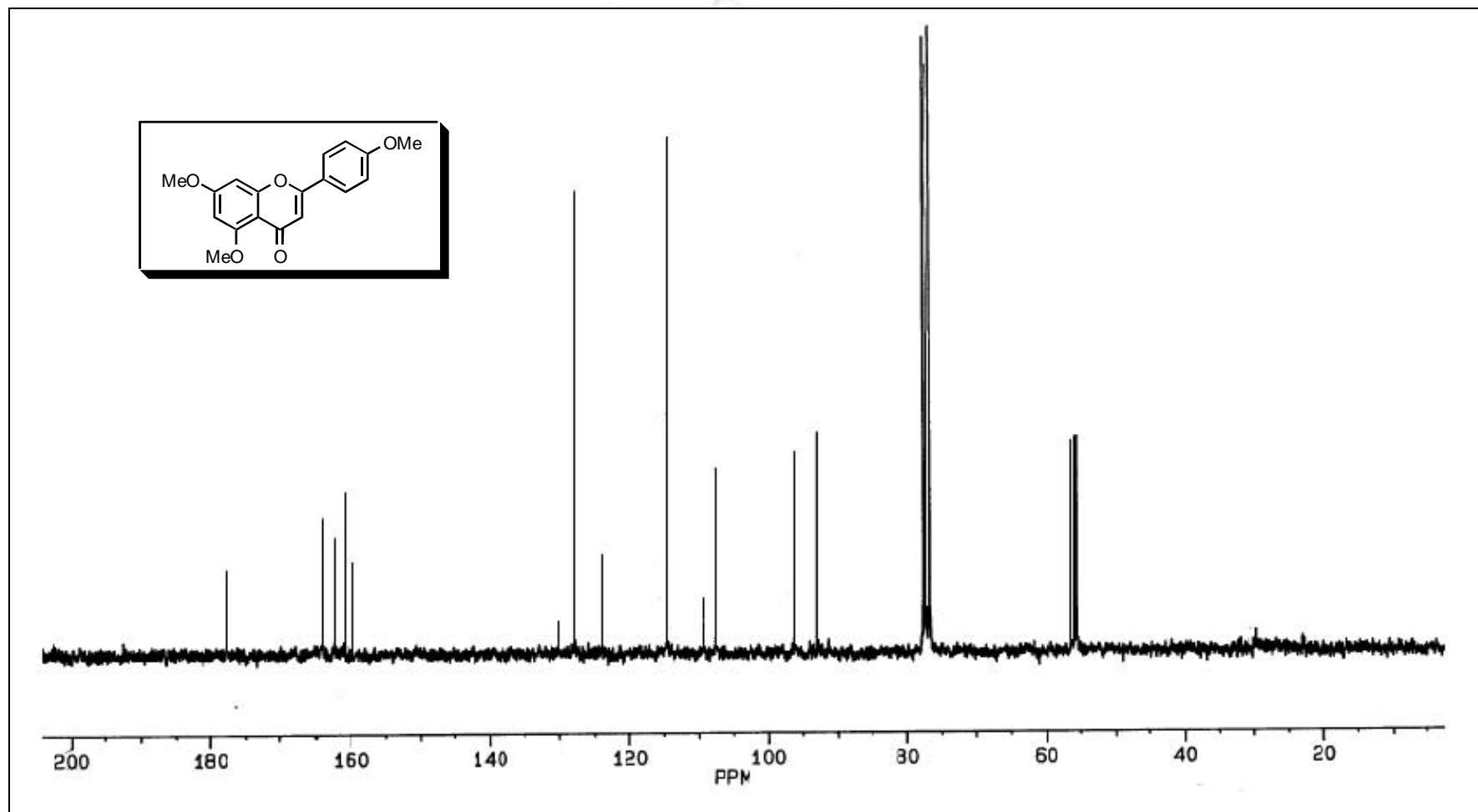


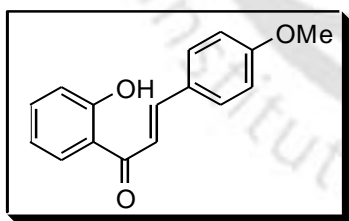
Figure 18: ¹³C-NMR spectrum of 5,7-Dimethoxy-2-(4-methoxyphenyl)-4H-1-benzopyran-4-one (62.5 MHz, CDCl₃) (**88b**)

Experimental

General procedure for preparation of 2'-hydroxy chalcone:

Into a 50 mL round bottom flask 2-hydroxyacetophenone (**82a**) or 2-hydroxy-4,6-dimethoxyacetophenone (**82b**) (5 mmol) is taken in ethanol (10 mL) and cooled it at ice bath temperature. Into it 0.25 g of NaOH (6.25 mmol) is added by dissolving in ethanol-water mixture (4:1, 5 mL) dropwise by using a dropping funnel and stirring is continued. After addition of NaOH solution, the reaction mixture is dissolved and the precipitate is reappeared slowly after 5 min. Then, aromatic aldehyde **83a-e** (5 mmol) is added slowly by dissolving in ethanol (5 mL) as followed earlier. Stirring is continued further for the period of 24-48 hrs to complete the reaction. Then, the solvent is removed *in vacuo* and 5% HCl solution is added to neutralize it (as confirmed by a pH paper). After neutralization, the yellow solid is appeared, which is filtered off in a Buchner funnel and washed thoroughly with water (2 x 25 mL). The solid product is then dried in air and finally recrystallizes with ethyl acetate-hexane mixture. The products **84a-f** are obtained in 69-90% yields as yellow crystalline solids.

1-(2-Hydroxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one (**84a**)



Reaction time: 24 hrs

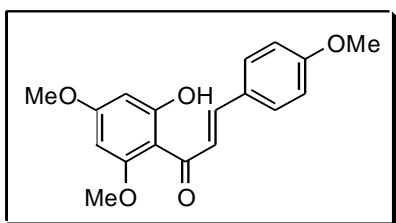
Yield: 69 %, yellow plates

Melting point: 93-94 °C (lit.⁷⁵ m.p. 93-94 °C)

R_f: 0.77 (EtOAc/hexane 1: 19)

IR (KBr): cm⁻¹ 1648,1600, 1568, 1514, 1210

1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one (**84b**)



Reaction time: 36 hrs

Yield: 90 %, yellow crystalline solid

Melting point: 110- 111 °C (lit.⁷⁶ m.p. 112-113 °C)

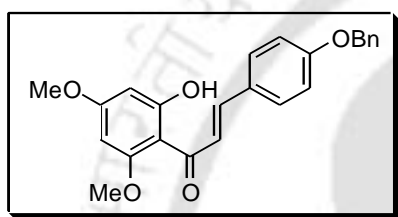
R_f: 0.63 (EtOAc/hexane 1: 9)

IR (KBr): cm^{-1} 1625, 1578, 1514, 1221.

^1H NMR (250 MHz, CDCl_3/TMS): δ 3.80 (s, 3H, $-\text{OCH}_3$), 3.82 (s, 3H, $-\text{OCH}_3$), 3.88 (s, 3H, $-\text{OCH}_3$), 5.93 (d, 1H, $J = 2.3$ Hz, ArH), 6.08 (d, 1H, $J = 2.3$ Hz, ArH), 6.90 (d, 2H, $J = 8.78$ Hz, ArH), 7.53 (d, 2H, $J = 8.78$ Hz, ArH), 7.77 (s, 2H, $-\text{COCH}=\text{CHPh}$), 14.18 (s, 1H, $-\text{OH}$).

^{13}C NMR (62.5 MHz, CDCl_3/TMS): δ 55.31, 55.45, 55.75, 91.15, 93.84, 106.32, 114.32 (2C), 125.11, 128.29, 130.02 (2C), 142.35, 161.34, 162.44, 165.99, 168.31, 192.52.

3-(4-Benzyloxyphenyl)-1-(2-hydroxy-4,6-dimethoxyphenyl)-2-propen-1-one (84c)



Reaction time: 24 hrs

Yield: 88 %, yellow solid

Melting point: 145-146 °C

R_f: 0.62 (EtOAc/hexane 1: 9)

IR (KBr): cm^{-1} 1612, 1557, 1514, 1225.

^1H NMR (400 MHz, $\text{CD}_3\text{COCD}_3/\text{TMS}$): δ 3.80 (s, 3H, $-\text{OCH}_3$), 3.89 (s, 3H, $-\text{OCH}_3$), 5.05 (s, 2H, $-\text{OCH}_2-$), 5.94 (d, 1H, $J = 2.2$ Hz, ArH), 6.09 (d, 1H, $J = 2.4$ Hz, ArH), 6.98 (d, 2H, $J = 8.8$ Hz, Ar-H), 7.33-7.43 (m, 5H, ArH), 7.54 (d, 2H, $J = 8.8$ Hz, ArH), 7.78 (s, 2H, $-\text{COCH}=\text{CHPh}$), 14.03 (s, 1H, $-\text{OH}$).

^{13}C NMR (100 MHz, CDCl_3/TMS): δ 55.49, 55.75, 69.99, 91.12, 93.69, 106.21, 115.13 (2C), 125.11, 127.42 (2C), 128.09, 128.40, 128.60 (2C), 130.05 (2C), 136.39, 142.33, 160.42, 162.36, 165.95, 168.30, 192.47.

Elemental Analysis

M. F. $\text{C}_{24}\text{H}_{22}\text{O}_5$
(390.44)

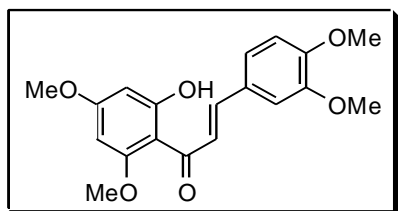
Calculated

C 73.83
H 5.68

Found

73.99
5.60

1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)-2-propen-1-one (84d)



Reaction time: 36 hrs

Yield: 86 %, yellow crystalline solid

Melting point: 150-151 °C (lit.⁷⁷ m.p. 151-153 °C)

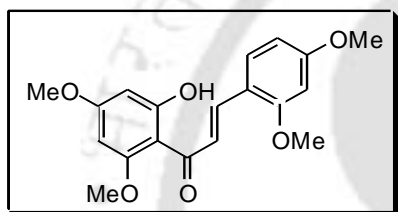
R_f: 0.37 (EtOAc/hexane 3: 7)

IR (KBr): cm^{-1} 1621, 1546, 1456, 1219, 1147.

^1H NMR (250 MHz, CDCl_3/TMS): δ 3.81 (s, 3H, $-\text{OCH}_3$), 3.89 (s, 3H, $-\text{OCH}_3$), 3.91 (s, 3H, $-\text{OCH}_3$), 3.92 (s, 3H, $-\text{OCH}_3$), 5.94 (d, 1H, $J = 2.3$ Hz, ArH), 6.09 (d, 1H, $J = 2.3$ Hz, ArH), 6.88 (d, 1H, $J = 8.3$ Hz, ArH), 7.11 (d, 1H, $J = 1.9$ Hz, ArH), 7.19 (dd, 1H, $J = 8.3$ Hz, 2.0 Hz, ArH), 7.75 (s, 2H, $-\text{COCH}=\text{CHPh}$), 14.29 (s, 1H, $-\text{OH}$).

^{13}C NMR (62.5 MHz, CDCl_3/TMS): δ 55.43, 55.67, 55.77, 55.88, 91.15, 93.81, 106.25, 110.51, 111.18, 122.53, 125.38, 128.56, 142.48, 149.11, 151.04, 162.34, 165.97, 168.30, 192.34.

1-(2-Hydroxy-4,6-dimethoxyphenyl)-3-(2,4-dimethoxyphenyl)-2-propen-1-one (84e)



Reaction time: 40 hrs

Yield: 84 %, redish yellow needles

Melting point: 150-151 $^{\circ}\text{C}$ (lit.⁷⁸ m.p. 152-153 $^{\circ}\text{C}$)

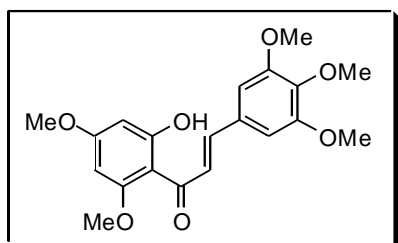
R_r: 0.60 (EtOAc/hexane 1: 4)

IR (KBr): cm^{-1} 1616, 1546, 1456, 1218, 1147.

^1H NMR (400 MHz, CDCl_3/TMS): δ 3.81 (s, 3H, $-\text{OCH}_3$), 3.84 (s, 3H, $-\text{OCH}_3$), 3.88 (s, 3H, $-\text{OCH}_3$), 3.89 (s, 3H, $-\text{OCH}_3$), 5.94 (d, 1H, $J = 2.2$ Hz, Ar-H), 6.09 (d, 1H, $J = 2.2$ Hz, Ar-H), 6.45 (d, 1H, $J = 2.2$ Hz, ArH), 6.51 (dd, 1H, $J = 8.5$ Hz, 2.2 Hz, ArH), 7.53 (d, 1H, $J = 8.5$ Hz, ArH), 7.90 (d, 1H, $J = 15.6$ Hz, $-\text{COCH}=\text{}$), 8.10 (d, 1H, $J = 15.8$ Hz, $=\text{CHPh}$ -), 14.16 (s, 1H, $-\text{OH}$).

^{13}C NMR (100 MHz, CDCl_3/TMS): δ 55.41 (2C), 55.46, 55.65, 91.03, 93.70, 98.25, 105.37, 106.35, 117.60, 125.20, 130.38, 138.23, 160.14, 162.38, 162.73, 165.73, 168.26, 192.95.

1-(2-Hydroxy-4,6-dimethoxy phenyl)-3-(3,4,5-trimethoxy phenyl) prop-2-en-1-one (84f)



Reaction time: 48 hrs

Yield: 82 %, yellow plates

Melting point: 184-185 $^{\circ}\text{C}$

R_r: 0.48 (EtOAc/hexane 1:4)

IR (KBr): cm^{-1} 1639, 1568, 1507, 1220, 1120.

¹H NMR (300 MHz, CDCl₃/TMS): δ 3.88 (s, 3H, -OCH₃), 3.89 (s, 3H, -OCH₃), 3.90 (s, 3H, -OCH₃), 3.91 (s, 6H, -OCH₃), 5.96 (d, 1H, *J* = 2.3 Hz, ArH), 6.10 (d, 1H, *J* = 2.3 Hz, ArH), 6.83 (s, 2H, ArH), 7.69 (d, 1H, *J* = 15.5 Hz, -COCH=), 7.80 (d, 1H, *J* = 15.5 Hz, =CHPh-), 14.40 (s, 1H, -OH).

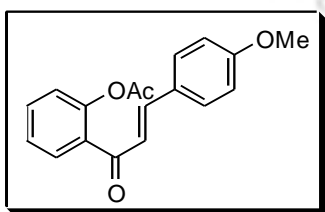
¹³C NMR (75 MHz, CDCl₃/TMS): δ 55.61, 55.80, 56.11 (2C), 61.02, 91.32, 93.84, 105.53 (2C), 106.26, 126.91, 131.14, 140.03, 142.40, 153.38 (2C), 162.40, 166.22, 168.43, 192.35.

Elemental Analysis	Calculated	Found
M. F. C ₂₀ H ₂₂ O ₇ (374.39)	C 64.16 H 5.92	63.93 5.91

General procedure for the preparation of 2'-acetoxychalcones:

The substrates 2'-hydroxychalcone **84a-f** (3.00 mmol) and pyridine (5 mL) are taken into a 50 mL round bottom flask. Then, acetic anhydride (0.6 mL, 6.3 mmol) is added into it and stirred at room temperature. The reaction is completed within 4-6 h as monitored by TLC. Then, the reaction mixture is co-evaporated by adding toluene (10 mL). The same procedure is followed twice. The crude residue is neutralized with a 5% hydrochloric acid solution as checked with a pH paper (pH = 6-7). The oily liquid, that solidified slowly, is filtered off in a Buchner funnel. The precipitate is washed thoroughly with distilled water until it becomes neutral. The solid product is dried and recrystallized in ethyl acetate-hexane. The products **85a-f** are obtained in 89-96% yields as solid.

1-(2-Acetoxy phenyl)-3-(4-methoxy phenyl) prop-2-en-1-one (**85a**)



Reaction time: 4 hrs

Yield: 96 %, yellow solid

Melting point: 84-85 °C

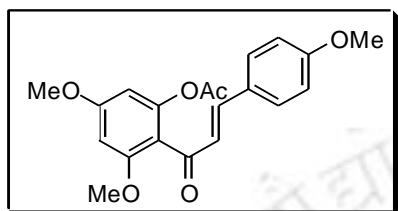
R_f: 0.45 (EtOAc/hexane 1:19)

IR (KBr): cm⁻¹ 1767, 1611, 1600, 1195.

¹H NMR (200 MHz, CDCl₃/TMS): δ 2.23 (s, 3H, -COCH₃), 3.85 (s, 3H, -OCH₃), 6.90-7.70 (m, 10H, ArH, -COCH=CHPh-).

^{13}C NMR (75 MHz, CDCl_3/TMS): δ 20.99, 54.48, 114.49 (2C), 123.11, 123.43, 126.02, 127.19, 129.77, 130.27 (2C), 132.23, 132.57, 145.51, 148.62, 161.84, 169.43, 191.79.

1-(2-Acetoxy-4,6-dimethoxyphenyl)-3-(4-methoxyphenyl)-2-propen-1-one (85b)



Reaction time: 4 hrs

Yield: 96 %, yellow solid

Melting point: 107- 108 °C

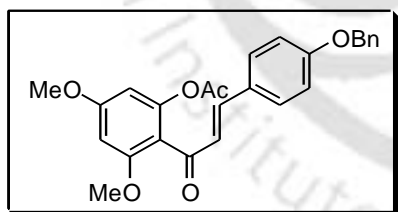
R_f: 0.44 (EtOAc/hexane 3:7)

IR (KBr): cm^{-1} 1765, 1663, 1620, 1600, 1204.

^1H NMR (250 MHz, CDCl_3/TMS): δ 2.15 (s, 3H, $-\text{COCH}_3$), 3.78 (s, 3H, $-\text{OCH}_3$), 3.82 (s, 6H, $-\text{OCH}_3$), 6.29 (d, 1H, $J = 2.1$ Hz, ArH), 6.40 (d, 1H, $J = 2.1$ Hz, ArH), 6.86 (d, 1H, $J = 16.1$ Hz, $-\text{COCH}=\text{}$), 6.88 (d, 2H, $J = 8.7$ Hz, ArH), 7.38 (d, 1H, $J = 16.0$ Hz, $=\text{CHPh-}$), 7.48 (d, 2H, $J = 8.7$ Hz, ArH).

^{13}C NMR (62.5 MHz, CDCl_3/TMS): δ 20.76, 55.29, 55.54, 55.98, 96.70, 100.22, 114.32 (2C), 116.09, 125.91, 127.42, 138.08 (2C), 144.42, 149.85, 158.98, 161.55, 161.84, 168.99, 191.66.

1 (2-Acetoxy-4,6-dimethoxyphenyl)-3-(4-benzyloxyphenyl)-2-propen-1-one (85c)



Reaction time: 4.5 hrs

Yield: 94 %, yellow solid

Melting point: 104-105 °C

R_f: 0.47 (EtOAc/hexane 3:7)

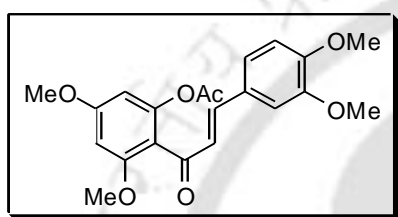
IR (KBr): cm^{-1} 1767, 1612, 1510, 1205.

^1H NMR (200 MHz, CDCl_3/TMS): δ 2.15 (s, 3H, $-\text{COCH}_3$), 3.80 (s, 3H, $-\text{OCH}_3$), 3.84 (s, 3H, $-\text{OCH}_3$), 5.09 (s, 2H, $-\text{OCH}_2-$), 6.26 (d, 1H, $J = 2.1$ Hz, ArH), 6.39 (d, 1H, $J = 2.1$ Hz, ArH), 6.87 (d, 1H, $J = 16.0$ Hz, $-\text{COCH}=\text{}$), 6.90 (d, 2H, $J = 8.8$ Hz, ArH), 7.28-7.40 (m, 6H, $=\text{CHPh-}$, ArH), 7.49 (d, 2H, $J = 8.8$ Hz, ArH).

^{13}C NMR (75 MHz, CDCl_3/TMS): δ 20.90, 55.61, 56.02, 70.05, 96.74, 100.13, 115.22, 116.02, 126.01, 127.44, 127.66, 128.15, 128.65 (3C), 130.21 (3C), 136.40, 144.55, 149.87, 159.01, 160.72, 161.90, 169.18, 191.86.

Elemental Analysis	Calculated	Found
M. F. $\text{C}_{26}\text{H}_{24}\text{O}_6$ (432.48)	C 72.21 H 5.59	72.42 5.51

1-(2-Acetoxy-4,6-dimethoxyphenyl)-3-(3,4-dimethoxyphenyl)-2-propen-1-one (85d)



Reaction time: 5.0 hrs

Yield: 95 %, yellow crystalline solid

Melting point: 119-120 °C

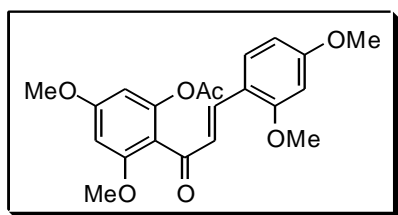
R_f: 0.60 (EtOAc/hexane 2:3)

IR (KBr): cm^{-1} 1759, 1612, 1506, 1225.

^1H NMR (250 MHz, CDCl_3/TMS): δ 2.15 (s, 3H, $-\text{COCH}_3$), 3.79 (s, 3H, $-\text{OCH}_3$), 3.83 (s, 3H, $-\text{OCH}_3$), 3.89 (s, 3H, $-\text{OCH}_3$), 3.90 (s, 3H, $-\text{OCH}_3$), 6.31 (d, 1H, $J = 2.1$ Hz, ArH), 6.42 (d, 1H, $J = 2.1$ Hz, ArH), 6.85 (d, 1H, $J = 16.0$ Hz, $-\text{COCH}=\text{C}$), 6.85 (d, 1H, $J = 8.3$ Hz, ArH), 7.06 (d, 1H, $J = 1.8$ Hz, ArH), 7.09 (dd, 1H, $J = 8.3$ Hz, 1.8 Hz, ArH), 7.35 (d, 1H, $J = 16.0$ Hz, $=\text{CHPh}$).

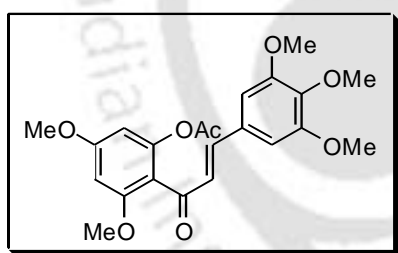
^{13}C NMR (62.5 MHz, CDCl_3/TMS): δ 20.54, 55.33, 55.65, 55.71, 55.78, 96.48, 100.08, 110.02, 110.99, 115.82, 122.73, 125.95, 127.49, 144.50, 149.02, 149.62, 151.13, 158.75, 161.67, 168.76, 191.42.

Elemental Analysis	Calculated	Found
M. F. $\text{C}_{21}\text{H}_{22}\text{O}_7$ (386.40)	C 65.27 H 5.74	65.42 5.66

1-(2-Acetoxy-4,6-dimethoxyphenyl)-3-(2,4-dimethoxyphenyl)-2-propen-1-one (85e)**Reaction time:** 4.5 hrs**Yield:** 94 %, yellow crystalline solid**Melting point:** 116-117 °C**R_f** : 0.63 (EtOAc/hexane 2 : 3)**IR (KBr):** cm⁻¹ 1772, 1613, 1466, 1202.

¹H NMR (300 MHz, CDCl₃/TMS): δ 2.16 (s, 3H, -COCH₃), 3.78 (s, 3H, -OCH₃), 3.82 (s, 6H, -OCH₃), 3.83 (s, 3H, -OCH₃), 6.30 (d, 1H, *J* = 2.1 Hz, Ar-H), 6.40 (d, 1H, *J* = 2.1 Hz, Ar-H), 6.43 (d, 1H, *J* = 2.3 Hz, ArH), 6.49 (dd, 1H, *J* = 8.5 Hz, 2.3 Hz, ArH), 7.02 (d, 1H, *J* = 16.0 Hz, -COCH=), 7.44 (d, 1H, *J* = 8.5 Hz, ArH), 7.66 (d, 1H, *J* = 16.0 Hz, =CHPh-).

¹³C NMR (75 MHz, CDCl₃/TMS): δ 20.91, 55.46, 55.61 (2C), 56.02, 96.74, 98.39, 100.13, 105.32, 116.45, 116.87, 126.44, 131.07, 140.41, 149.86, 159.04, 160.28, 161.72, 162.99, 169.16, 192.80.

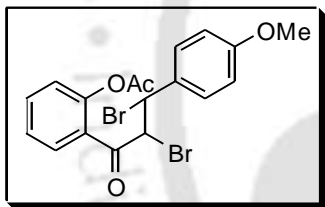
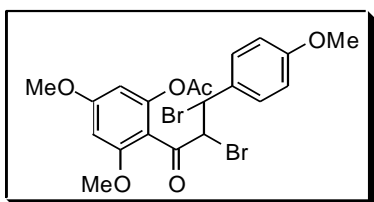
1-(2-Acetoxy-4,6-dimethoxyphenyl)-3-(3,4,5-trimethoxyphenyl)-2-propen-1-one (85f)**Reaction time:** 6 hrs**Yield:** 89 %, pale yellow crystal**Melting point:** 126-127 °C**R_f** : 0.66 (EtOAc/hexane 2:3)**IR (Neat):** cm⁻¹ 1770, 1610, 1466, 1200.

¹H NMR (300 MHz, CDCl₃/TMS): δ 2.17 (s, 3H, -COCH₃), 3.80 (s, 3H, -OCH₃), 3.84 (s, 6H, -OCH₃), 3.87 (s, 6H, -OCH₃), 6.31 (d, 1H, *J* = 2.0 Hz, Ar-H), 6.42 (d, 1H, *J* = 2.0 Hz, Ar-H), 6.76 (s, 2H, ArH), 6.88 (d, 1H, *J* = 15.9 Hz, -COCH=), 7.32 (d, 1H, *J* = 15.9 Hz, =CHPh-).

¹³C NMR (75 MHz, CDCl₃/TMS): δ 20.91, 55.64, 56.08, 56.14 (2C), 60.98, 96.74, 100.14, 105.86 (2C), 115.83, 127.44, 130.21, 140.24, 144.92, 149.87, 153.44 (2C), 159.03, 162.03, 169.25, 191.92.

General procedure for the preparation of dibromochalcones:

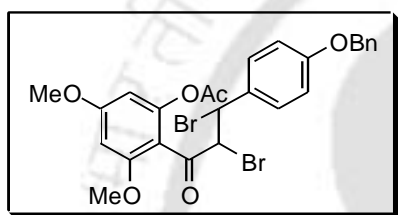
Into a 100 ml of round bottom flask the substrate **85a-f** (2 mmol) is dissolved in dry CH_2Cl_2 (15mL) and stirred at ice bath temperature for 5 min. Then, TBATB (1.060 g, 2.2 mmol) is added into it and stirring is continued at the same temperature until all the reactants are converted into the product. The reaction is completed within 0.75-2.25 hrs as monitored by TLC. After completion, the reaction mixture is quenched by adding two drops of 5% sodium metabisulfite solution. The reaction mixture is then extracted with CH_2Cl_2 (25 mL) and washed thoroughly with water (2 x 20 mL). The combined organic part is dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude reaction mixture finally purified by column chromatography using ethylacetate-hexane mixture as eluent. The products **86a-f** are obtained in 70-80% yields.

1-(2-Acetoxyphenyl)-2,3-dibromo-3-(4-methoxyphenyl)propan-1-one (86a)**Reaction time:** 2.25 hrs**Yield:** 75 %, oil**R_f:** 0.50 (EtOAc/hexane 1:4)**IR (Neat):** cm^{-1} 1770, 1690, 1600, 1258, 1184.**¹H-NMR (250 MHz, CDCl_3/TMS):** δ 2.37 (s, 3H, $-\text{COCH}_3$), 3.82 (s, 3H, $-\text{OCH}_3$), 5.11 [d, 1H, $J = 8.9$ Hz, $-\text{CH}(\text{Br})\text{Ph}-$], 5.71 [d, 1H, $J = 8.8$ Hz, $-\text{COCH}(\text{Br})-$], 6.92 (d, 2H, $J = 8.8$ Hz, ArH), 7.18 (d, 1H, $J = 8.1$ Hz, ArH), 7.32-7.40 (m, 3H, ArH), 7.56-7.62 (m, 1H, ArH), 7.82-7.85 (m, 1H, ArH).**1-(2-Acetoxy-4,6-dimethoxyphenyl)-2,3-dibromo-3-(4-methoxyphenyl)propan-1-one (86b)****Reaction time:** 1 hr**Yield:** 70 %, oil**R_f:** 0.45 (EtOAc/hexane 3:7)**IR (KBr):** cm^{-1} 1667, 1695, 1594, 1511, 1203.

^1H NMR (250 MHz, CDCl_3/TMS): δ 2.31 (s, 3H, $-\text{COCH}_3$), 3.82 (s, 3H, $-\text{OCH}_3$), 3.85 (s, 3H, $-\text{OCH}_3$), 3.95 (s, 3H, $-\text{OCH}_3$), 5.53 [d, 1H, $J = 11.4$ Hz, $-\text{CH}(\text{Br})\text{Ph}-$], 5.79 [d, 1H, $J = 11.4$ Hz, $-\text{COCH}(\text{Br})-$], 6.32 (d, 1H, $J = 2.2$ Hz, ArH), 6.41 (d, 1H, $J = 2.2$ Hz, ArH), 6.91 (d, 2H, $J = 8.8$ Hz, ArH), 7.31 (d, 2H, $J = 8.8$ Hz, ArH).

^{13}C NMR (62.5 MHz, CDCl_3/TMS): δ 20.89, 49.59, 53.43, 55.29, 55.73, 56.10, 96.85, 101.86, 113.73, 114.14 (2C), 129.45 (2C), 131.18, 152.17, 159.97, 160.11, 163.58, 169.26, 190.04.

1-(2-Acetoxy-4,6-dimethoxyphenyl)-3-(4-benzyloxyphenyl)-2,3-dibromopropan-1-one (86c)



Reaction time: 1 hr

Yield: 78 %, off white solid

Melting point: 132-133 °C

R_f: 0.46 (EtOAc/hexane 3:7)

UV (MeOH): $\lambda_{\text{max}}/\text{nm}$ 304.5 ($\epsilon = 18,280 \text{ M}^{-1}\text{cm}^{-1}$)
276.0 ($\epsilon = 27,400 \text{ M}^{-1}\text{cm}^{-1}$)

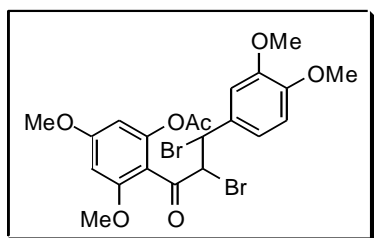
IR (Neat): cm^{-1} 1771, 1689, 1607, 1203, 1100.

^1H NMR (400 MHz, CDCl_3/TMS): δ 2.30 (s, 3H, $-\text{COCH}_3$), 3.84 (s, 3H, $-\text{OCH}_3$), 3.93 (s, 3H, $-\text{OCH}_3$), 5.06 (s, 2H, $-\text{OCH}_2-$), 5.53 [d, 1H, $J = 11.4$ Hz, $-\text{CH}(\text{Br})\text{Ph}-$], 5.79 [d, 1H, $J = 11.4$ Hz, $-\text{COCH}(\text{Br})-$], 6.32 (d, 1H, $J = 2.2$ Hz, ArH), 6.41 (d, 1H, $J = 2.2$ Hz, ArH), 6.97 (d, 2H, $J = 8.6$ Hz, ArH), 7.31-7.43 (m, 7H, ArH).

^{13}C NMR (100MHz, CDCl_3/TMS): δ 20.93, 49.89, 53.36, 55.76, 56.11, 70.10, 96.83, 101.80, 114.56, 114.97 (2C), 127.54 (2C), 128.12, 128.64 (2C), 129.49 (2C), 131.38, 136.63, 152.14, 159.18, 160.10, 163.59, 169.38, 190.12.

Elemental Analysis	Calculated	Found
M. F. $\text{C}_{26}\text{H}_{24}\text{Br}_2\text{O}_6$	C 52.72	52.56
(592.28)	H 4.08	3.98

1-(2-Acetoxy-4,6-dimethoxyphenyl)-2,3-dibromo-3-(3,4-dimethoxyphenyl)propan-1-one (86d)



Reaction time: 0.75 hr

Yield: 80 %, off white crystals

Melting point: 137-138 °C

R_f: 0.37 (EtOAc/hexane 2:3)

IR (KBr): cm⁻¹ 1755, 1692, 1603, 1250, 1190.

¹H NMR (250 MHz, CDCl₃/TMS): δ 2.31 (s, 3H, -COCH₃), 3.85 (s, 3H, -OCH₃), 3.89 (s, 3H, -OCH₃), 3.91 (s, 3H, -OCH₃), 3.95 (s, 3H, -OCH₃), 5.52 [d, 1H, *J* = 11.5 Hz, -CH(Br)Ph-], 5.76 [d, 1H, *J* = 11.5 Hz, -COCH(Br)-], 6.33 (d, 1H, *J* = 2.2 Hz, ArH), 6.42 (d, 1H, *J* = 2.2 Hz, ArH), 6.86 (d, 1H, *J* = 8.3 Hz, ArH), 6.92 (d, 1H, *J* = 2.0 Hz, ArH), 7.03 (dd, 1H, *J* = 8.3 Hz, 2.1 Hz, ArH).

¹³C NMR (100MHz, CDCl₃/TMS): δ 21.32, 50.79, 53.78, 56.17, 56.30, 56.42, 56.51, 97.24, 102.27, 111.39, 111.73, 113.68, 121.29, 131.78, 149.35, 149.98, 160.51, 164.03, 169.73, 171.52, 190.50.

Elemental Analysis

M. F. C₂₁H₂₂Br₂O₇
(546.21)

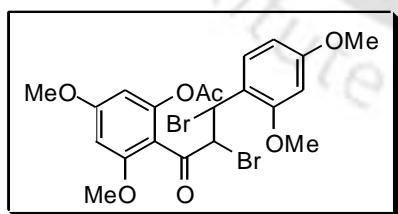
Calculated

C 46.18
H 4.06

Found

46.32
4.11

1-(2-Acetoxy-4,6-dimethoxyphenyl)-2,3-dibromo-3-(2,4-dimethoxyphenyl)propan-1-one (86e)



Reaction time: 1 hr

Yield: 75 %, oil

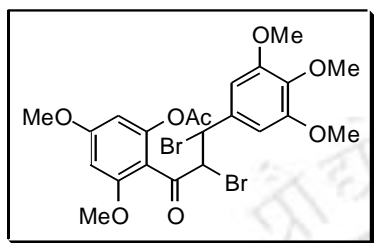
R_f: 0.42 (EtOAc/hexane 2:3)

IR (KBr): cm⁻¹ 1766, 1683, 1600, 1460, 1203, 1077.

¹H NMR (300 MHz, CDCl₃/TMS): δ 2.31 (s, 3H, -COCH₃), 3.84 (s, 3H, -OCH₃), 3.88 (s, 6H, -OCH₃), 3.89 (s, 3H, -OCH₃), 3.91 (s, 3H, -OCH₃), 5.35 [d, 1H, *J* = 11.5 Hz, -CH(Br)Ph-], 5.56 [d, 1H, *J* = 11.5 Hz, -COCH(Br)-], 6.31 (d, 1H, *J* = 2.2 Hz, Ar-H), 6.42 (d, 1H, *J* =

2.2 Hz, Ar-H), 6.44 (d, 1H, $J = 2.3$ Hz, ArH), 6.47 (dd, 1H, $J = 8.4$ Hz, 2.3 Hz, ArH), 7.41 (d, 1H, $J = 8.4$ Hz, ArH).

1-(2-Acetoxy-4,6-dimethoxyphenyl)-2,3-dibromo-3-(3,4,5-trimethoxyphenyl)propan-1-one (86f)



Reaction time: 2 hrs

Yield: 80 %, off white crystal

Melting point: 147-148 °C

R_f: 0.50 (EtOAc/hexane 2:3)

IR (KBr): cm^{-1} 1770, 1694, 1614, 1209, 1128.

¹H NMR (400 MHz, CDCl₃/TMS): δ 2.31 (s, 3H, -CH₃), 3.85 (s, 3H, -OCH₃), 3.86 (s, 3H, -OCH₃), 3.89 (s, 6H, -OCH₃), 3.95 (s, 3H, -OCH₃), 5.46 [d, 1H, $J = 11.3$ Hz, -CH(Br)Ph-], 5.71 [d, 1H, $J = 11.3$ Hz, -COCH(Br)-], 6.34 (d, 1H, $J = 2.1$ Hz, ArH), 6.42 (d, 1H, $J = 2.1$ Hz, ArH), 6.65 (s, 2H, ArH).

¹³C NMR (100 MHz, CDCl₃/TMS): δ 20.91, 50.45, 53.19, 55.82, 56.26 (2C), 60.38, 60.88, 96.81, 101.94, 105.54 (2C), 113.16, 134.26, 138.55, 152.11, 153.39 (2C), 160.11, 163.68, 169.34, 190.06.

Elemental Analysis

M. F. C₂₂H₂₄Br₂O₈
(576.23)

Calculated

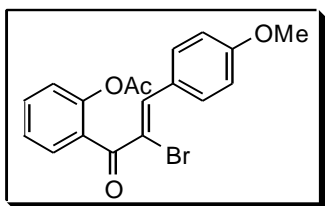
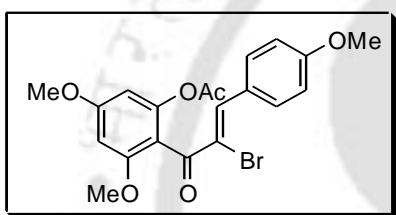
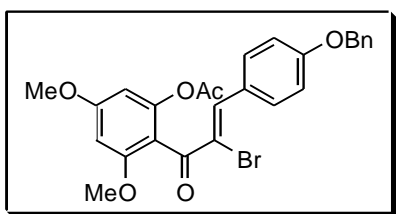
C 45.85
H 4.19

Found

45.52
4.08

General procedure of dehydrobromiantion of 2'-acetoxychalcone dibromide:

To a well-stirred solution of 2'-acetoxychalcone dibromide **86a-f** (1 mmol) in dry CH₂Cl₂ (5mL) at 0-5 °C is added triethylamine (0.3 mL, 2.1 mmol) or K₂CO₃ (0.41 g, 3 mmol) and stirring is continued for 3-5 hrs. The progress of reaction is monitored by TLC. In case of Et₃N, CH₂Cl₂ (15 mL) is added to the reaction mixture and neutralized the reaction mixture with a 5% solution of HCl (pH = 6-7). The organic part is washed with brine (10 mL) and then water (2 x 15 mL), dried over anhy. Na₂SO₄ and concentrated *in vacuo*. The crude reaction mixture is finally purified by column chromatography using ethyl acetate-hexane as eluent. The pure products **87a-f** are obtained as oil in 80-90% yield. In case of K₂CO₃, the solid residue is filtered off and the reaction mixture is concentrated, and finally purified by column chromatography as usual manner.

1-(2-Acetoxyphenyl)-2-bromo-3-(4-methoxyphenyl)-2-propen-1-one (87a)**Reaction time:** 3 hrs**Yield:** 80 %, oil**R_f:** 0.65 (EtOAc/hexane 1:4)**IR (Neat):** cm⁻¹ 1772, 1606, 1208.**¹H NMR (250 MHz, CDCl₃/TMS):** δ 2.20 (s, 3H, -COCH₃), 3.84 (s, 3H, -OCH₃), 6.90 (d, 2H, *J* = 8.7 Hz, ArH), 7.15-7.72 (m, 6H, ArH), 7.76 (s, 1H, =CHPh-).**1-(2-Acetoxy-4,6-dimethoxyphenyl)-2-bromo-3-(4-methoxyphenyl)-2-propen-1-one (87b)****Reaction time:** 4.5 hrs**Yield:** 80 %, oil**R_f:** 0.54 (EtOAc/hexane 3:7)**IR (Neat):** cm⁻¹ 1774, 1677, 1613, 1466, 1255.**¹H NMR (250 MHz, CDCl₃/TMS):** δ 2.12 (s, 3H, -CH₃), 3.76 (s, 3H, -OCH₃), 3.83 (s, 3H, -OCH₃), 3.84 (s, 3H, -OCH₃), 6.33 (d, 1H, *J* = 2.1 Hz, ArH), 6.40 (d, 1H, *J* = 2.1 Hz, ArH), 6.92 (dd, 2H, *J* = 6.9 Hz, 2.1 Hz, ArH), 7.74 (s, 1H, =CHPh-), 7.89 (dd, 2H, *J* = 6.9 Hz, 2.1 Hz, ArH).**¹³C NMR (62.5 MHz, CDCl₃/TMS):** δ 20.69, 54.34, 55.62, 56.05, 96.69, 100.26, 113.87 (2C), 114.12, 122.38, 126.17, 132.91 (2C), 143.66, 149.47, 158.64, 161.57, 162.07, 168.74, 187.67.**Mass (m/z; MALDI):** 434/432.**1-(2-Acetoxy-4,6-dimethoxyphenyl)-3-(4-benzyloxyphenyl)-2-bromo-2-propen-1-one (87c)****Reaction time:** 3.5 hrs**Yield:** 90 %, oil**R_f:** 0.52 (EtOAc/hexane 3:7)

UV (MeOH): λ_{\max}/nm 332.0 ($\epsilon = 61.259 \text{ M}^{-1}\text{cm}^{-1}$)

IR (Neat): cm^{-1} 1767, 1667, 1598, 1219, 1101.

^1H NMR (400 MHz, CDCl_3/TMS): δ 2.12 (s, 3H, $-\text{CH}_3$), 3.75 (s, 3H, $-\text{OCH}_3$), 3.83 (s, 3H, $-\text{OCH}_3$), 5.10 (s, 2H, $-\text{OCH}_2-$), 6.33 (d, 1H, $J = 2.2 \text{ Hz}$, ArH), 6.39 (d, 1H, $J = 2.2 \text{ Hz}$, ArH), 6.99 (d, 2H, $J = 9.04 \text{ Hz}$, ArH), 7.32-7.43 (m, 5H, ArH), 7.74 (s, 1H, $=\text{CHPh-}$), 7.89 (d, 2H, $J = 9.04 \text{ Hz}$, ArH).

^{13}C NMR (100 MHz, CDCl_3/TMS): δ 20.73, 55.63, 56.03, 70.02, 96.66, 100.11, 113.99, 114.70 (2C), 122.42, 126.32, 127.42 (2C), 128.16, 128.64 (2C), 132.97 (2C), 136.23, 143.78, 149.40, 158.59, 160.68, 162.04, 168.85, 187.77.

Elemental Analysis

M. F. $\text{C}_{26}\text{H}_{23}\text{BrO}_6$

(511.368)

Calculated

C 61.06

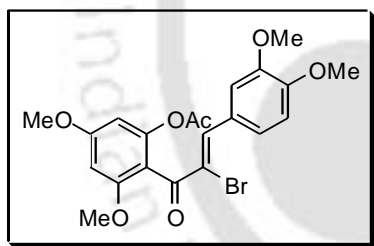
H 4.53

Found

59.83

5.58

1-(2-Acetoxy-4,6-dimethoxyphenyl)-2-bromo-3-(3,4-dimethoxyphenyl)-2-propen-1-one (87d)



Reaction time: 3 hrs

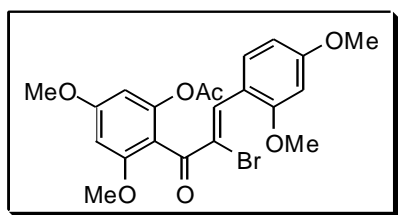
Yield: 88 %, oil

R_f: 0.50 (EtOAc/hexane 2:3)

IR (Neat): cm^{-1} 1773, 1680, 1618, 1265, 1219, 1163.

^1H NMR (400 MHz, CDCl_3/TMS): δ 2.30 (s, 3H, $-\text{COCH}_3$), 3.61 (s, 3H, $-\text{OCH}_3$), 3.82 (s, 3H, $-\text{OCH}_3$), 3.88 (s, 3H, $-\text{OCH}_3$), 3.89 (s, 3H, $-\text{OCH}_3$), 6.27 (d, 1H, $J = 2.4 \text{ Hz}$, ArH), 6.27 (d, 1H, $J = 2.2 \text{ Hz}$, ArH), 6.80-6.96 (m, 3H, ArH), 7.74 (s, 1H, $=\text{CHPh-}$).

1-(2-Acetoxy-4,6-dimethoxyphenyl)-2-bromo-3-(2,4-dimethoxyphenyl)-2-propen-1-one (87e)



Reaction time: 4 hrs

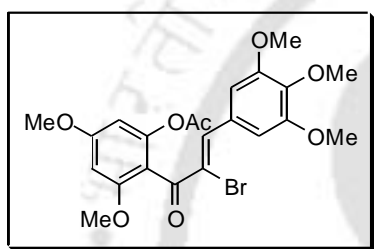
Yield: 83 %, oil

R_f: 0.50 (EtOAc/hexane 2:3)

¹H NMR (400 MHz, CDCl₃/TMS): δ 2.16 (s, 3H, -CH₃), 3.74 (s, 3H, -OCH₃), 3.76 (s, 3H, -OCH₃), 3.83 (s, 3H, -OCH₃), 3.84 (s, 3H, -OCH₃), 6.38 (s, 1H, ArH), 6.39 (s, 1H, ArH), 6.40 (s, 1H, ArH), 6.56 (dd, 1H, *J* = 8.8 Hz, 2.2 Hz, ArH), 8.06 (s, 1H, =CHPh-), 8.28 (d, 1H, *J* = 8.8 Hz, ArH).

¹³C NMR (100 MHz, CDCl₃/TMS): δ 20.83, 55.47, 55.64 (2C), 55.96, 96.47, 97.98, 99.98, 104.37, 114.13, 115.85, 122.87, 131.25, 138.82, 149.58, 158.56, 159.73, 161.88, 163.06, 168.57, 187.91.

1-(2-Acetoxy-4,6-dimethoxyphenyl)-2-bromo-3-(3,4,5-trimethoxyphenyl)-2-propen-1-one (87f)



Reaction time: 5 hrs

Yield: 85 %, oil

R_f: 0.56 (EtOAc/hexane 2:3)

IR (Neat): cm⁻¹ 1767, 1674, 1247, 1212, 1114.

¹H NMR (400 MHz, CDCl₃/TMS): δ 2.15 (s, 3H, -CH₃), 3.76 (s, 3H, -OCH₃), 3.85 (s, 3H, -OCH₃), 3.88 (s, 6H, -OCH₃), 3.90 (s, 3H, -OCH₃), 6.19 (s, 1H, ArH), 6.41 (s, 1H, ArH), 7.17 (s, 2H, ArH), 7.71 (s, 1H, =CHPh-).

¹³C NMR (100 MHz, CDCl₃/TMS): δ 20.83, 55.66, 56.13, 56.25 (2C), 60.93, 94.41, 96.75, 100.24, 105.67, 108.40 (2C), 113.90, 123.84, 128.78, 143.65, 152.85 (2C), 158.76, 162.24, 168.96, 187.76.

Elemental Analysis

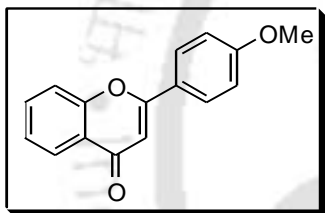
M. F. C₂₂H₂₃BrO₈
(495.32)

Calculated	
C	53.34
H	4.68

Found	
C	53.08
H	4.62

General procedure for the synthesis of flavones:

Into a 50 mL round bottom flask the substrate **87a-f** (1 mmol) is taken in dry methanol (3 mL) and stirred at ice bath temperature for 5 min. Into it a freshly prepared solution of 0.1 M NaOMe in methanol (10 mL, 1 mmol) is added dropwise over 5 min. The stirring is continued for 1.0 -2.25 hrs as monitored by TLC. After completion of reaction, methanol is removed *in vacuo*. The reaction mixture is extracted in CH₂Cl₂ (15 mL) and neutralized with a 2% solution of HCl (pH = 6-7). The organic part is finally washed with water (2 x 10 mL), dried over anhydrous Na₂SO₄ and concentrated *in vacuo*. The crude residue is then purified by column chromatography using ethyl acetate-hexane mixture as eluent. The flavones **88a-f** are obtained in 60-88% as solid.

2-(4-Methoxyphenyl)-4H-1-benzopyran-4-one (88a)**Reaction time:** 2.25 hrs**Yield:** 60 %**Melting point:** 156-157 °C (lit.⁷⁹ m.p. 158-159°C)**R_f:** 0.32(EtOAc/hexane 1:1)**IR (Neat):** cm⁻¹ 1653, 1610, 1470, 1352, 1260.

¹H NMR (400 MHz, CDCl₃/TMS): δ 3.89 (s, 3H, -OCH₃), 6.76 (s, 1H, -COCH=), 7.03 (d, 2H, J = 8.7 Hz, ArH), 7.41 (t, 1H, J = 7.5 Hz, ArH), 7.55 (d, 1H, J = 8.3 Hz, ArH), 7.68 (m, 1H, ArH), 7.89 (d, 2H, J = 9.0 Hz, ArH), 8.23 (dd, 1H, J = 7.8 Hz, 1.5 Hz, ArH).

Elemental AnalysisM. F. C₁₆H₁₂O₃

(252.26)

Calculated

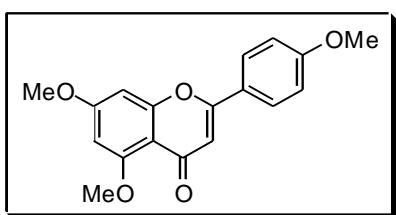
C 76.18

H 4.79

Found

76.27

4.73

5,7-Dimethoxy-2-(4-methoxyphenyl)-4H-1-benzopyran-4-one (88b)**Reaction time:** 1 hr**Yield:** 78 %, off white solid**Melting point:** 155-156 °C (lit.^{79,80} m.p. 156-157 °C)**R_f:** 0.29 (EtOAc/hexane 4:1)

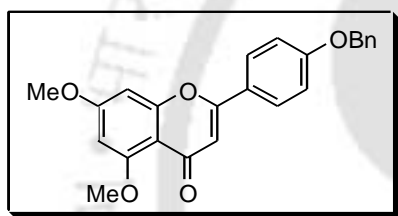
IR (KBr): cm^{-1} 1653, 1610, 1470, 1352, 1260.

^1H NMR (250 MHz, CDCl_3/TMS): δ 3.84 (s, 3H, $-\text{OCH}_3$), 3.87 (s, 3H, $-\text{OCH}_3$), 3.91 (s, 3H, $-\text{OCH}_3$), 6.32 (d, 1H, $J = 2.3$ Hz, ArH), 6.52 (d, 1H, $J = 2.3$ Hz, ArH), 6.59 (s, 1H, $-\text{COCH}=\text{)$, 6.95 (d, 2H, $J = 9.0$ Hz, ArH), 7.77 (d, 2H, $J = 8.9$ Hz, ArH).

^{13}C NMR (62.5 MHz, CDCl_3/TMS): δ 55.36, 55.66, 56.29, 92.78, 96.06, 107.29, 108.94, 114.27 (2C), 123.63, 127.54 (2C), 159.74, 160.79 (2C), 162.06, 163.95, 177.46.

Elemental Analysis	Calculated	Found
M. F. $\text{C}_{18}\text{H}_{16}\text{BrO}_5$ (312.32)	C 69.22 H 5.16	69.38 5.18

2-(4-Benzyloxyphenyl)-5,7-dimethoxy-4H-1-benzopyran-4-one (88c)



Reaction time: 1.5 hrs

Yield: 70 %

Melting point: 181-182 °C

R_r: 0.27 (EtOAc/hexane 4:1)

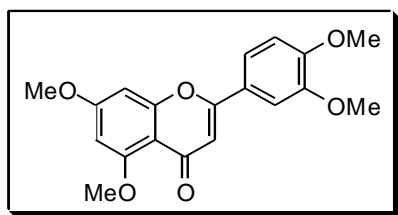
UV (MeOH): $\lambda_{\text{max}}/\text{nm}$ 325.0 ($\epsilon = 31,269 \text{ M}^{-1}\text{cm}^{-1}$)
326.0 ($\epsilon = 27,508 \text{ M}^{-1}\text{cm}^{-1}$)

IR (KBr): cm^{-1} 1653, 1613, 1515, 1249, 1171.

^1H NMR (400 MHz, CDCl_3/TMS): δ 3.90 (s, 3H, $-\text{OCH}_3$), 3.94 (s, 3H, $-\text{OCH}_3$), 5.13 (s, 2H, $-\text{OCH}_2-$), 6.35 (d, 1H, $J = 2.2$ Hz, ArH), 6.54 (d, 1H, $J = 2.4$ Hz, ArH), 6.59 (s, 1H, $-\text{COCH}=\text{)$, 7.06 (d, 2H, $J = 8.8$ Hz, ArH), 7.33-7.45 (m, 5H, ArH), 7.80 (d, 2H, $J = 8.8$ Hz, ArH).

^{13}C NMR (62.5 MHz, CDCl_3/TMS): δ 55.68, 56.34, 70.08, 92.72, 96.00, 107.59, 109.08, 115.14 (2C), 123.93, 127.41 (2C), 127.54 (2C), 128.16, 128.63 (2C), 136.19, 159.75, 160.56, 160.78, 161.11, 163.85, 177.61.

Elemental Analysis	Calculated	Found
M. F. $\text{C}_{24}\text{H}_{20}\text{O}_5$ (388.41)	C 74.21 H 5.19	74.44 5.11

2-(3,4-Dimethoxyphenyl)-5,7-dimethoxy-4H-1-benzopyran-4-one (88d)**Reaction time:** 2 hrs**Yield:** 65 %**Melting point:** 179-180 °C (lit.⁸¹ m.p. 179-180 °C)**R_f:** 0.23 (EtOAc/hexane 4:1)**IR (KBr):** cm⁻¹ 1655, 1585, 1437, 1275, 1150.

¹H NMR (500 MHz, CDCl₃/TMS): δ 3.91 (s, 3H, -OCH₃), 3.95 (s, 3H, -OCH₃), 3.96 (s, 3H, -OCH₃), 3.97 (s, 3H, -OCH₃), 6.37 (d, 1H, *J* = 1.7 Hz, ArH), 6.56 (d, 1H, *J* = 1.7 Hz, ArH), 6.60 (s, 1H, -COCH=), 6.95 (d, 1H, *J* = 6.8 Hz, ArH), 7.31 (d, 1H, *J* = 1.6 Hz, ArH), 7.50 (dd, 1H, *J* = 6.8 Hz, 1.6 Hz, ArH).

Elemental AnalysisM. F. C₁₉H₁₈O₆

(342.34)

Calculated

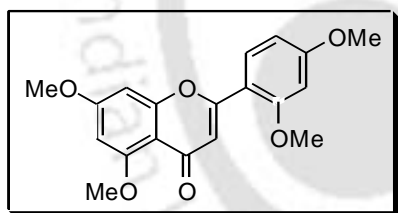
C 66.66

H 5.30

Found

66.47

5.23

2-(2,4-Dimethoxyphenyl)-5,7-dimethoxy-4H-1-benzopyran-4-one (88e)**Reaction time:** 1.0 hr**Yield:** 88 %, off white solid**Melting point:** 176-177 °C (lit.⁸² m.p. 179-180 °C)**R_f:** 0.16 (EtOAc/hexane 4:1)**IR (KBr):** cm⁻¹ 1648, 1593, 1497, 1110.

¹H NMR (400 MHz, CDCl₃/TMS): δ 3.88 (s, 3H, -OCH₃), 3.90 (s, 3H, -OCH₃), 3.91 (s, 3H, -OCH₃), 3.95 (s, 3H, -OCH₃), 6.35 (d, 1H, *J* = 2.2 Hz, ArH), 6.52 (d, 1H, *J* = 2.2 Hz, ArH), 6.54 (d, 1H, *J* = 2.2 Hz, ArH), 6.61 (dd, 1H, *J* = 8.8 Hz, 2.2 Hz, ArH), 6.99 (s, 1H, -COCH=), 7.84 (d, 1H, *J* = 8.8 Hz, ArH).

¹³C NMR (100 MHz, CDCl₃/TMS): δ 55.46, 55.61, 55.62, 56.36, 92.63, 95.79, 98.77, 105.08, 112.64, 113.25, 129.99, 158.08, 159.47, 159.92, 160.75, 162.88, 163.72 (2C), 178.22.

Elemental AnalysisM. F. C₁₉H₁₈O₆

(342.34)

Calculated

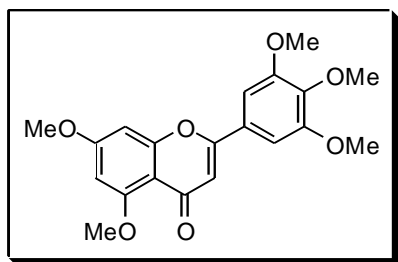
C 66.66

H 5.30

Found

66.54

5.27

2-(3,4,5-Trimethoxyphenyl)-5,7-dimethoxy-4H-1-benzopyran-4-one (88f)**Reaction time:** 1.5 hrs**Yield:** 74 %, white crystalline solid**Melting point:** 190-191 °C (lit.⁸³ m.p. 196-197 °C)**R_f:** 0.18 (EtOAc/hexane 7:3)**IR (KBr):** cm⁻¹ 1645, 1598, 1501, 1461, 1124.**¹H NMR (500 MHz, CDCl₃/TMS):** δ 3.92 (s, 3H, -OCH₃), 3.93 (s, 3H, -OCH₃), 3.95 (s, 6H, -OCH₃), 3.96 (s, 3H, -OCH₃), 6.39 (d, 1H, *J* = 2.1 Hz, ArH), 6.57 (d, 1H, *J* = 2.2 Hz, ArH), 6.62 (s, 1H, -COCH=), 7.08 (s, 2H, ArH).**¹³C NMR (100 MHz, CDCl₃/TMS):** δ 55.86, 56.18, 56.23 (2C), 60.03, 90.72, 92.95, 96.25, 103.45 (2C), 108.71, 126.70, 140.93, 153.54 (2C), 160.62, 160.92, 164.17 (2C), 177.56.**Elemental Analysis**

	Calculated	Found
M. F. C ₂₀ H ₂₀ O ₇	C 61.51	61.33
(372.38)	H 5.41	5.28



PRESENT WORK ON THE BROMINATION OF VARIOUS 2'-ACETOXYCHALCONES TO THE CORRESPONDING 2'-ACETOXY- α -BROMOCHALCONES AND THEIR APPLICATIONS TOWARDS FLAVONE SYNTHESIS

Experimental

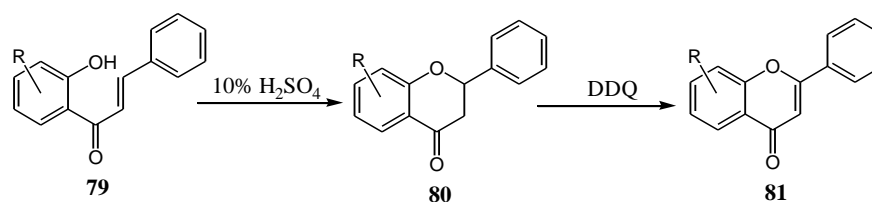
Discussion

After successful preparation of various α -bromo-enones from their corresponding enones using organic ammonium tribromide,⁴⁸ our next goal is to synthesize various substituted flavones from 2'-acetoxychalcones by Kostanecki route as already been highlighted in chapter 1. Prior to discuss the details of our present work we would like to focus some of the important aspects of flavones and their synthesis.

Flavonoids are a group of naturally occurring, low molecular weight *O*-heterocycles that are widely distributed in the plant kingdom and represent a significant part of the average Western daily diet.⁴⁹ Many types of compounds comprise the flavonoids, one of the most abundant being the flavones.⁵⁰ They are well known in literature due to their wide range of biological activities.⁵¹ Among the various flavones, particularly ring-A hydroxylated flavones are of current interest because they exhibit a variety of roles in biological systems⁵², including inhibition of retroviral-reverse transcriptases,⁵³ protein-tyrosine kinases⁵⁴ and serine/threonine kinases.⁵⁵ They also possess anticancer⁵⁶ and chemo preventative activities.⁵⁷ Apigenin, Luteloin and related compounds have attracted special attention in the chemotherapy of a retrovirus-associated human diseases (AIDS) namely rauscher murine leukemia (RLV) and human immunodeficiency diseases (HIV).⁵⁸⁻⁶⁰ Therefore, the syntheses of these compounds are still having interest largely on account of their biological activities.

There are number of methods available for the synthesis of flavone,⁶¹ viz the Allan-Robinson synthesis,⁶² the Baker-Venkataraman method,⁶³ synthesis from chalcone⁶⁴⁻⁶⁹ and synthesis via intramolecular Wittig approach.⁷⁰ Among these, the method which uses chalcone as the starting material would be the most promising one for the synthesis of flavone.

The synthesis of flavone can be achieved from chalcone either by cyclisation with a mineral acid like 10% H₂SO₄ in methanol followed by dehydrogenation with DDQ,⁷¹ as mentioned in scheme 33 or it can be prepared by bromination followed by dehydrobromination with base, and finally cyclisation.

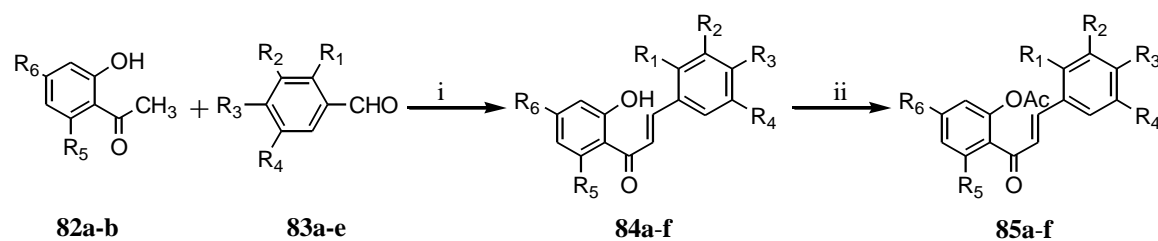


Scheme 33

The existing methods, which are based on bromination of chalcone followed by cyclisation with a base, have some serious drawbacks. As for example, 2'-hydroxychalcone possessing a phloroglucinol oxygenation pattern in ring-A, give the 5,7-dihydroxy substituted flavone only in very low yield.³¹ or not at all²³ and in most of the cases mixture of products are obtained.²⁴ The required chalcone dibromides or α -bromo-chalcones are usually prepared by employing molecular bromine as discussed earlier. We have already pointed out the drawbacks associated with the molecular bromine in chapter 2 part I. Recently, we have demonstrated that the solid organic ammonium tribromides, particularly *n*-tetrabutylammonium tribromide (TBATB) has been used as a versatile reagent in organic synthesis.^{72,73}

From the unique behavior of the reagent, we have inclined to study the bromination of 2'-hydroxychalcones or 2'-acetoxychalcones with this novel brominating agent i.e. *n*-tetrabutylammonium tribromide (TBATB) because it works efficiently, easy to handle and by maintaining the stoichiometric ratio it might be possible to carry out the reaction chemoselectively.

As per our requirement, we have prepared various substituted 2'-hydroxychalcones **84a-f** by reaction with 2'-hydroxyacetophenones **82a** or **82b** and the appropriate aromatic aldehydes **83a-e**, by following Claisen-Schmidt reaction.⁴⁴ Then, the compound **84a-f** are transformed into the required 2'-acetoxychalcones **85a-f** by acetylation using acetic anhydride and pyridine as depicted in Scheme 34. The results are summarized in the table 8.



82a: R ₅ = R ₆ = H	83a: R ₁ = R ₂ = R ₄ = H, R ₃ = OMe	84a: R ₁ = R ₂ = R ₄ = R ₅ = R ₆ = H, R ₃ = OMe
82b: R ₅ = R ₆ = OMe	83b: R ₁ = R ₂ = R ₄ = H, R ₃ = OBn	84b: R ₁ = R ₂ = R ₄ = H, R ₃ = R ₅ = R ₆ = OMe
	83c: R ₁ = R ₄ = H, R ₂ = R ₃ = OMe	84c: R ₁ = R ₂ = R ₄ = H, R ₃ = OBn, R ₅ = R ₆ = OMe
	83d: R ₁ = R ₃ = OMe, R ₂ = R ₄ = H	84d: R ₁ = R ₄ = H, R ₂ = R ₃ = R ₅ = R ₆ = OMe
	83e: R ₁ = H, R ₂ = R ₃ = R ₄ = OMe	84e: R ₁ = R ₃ = R ₅ = R ₆ = OMe, R ₂ = R ₄ = H
		84f: R ₁ = H, R ₂ = R ₃ = R ₄ = R ₅ = R ₆ = OMe

Reagents and Conditions: i) NaOH (1.25 equiv.), 0-rt., 24-48 h, 69-90%; ii) Ac₂O, Pyridine, rt., 4-6 h, 89-96%.

Scheme 34

Table 8. Preparation of different substituted 2'-hydroxy chalcones and the corresponding 2'-acetoxy chalcones

2'-Hydroxy acetophenone (82)	Aromatic aldehyde (83)	Time (h)	2'-Hydroxy chalcone (84)	Yield (%)	Time (h)	2'-Acetoxy chalcone (85)	Yield (%)
82a	83a	24	84a	69	4.0	85a	96
82b	83a	36	84b	90	4.5	85b	96
82b	83b	24	84c	88	4.5	85c	96
82b	83c	36	84d	86	6.0	85d	95
82b	83d	40	84e	84	5.0	85e	94
82b	83e	48	84f	82	4.0	85f	89

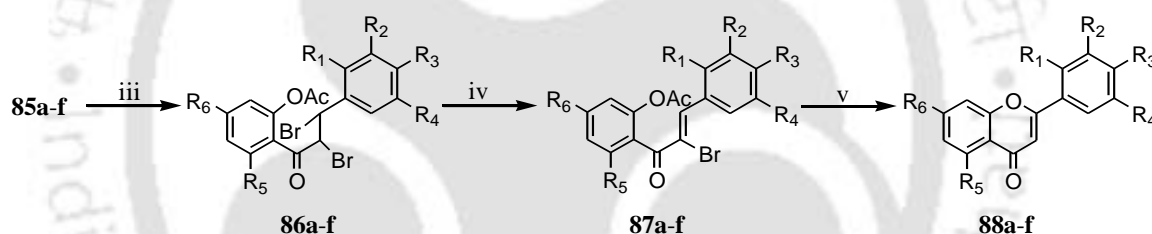
All the compounds **84b-f** and acetates **85a-f** are characterized by IR, ¹H NMR (figure 8 and figure 10), ¹³C NMR (figure 9 and figure 11) and/or elemental analysis. The compound **84a** is characterized by comparing the melting point with the authentic compound. Then, we perform the bromination reactions of various 2'-acetoxychalcones **85a-f** with *n*-tetrabutylammonium tribromide (TBATB) in CH₂Cl₂ to obtain dibromo compounds **86a-f**. As a representative case, when the compound **85b** is treated with

TBATB in CH_2Cl_2 at 0-5 °C, it provides the dibromo compound **86b** in good yield. The product **86b** is characterized by IR, ^1H NMR (figure 12), ^{13}C NMR (figure 13) and also by elemental analysis. The ^1H NMR of compound **86b** shows the disappearance of two olefinic proton signals at δ 6.86 ($J = 16.1$ Hz) and δ 7.38 ($J = 16.1$ Hz) and the appearance of two new signals as doublet at δ 5.53 ($J = 11.4$ Hz) and δ 5.79 ($J = 11.4$ Hz), indicates the *trans*-bromination of the enone double bond. In ^{13}C NMR, it shows two characteristic signals at δ 49.59 and δ 53.43 for the two brominated carbon atoms.

The α -bromochalcones **87b** is prepared from compound **86b** on treatment with Et_3N in CH_2Cl_2 . The same compound **87b** can also be obtained from **86b** using K_2CO_3 in CH_2Cl_2 . We have isolated only (*Z*)- α -bromochalcone **87b** after dehydrobromination of dibromo dihydrochalcone **86b**. The *E*-isomer of **87b** slowly converts into the thermodynamically stable *Z*-form on standing, which was also observed by others.³⁶ The (*Z*) α -bromochalcone **87b** is characterized by IR, ^1H NMR (figure 14), ^{13}C -NMR (figure 15), mass spectra (figure 16) as well as elemental analysis. The ^1H NMR and ^{13}C NMR spectral data are in full agreement with the expected product. The characteristic changes are the disappearance two signals at δ 5.53 ($J = 11.4$ Hz) and δ 5.79 ($J = 11.4$ Hz) indicates dehydrobromination, which is also supporting by the appearance of a new signal as singlet at δ 7.72 due to the presence of β -proton in α -bromochalcone **87b**. On the other hand, ^{13}C NMR shows the absence of signals at δ 49.59 and δ 53.43 in compound **87b** and exhibits two new signals at δ 114.12 (quaternary, α -carbon) and δ 143.66 (β -carbon) for the two olefinic carbons.

By following the same typical bromination procedure various 2'-acetoxychalcones **85a** and **85c-f** are smoothly converted to the corresponding 2'-acetoxychalcone dibromides **86a** and **86c-f** respectively, on bromination with TBATB and subsequently converted them to the corresponding 2'-acetoxy- α -bromochalcones **87a** and **87c-f** on dehydrobromination, on treatment with triethylamine or K_2CO_3 under similar reaction conditions. Our next objective is to find out the more appropriate reaction conditions to synthesize flavones **88a-f** from the compounds **87a-f**. After several trial reactions, we have found that the flavone **88b** is obtained in maximum yield from the compound **87b**, on treatment with 0.1 M NaOMe (freshly prepared from metallic Na in dry methanol) in methanol.

Subsequently, all the α -bromochalcones **87a** and **87c-f** are transformed into the corresponding flavones **88a** and **88c-f** under identical reaction conditions. The final product 4,4',6- trimethyl ether of apegenin (**88b**) is assigned by IR, ^1H NMR, ^{13}C NMR, mass spectra and elemental analysis, and by checking m.p., which is also matched with the reported compound.⁷⁹ The disappearance of acetate peak at δ 2.12 as well as appearing of new signal at δ 6.57 indicates the cyclisation at the β -position of α -bromochalcone **87b** (figure 13). The ^{13}C -NMR spectrum of compound **88b** is also in full agreement (figure 14). Subsequently, we have achieved the cyclisation of α -bromochalcones **87a** and **87c-f** into the desired flavones **88a** and **88c-f**. The details of reaction conditions are shown in scheme 35 and the results are summarized in Table 9. All the products are characterized by recording IR, ^1H -NMR, ^{13}C -NMR, elemental analyses or/and mass spectra. Therefore, we have demonstrated an environmentally benign protocol for the synthesis of substituted flavones derivatives.



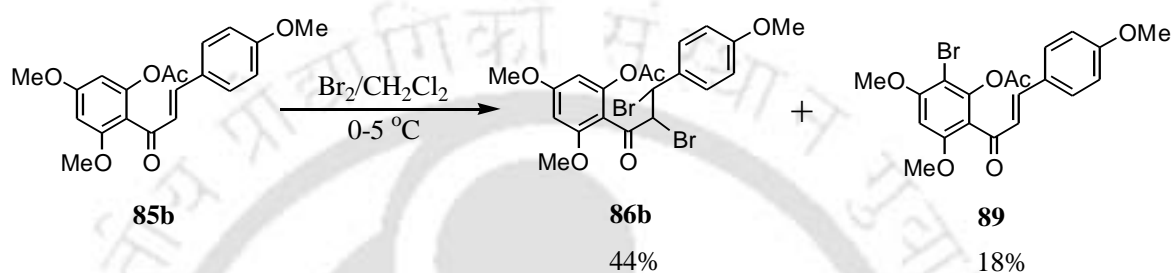
Reagents and Conditions: iii) TBATB (1.1 equiv.), CH_2Cl_2 , 0-5 $^\circ\text{C}$, 0.75-2.25 h, 70-80%; iv) Et_3N or K_2CO_3 , CH_2Cl_2 , rt, 3-5 h, 80-90 %; v) 0.1 M NaOMe, MeOH, 0-5 $^\circ\text{C}$, 1.0-2.25h, 60-88 %.

Scheme 35

Table 9. Preparation of different substituted flavones

Entry (85)	Time (h.)	Dibromo product (86)	Yield (%)	Time (h)	α -Bromo product (87)	Yield (%)	Time (h)	Flavone (88)	Yield (%)
85a	2.25	86a	75	3.0	87a	80	2.25	88a	60
85b	1.0	86b	70	4.5	87b	80	1.0	88b	78
85c	1.0	86c	78	3.5	87c	90	1.5	88c	70
85d	0.75	86d	80	3.0	87d	88	2.0	88d	65
85e	1.0	86e	75	4.0	87e	83	1.0	88e	88
85f	2.0	86f	80	5.0	87f	85	1.5	88f	74

In order to gain more insight into such chemical transformations, we have conducted the similar reaction with molecular bromine. We observed that the compound **85b** on treatment with elemental bromine under the identical reaction conditions gives a mixture of products with 2'-acetoxychalcone dibromide **86b** and 2'-acetoxy-3'-bromochalcone **89** as the major components (shown in scheme 36). This result is also proved that TBATB is more selective reagent than molecular bromine.



Scheme 36

In conclusion, we have shown TBATB can be utilized for bromination of 2'-acetoxychalcones, particularly ring-substituted chalcones without nuclear ring bromination.³³ as well as without affecting the other substituents. In addition, we have accomplished the synthesis of ring-A hydroxylated naturally occurring flavone derivatives such as methyl ether of Apigenin (**88b**), Norartocarpetin (**88e**), Tricetin (**88f**), Luteolin (**88d**), which are difficult to prepare earlier by following Konstanekki route.

PRESENT WORK ON THE BROMINATION OF VARIOUS 2'-ACETOXYCHALCONES TO THE CORRESPONDING 2'-ACETOXY- α -BROMOCHALCONES AND THEIR APPLICATIONS TOWARDS FLAVONE SYNTHESIS

DISCUSSION

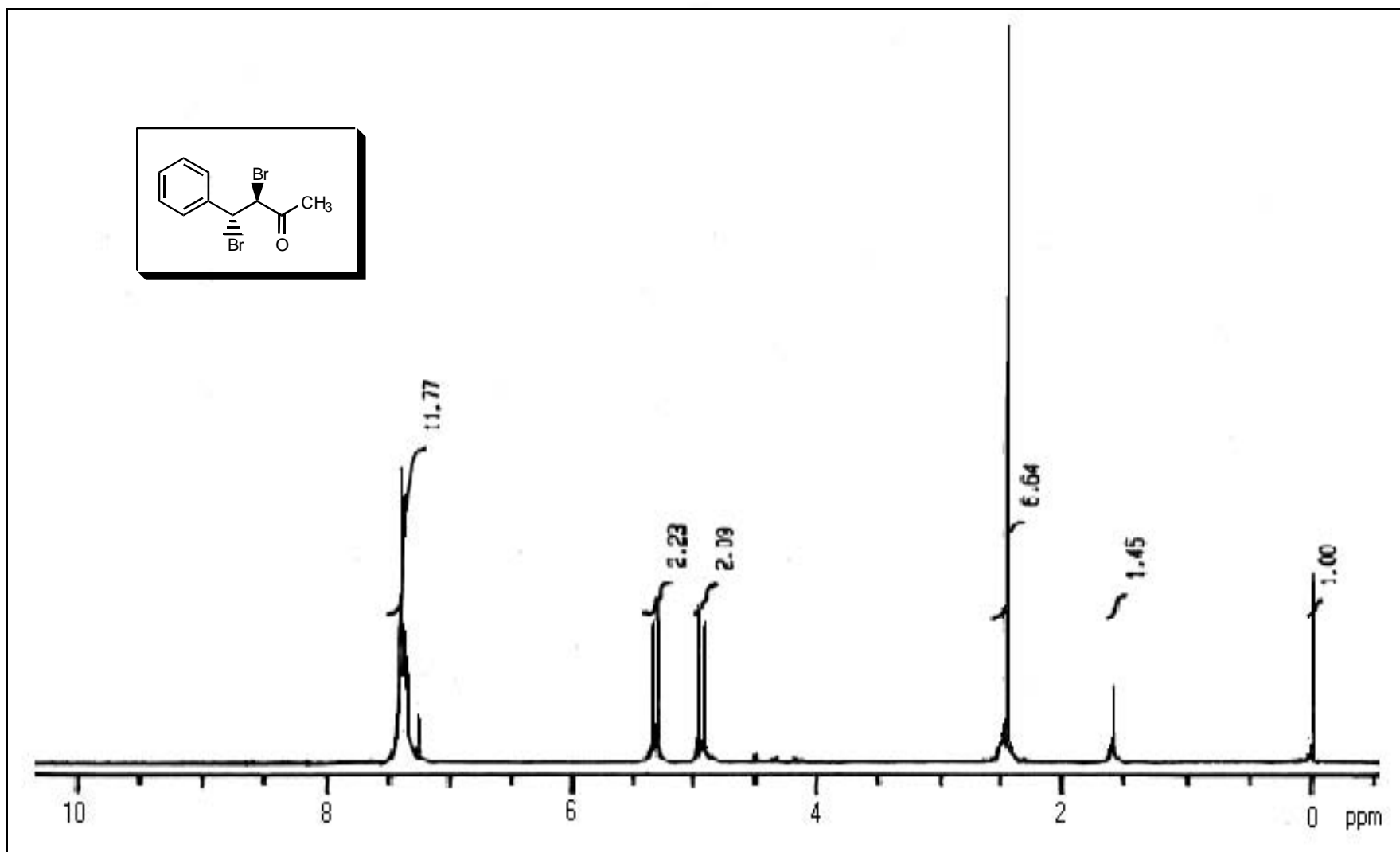


Figure 1: ¹H-NMR spectrum of 3,4-Dibromo-4-phenylbutan-2-one (400 MHz, CDCl₃) (**75a**)

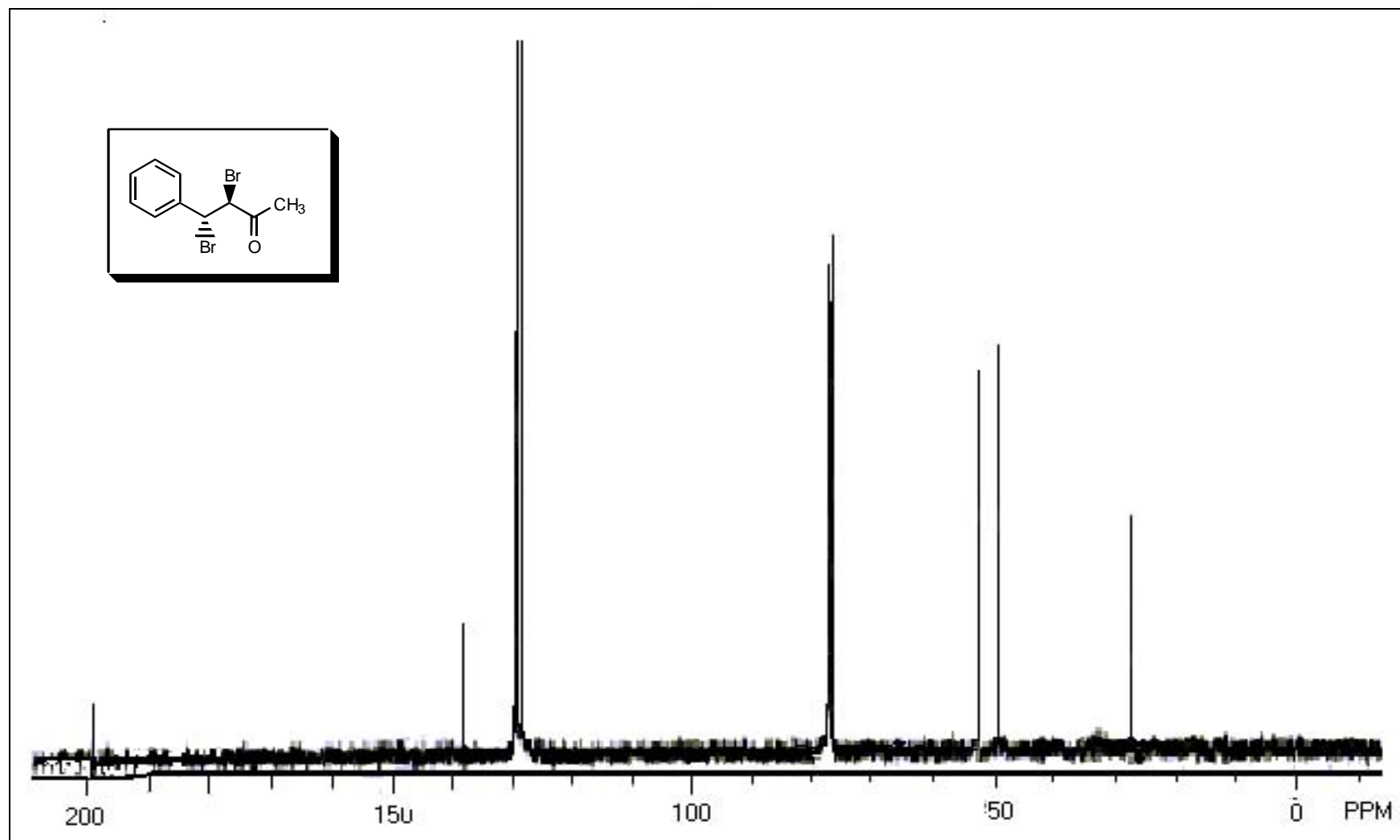


Figure 2: ^{13}C -NMR spectrum of 3,4-Dibromo-4-phenylbutan-2-one (100 MHz, CDCl_3) (**75a**)

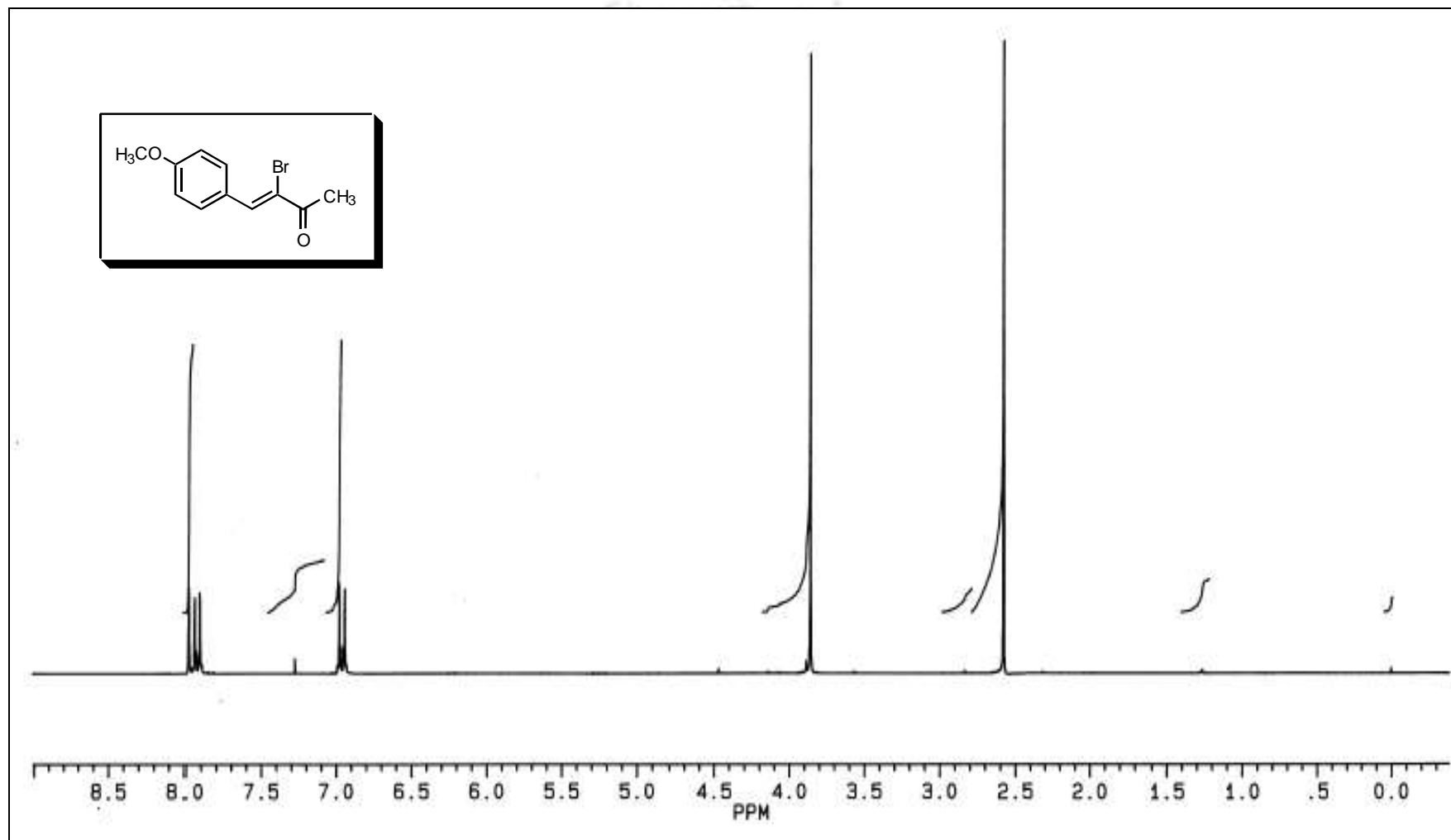


Figure 3: ¹H-NMR spectrum of 3-Bromo-4-(4-methoxyphenyl)-3-buten-2-one (250 MHz, CDCl₃) (**76b**)

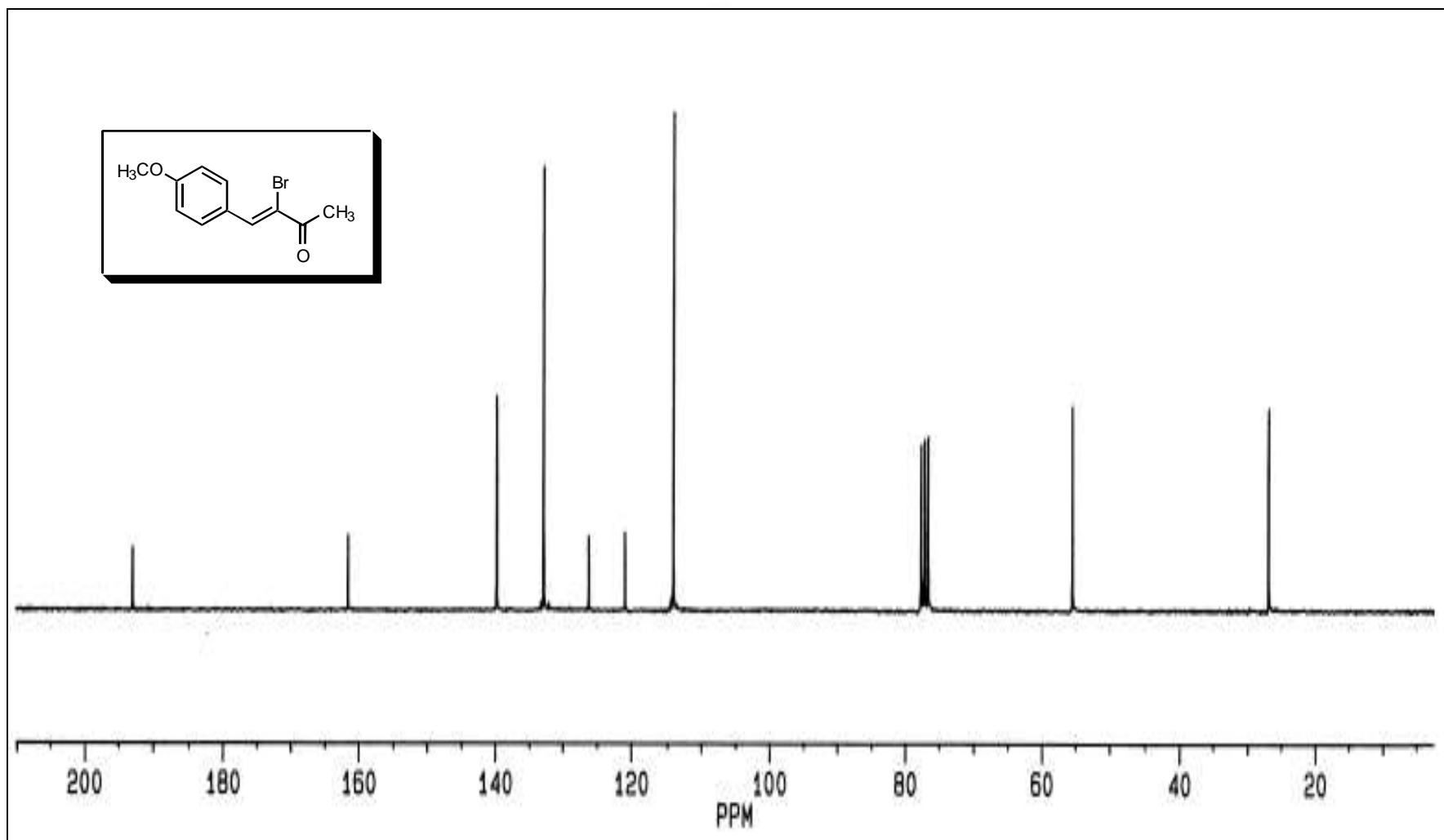


Figure 4: ¹³C-NMR spectrum of 3-Bromo-4-(4-methoxyphenyl)-3-buten-2-one (62.5 MHz, CDCl₃) (**76b**)

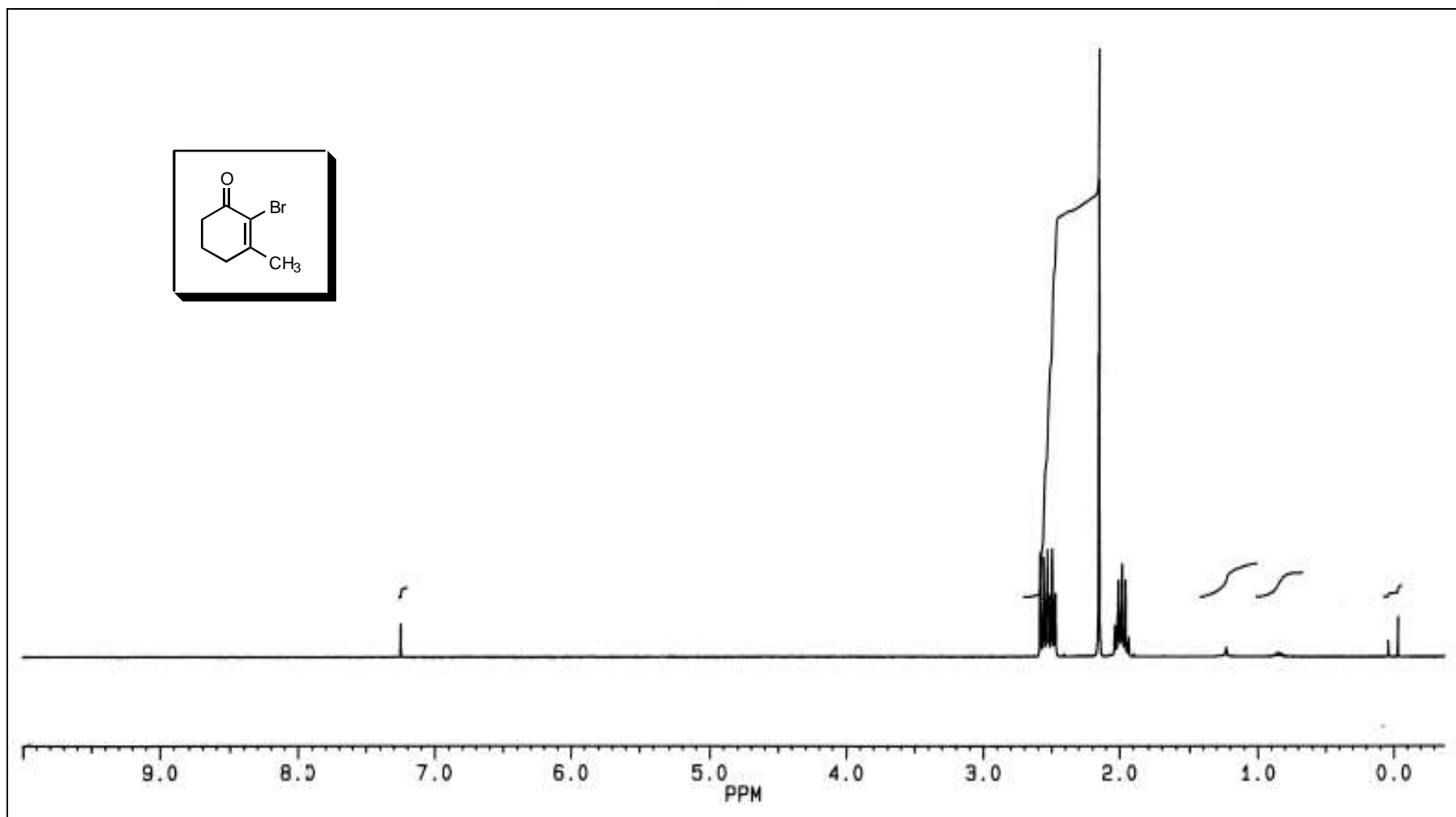


Figure 5: ¹H-NMR spectrum of 2-Bromo-3-methyl-2-cyclohexen-1-one (250 MHz, CDCl₃) (**78d**)

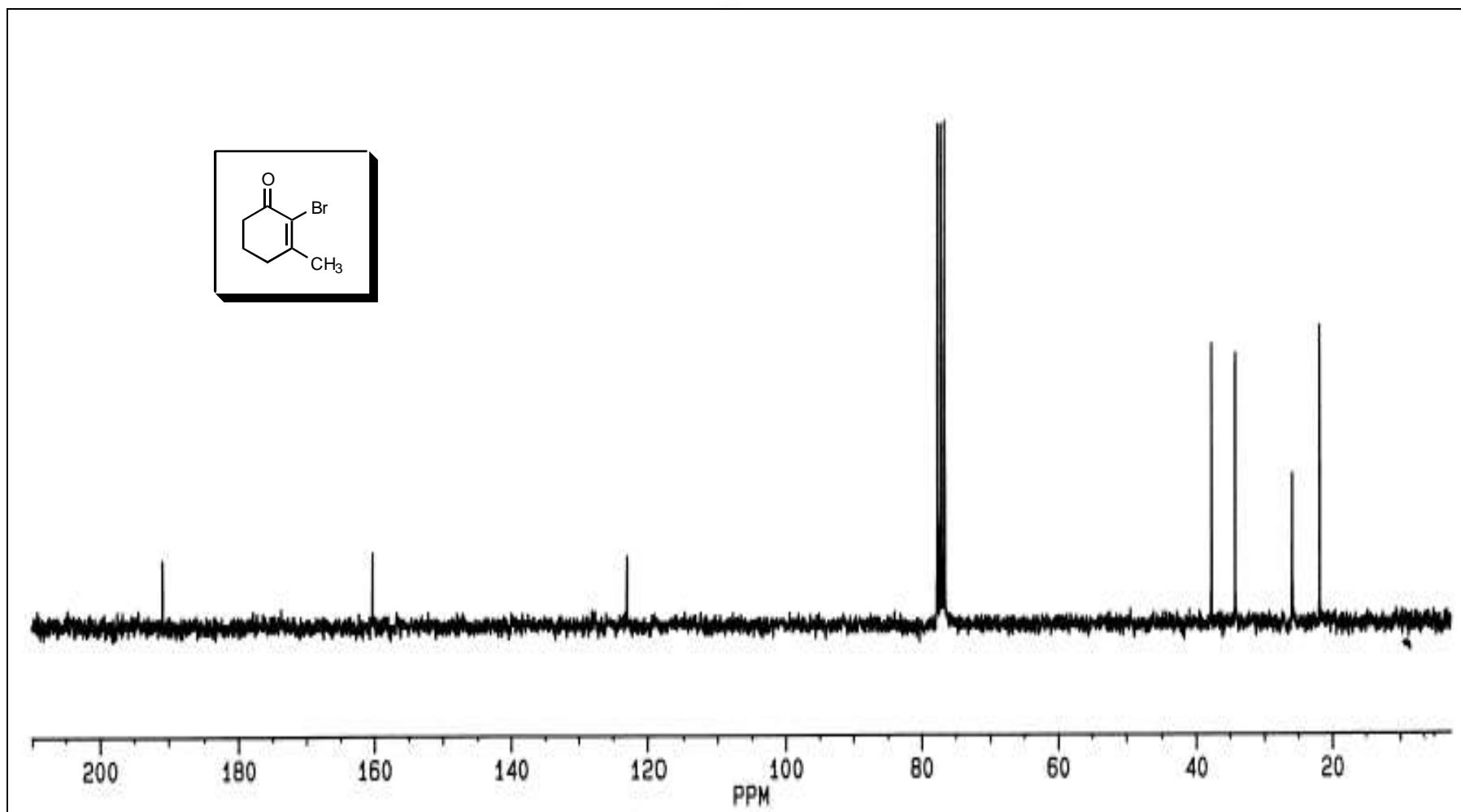


Figure 6: ^{13}C -NMR spectrum of 2-Bromo-3-methyl-2-cyclohexen-1-one (62.5 MHz, CDCl₃) (**78d**)

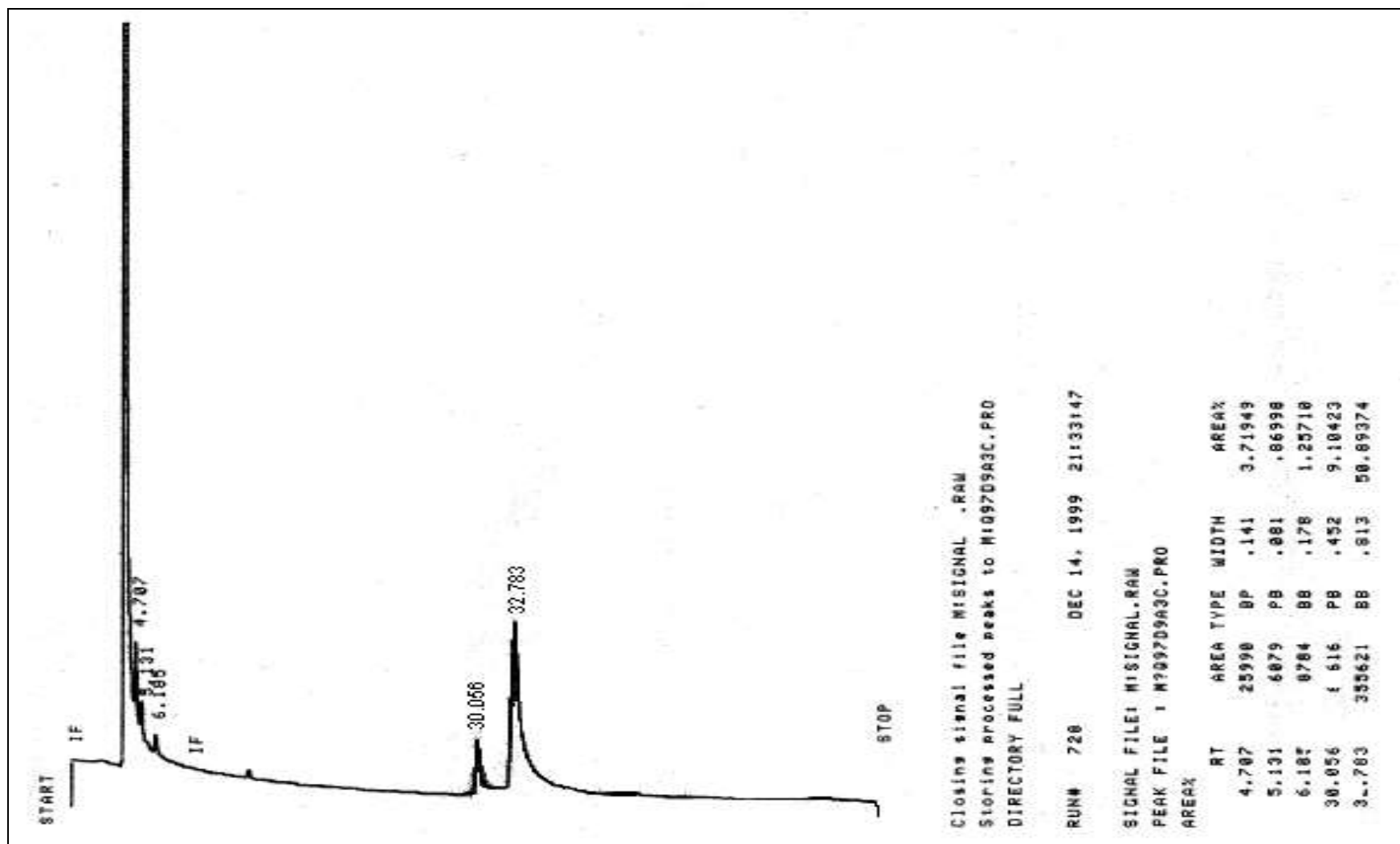


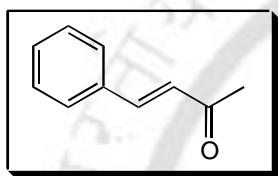
figure 7: Gas Chromatography of 2-Bromo-3-methoxyphenyl-1-phenyl-2-propen-1-one (76d):

Experimental

General procedure for the preparation of acyclic enones:

All the acyclic enones **74a-f** are prepared by following the literature procedure.⁴⁴ The compound **74g** is prepared by following the literature procedure.⁴⁵

4-Phenyl-3-buten-2-one (**74a**)



Reaction time: 12 hrs

Yield: 73 %, pale yellow solid

Melting point: 42-43 °C (lit.⁴⁴ m. p. 42 °C)

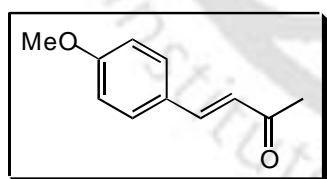
R_f: 0.48 (EtOAc: Hexane 1:9)

UV (MeOH): λ_{\max} /nm 221.5, 288.

IR (Neat): cm⁻¹ 1682, 1610.

¹H NMR (60 MHz, CDCl₃/TMS): δ 2.16 (s, 3H, -CH₃), 6.38 (d, 1H, J = 16.0 Hz, =CHPh), 6.96-7.33 (m, 6H, ArH, -COCH=).

4-(4-Methoxyphenyl)-3-buten-2-one (**74b**)



Reaction time: 12 hrs

Yield: 75 %, white solid

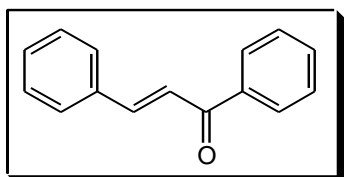
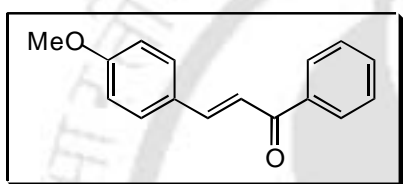
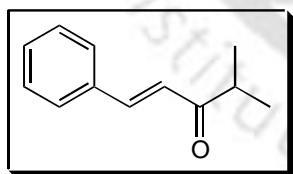
Melting point: 58-59 °C

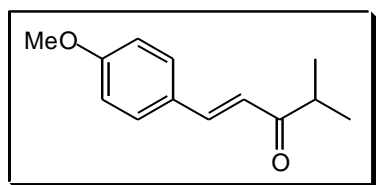
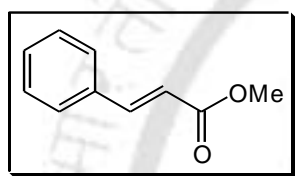
R_f: 0.40 (EtOAc: Hexane 1:9)

UV (MeOH): λ_{\max} /nm 233.5, 319.0

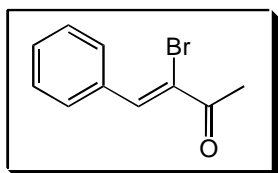
IR (Neat): cm⁻¹ 1659, 1606.

¹H NMR (60 MHz, CDCl₃/TMS): δ 2.24 (s, 3H, -CH₃), 3.71 (s, 3H, -OCH₃), 6.20-7.36 (m, 6H, ArH, -COCH=CHPh-).

1,3-Diphenyl-2-propen-1-one (74c)**Reaction time:** 24 hrs**Yield:** 82%, pale yellow solid**Melting point:** 57-58 °C (lit.⁴⁴ m. p. 56-57 °C)**R_f:** 0.63 (EtOAc: Hexane 1:19)**UV (MeOH):** λ_{max} /nm 305.5, 206.0, 224.5.**IR (KBr):** cm^{-1} 1665, 1606.**¹H NMR (60 MHz, CDCl₃/TMS):** δ 7.00-7.85 (m, 12H, ArH, -COCH=CH-).**3-(4-Methoxyphenyl)-1-phenyl-2-propen-1-one (74d)****Reaction time:** 12 hrs**Yield:** 80 %, pale yellow solid**Melting point:** 73-74 °C (lit.⁴⁷ m. p. 72 °C)**R_f:** 0.30 (EtOAc: Hexane 3:17)**UV (MeOH):** λ_{max} /nm 344, 240.**IR (Neat):** cm^{-1} 1657, 1598.**¹H NMR (60 MHz, CDCl₃/TMS):** δ 3.85 (s, 3H, -CH₃), 6.92 (d, 2H, J = 8.0 Hz, ArH), 7.45-7.80 (m, 7H, ArH, -COCH=CH-), 8.05 (d, 2H, J = 8.0 Hz, ArH).**4-Methyl-1-phenyl-1-penten-3-one (74e)****Reaction time:** 24 hrs**Yield:** 75%**Melting point:** 42-43 °C**R_f:** 0.52 (EtOAc: Hexane 1:19)**UV (MeOH):** λ_{max} /nm 221.5, 288.**IR (KBr):** cm^{-1} 1688, 1664, 1609.**¹H NMR (60 MHz, CDCl₃/TMS):** δ 0.86-1.03 (m, 6H, -CH₃), 2.4-2.7 [m, 1H, -CH(CH₃)₂], 6.8-7.4 (m, 7H, ArH, olifinic-H).

1-(4-Methoxyphenyl)-4-methyl-1-penten-3-one (74f)**Reaction time:** 24 hrs**Yield:** 69%, oil**R_f:** 0.38 (EtOAc: Hexane 1:19)**IR (KBr):** cm⁻¹ 1680, 1596, 1253.**¹H NMR (60 MHz, CDCl₃/TMS):** δ 1.00-1.03 (m, 6H, -CH₃), 2.50-2.90 [m, 1H, -CH(CH₃)₂], 3.65 (s, 3H, -OCH₃), 6.53-7.47 (m, 7H, ArH, olifinic-H).**3-Phenylmethylpropionate (74g)****Reaction time:** 24 hrs**Yield:** 84%**Melting point:** 35-35 °C (lit.⁴⁵ m. p. 36-38 °C)**R_f:** 0.61 (EtOAc: Hexane 1:19)**IR (Neat):** cm⁻¹ 1728, 1618, 1184.**¹H NMR (400 MHz, CDCl₃/TMS):** δ 3.89 (s, 3H, -CH₃), 6.45 (d, 2H, J = 7.8 Hz, ArH), 7.36-7.55 (m, 5H, ArH), 7.67 (d, 2H, J = 7.8 Hz, ArH),**General procedure for the preparation of acyclic α-bromoenones:**

To a well-stirred solution of the acyclic enone **74a-g** (5 mmol) in CH₂Cl₂ (10 mL) at ice bath temperature is added cetyltrimethylammonium tribromide (2.62 g, 5 mmol; method A) or *n*-tetrabutylammonium tribromide (2.41 g, 5 mmol; method B) and stirring is continued at the same temperature. After 45 min of stirring, K₂CO₃ (2.07 g, 15.0 mmol) is added to the reaction mixture and the stirring is continued at rt. monitored by TLC. After completion of reaction, the white solid is filtered off and the residue is washed with dichloromethane (2 x 20 mL). Then, the combined solution is concentrated in rotavapor. The crude product is purified finally by column chromatography using ethyl acetate-hexane mixture as eluent. All the products **76a-g** are obtained as gummy liquids in 68-88% yields.

3-Bromo-4-phenyl-3-buten-2-one (76a)**Reaction time:** 6.0 hrs (A); 6.5 hrs (B)**Yield:** 68% (A); 71% (B), oil**R_f:** 0.50 (EtOAc: Hexane 1:9)**IR (Neat):** cm^{-1} 1684, 1601.**¹H NMR (400 MHz, CDCl₃/TMS):** δ 2.66 (s, 3H, -CH₃), 7.42-7.45 (m, 3H, ArH), 7.86-7.88 (m, 2H, ArH), 8.03 (s, 1H, =CHCH₃).**¹³C NMR (75 MHz, CDCl₃/TMS):** δ 27.00, 123.23, 128.46 (2C), 130.40, 130.43 (2C), 133.62, 139.97, 193.12.**Mass (m/z, EIMS):** 226/224 (M⁺)**Elemental Analysis**M. F. C₁₀H₉BrO

(225.09)

Calculated

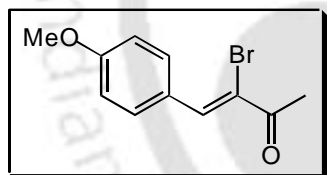
C 53.36

H 4.03

Found

53.13

3.98

3-Bromo-4-(4-methoxyphenyl)-3-buten-2-one (76b)**Reaction time:** 4.0 hrs (A); 3.0 hrs (B)**Yield:** 70% (A); 75% (B), oil**R_f:** 0.38 (EtOAc: Hexane 1:9)**IR (Neat):** cm^{-1} 1675, 1589, 1174.**¹H NMR (300 MHz, CDCl₃/TMS):** δ 2.57 (s, 3H, -CH₃), 3.85 (s, 3H, -OCH₃), 6.95 (d, 2H, J = 8.8 Hz, ArH), 7.92 (d, 2H, J = 8.7 Hz, ArH), 7.98 (s, 1H, =CHPh-).**¹³C NMR (100 MHz, CDCl₃/TMS):** δ 26.80, 55.32, 113.93 (2C), 120.74, 126.03, 132.69 (2C), 139.61, 161.43, 192.89.**Mass (m/z, EIMS):** 256/254 (M⁺), 151 (base peak)**Elemental Analysis**M. F. C₁₁H₁₁BrO₂

(255.11)

Calculated

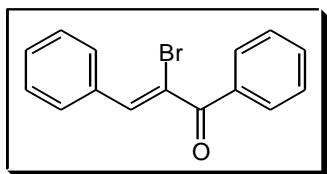
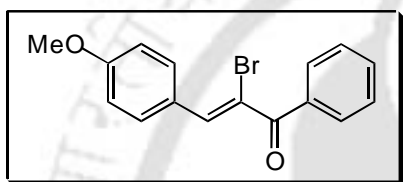
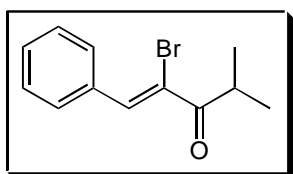
C 51.79

H 4.34

Found

51.55

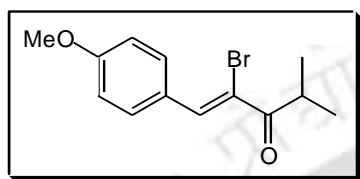
4.32

2-Bromo-1,3-diphenyl-2-propen-1-one (76c)**Reaction time:** 8.0 hrs (A); 6.0 hrs (B)**Yield:** 70% (A); 72% (B), oil**R_f:** 0.67 (EtOAc: Hexane 1:19)**IR (Neat):** cm⁻¹ 1662, 1596.**¹H NMR (300 MHz, CDCl₃/TMS):** δ 7.42-7.45 (m, 4H, Ar-H), 7.48 (t, 1H, J = 7.8 Hz, ArH), 7.59 (m, 1H, ArH), 7.69 (s, 1H, =CHPh-), 7.79-7.85 (m, 4H, ArH).**2-Bromo-3-(4-methoxyphenyl)-1-phenyl-2-propen-1-one (76d)****Reaction time:** 9.5 hrs (A); 7.5 hrs (B)**Yield:** 85% (A); 88% (B), oil**R_f:** 0.32 (EtOAc: Hexane 1:9)**IR (Neat):** cm⁻¹ 1668, 1592**¹H NMR (300 MHz, CDCl₃/TMS):** *Trans*-isomer δ 3.85 (s, 3H, -CH₃), 6.95 (d, 2H, J = 8.8 Hz, ArH), 7.39-7.52 (m, 3H, ArH), 7.68 (s, 1H, =CHPh-), 7.74-7.77 (m, 2H, ArH), 7.89 (d, 2H, J = 8.7 Hz, ArH). *Cis*-isomer δ 3.71 (s, 3H, -CH₃), 6.68 (d, 2H, J = 8.8 Hz, ArH), 7.09 (d, 2H, J = 8.7 Hz, ArH), 7.30 (s, 1H, =CHPh-), 7.54-7.62 (m, 3H, ArH), 7.96-7.99 (m, 2H, ArH).**Elemental Analysis**M. F. C₁₆H₁₃BrO₂
(317.18)**Calculated**C 48.27
H 3.64**Found**48.44
3.55**2-Bromo-4-methyl-1-phenyl-1-penten-3-one (76e)****Reaction time:** 9.0 hrs (A); 8.0 hrs (B)**Yield:** 69% (A); 70% (B), oil**R_f:** 0.46 (EtOAc: Hexane 1:19)**IR (Neat):** cm⁻¹ 1685, 1598.**¹H NMR (300 MHz, CDCl₃/TMS):** δ 1.21 (s, 3H, -CH₃), 1.24 (s, 3H, -CH₃), 3.50-3.65

[m, 1H, -CH(CH₃)₂], 7.28-7.31 (m, 2H, ArH), 7.42-7.46 (m, 3H, ArH), 7.81 (s, 1H, =CHPh-).

¹³C NMR (75 MHz, CDCl₃/TMS): δ 18.52, 18.59, 44.89, 121.34, 126.92 (2C), 131.19, 131.54 (2C), 132.33, 140.17, 197.72.

2-Bromo-1-(4-methoxyphenyl)- 4-methyl-1-penten-3-one (76f)



Reaction time: 9.0 hrs (A); 7.5 hrs (B)

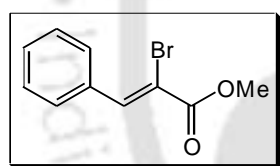
Yield: 78% (A); 81% (B), oil

R_f: 0.49 (EtOAc: Hexane 1:19)

IR (Neat): cm⁻¹ 1681, 1600, 1253.

¹H NMR (60 MHz, CDCl₃/TMS): δ 1.23 (s, 3H, -CH₃), 1.24 (s, 3H, -CH₃), 3.30-3.65 [m, 1H, -CH(CH₃)₂], 3.81 (s, 3H, -CH₃), 6.70-7.67 (m, 4H, ArH), 7.83 (s, 1H, =CHPh-).

2-Bromo-4-phenylmethylpropionate (76g)



Reaction time: 55.0 hrs (A); 50.0 hrs (B)

Yield: 68% (A); 70% (B), oil

R_f: 0.49 (EtOAc: Hexane 1:19)

IR (Neat): cm⁻¹ 1723, 1639, 1174

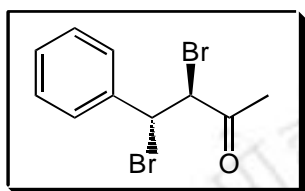
¹H NMR (60 MHz, CDCl₃/TMS): δ 3.78 (s, 3H, -OCH₃), 7.87-7.92 (m, 5H, ArH), 8.32 (s, 1H, =CHPh-).

General procedure for the bromination of acyclic enones:

Into a 50 mL round bottom flask the substrate 4-phenyl-3-buten-2-one (**74a**) (0.440 g, 3.0 mmol) is dissolved in dichloromethane (10 mL) and kept for stirring at ice-bath temperature. To this solution is added cetyltrimethylammonium tribromide (CetTATB, method A) (1.570 g, 3.0 mmol) or *n*-tetrabutylammonium tribromide (TBATB, method B) (1.450 g, 3.0 mmol) and stirring is continued for additional 1.5 hrs (method A) or 1.0 hrs (method B) at the same temperature, as monitored by TLC. Then the reaction mixture is quenched by adding a drop of 5% sodium metabisulfite solution and extracted with CH₂Cl₂ (2 x 10 mL), washed with water and finally dried over anhydrous Na₂SO₄. The

organic extract is concentrated *in vacuo* and the crude residue is purified by column chromatography on SiO₂ (60-120 mesh) using ethyl acetate-hexane as eluent. The product is obtained as white solid (0.673 g, 73%; method A/ 0.728 g, 79%; method B).

3,4-Dibromo-4-phenylbutan-2-one (75a)



Reaction time: 1.5 hrs. (A); 1.0 hrs. (B)

Yield: 73% (A); 79 % (B), white solid

Melting point: 131-132 °C

R_f: 0.56 (EtOAc: Hexane 1:9)

UV (MeOH): λ_{\max}/nm 233.5.

IR (Neat): cm^{-1} 1722, 1584, 1225.

¹H NMR (300 MHz, CDCl₃/TMS): δ 2.46 (s, 3H, -CH₃), 4.88 [d, 1H, J = 11.6 Hz, -CH(Br)Ph], 5.29 [d, 1H, J = 11.6 Hz, -COCH(Br)-], 7.38 (br, 5H, ArH).

¹³C NMR (75 MHz, CDCl₃/TMS): δ 26.50, 49.44, 52.72, 128.08 (2C), 128.87 (2C), 129.33, 137.70, 198.41.

Elemental Analysis

M. F. C₁₀H₁₀Br₂O

(306.00)

Calculated

C 39.25

H 3.29

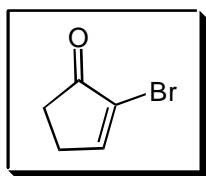
Found

39.12

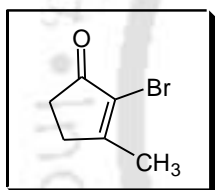
3.22

General procedure for the preparation of cyclic α -bromoenones:

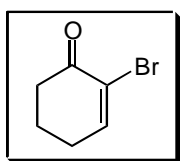
To a well-stirred solution of cyclic enone **77a** (3 mmol) in CH₂Cl₂ (10 mL) are added cetyltrimethylammonium tribromide (1.57 g, 3 mmol; method A) or tetrabutylammonium tribromide (1.45 g, 3 mmol; method B) and K₂CO₃ (1.24 g, 9 mmol) at 0-5 °C. Stirring is continued at the same temp for 10 min and then it is brought slowly to the room temp. The reaction is monitored by TLC. Then, the white solid is filtered off and washed the solid residue with 20 mL of dichloromethane. The combined filtrate is concentrated in rotavapor and the crude product is purified by chromatography on silica gel (60-120 mesh). The compound is eluted with ethylacetate-hexane mixture and the product **78a** is obtained as a gummy liquid in 70/65 yield. Similarly, the cyclic α -bromoenones **78b-e** are prepared from the compounds **77b-e** by following the identical procedure.

2-bromo-2-cyclopentene-1-one (78a)**Reaction time:** 40 min (A); 15 min (B)**Yield:** 70% (A); 65% (B), white solid**Melting point:** 38 °C (lit.¹³ m.p. 39-39.5 °C)**R_f:** 0.43 (EtOAc: Hexane 3:7)**IR (Neat):** cm⁻¹ 1720, 1595.**¹H NMR (400 MHz, CDCl₃/TMS)** δ 2.52-2.66 (m, 2H, =CHCH₂-), 2.70-2.74 (m, 2H, -COCH₂-), 7.81 (t, 1H, J = 3 Hz, =CH-).**Mass (m/z, EIMS):** 162/160 (M⁺), 132/134, 53 (base peak).

Elemental Analysis	Calculated	Found
M. F. C ₅ H ₅ BrO (161.00)	C 37.30 H 3.13	37.26 3.09

2-bromo-3-methyl-2-cyclopentene-1-one (78b)**Reaction time:** 240 min (A); 180 min (B)**Yield:** 68% (A); 72% (B), white plates**Melting point:** 51-52 °C (lit.¹² m.p. 52-53 °C)**R_f:** 0.37 (EtOAc: Hexane 1:4)**IR (Neat):** cm⁻¹ 1730, 1600.**¹H NMR (400 MHz, CDCl₃/TMS):** δ 2.17 (s, 3H, -CH₃), 2.53-2.56 (m, 2H, -COCH₂CH₂-), 2.63-2.67 (m, 2H, -COCH₂-).**¹³C NMR (100 MHz, CDCl₃/TMS):** δ 18.96, 32.20, 33.25, 123.11, 173.43, 201.47.

Elemental Analysis	Calculated	Found
M. F. C ₆ H ₇ BrO (175.03)	C 41.17 H 4.03	40.95 4.08

2-bromo-2-cyclohexene-1-one (78c)**Reaction time:** 140 min (A); 120 min (B)**Yield:** 80% (A); 75% (B), pale yellow needles**Melting point:** 71 °C (lit.¹³ m.p. 75-76 °C)**R_f:** 0.45 (EtOAc: Hexane 1:9)**UV (MeOH):** λ_{max}/nm 238**IR (Neat):** cm⁻¹ 1689, 1598.

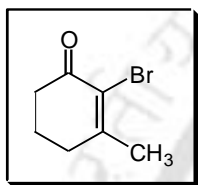
^1H NMR (400 MHz, CDCl_3/TMS): δ 2.05-2.11 (m, 2H, $-\text{COCH}_2\text{CH}_2-$), 2.43-2.47 (m, 2H, $-\text{COCH}_2-$), 2.62-2.65 (m, 2H, $=\text{CHCH}_2-$), 7.43 (t, 1H, $J = 4.3$ Hz, $=\text{CH}-$).

^{13}C NMR (100 MHz, CDCl_3/TMS): δ 22.62, 28.31, 38.30, 123.87, 151.66, 191.18.

Mass (m/z, EIMS) 176/174(M^+), 148/146, 67 (base peak).

Elemental Analysis	Calculated	Found
M. F. $\text{C}_6\text{H}_7\text{BrO}$	C 41.17	40.89
(175.03)	H 4.03	3.96

2-bromo-3-methyl-2-cyclohexene-1-one (78d)



Reaction time: 150 min (A); 120 min (B)

Yield: 72% (A); 75% (B), oil

R_f: 0.53 (EtOAc: Hexane 1:4)

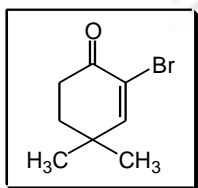
IR (Neat): cm^{-1} 1684, 1588.

^1H NMR (250 MHz, CDCl_3/TMS): δ 1.94-2.02 (m, 2H, $-\text{COCH}_2\text{CH}_2-$), 2.14 (s, 3H, $-\text{CH}_3$), 2.46-2.58 (m, 4H, $-\text{COCH}_2\text{CH}_2\text{CH}_2-$).

^{13}C NMR 62.5 MHz, CDCl_3/TMS): δ 21.78, 25.79, 34.13, 37.61, 122.79, 160.12, 190.77.

Elemental Analysis	Calculated	Found
M. F. $\text{C}_7\text{H}_9\text{BrO}$	C 44.47	44.23
(189.09)	H 4.80	4.78

2-bromo-4,4-dimethyl-2-cyclohexene-1-one (78e)



Reaction time: 150 min (A); 120 min (B)

Yield: 65% (A); 68% (B), white needles

Melting point: 28-29 °C (lit.¹⁵ m. p. 29 °C)

R_f: 0.45 (EtOAc: Hexane 1:19)

IR (Neat): cm^{-1} 1679, 1684.

^1H NMR (400 MHz, CDCl_3/TMS): δ 1.25 (s, 6H, $-\text{CH}_3$), 1.92 (t, 2H, $J = 6.8$ Hz, $-\text{COCH}_2\text{CH}_2-$), 2.66 (t, 2H, $J = 6.5$ Hz, $-\text{COCH}_2-$), 7.15 (s, 1H, $-\text{CH}=\text{CBr}-$).

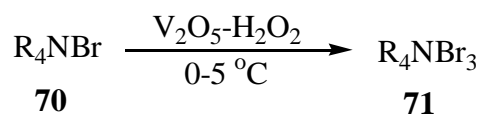
Elemental Analysis	Calculated	Found
M. F. $\text{C}_8\text{H}_{11}\text{BrO}$	C 47.31	47.19
(203.08)	H 5.45	5.38

PRESENT WORK ON THE BROMINATION OF VARIOUS ACYCLIC AND CYCLIC ENONES TO THE CORRESPONDING α -BROMOENONES USING ORGANIC AMMONIUM TRIBROMIDE (OATB)

EXPERIMENTAL

Discussion:

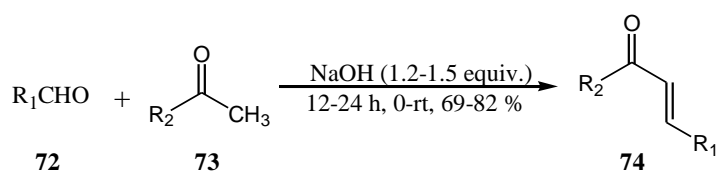
α -Bromo-enones are well-known as useful synthetic precursors for natural^{7,12} and non-natural products synthesis.^{6,13,14} They also serve as important intermediates in organic synthesis such as for functionalization at the α -position through the generation of α -keto vinyl carbanion.¹⁶ For example, α -bromo-2-cyclopentenone (**78a**) has been used for the preparation of α -hydroxymethyl cyclopentenone, which is a valuable starting material for cyclopentanoid natural products synthesis.³⁷ In addition, some α -bromo-enones are found in nature as such.³⁸ Although there are several methods of preparation of α -bromo-enones in the literature, many of them have one or more serious drawbacks. The existing methods³⁹ are i) bromination of enones with elemental bromine followed by dehydrobromination using a suitable base,^{6,9} such as triethyl amine¹⁵ or sodium bicarbonate¹² ii) reaction of enones with excess phenylselenium bromide, followed by treatment with a base pyridine¹⁷ iii) epoxidation of enones using dimethyldioxirane followed by epoxide ring opening with alkali metal bromide such as sodium bromide and subsequent dehydration.¹⁸ All these methods have some drawbacks, such as the use of hazardous molecular bromine, long reaction time, harsh reaction conditions, low yield and operational difficulty. Apart from these, it is difficult to maintain stoichiometric ratio with liquid bromine. On the other hand, the reagent phenylselenium bromide is toxic, expensive and it also requires much longer reaction time to obtain the desired product. Sometimes it failed to obtain β -substituted cyclic α -bromo-enones by using elemental bromine.¹³ Therefore, a clean preparation of α -bromo-enone is highly desirable. Recently, Chaudhuri *et al* have reported⁴⁰, the preparation of various organic ammonium tribromide by involving V_2O_5 - H_2O_2 catalyzed oxidation of quaternary organic ammonium bromide under a mild and environmentally favorable condition (shown in scheme 29) and some of its applications are disclosed. They have also demonstrated⁴¹ the bromination of various organic substrates *in situ* by employing V_2O_5 - H_2O_2 catalyzed oxidation of quaternary organic ammonium bromide.



Scheme 29

Among these various organic ammonium tribromides (OATB), tetrabutyl ammonium tribromide (TBATB) is one of the potent reagents for bromination reaction⁴² in literature. However, this reagent was not exploited extensively in organic synthesis due to non-availability of efficient methods of preparation. Earlier, it was prepared⁴³ only by reaction of *n*-tetrabutylammonium bromide with molecular bromine. By this method the prepared reagent undergoes decomposition within a shorter period due to the presence of HBr associated with it during its preparation. Due to its potentiality as a mild and efficient brominating agent,⁴⁰ it is expected to be possible to get an easy access to α -bromoenones by bromination of enones. Among the various organic ammonium tribromides, we have selected cetyltrimethylammonium tribromide (CetTMATB) and tetrabutylammonium tribromide (TBATB) for our investigations because their precursors are readily available as well as inexpensive in comparison to other organic ammonium bromides. The results of our successful attempts are discussed below-

For our investigation, we have prepared a wide variety of acyclic enones **74a-f**, by following Claisen-Schmidt reaction.⁴⁴ The method involves the reaction of aldehydes **72a** or **72b** with the ketones **73a-c** in the presence of dil. NaOH as shown in the Scheme 30. The results are summarized in Table 5 and the products were characterized by usual spectroscopic techniques as well as by comparison of melting points with the authentic compounds. The compound **74g** is prepared from cinnamic acid by esterification following the literature procedure.⁴⁵



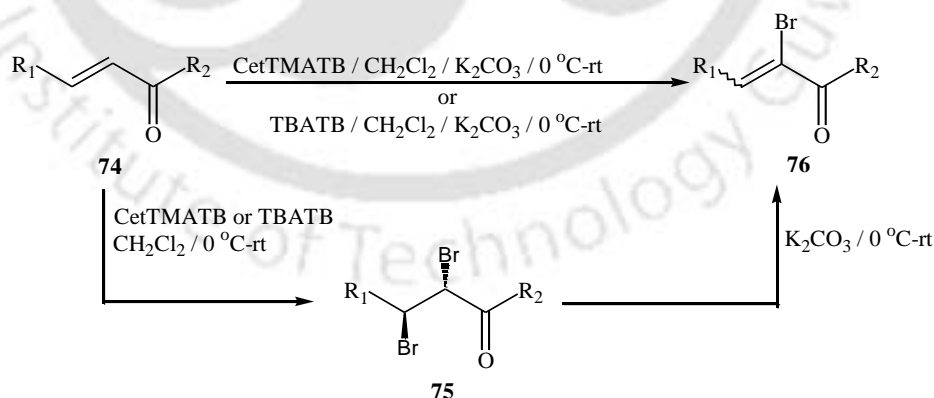
Scheme 30

Table 5: Preparation of various acyclic enones

Aldehyde (72)	Ketone (73)	Reaction time (h)	Enone (74)	Yield (%)
72a: R ₁ = Ph	73a: R ₂ = Me	12	74a: R ₁ = Ph, R ₂ = Me	73
72b: R ₁ = 4-OMePh	73a: R ₂ = Me	12	74b: R ₁ = 4-OMePh, R ₂ = Me	75
72a: R ₁ = Ph	73b: R ₂ = Ph	24	74c: R ₁ = Ph, R ₂ = Ph	82
72b: R ₁ = 4-OMePh	73b: R ₂ = Ph	12	74d: R ₁ = 4-OMePh, R ₂ = Ph	80
72a: R ₁ = Ph	73c: R ₂ = CH(Me) ₂	24	74e: R ₁ = Ph, R ₂ = CH(Me) ₂	75
72b: R ₁ = 4-OMePh	73c: R ₂ = CH(Me) ₂	24	74f: R ₁ = 4-OMePh, R ₂ = CH(Me) ₂	69

Thus, the reaction of *trans*-4-phenyl-3-buten-2-one (**74a**) with CetTMATB in CH₂Cl₂ at 0–5 °C, followed by treatment with K₂CO₃ at room temp. gives *E/Z* (28/72) mixture of 3-bromo-4-phenyl-3-buten-2-one (**76a**) in a very good yield. (Method A). The compound **76a** is also prepared from the compound **74a** using TBATB in similar solvent system at 0 °C–rt (Method B, Scheme 31). It may be noted that no bromination takes place at C-1 position of **74a**. The *E/Z* ratio is ascertained by GC and ¹H NMR. We have observed that when the compound **74a** is treated with TBATB or CetTMATB in absence of base, the dibromo product **75a** is obtained. It clearly indicates that in presence of a base, the product **76a** is obtained through the dibromo intermediate. The spectroscopic studies shows that in dibromo compound **75a**, the IR stretching frequency for carbonyl group is appeared at 1722 cm⁻¹ due to lack of conjugation whereas its parent compound **74a** shows carbonyl stretching frequency at 1682 cm⁻¹. The appearance of two doublets at δ 4.88 and δ 5.29 with J = 11.6 Hz in ¹H NMR spectrum of compound **75a** shows the formation of *trans*-dibromo product **75a** (fig. 1). In ¹³C NMR spectrum, there are two characteristic signals at δ 49.44 and δ 52.72 for compound **75a** (fig. 2) due to two brominated carbon atoms at the α- and β- position, respectively. After dehydrobromination of compound **75a**, we usually get two products as *E/Z* mixture (confirmed by GC). Among the two products, we have characterized *Z*-isomer only since *E*-isomer is obtained as minor amount. The compound α-bromoenone **76a** (*Z*-isomer) is confirmed by IR, ¹H NMR and ¹³C NMR. In IR spectrum, the band at 1684 cm⁻¹ gives the preliminary confirmation for the formation of

enone double bond. In ^1H NMR spectrum, the two signals at δ 4.88 and δ 5.29 are disappeared and new signal as singlet at δ 8.03 is appeared due to β -hydrogen in **76a**. This is also confirmed by ^{13}C NMR spectrum in which two signals at δ 49.44 and δ 52.72 are disappeared and two new signals at δ 123.23 and δ 139.97 are observed due to two-olefinic carbon. Likewise, the reaction of 4-(4'-methoxyphenyl)-3-buten-2-one (**74b**) with CetTMATB or TBATB in presence of K_2CO_3 in CH_2Cl_2 at 0-5 $^\circ\text{C}$ affords 3-bromo-4-(4-methoxyphenyl)-3-buten-2-one (**76b**) as *E/Z* mixture (Scheme 31). We have isolated only the *Z*-isomer, which is thermodynamically stable. The final product 4-(4-methoxyphenyl)-3-buten-2-one (**76b**) is also characterized by spectral data such as IR, ^1H NMR (fig. 3) and ^{13}C NMR (fig. 4). The base K_2CO_3 is usually added to reaction mixture after 45 min except the compound **74c** ($\text{R}_1 = \text{R}_2 = \text{Ph}$), in which the addition is made after 3.5 hrs. Similarly, the substrates **74c**, **74d**, **74e** and **74f** are successfully converted into the corresponding α -bromo enones **76c**, **76d**, **76e** and **76f** respectively at 0 $^\circ\text{C}$ to room temperature (Table 6) and are fully characterized by usual spectroscopic techniques as mentioned above. Also, the reaction of an α,β -unsaturated ester, *viz.*, methyl cinnamate **74g**, with CetTMATB or TBATB followed by treatment with K_2CO_3 , provided α -bromo- α,β -unsaturated ester **76g**, which is usually prepared⁴⁶ *via* arsonium ylides.



Scheme 31

Table 6. Bromination of various acyclic enones by organic ammonium tribromides

Entry (74)	Substrate	Method	Time (h)	Product ^a (76)	Yield ^b / %	[E/Z] ^c
a	R ₁ = Ph, R ₂ = Me	A	6.0	a	68	28:72
		B	6.5		71	30:70
b	R ₁ = 4-OMePh, R ₂ = Me	A	4.0	b	70	15:85
		B	3.0		75	10:90
c	R ₁ = Ph, R ₂ = Ph	A	8.0	c	70	10:90
		B	6.0		72	10:90
d	R ₁ = 4-OMePh, R ₂ = Ph	A	9.5	d	85	20:80
		B	7.5		88	15:85
e	R ₁ = Ph, R ₂ = CH(Me) ₂	A	9.0	e	69	22:78
		B	8.0		70	20:80
f	R ₁ = 4-OMePh, R ₂ = CH(Me) ₂	A	9.0	f	78	28:72
		B	7.5		81	30:70
g	R ₁ = Ph, R ₂ = OMe	A	55	g	68	50:50
		B	50		70	50:50

^aProducts are characterized by IR, ¹H-NMR, ¹³C-NMR and mass spectra. ^bIsolated yield. ^cE/Z ratio is determined by GC and ¹H-NMR analysis. Method A-CetTMATB, Method B-TBATB.

Similarly, various cyclic enones (**77a-e**) are reacted with CetTMATB or TBATB in presence of K₂CO₃ at 0 °C-rt to provide readily the cyclic α -bromo enones (**78a-e**) in good yields (Scheme 32, Table 7). The generation of α -bromo enones can be explained by the initial formation of dibromo ketones, followed by dehydrobromination by a base such as K₂CO₃. All the products are characterized by comparing melting point with the authentic compounds as well as by using spectroscopic techniques like IR, ¹H NMR (figure 5), ¹³C NMR (figure 6) and/or mass spectra. Elemental analysis of all the compounds **78a-e** gives the satisfactory results.

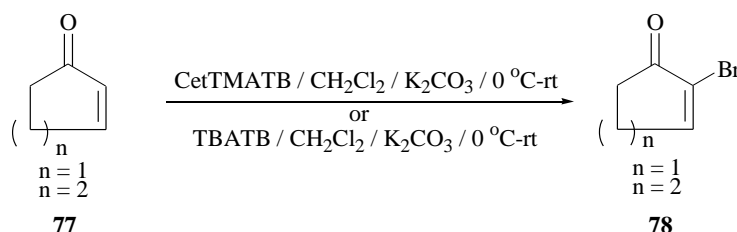
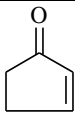
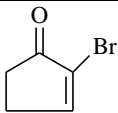
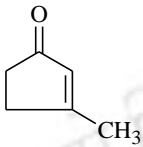
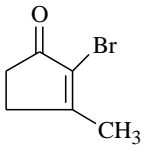
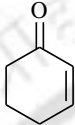
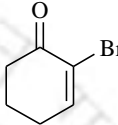
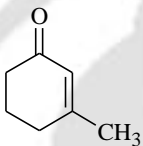
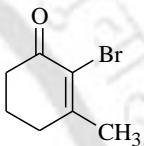
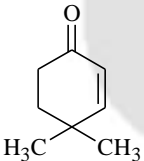
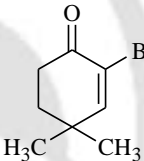
**Scheme 32**

Table 7: Bromination of various cyclic enones by organic ammonium tribromides.

Entry (77)	Substrate	Method	Time (min)	Product ^a (78)	Yield ^b / %
a		A	40		70
		B	15		65
b		A	240		68
		B	180		72
c		A	140		80
		B	120		75
d		A	150		72
		B	120		75
e		A	150		65
		B	120		68

^aProducts have been characterized by IR, ¹H-NMR, ¹³C-NMR and mass spectra. ^bIsolated yield.

In conclusion, we have demonstrated a simple and useful method for the synthesis of α -bromoenones from enones by employing organic ammonium tribromide, such as cetyltrimethylammonium tribromide (CetTMATB) or *n*-tetrabutylammonium tribromide (TBATB) as brominating agent under mild and environmentally favorable conditions. In addition, we have also achieved the preparation of β -substituted cyclic α -bromoenones. Owing to its operational simplicity, generality and efficacy, this method is expected to have wide utility in organic synthesis.

PRESENT WORK ON THE BROMINATION OF VARIOUS ACYCLIC AND CYCLIC ENONES TO THE CORRESPONDING α -BROMOENONES USING ORGANIC AMMONIUM TRIBROMIDE (OATB)

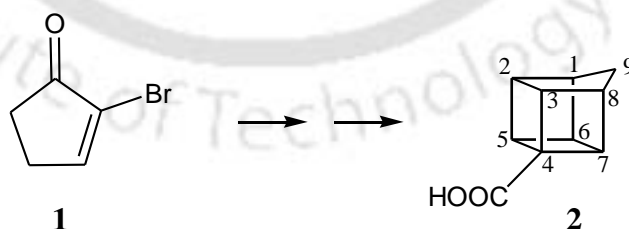
DISCUSSION

Introduction :

The importance of bromo compounds is well known in organic synthesis from the early days of chemistry. Many of them are naturally occurring having structural diversity ranging from a simple to a very complex one.¹ Interestingly, some of them possess remarkable biological activities such as antitumor, antibacterial, antifungal, antineoplastic, antiviral, antioxidizing agent.² They also serve as industrial intermediates in the manufacture of chemicals, pharmaceuticals and agrochemicals. In addition, bromo compounds are valuable precursors in organic synthesis. For examples, they are used in the preparation of Wittig salts,³ in Grignard reactions⁴ and sometimes they also serve as electrophiles in the alkylation reactions.⁵

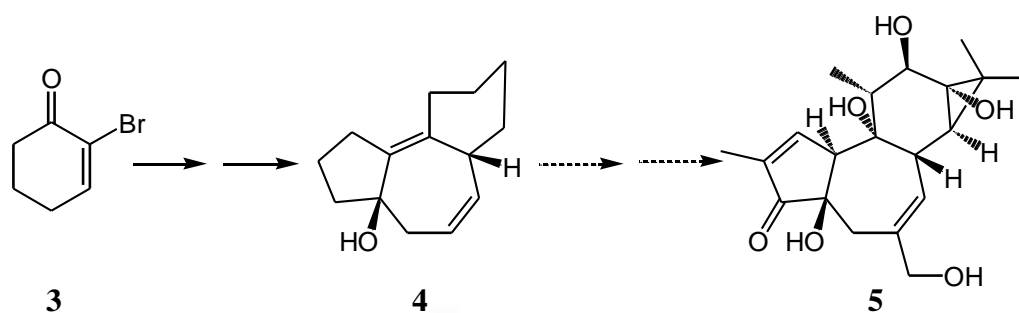
Among the various organobromine compounds, α -bromo enone has attracted considerable interest to synthetic chemists during the last few years. From literature survey, it has been found that α -bromo enone is used as valuable building block in natural and non-natural products synthesis. Some of their useful applications in organic synthesis are highlighted below –

Hoover *et al* first reported⁶ the synthesis of pentacyclo[4.3.0.0^{2,5}.0^{3,8}.0^{4,7}]nonane (Homocubane) (**2**) starting from 2-bromo-2-cyclopentenone (**1**), as shown in scheme 1.



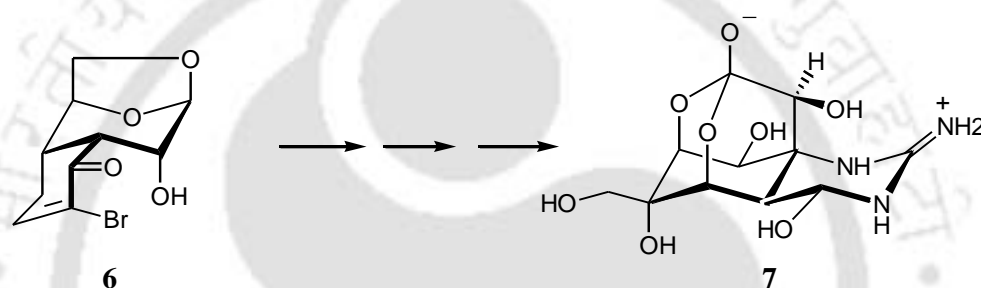
Scheme 1

Later, Wender and his group have employed⁷ 2-bromo-2-cyclohexenone (**3**) in the constructions of the backbone of the tiglianes, daphnanes and ingenanes families of natural products as depicted in scheme 2.



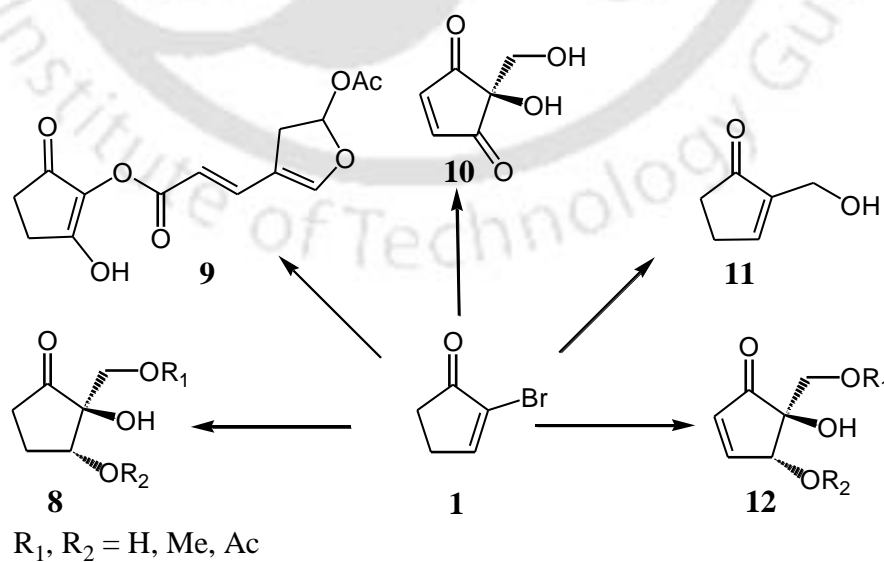
Scheme 2

Ishobe *et al* have utilized⁸ the compound **6** containing 2-bromo-2-cyclohexenone moiety towards the synthetic studies of Tetrodotoxin (**7**), as represented in scheme 3.



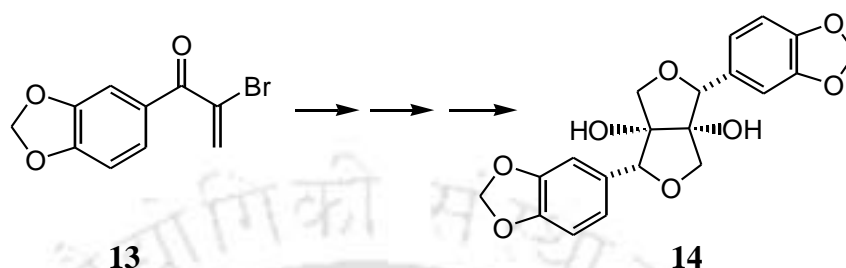
Scheme 3

A. B. Smith III and his co-workers have shown⁹ the remarkable application of 2-bromo-2-cyclopentenone (**1**) for the synthesis of a wide variety of cyclopentanoid natural products. Some of them are shown in scheme 4.



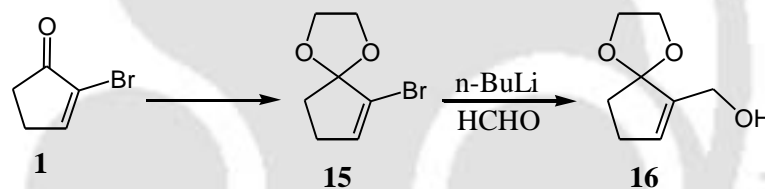
Scheme 4

Very recently, E. J. Corey and his group have reported¹⁰ the enantioselective total synthesis of (-)-Wodeshiol (**14**) by using α -bromovinyl ketone derivative (**13**) as depicted in scheme 5.



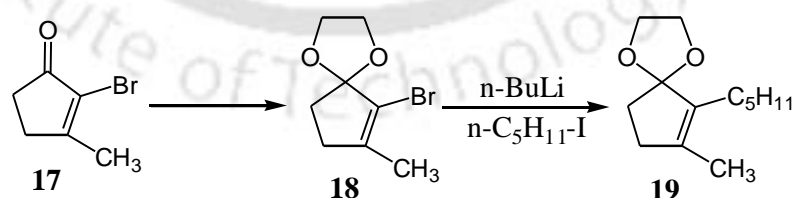
Scheme 5

The bromo functionality in α -bromo enone can be utilized for the generation of α -keto vinyl carbanion equivalent for functional group transformations such as incorporation of hydroxymethyl group at the α -position, as shown in scheme 6, which was demonstrated by A. B. Smith III and his group.¹¹



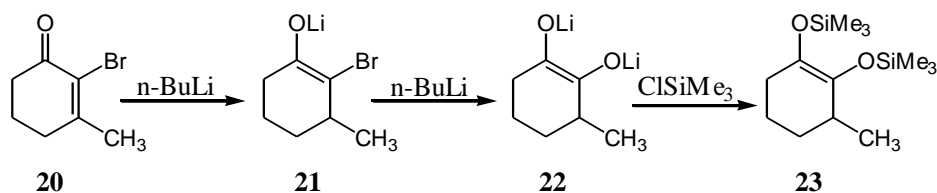
Scheme 6

Godefroi and his co-workers have shown¹² the application of the generated carbanion equivalent for the synthesis of dihydrojasnoneacetal (**19**), as shown in scheme 7.



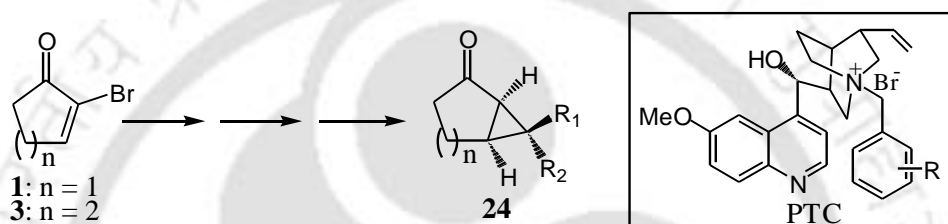
Scheme 7

The generation of α -ketodianion (**22**) from α -bromo enone (**20**) has been exploited by Kowalski and his co-workers,¹³ which reacts with chlorotrimethylsilane to form **23**, as represented in scheme 8. They can also be used directly for conjugate addition reaction.



Scheme 8

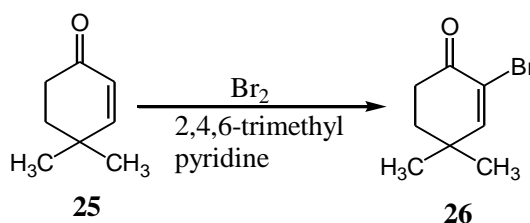
Recently, Shioiri *et al* demonstrated¹⁴ that the double bond of α -bromo enones can be utilized for the asymmetric cyclopropanation reactions (**24**, $R_1, R_2 = \text{H}, \text{NO}_2, \text{CN}, \text{CO}_2\text{Bn}$) using a phase transfer catalyst ($R = \text{Me}, 2,4\text{-Me}_2, \text{vinyl}$ etc.), as depicted in scheme 9.



Scheme 9

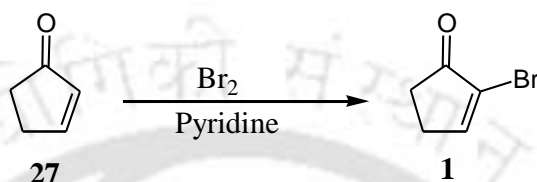
From the literature survey, we have observed that α -bromo enones are employed as valuable synthons for the natural and non-natural products synthesis. In addition, they can also be applied for organic functional group transformations. Then, we became interested in the literature procedure for the preparation of α -bromo enones. The existing methods of preparation of α -bromo enones are described below-

Wellman *et al* first reported¹⁵ the preparation of α -bromo enones from their corresponding enones, by bromination involving molecular bromine followed by dehydrobromination on treatment with a base like 2,4,6-trimethyl pyridine. As for example, they have prepared 2-bromo-4,4-dimethyl-2-cyclohexenone (**26**) from the compound 4,4-dimethyl-2-cyclohexenone (**25**) under the above mentioned reaction condition, as given below in scheme 10.



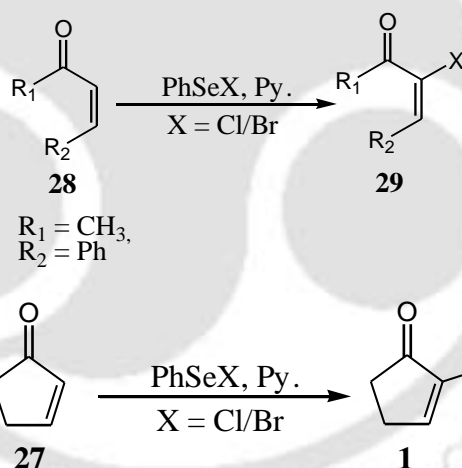
Scheme 10

Similarly, Hoover *et al* also prepared⁶ the cyclic α -bromoenones viz. 2-bromo-2-cyclopentenone (**1**) starting from 2-cyclopentenone (**27**) by bromination using molecular bromine followed by dehydrobromination in the presence of a base such as pyridine, as depicted in scheme 11. The same procedure was followed by others¹⁶ for the preparation of α -bromoenones from their respective enones.



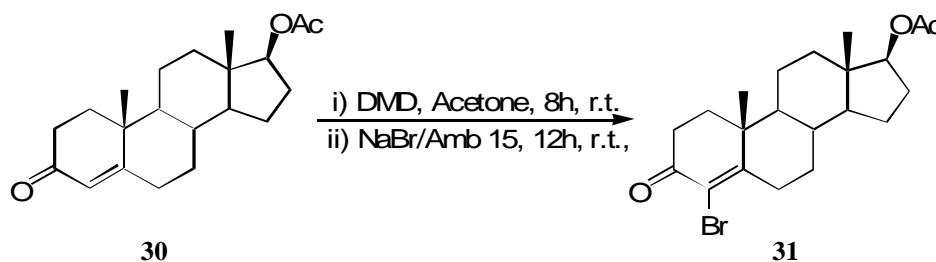
Scheme 11

A few years ago, Ley *et al* have devised¹⁷ an alternate procedure for the preparation of both acyclic as well as cyclic α -haloenones using excess amount of phenylselenium halide in the presence of pyridine as shown in scheme 12.



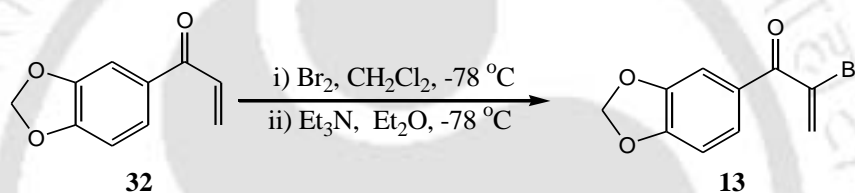
Scheme 12

Recently, Righi and his group have reported¹⁸ another new synthetic protocol for the preparation of cyclic α -haloenones, which is based on three steps sequence in one pot reaction. In this procedure, the double bond of the enone is first epoxidized by dimethyldioxirane (DMD) in acetone, followed by epoxide ring opening with NaBr and finally dehydration in presence of Amberlyst 15 catalyst, as mentioned in scheme 13.



Scheme 13

Very recently, Corey and his co-worker have reported¹⁰ the preparation of acyclic α -bromo enones **13** from the acyclic enone **32**, which is required in the synthesis of (-)-Wodeshiol (**14**), by bromination using molecular bromine in CH_2Cl_2 at -78°C , followed by dehydrobromination with Et_3N at the same temperature, as mentioned in scheme 14.

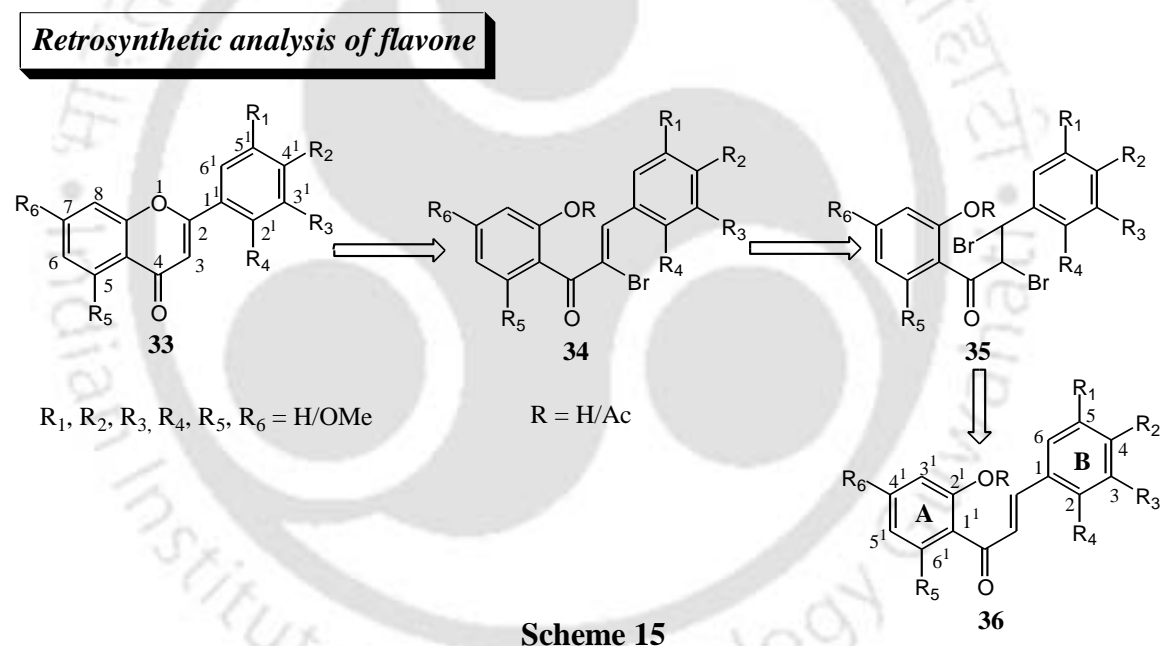


Scheme 14

It is evident from the literature survey that molecular bromine and a suitable base are usually required for the preparation of α -bromo enones from their corresponding enones. A considerable emphasis has been given in recent years on environmental impact of chemical reactions. In view of this, the above-mentioned procedure presents several drawbacks such as molecular bromine is volatile, hazardous, difficult to handle and also difficult to maintain stoichiometric ratio while carrying out the reaction. The second method, which is based on phenylselenium halide has also some disadvantages as it is an expensive reagent, highly toxic and requires relatively longer reaction time. The third method, which is reported by Righi and his co-workers, associated with some drawbacks like DMD is explosive, difficult to handle, has to be prepared prior to use and requires longer reaction time. Therefore, there exist a great scope to find better alternatives that might work faster, economically viable, environmentally favorable and proceeds under much milder reaction conditions. These factors are important due to current working practices with greener alternatives.¹⁹ Based on the overview presented above, the preparation α -bromo enones from enones by employing a new methodology with a new

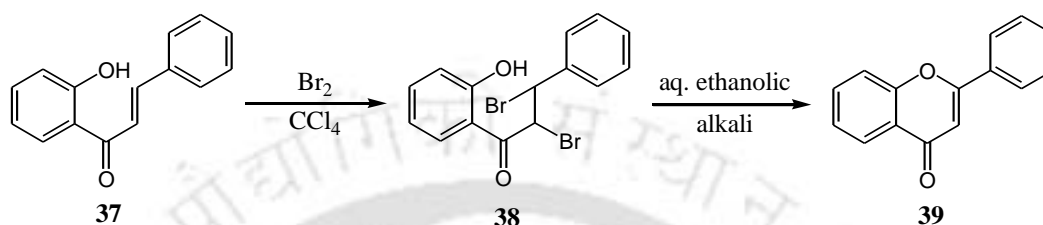
and novel reagent (which is the equivalent source of molecular bromine but works under a mild, environmentally friendly and less hazardous reaction conditions) has been chosen as my Ph. D. problem.

From the literature survey, it is revealed that α -bromoenones are valuable synthons for both natural as well as non-natural products synthesis. At the same time we have realized that the methodology can be extended further for the synthesis of flavones. α -Bromo-2'-hydroxychalcones or α -bromo-2'-acetoxychalcones, which are equivalent to the α -bromoenones, could be considered as important building blocks for the synthesis of naturally occurring various substituted flavones, as shown in the retrosynthetic analysis in scheme 15.



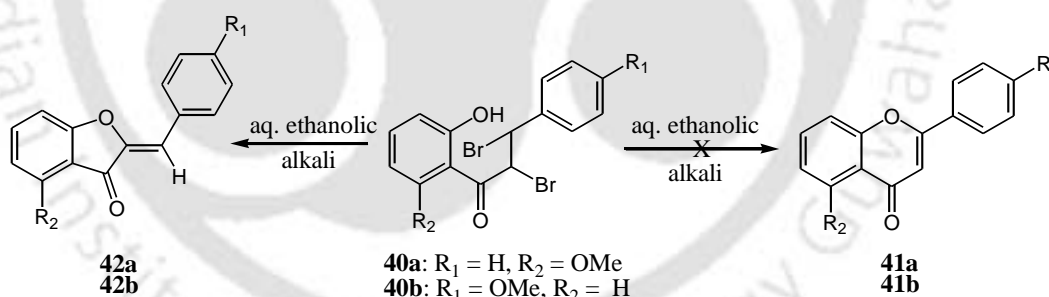
From the retrosynthetic analysis, it seems that α -bromo chalcones (**34**) are the appropriate precursors for the synthesis of naturally occurring hydroxy substituted flavones. Compounds **34** can be easily accessed from chalcones **36** via chalcone dibromides **35**, as shown in scheme 15. We have gone through the literature to know whether chalcone dihalides **35** (which are key precursors of α -bromo-2'-hydroxychalcones) could be exploited for the synthesis of flavones or not. Interestingly, we have found that good amount of work has been done on the synthesis of flavones either from chalcone dibromides **35** or α -bromo chalcones **34**. Some of these works are represented below-

Emilewicz and Kostanecki have first demonstrated²⁰ the synthesis of flavone **39** from the chalcone **37** via chalcone dihalide **38**, which was prepared by bromination using molecular bromine in CCl₄ followed by cyclisation on treatment with aqueous ethanolic alkali, as shown in scheme 16.



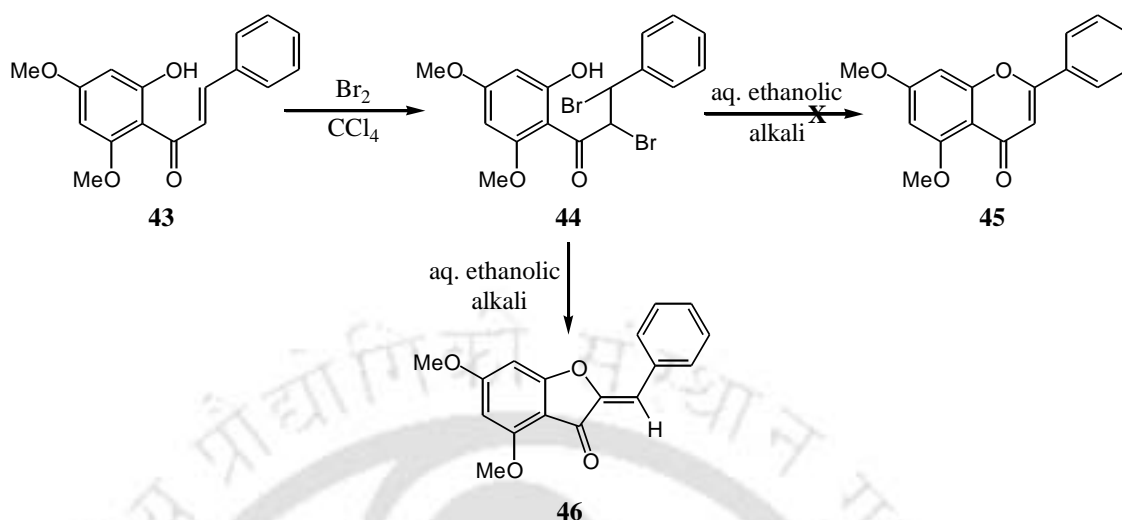
Scheme 16

Konstanecki and his group^{21,22} have tried to explore further their synthetic strategy to synthesize naturally occurring flavones such as 5-alkoxyflavone (**41a**) and 4'-alkoxyflavone (**41b**). Unfortunately, both the reactions were unsuccessful to get the desired flavones **41a** and **41b**. However, they obtained structurally isomeric compound aurones **42a** and **42b**, respectively instead of the expected flavones **41a** and **41b**, as shown in scheme 17.

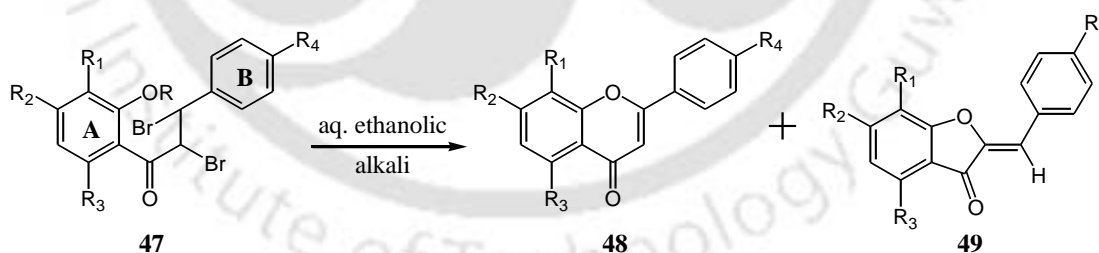


Scheme 17

The similar strategy was further exploited by Wheeler *et al*²³ to prepare 5,7-disubstituted flavones because they are widely distributed in nature having significant biological activities. While carrying out the reactions with chalcone dihalide **44**, they had obtained 4,6-dimethoxy aurone (**46**) rather than the desired 5,7-dimethoxy flavone (**45**), as mentioned in Scheme 18. From the observations of Konstanecki and Wheeler, it is quite obvious that 5-alkoxy, 4'-alkoxy and 5,7-dialkoxy substituted flavones cannot be easily accessible from their corresponding chalcone dihalides.



Later, Donnelly and his co-workers²⁴ have reinvestigated the same reactions to get the desired 5-substituted flavones as well as 5,7-disubstituted flavones. They have chosen various chalcone dibromides and treated them with aqueous ethanolic alkali, as shown in scheme 19. They found that the products were a mixture in which the flavone is the major component. From this result, they came to conclusion that the steric effects of the two substituents at the position 3' and 6' in ring A of the chalcone play a vital role for the formation of flavones over aurones.

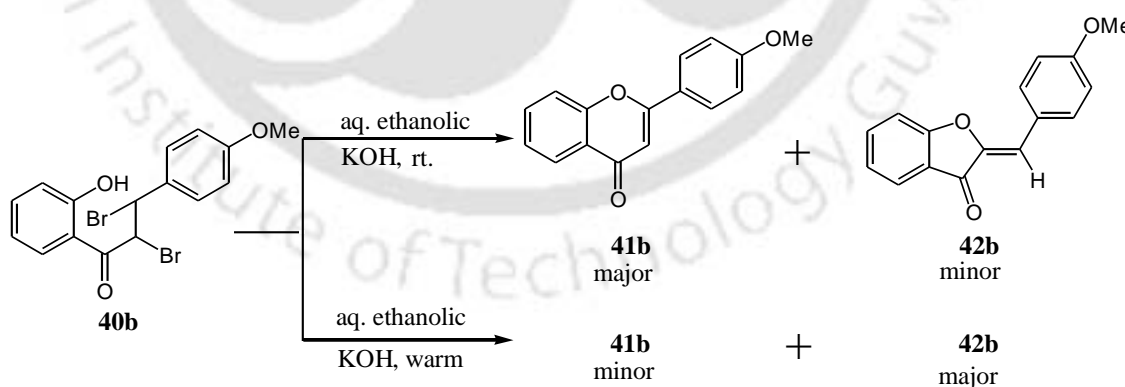


It is clear from their observation that ortho substituents in the ring A favor the formation of aurone in comparison to flavone. For instance, when a bromo group is placed at 3'-position of compound **47a** (i.e. compound **47b**), then the percentage composition of flavone decreases enormously from 89% (**48a**) to 46% (**48b**) (mentioned in table 1). However, it is not possible to access exclusively either flavones or aurones under the above reaction conditions.

Table 1: Product composition of flavones and aurones

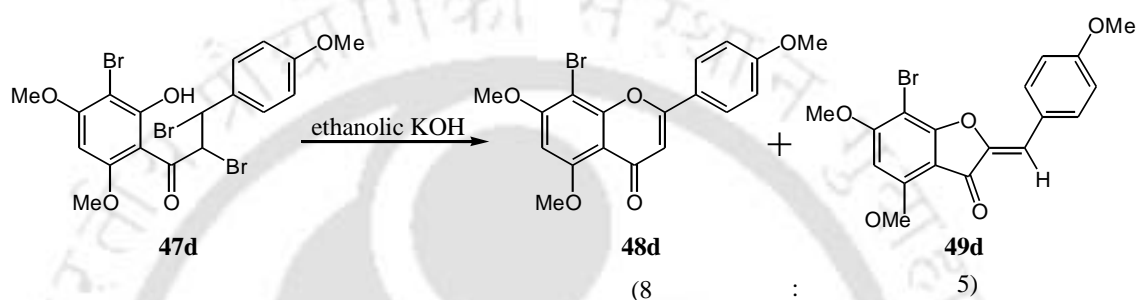
Entry (47)	Substituents	Products composition (%)	
		Flavone (48)	Aurone (49)
a	R = Ac, R ₁ = R ₂ = R ₄ = H, R ₃ = OMe	89	11
b	R = Ac, R ₁ = Br, R ₂ = R ₄ = H, R ₃ = OMe	46	54
c	R = R ₄ = H, R ₁ = Br, R ₂ = R ₃ = OMe	54	46
d	R = H, R ₁ = Br, R ₂ = R ₃ = R ₄ = OMe	62	38

Next, Donnelly *et al* were interested again to see the effect of substituents in the ring B particularly at the position 4 of the chalcone dibromide for the preparation of flavone. Prior to their investigation, Auwers and Anschutz found²⁵ that the chalcone dihalides containing substituent at the 2- or 4-position of the ring B provided flavones and/or aurones, on treatment with aqueous ethanolic alkali. In the mean time, Wheeler and Gowan²⁶ modified the reaction condition to get either flavone or aurone from the chalcone dihalide having substituent at the 4-position. They have noticed that the product flavone **41b** predominates if the reaction is carried out in an ethanolic suspensions of KOH at room temperature, whereas aurone **42b** predominates if the reaction is carried out in a warm ethanolic KOH solution, as shown in scheme 20.

**Scheme 20**

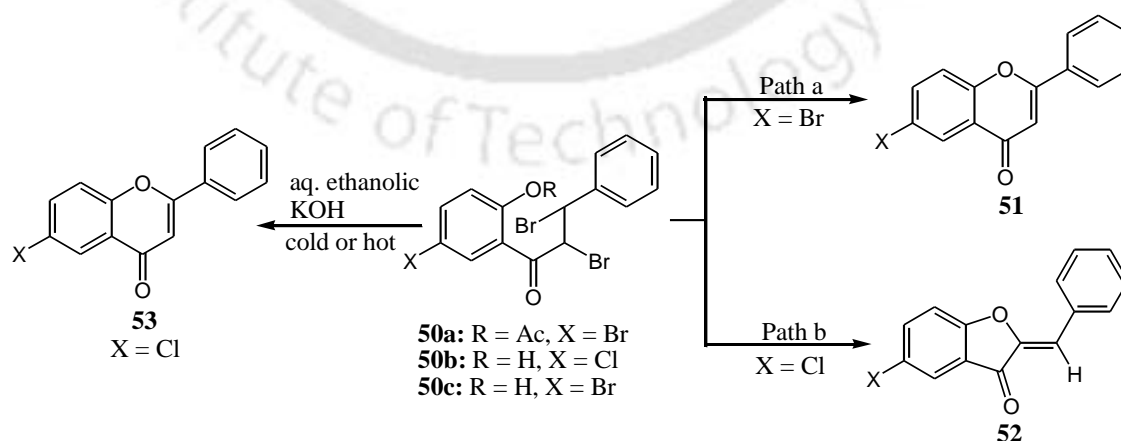
In continuation of their study to examine the effect of ring substituents of chalcone dihalides, Donnelly *et al*²⁷ had selected a chalcone dibromide having substituents at 3',4'- and 6'- positions in the ring-A and at the position 4 in ring-B such as **47d**. They had

reported that the compound **47d** on treatment with ethanolic KOH at room temperature provided both flavone **48d** and aurone **49d** in the ratio 8:5 as depicted in Scheme 21. Interestingly, they have reported that compounds **48d** and **49d** are having nearly the same melting point. Perhaps, they have wrongly assigned the compound 8-bromo-4',5,7-trimethoxyflavone (**48d**) on the basis of melting point, which is merely 2 °C different from the aurone **49d**.



Scheme 21

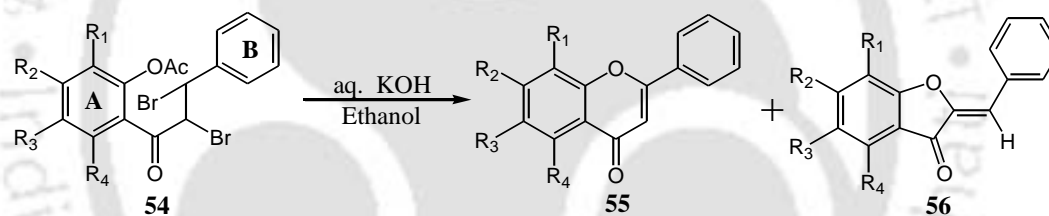
Again, Donnelly and his co-workers²⁸ were interested to find out the effect of substituent at the 5'- position in ring A of chalcone dihalides. By the time, Konstanecki and Ludwig²⁹ found that 2'-acetoxy-5'-bromochalcone dibromide (**50a**) on treatment with aqueous NaOH solution (path a, scheme 22) provided 6-bromoflavone (**51**). On the other hand, Shah and Parikh³⁰ reported that the closely related compounds 5-chloro-2'-hydroxychalcone dibromide (**50b**) under similar reaction condition (path b, scheme 22) gave the corresponding aurone **52**.



Scheme 22

However, by changing the base from NaOH to KOH, Donnelly *et al* were able to prepare²⁸ 6-bromoflavone (**51**) and 6-chloroflavone (**53**) from the compound **50b** and **50c**, respectively, as shown in scheme 22. From these results, it is obvious that the substituent at 5'- position does not have any effect for the formation of flavone or aurone.

After studying a wide variety of chalcone dibromides such as 3'-substituted, 6'-substituted and 3',6'-disubstituted chalcone dibromides, Donnelly frustrated to scrutinize the cyclisation of chalcone dihalides containing substituent at 3'-, 4'- and 6'-positions of ring-A, as shown in scheme 23. They observed³¹ that if there is an additional substituent at 4'- position, there is an increase in the yield of aurone. For instance, if there is a methoxy group at 4'-position of **54c** (\equiv **54d**), the percentage of aurone is increased from 12.3% to 20%, as mentioned in table 2. From this study, we may conclude that a substituent at 4'- position of chalcone dihalide gives only insignificant amount of aurone.



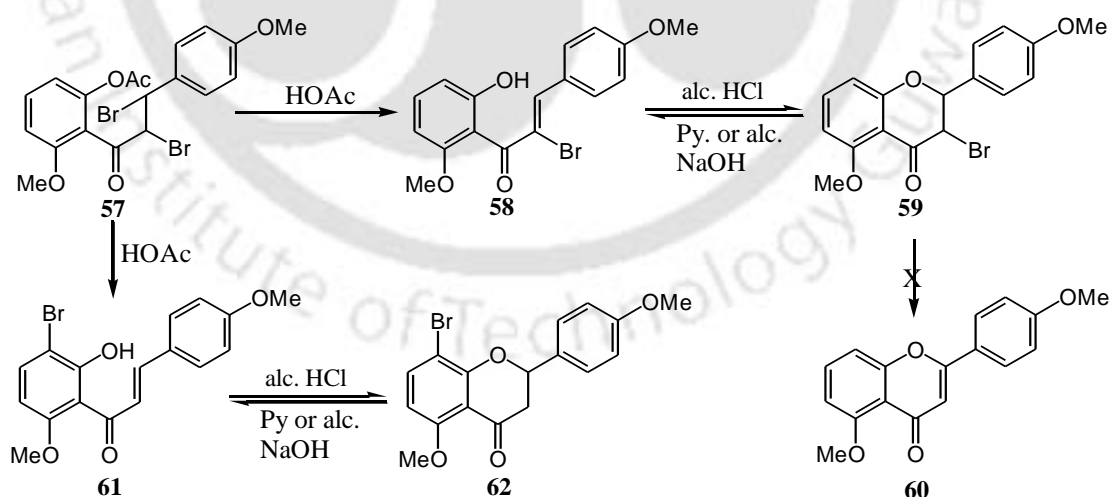
Scheme 23

Table 2: Effect of ring substituents in the formation of flavone and aurone

Entry (54)	Substituent	Flavone (%) (55)	Aurone (%) (56)
a	R ₁ = R ₃ = Br, R ₂ = R ₄ = H	58.5	0.0
b	R ₁ = R ₂ = R ₃ = H, R ₄ = OMe	98.2	1.4
c	R ₁ = Br, R ₂ = R ₃ = H, R ₄ = OMe	43	12.3
d	R ₁ = Br, R ₂ = R ₄ = OMe, R ₃ = H	42	20

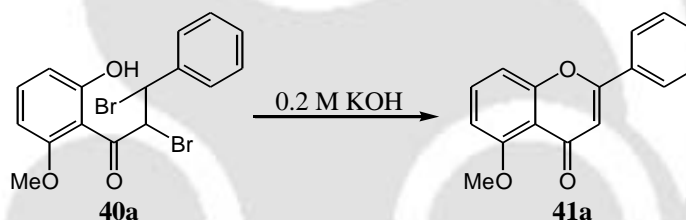
Pendse³² was motivated to examine the cyclisation of chalcone dihalide having substituent at 4 and 6'-position under acidic conditions since both 4-substituted chalcone dihalide **40a** or 6'-substituted chalcone dihalide **40b** provide preferentially aurone over flavone under alkaline conditions as mentioned earlier in scheme 17.

Therefore, he had selected the chalcone dihalide having the substituents at both 4- and 6'-positions for his investigation under acidic condition. He reported that the compound 2'-acetoxy-4,6'-dimethoxychalcone dibromide (**57**) on reaction with acetic acid gave α -bromo-2'-hydroxy-4,6'-dimethoxychalcone (**58**), which on cyclisation with alcoholic HCl provided an epimeric compound 3-bromo-4',5-dimethoxyflavanone (**59**). However, he was unable to prepare the flavone **60** from **59** by dehydrobromination on treatment with alkali. So, he suggested that the compound **59** preferably undergoes ring opening rather than dehydrobromination to provide **58** due to its inherent stability under basic conditions. Donnelley got confused by the unexpected stability of the compound **58** in base and its surprising formation—instead of 4',5-dimethoxyflavone (**60**), because the α -bromo chalcone **58** is the probable intermediate for the synthesis of flavone as proposed by Kostanecki.²⁰ He found³³ that under similar reaction conditions, the chalcone dibromide **57** underwent deacetylation, debromination followed by nuclear ring bromination and ultimately provided compound **61**, which on cyclisation gave flavanone **62** instead of compound **59** as mentioned in scheme 24. Therefore, Pendse had wrongly assigned the compound **62** as **59**.



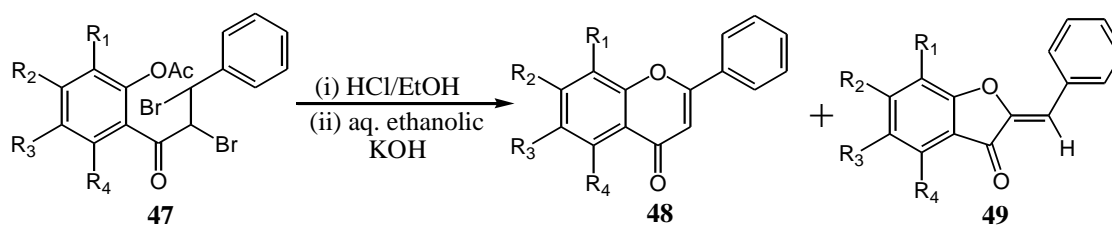
Scheme 24

As per literature report as discussed above, we found that the ring substituted flavones particularly 5-alkoxy and 5,7-dialkoxyflavones, which are widely distributed in nature, can not be accessed readily from their respective chalcone dihalides either by base or acid catalyzed cyclisation (scheme 17 and 18). However, Wheeler and Gowan had shown²⁶ that 4'-alkoxyflavone (**41b**) can be achieved from the corresponding chalcone dihalide (**40b**) if the reaction is performed in cold condition with base rather than in refluxing conditions (shown in scheme 20). Subsequently, Donnelly and his coworkers³⁴ had overcome the preparation of 5-alkoxy flavones by tuning the reaction condition mainly by lowering the base concentration in the cyclisation step. They had optimized the reaction condition and came to conclusion that an approximately 0.2 M base concentration is most suitable base concentration to get the expected product flavone (**41a**) in good yield, as mentioned in scheme 25.



Scheme 25

After their successful result, Donnelly and his co-workers had attempted³⁵ to synthesize different ring substituted flavones exclusively by involving 0.2 M KOH solution. In addition, they were also interested to investigate the effect of base concentrations in the cyclisation of chalcone dibromide. After several experiments on the cyclisation of different substituted chalcone dihalides under various base concentrations (scheme 26), they came to conclusion that in higher base concentration the formation of aurone is favored. The details of the product compositions under different base concentrations, as observed by them, are presented in table 3. It is clear from their observation that flavones were obtained in maximum composition when the cyclisation was performed in 0.2 M KOH solution only.



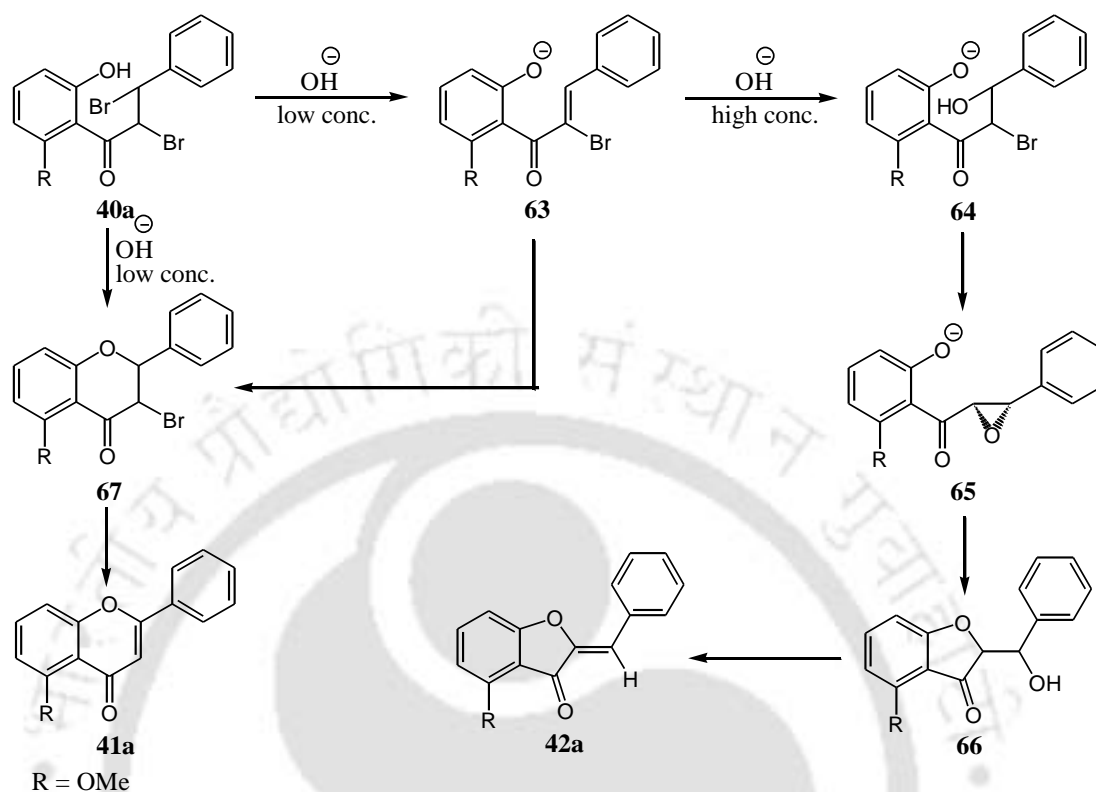
- a** : R₁ = R₂ = R₃ = H, R₄ = OMe
b : R₁ = Br, R₂ = R₃ = H, R₄ = OMe
c : R₁ = R₃ = H, R₂ = R₄ = OMe
d : R₁ = Br, R₃ = H, R₂ = R₄ = OMe

Scheme 26

Table 3: Product composition of flavones and aurones under different base conc.

Added base conc.	Product composition of flavones and aurones							
	48a	49a	48b	49b	48c	49c	48d	49d
0.2 M	100.0	0.0	100.0	6.7	96.4	5.7	100.0	0.0
1.0 M	100.0	3.7	88.9	13.3	94.6	7.6	81.4	5.5
4.0 M	79.0	6.5	59.1	11.5	91.4	12.0	66.4	22.5
10.0 M	72.7	15.6	-	-	68.0	24.9	28.0	57.1

In support for the formation of flavone, they proposed the mechanism as follows: the chalcone dihalide **40a** first undergoes dehydrobromination to form α -bromo phenoxide ion intermediate (**63**). At lower base concentration, the intermediate **63** undergoes intramolecular Michael type reaction by the phenoxide ion to give 3-bromoflavanone (**67**), which on dehydrobromination provides flavone (**41a**). The compound **41a** might also be obtained from **40a** by direct intramolecular nucleophilic substitution reaction by the generated phenoxide ion preferably at the β -position followed by dehydrobromination.



Scheme 27

In favor of the formation of aurones they proposed that at higher base concentration, there is a competition between the intermolecular Michael type reaction due to the presence of excess of hydroxide ion and the intramolecular Michael type reaction by the phenoxide ion in which the former predominates to provide bromohydrin intermediate (**64**). The intermediate **64** is then cyclised to the hydrated aurone **66** and finally aurone **42a** by dehydration.

Then, Donnelly *et al* were inspired to examine³⁶ the cyclisation of α -bromo chalcone under different base concentrations because they assumed α -bromo chalcone anion **63** as one of the intermediates during the cyclisation of chalcone dihalide **40a**. They have studied thoroughly and observed that α -bromo chalcone (which is a mixture *cis* and *trans* isomer such as **68** and **69**) gives preferably flavone in lower base concentration. In addition, they have also investigated the cyclisation of *cis* α -bromo chalcone **68** and *trans* α -bromo chalcone **69** individually at different base concentrations. They found that *cis* isomer **68** gave flavone as exclusive product, whereas the *trans* isomer gave little amount

of aurone, even at lower base concentration. However, at higher base concentration, both *cis* and *trans* isomers provide mixture of flavone **48c** and aurone **49c** as mentioned in scheme 28. Interestingly, the *trans* isomer (which is the major product during dehydrobromination of chalcone dibromide **47c**) gives almost equal amount of **48c** and **49c** at higher base concentration. So, it is very difficult to get either flavone or aurone exclusively from α -bromochalcones since the thermodynamically stable *trans* isomer is obtained as major product after dehydrobromination of the chalcone dihalide. From these observations it is quite clear that α -bromochalcone is a suitable precursor for the synthesis of flavone at lower base concentration. Unfortunately, it is not a good precursor for the synthesis of aurone even at higher base concentration as mentioned in table 4.

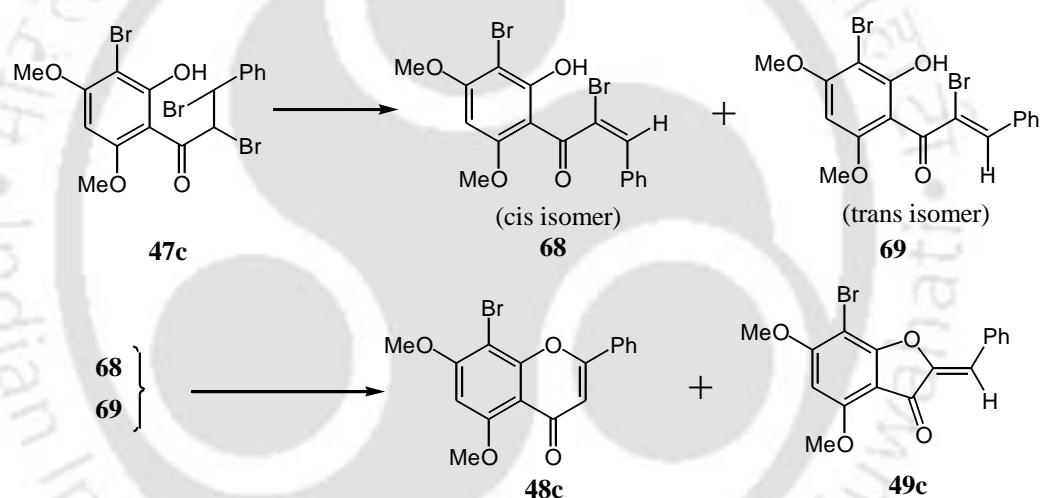


Table 4: Effect of base conc. on the *cis* and *trans* α -bromochalcone

Base conc.	α -Bromochalcone	Product composition	
		Flavone (48c)	Aurone (49c)
0.2 M	68	100.0	0.0
0.2 M	69	99.7	0.3
4.0 M	68	88.7	11.3
4.0 M	69	56.1	43.9

From the above literature review it is evident that 2'-hydroxy chalcone dibromides are suitable building blocks (which have to be prepared from 2'-hydroxy chalcones by bromination involving molecular bromine) for the synthesis of flavones without having any substituent either in ring-A or ring-B or both. This strategy was first formulated by Konstanecki and his group.²⁰ Unfortunately, various hydroxy substituted flavones, which are naturally occurring as well as biologically active can not be accessed easily by this route because they undergo nuclear ring brominations under the above mentioned reaction conditions. Again, such reaction sometimes lead to unwanted side product aurone during cyclisation, which was already observed by Donnelly and his group.³⁵ That is why, this route (which is based on bromination of 2'-hydroxy chalcones followed by cyclisation with a base) has not been exploited much for the synthesis of hydroxy substituted flavones. Therefore, it appears that substituted 2'-hydroxy chalcone is the most appropriate starting material for flavone synthesis. From Donnelly and his group's exhaustive studies of 2'-hydroxy chalcone dibromides and α -bromo-2'-hydroxy chalcones, we have realized that α -bromo-2'-hydroxy chalcones are the more appropriate synthons in comparison to chalcone dihalides for the synthesis of naturally occurring flavones. However, they have also observed that between the two α -bromo chalcones, *cis* isomer is a better choice for flavone synthesis. Interestingly, the *trans* isomer, being thermodynamically more stable, is the major product obtained after dehydrobromination of chalcone dihalides. Therefore, it is obvious that overall chemical yield of flavone would always be lower.

From the foregoing overview it emerges that there still exists a few problems associated with the synthesis of flavone, particularly hydroxy substituted flavone, either from 2'-hydroxy chalcone dibromide or α -bromo chalcone. Therefore, we have chosen the other part of the research problem to develop a new methodology for the synthesis of flavone from α -bromo chalcone. Some of the aspects of the methodology to be addressed are clean synthesis, high yield and selectivity, and mild reaction conditions.

CHAPTER 1

A BRIEF REVIEW ON THE IMPORTANCE OF α -BROMOENONES AND THEIR PREPARATION, SYNTHESIS OF FLAVONE FROM CHALCONE BY BROMINATION FOLLOWED BY CYCLISATION

REVIEW OF LITERATURE



Dedicated to my beloved mother

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY, GUWAHATI
INDIA

CERTIFICATE-I

This is to certify that Mr. Gopal Bose has satisfactorily completed all the courses required for the Ph. D. degree programme.

These courses include:

CHM 601	Physical Methods in Chemistry
CHM 610	Organometallics
CHM 620	Art in Organic Synthesis
CHM 621	Newer Reagents in Organic Synthesis

Mr. Gopal Bose successfully completed his Ph. D. qualifying examination in March 1998.

(Professor M. K. Chaudhuri)
Head
Department of Chemistry
I. I. T. Guwahati

Dr (Mrs.) A. Paul
Secretary
Departmental Post Graduate Committee
Department of Chemistry
I. I. T. Guwahati



Indian Institute of Technology, Guwahati
North Guwahati, Guwahati, 781 039, India

Tel. No.: 0091-361-690321-8 extn.2096

Fax No.: 0091-361-690762

E. mail: atk@iitg.ernet.in

atk@postmark.net

Dr. Abu T. Khan

Associate Professor, Department of Chemistry

CERTIFICATE – II

Dated: March 20, 2002

This is to certify that Mr. Gopal Bose has been working under my supervision since September 9, 1997. I am forwarding his thesis entitled “INVESTIGATION OF BROMINATION REACTIONS USING ORGANIC AMMONIUM TRIBROMIDE AND THEIR APPLICATIONS TOWARDS BIOACTIVE NATURAL PRODUCTS SYNTHESIS” 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.

(Dr. A. T. Khan)

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology, Guwahati, India under the guidance of Dr. Abu T. Khan.

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.

Guwahati

Gopal Bose

February 28, 2002

INDIAN INSTITUTE OF TECHNOLOGY, GUWAHATI

Ph. D. GRADE CARD

ROLL NO. : 974504
Name : Gopal Bose

DEPT. : Chemistry

Semester (July – November, 1997)

Course	Course Name	Credit	Grade
CHM 601	Physical Methods in Chemistry	6	AB
CHM 610	Organometallics	6	BB
CHM 620	Art in Organic Synthesis	6	AA
CHM 621	Newer Reagents in Organic Synthesis	6	AB

Semester Performance Index (S. P. I) : 9.00

Cumulative Performance Index (C. P. I) : 9.00

Date:

Assistant Registrar (Academic)

ACKNOWLEDGEMENTS

The author takes this opportunity to express his deepest sense of gratitude to his supervisor Dr. Abu T. Khan, Associate Professor, Department of Chemistry, Indian Institute of Technology, Guwahati for his able guidance, helpful discussion, boundless encouragement and invaluable suggestions, and due attention throughout the course of this investigation and providing laboratory facilities that enabled him to complete the thesis work.

The author is also profoundly grateful to Professor Mihir K. Chaudhuri, Head and Dean of Students' Affairs, Department of Chemistry, I.I.T. Guwahati, for his constant help, co-operation and suggestion throughout the course of this work.

Acknowledgement of the author will be incomplete if the author does not thank to Dr. Bhisma K. Patel and Dr. Nikhil Guchhait for their help and relentless encouragements. The author also acknowledges all other faculty members and staff of the department for their continuous co-operation.

The author highly indebted to Dr. Nabin C. Barua, Dr. Jadab C. Sharma and Dr. Manobjyoti Bordoloi, Scientists, Natural Products Chemistry Division, Regional Research Laboratory, Jorhat; Prof. K. C. Majumdar, Department of Chemistry, Kalyani University and Professor A. Srikrishna, Department of Organic Chemistry, Indian Institute of Science, Bangalore for helping him in recording IR, $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectral measurements.

The author expresses deep sense of gratitude to Pankaj da, Dipak da, Ejabul, Priti, Deepa di, Tridib, Devasish, Alam, Sudipta, Upasana, Subhajit, Amrit da, Gopinath, Sarala, Arup, Akshay Pattnayak, Dibakar, Panchanan, Indrajit, Manoranjan, Sidananda, Chandan, Lokesh, Pankaj, Sabeena, Pompei Hazarika, and all other friends and juniors for their active co-operation on various pertinent issues. The spontaneous help that they afforded on various matters at different stages of Ph. D. work will always be thankfully remembered. Sujit da and Siddhartha are specially acknowledged for their immense moral support and help during the entire tenure of Ph. D. work.

The author is thankful to the Gauhati University, RSIC-Shillong, CDRI-Lucknow, Indian Institute of Chemical Biology-Kolkata, Bose Institute-Kolkata, Indian Institute of Chemical Technology-Hyderabad for recording IR, $^1\text{H-NMR}$ and mass spectra.

Acknowledgement

Financial help from the Indian Institute of Technology, Guwahati through the institute fellowship and the Council of Scientific and Industrial Research, New Delhi through Senior Research Fellowship is duly acknowledged.

All the family members of the author are thankfully acknowledged for their invaluable support.

Above all, the author expresses his gratefulness to his mother without whose moral support and wishes the completion of this work could not have been possible.

(Gopal Bose)

SUMMARY

This dissertation describes the successful and unsuccessful results for the preparation of various α -bromoenones from their corresponding acyclic and cyclic enones using organic ammonium tribromides; synthesis of various ring substituted flavones and aurones (which are structurally isomeric with flavones) from their corresponding 2'-acetoxychalcones by bromination, followed by cyclisation as well as synthesis of 7-bromoaurones and 8-bromoflavones from 2'-hydroxychalcones.

Chapter 1 of this dissertation includes the review on α -bromoenone, α -bromo-2'-acetoxychalcone and their applications towards the synthesis of flavone.

Chapter 2 in part I describes the results of our successful efforts on the preparation of both acyclic and cyclic α -bromoenones from the corresponding enones in one pot, by bromination using organic ammonium tribromide (OATB), followed by dehydrobromination by employing a base such as K_2CO_3 . Thus, various acyclic enones **74a-g** on bromination with cetyltrimethylammonium tribromide (CetTMATB) in CH_2Cl_2 followed by dehydrobromination with K_2CO_3 furnish α -bromoenones **76a** (68%), **76b** (70%), **76c** (70%), **76d** (85%), **76e** (69%), **76f** (78%) and **76g** (68%) as E/Z mixture, which are determined by GC. On the other hand, the same substrates **74a-g** on reaction with *n*-tetrabutylammonium tribromide (TBATB) under identical reaction conditions afford α -bromoenones **76a** (71%), **76b** (75%), **76c** (72%), **76d** (88%), **76e** (70%), **76f** (81%) and **76g** (70%) as E/Z mixture. From the reaction time we may conclude that TBATB is relatively better brominating reagent than CetTMATB. Similarly, a wide variety of cyclic enones **77a-e** are successfully transformed into the corresponding cyclic α -bromoenones **78a** (70%/65%), **78b** (68%/72%), **78c** (80%/75%), **78d** (72%/75%), **78e** (65%/68%) involving CetTMATB/ TBATB in the presence of K_2CO_3 under identical reaction conditions.

Chapter 2 in part II describes bromination of various 2'-acetoxychalcones using TBATB, which are then transformed to the α -bromo-chalcones and finally utilized them for flavone synthesis. Various 2'-acetoxychalcones **85a-f** are brominated with TBATB

Summary

in CH₂Cl₂ to provide dibromo compounds **86a** (75%), **86b** (70%), **86c** (78%), **86d** (80%), **86e** (75%) and **86f** (80%) in good yields. Then, the compounds **86a-f** are converted to the corresponding α -bromochalcones **87a** (80%), **87b** (80%), **87c**(90%), **87d** (88%), **87e** (83%), **87f** (85%) by dehydrobromination on treatment with Et₃N or K₂CO₃, which are finally cyclised to the flavones **88a-f** on treatment with 0.1 M NaOMe solution. The flavones **88a** (60%), **88b** (78%), **88c** (70%), **88d** (65%), **88e** (88%) and **88f** (74%) are obtained. Thus, we have demonstrated a new synthetic protocol for the synthesis of various substituted flavones which are not accessible earlier by this route.

Chapter 3 in part I of this dissertation describes the literature survey on the synthesis of aurone and 7-bromoaurone.

Chapter 3 in part II of this dissertation describes the novel synthesis of a wide variety of substituted aurones from 2'-acetoxychalcones by bromination employing TBATB under different reaction conditions and finally cyclisation. Various substituted 2'-acetoxychalcones **29a-f** on reaction with TBATB in CH₂Cl₂-MeOH (5:2) solvent system afford 2'-acetoxy- α -bromo- β -methoxy-dihydrochalcones **30a** (80%), **30b**(75%), **30c** (85%), **30d** (84%), **30e** (86%) and **30f** (80%), respectively. The cyclisation of brominated products **30a-f** on reaction with 2.0 M KOH in aqueous ethanol provide the expected aurones **31a** (85%), **31b** (91%), **31c** (87%), **31d** (95%), **31e** (86%) and **31f** (87%) as sole products.

Chapter 3 in part III of this dissertation describes our successful efforts on the synthesis of 7-bromoaurone and unsuccessful efforts on the synthesis of 8-bromoflavones from 2'-hydroxychalcones. Various substituted 2'-hydroxychalcones **26b-f** on reaction with TBATB in CH₂Cl₂-MeOH (5:2) solvent system give $\alpha,3'$ -dibromo-2'-hydroxy- β -methoxy-dihydrochalcones **27b** (73%), **27c**(74%), **27d** (82%), **27e** (90%) and **27f** (75%) in good yields. The desired products 7-bromoaurones **28b** (92%), **28c** (77%), **28d** (68%), **28e** (44%) and **28f** (72%) are obtained from compounds **27b-f** on cyclisation with 2.0 M KOH in aqueous ethanol.

contents

	pages
Chapter 1 A brief literature survey on the preparation of α -bromo enones and their applications, bromination of chalcones and their applications towards flavone synthesis.	--1 – 18
Chapter 2	
Part I Bromination of various acyclic and cyclic enones to the corresponding α -bromo enones using organic ammonium tribromide (OATB)	
A: Present work (Discussion)	--19 – 24
B: Present work (Experimental)	--25 – 40
Part II Bromination of various 2'-acetoxychalcones to the corresponding α -bromo chalcones using <i>n</i> -tetrabutylammonium tribromide (TBATB) and their applications towards flavone synthesis	
A: Present work (Discussion)	--41 – 46
B: Present work (Experimental)	--47 – 75
C: References	--76 – 80
Chapter 3	
Part I A brief review on the preparation of aurones and 7-bromoaurones	--81 – 85
Part II Bromination of a wide variety of 2'-acetoxychalcones to the corresponding 2'-acetoxy- α -bromo- β -methoxy-dihydrochalcones and their applications towards aurone synthesis.	
A: Present work (Discussion)	--86 – 89
B: Present work (Experimental)	--90 – 103
Part III Bromination of various 2'-hydroxychalcones employing <i>n</i> -tetrabutylammonium tribromide (TBATB) and their application towards 7-bromoaurone synthesis.	
A: Present work (Discussion)	--104 – 106
B: Present work (Experimental)	--107 – 120
C: References	--121 – 122
Appendix Conclusion and future scope of the work List of Author's Publications	

GENERAL REMARKS

The present investigations were carried out in the Department of Chemistry, Indian Institute of Technology-Guwahati, Guwahati -781 039, Assam, during the period September 9, 1997 to December 31, 2001.

The analytical samples were routinely dried *in vacuo* at 60 °C for 8 hours. Column chromatography was carried out with silica gel of 60-120 mesh (Merck, SRL or Qualigen) for purifications of reaction mixture. After purification, the solvent was usually removed in rotavapour using Buechi R-114V instrument. In TLC experiments, silica gel G (SRL) or silica gel GF 254 (SRL) were employed as adsorbent and spots were detected by staining with iodine vapour or under UV light or charring 10% MeOH in Conc. H₂SO₄. The ultraviolet spectra were recorded on a Hitachi U-2001 instrument. ¹H-Nuclear Magnetic Resonance spectra and ¹³C-Nuclear Magnetic Resonance spectra were recorded on Bruker (250 MHz), Bruker (300 MHz), Jeol (400 MHz), Bruker (400 MHz) and Bruker (500 MHz) instruments using tetramethyl silane (TMS) as an internal standard and CDCl₃ as solvent. The chemical shift values are expressed in δ scale and their multiplications are described using the following symbols: s-singlet, d-doublet, t-triplet, q-quartet, quin-quintet, m- multiplet, br-broad, brs-broad singlet.

The infrared spectra were recorded in KBr pellets or in liquid film on a Perkin Elmer 1330 and Nicolet Impact 410 instruments, respectively. Mass spectra were recorded on a Jeol JMS- D 300 mass spectrometer from CDRI, Lucknow. Melting points were determined on a sulphuric acid bath or Buechi B-540 instrument and are uncorrected. The elemental analyses were done at Natural Products Chemistry Division, Regional Research Laboratory-Jorhat, Jorhat-785 006, Assam and Department of Chemistry, IIT-Guwahati, using Perkin Elmer CHNS/O-2400 instrument. All the solvents and reagents employed were purified using recommended procedures in literature.