Chapter 1

Serendipitous one-pot synthesis of

3,4-dihydro-3-hydroxyisochroman-1-one from indene

and synthesis of its novel acetal derivatives
1.1 Abstract

One-pot synthesis of 3,4-dihydro-3-hydroxyisochroman-1-one (lactol) 20 from indene using tungstic acid-hydrogen peroxide is reported and a plausible mechanism of its formation is also proposed by different experimental studies. The lactol was further converted into its novel acetal derivatives 46 (a-h).
1.2 Introduction

The dihydroxylation of alkenes is one of the most important transformations in organic synthesis. The product obtained from the dihydroxylation of alkene i.e. 1,2-diol plays an important role in the production of numerous commodity materials which find wide application in all areas of life for example polymers, fine chemicals, pharmaceuticals, cosmetics, fragrant, photographic plates, lubricants, cleaners, etc. The diol compounds are also employed as solvents and additives in various synthetic reactions.

The 1,2-diol is found as a basic structural unit in many natural products, that exerts a wide spectrum of biological and pharmaceutical activities such as syributin\textsuperscript{1} acts as nonproteinaceous C-glycosidic elicitors; lentiginosine\textsuperscript{2} 2 inhibits the amyloglucosidase enzyme and shows good glycosidase inhibitory activity; anthopleurine\textsuperscript{3} 3 is the alarm pheromone of the sea anemone; circumcin A\textsuperscript{4} 4 possesses neuroactivity; dopamine\textsuperscript{5} 5 is a neurotransmitter involved in the regulation of a range of physiological functions, including motor control, cognition and the ability to experience pleasure. (Figure 1.1)

![Structures of some bioactive natural products](image)

**Figure 1.1:** Structures of some bioactive natural products having 1,2-diol moiety
The compounds containing 1,2-diol moiety have enormous synthetic potential to act as a precursor in the synthesis of various natural products like multistriatin⁷ 6, brevicomin⁸ 7, disparlure⁹ 8, etc. (Figure 1.2)

![Chemical structures of Multistriatin 6, Brevicomin 7, and Disparlure 8](image)

**Figure 1.2:** 1,2-diol mediated synthesis of natural products

Owing to its importance, a number of methods have been developed for the synthesis of 1,2-diols from various alkenes such as Prevost reaction, Woodward reaction, Upjohn dihydroxylation, Sharpless dihydroxylation and many more.¹⁰ Depending on the reagent used, *cis*-diol or *trans*-diol is formed.

Generally, potassium permanganate, osmium tetroxide and iodine-silver benzoate are used for the synthesis of *cis*-diols from alkenes.¹¹ Among the reagents available, none have achieved more success than osmium tetroxide for the synthesis of *cis*-diols. A variety of co-oxidants have been used in the conjugation with osmium tetroxide in order to improve this transformation such as hydrogen peroxide,¹² metal chlorates,¹³ *t*-butyl hydroperoxide,¹⁴ *N*-methylmorpholine *N*-oxide¹⁵ and molecular oxygen.¹⁶ Despite of the widespread popularity of osmium tetroxide, the toxicity, high cost, volatile nature and high levels of inorganic waste are limitations of its extensive uses.¹⁷ Therefore, the metal catalysts like palladium,¹⁸ iron,¹⁹ ruthenium,²⁰ manganese,²¹ copper,²² cobalt²³ and molybdenum²⁴ have been used to convert alkenes into *cis*-1,2-diols as an alternate pathways. A variety of peroxy acids are also employed for the synthesis of *trans*-diols from alkenes such as performic acid, perbenzoic acid, potassium peroxymonosulfate and others.²⁵

The significance of HIV protease inhibitors in the treatment of acquired immune deficiency syndrome (AIDS) is now well known in the literature.²⁶ The crixivan ⁹, a leading drug was developed for the treatment of AIDS. The *cis*-1-amino-
2-indanol 10 is an important synthon for the synthesis of crixivan which can be synthesized from trans-1,2-indan diol 11.26 (Scheme 1.1)

![Chemical structure of crixivan and related compounds]

**Scheme 1.1: trans-1,2-indandiol as precursor**

Numerous methods have been developed for the synthesis of trans-1,2-indandiol 11 either chemically or biologically.27-29 Whalen *et al*28 have used Prevost dihydroxylation for the synthesis of trans-1,2-indandiol 11. Asano *et al*29 have prepared trans-1,2-indandiol 11 from indene in two steps. The bio-transformation of indene to trans-1,2-indandiol 11 using *Rhodococcus* strain I24 is reported by Sinskey *et al*.27 Though these methods work well, many of them involve use of expensive reagents, tedious workup procedure, toxic effluent.

Tungstic acid and hydrogen peroxide are commercially available reagents. Water is the only byproduct and the tungstic acid is easily recovered after completion of the reaction. The tungstic acid catalyzed trans addition of hydrogen peroxide to alkenes is well known for a long time.30

The first synthesis of trans-1,2-cyclohexane diol 13 using tungstic acid-hydrogen peroxide was reported by Payne *et al* in 1957.31 (Scheme 1.2)

![Chemical structure of trans-1,2-cyclohexane diol synthesis]

**Scheme 1.2: Synthesis of trans-1,2-cyclohexane diol**
Earlier our group has demonstrated the synthetic utility of tungstic acid–hydrogen peroxide to obtain the corresponding trans-diol 15 of (Z,Z)-cyclocta-1,5-diene 14.\(^3\)(Scheme 1.3) (Z,Z)-cyclocta-1,5-diene is known to pose considerable problems in hydroxylation with other hydroxylating agents owing to its propensity towards trans-annular cyclization.\(^3\)

The treatment of this reagent combination with endo-dicyclopentadiene 16 in t-butanol unexpectedly resulted in the formation of novel polycyclic oxetanes (17, 18).\(^3\)(Scheme 1.4)

Our continued interest in the dihydroxylation of olefins prompted us to explore the reaction of indene 19 with tungstic acid-hydrogen peroxide in order to prepare its trans-diol 11 which is an important intermediate for crixivan 9, an HIV protease inhibitor.

1.3 Results and discussion

In pursuing above objective, indene 19 was treated with tungstic acid–hydrogen peroxide in t-butanol for 14h which resulted in the formation of not only


**racemic** indan-trans-1,2-diol 11 but also racemic 3,4-dihydro-3-hydroxyisochroman-1-one (lactols or pseudoacid) 20. (Scheme 1.5)

![Scheme 1.5: Reaction of indene with hydrogen peroxide-tungstic acid](image)

The structures of compounds 11 and 20 were confirmed by mp, FTIR, $^1$H NMR, $^{13}$C NMR, Mass and elemental analysis.

![Scheme 1.6: 5-oxoacids exist as cyclic lactols](image)

During the reaction, the serendipitous formation of lactol encouraged us to investigate its route of formation. Since it is already known that certain 5-oxoacids such as 21 exist as pseudoacids or cyclic lactols 22,34 (Scheme 1.6) it was clear that 20 was formed as a result of cleavage of indene followed by *in situ* cyclization of the intermediate 2-carboxyphenylethanal 24 similar to 21.

To ascertain the source of the lactol 20, a few experiments were carried out. Initially, it was thought that indan-trans-1,2-diol 11 could be giving rise to 20 via 2-carboxyphenylethanal but the treatment of 11 with tungstic acid-hydrogen peroxide at 30°C in t-butanol left it unchanged even after 14 h. It was then contemplated that *cis*-dial of indene could be the source of 20. Thus, indan-cis-1,2-diol 23 was prepared by a reported method35 and was treated with tungstic acid-hydrogen peroxide under the
reaction condition which indeed gave 20 along with 11 in 28% and 63% yields respectively (Scheme 1.7). A similar conversion of 23 to 11 in the presence of nickel at 60°C was reported. It should be noted that the present method (Scheme 1.7) furnishes 11 from 23 in better yield (63%) under milder conditions.

![Scheme 1.7: Reaction of indan-cis-1,2-diol with hydrogen peroxide - tungstic acid.](image)

That the lactol 20 originates from 23 was further confirmed by spiking studies as described below. We added varying amounts of 23, a proposed precursor of 20, to the reaction mixture in order to prove its intermediacy or involvement in the formation of 20. Our contention was supported when enhancement in the yields of 20 and 11 was obtained on treatment of the mixtures of varying amounts of 23 and 19 under reaction condition (Scheme 1.8, Table 1.1).

![Scheme 1.8: Treatment of mixtures of 23 and 19 with hydrogen peroxide-tungstic acid](image)

<table>
<thead>
<tr>
<th>Indan-cis-1,2-diol (23)</th>
<th>Indan-trans-1,2-diol (11)</th>
<th>Lactol (20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of moles added</td>
<td>Rise found in no. of moles</td>
<td>Rise found in no. of moles</td>
</tr>
<tr>
<td>0.007</td>
<td>0.0036 (61.85%)</td>
<td>0.0020 (26.66%)</td>
</tr>
<tr>
<td>0.014</td>
<td>0.0081 (61.81%)</td>
<td>0.0037 (26.95%)</td>
</tr>
<tr>
<td>0.021</td>
<td>0.0155 (61.92%)</td>
<td>0.0056 (26.98%)</td>
</tr>
</tbody>
</table>
These observations also implied that 23 gives rise to lactol 20 via oxidative cleavage followed by cyclization under reaction condition. (Scheme 1.9) Similar cleavage of 11 does not take place during the reaction, perhaps due to the trans geometry of the hydroxyl groups in it.

Lactol scaffold is widely distributed in nature and is found as a core structural unit in various biologically active compounds (Figure 1.3) such as callipeltoside A 25,26 ginkgolides 26,28 dysidiolide 27,29 cladocorans B 28,30 acuminolide 29,31 spongianolide A 30,32 manoalide 31,33 cacospongionolide B 32,34 peniolactol 33,35 Lactols are also employed as important precursors of several compounds such as illudalic acid,46 benzopyran-1-ones,47 caronaldehyde,48 mevalonate and mevaldate.49
In past, lactol unit has been assembled via different routes by various research groups.\textsuperscript{46-50} Boukouvalas et al\textsuperscript{39} has reported the total synthesis of dysidiolide 27 in which lactol unit has been generated by photosensitized oxygenation of furan (Scheme 1.10) and in the same way the lactol units of cladocorans B 28, acuminolide 29, spongianolide A 30, manoalide 31 and cacospongionolide B\textsubscript{2} 32 have also been synthesized.
Many other route are also available in the literature like oxidative cleavage of olefins or diols followed by cyclization using various reagents like sodium metaperiodate, aqueous potassium hydroxide, trifluoroacetic acid, and ozonolysis followed by addition of dimethyl sulphate.

Schöpf and Kühne were the first to report lactol in four steps (Scheme 1.11) and its crystal structure was subsequently reported much later by Valente et al.
Abe et al\textsuperscript{52} have also synthesized the lactol 20 from silyl enol ethers 43 by photoxygenation sensitized by 9,10-dicyanoanthracene (DCA) or bipyridyl (BP) in three steps (Scheme 1.12).

\textbf{Scheme 1.12:} Synthesis of lactol 20 reported by Abe \textit{et al}

To the best of our knowledge, one-pot synthesis of 3,4-dihydro-3-hydroxyisochroman-1-one 20 from indene 19 under such mild conditions (Scheme 1.5) is hitherto unknown in the literature.
Literature survey revealed that various lactol derivatives show wide variety of biological activities, for example dysidiolide 27 acts as the inhibitor of phosphatase CDC25A and inhibits the growth of A-549 human lung carcinoma, cladocorans B 28 are used as inhibitor of protein phosphatase CDC25A, acuminolide 29 displays cytotoxic activity in human cancer cell lines and cultured P388 cells, spongianolide A 30 inhibits proliferation of the mammary tumor cell line MCF-7, manoalide 31 is an irreversible inhibitor of phospholipase A2 (PLA2), cacospiongionolide B 32 shows a significant activity on recombinant human synovial PLA2, illudalic acid is a potential human leukocyte common antigen-related (LAR) phosphatase inhibitor.

![Scheme 1.13: Synthesis of acetal derivatives of lactol](image)

We also found that the acetals of nepetalic acid exhibit prominent mosquito repellency. These interesting biological properties of lactol derivatives impelled us to prepare the acetal derivatives 46(a-h) (Scheme 1.13) and examine their antimicrobial activity as well as mosquito pathogenicity. As mentioned earlier, the lactols are known to coexist as open chain structure having free carboxylic acid functionality that can react with alcohols to form acetals.

The structures of acetal derivatives 46(a-h) were also confirmed by mp, FTIR, $^1$H NMR, $^{13}$C NMR, mass and elemental analysis. The FTIR spectrum of 46a showed bands at 1628, 1464 cm$^{-1}$ for aromatic ring and a strong band at 1729 cm$^{-1}$ for the carbonyl group. The $^1$H NMR spectrum of 46a displayed triplet of three methyl protons at $\delta$ 1.20, two doublet of doublet at $\delta$ 3.15 and 3.35 for two methylene protons and triplet at $\delta$ 5.55 for one methine proton. The multiplets between $\delta$ 7.2-8.2 showed the presence of four aromatic protons. The $^{13}$C NMR spectrum of 46a exhibited...
signals at δ 15.30 for methyl carbon, at δ 33.71, 65.35 for methylene carbon, at δ 101.14 for methine carbon and at δ 125.04, 127.70, 128.34, 129.97, 134.12 and 136.68 for aromatic carbons along with signal at δ 164.22 for carbonyl carbon. The structure of 46a was further confirmed by its mass spectrum which gave a molecular ion peak at 192. The elemental analysis was in good agreement with the required molecular formula for C₁₁H₁₂O₃ and it was found as C, 68.76; H, 6.23 and calculated; C, 68.74; H, 6.29.

Scheme 1.14: Dehydration of 3,4-dihydro-3-hydroxyisochroman-1-one

The catalyst quantity and the reaction temperature play an important role in the formation of acetal derivatives. It was observed that lactol 20 underwent dehydration by increasing either the temperature or the catalyst quantity beyond 12.5 mol%. (Scheme 1.14) Various acetal derivatives of lactol (46a-h) were prepared to examine the effect of spacer groups on their biological potency.

1.4 Experimental

General

FTIR spectra were recorded on a Shimadzu 8400S FTIR spectrometer using KBr. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker-400MHz NMR spectrometer (100 MHz for ¹³C NMR) using CDCl₃ or DMSO-d₆ (TMS as an internal standard). Mass spectra were obtained on a Shimadzu QP-5050 mass spectrometer. Column chromatography was carried out on Acme’s silica gel (60-120 mesh size) and eluted using mixtures of light petroleum and ethyl acetate. Thin layer chromatography was performed using Acme’s silica gel for TLC and spots were visualized in the iodine vapor. Percentage yields were reported based upon the recovery of starting materials.
The structures of all the compounds were confirmed by their mp, elemental analysis, FTIR, $^1$H NMR, $^{13}$C NMR and mass spectrometric data.

*Synthesis of 2,3-dihydro-1H-indan-trans-1,2-diol and 3,4-dihydro-3-hydroxyisochroman-1-one:*

To a stirred solution of indene (19) (43 mmol) in $t$-butanol (25 ml) was added a suspension of tungstic acid (0.5 g) and hydrogen peroxide (30%, 140 mmol). The reaction mixture was stirred for 14 hrs at room temperature (~30°C). After completion of the reaction (TLC), reaction mixture was filtered through a celite pad to remove the suspended catalyst. The filtrate was diluted with water (20 ml) and extracted with ethyl acetate (4 × 25 ml). The combined organic extracts were washed with water (15 ml), brine (10 ml) and dried over anhydrous sodium sulphate. Removal of solvent and column chromatography of the residue furnished the indan-trans-1,2-diol (11, 39%) and 3,4-dihydro-3-hydroxyisochroman-1-one (20, 16%). Prolonged reaction periods did not appreciably alter the product ratio.

**2,3-Dihydro-1H-indan-trans-1,2-diol (11)**

White crystalline solid (39%), mp. 156-160 °C; IR (ν max, cm$^{-1}$): 3226, 2911, 2849, 1559, 1477, 1458, 1354, 1057, 746, 645; $^1$H NMR: δH 2.74 (dd, 1H, CH$_2$ geminal, $J_1$ = 15.5 Hz, $J_2$ = 7.5 Hz), 3.18 (dd, 1H, CH$_2$ geminal, $J_1$ = 15.3 Hz, $J_2$ = 7.4 Hz), 4.25 (m, 1H, CH–OH), 5.04 (d, 1H, Ar–CH–OH, $J$ = 5.6 Hz), 4.88 and 4.86 (s, 2H, OH, both exchange with D$_2$O), 7.10-7.40 (m, 4H, aromatic H); $^{13}$C NMR: δC 37.69 (CH$_2$), 80.58, 81.10 (CH–OH), 123.89, 124.29, 126.31, 127.40 (aromatic), 138.99, 143.12 (quaternary aromatic). MS (EI): m/z 150(M$^+$). Anal. Calcd for C$_9$H$_{10}$O$_2$: C, 71.98; H, 6.71. Found: C, 71.80; H, 6.74.

**3,4-Dihydro-3-hydroxyisochroman-1-one (20)**

White crystalline solid (16%), mp. 95 °C; IR (ν max, cm$^{-1}$): 3276, 2923, 1702, 1603, 1439, 1393, 1133, 1067, 735. $^1$H NMR: δH 1.70 (broad s, 1H, OH, exchanges with D$_2$O), 3.15 (dd, 1H, CH$_2$, $J$ = 16.6 Hz, $J_2$ = 4.6 Hz), 3.35 (dd, 1H, CH$_2$, $J$ = 16.8 Hz, $J_2$ = 4.2 Hz), 5.95 (t, 1H, CH–OH, $J$ = 4.8 Hz), 7.20-8.20 (m, 4H, aromatic H). $^{13}$C NMR: δC 34.20 (CH$_2$), 96.17 (CH–OH), 124.76, 127.94, 128.66, 130.21 (aromatic), 138.99.

**Synthesis of Acetal derivatives of 3,4-dihydro-3-hydroxyisochroman-1-one 46(a-h):**

To a mixture of the lactol (20) (3.05 mmol) and the alcohol (3.65 mmol) in dry toluene (20 ml) was added conc. H₂SO₄ (0.4 ml) at room temperature under stirring. After completion of the reaction (TLC), solvent was removed and the reaction mixture was neutralized with saturated solution of sodium bicarbonate and extracted using ethyl acetate. The combined organic extracts were washed with water, brine, dried over anhydrous sodium sulphate. Removal of solvent and chromatography of the residue furnished 5 as light yellow liquid.

**3-Ethoxy-3,4-dihydroisochroman-1-one (46a)**

Light yellow liquid (72%), IR (ν_{max}, cm⁻¹): 2946, 2912, 2834, 1729, 1628, 1464, 1274, 1104, 1092, 738; ¹H NMR: δH 1.20 (t, 3H, OCH₂CH₃, \( J = 6.9 \) Hz), 3.15 (dd, 1H, CH₂, \( J_1 = 16.2 \) Hz, \( J_2 = 4.8 \) Hz), 3.35 (dd, 1H, CH₂, \( J_1 = 16.8 \) Hz, \( J_2 = 4.2 \) Hz), 3.70 (m, 1H, OCH₂CH₃), 3.98 (m, 1H, OCH₂CH₃), 5.55 (t, 1H, CH–OR, \( J = 4 \) Hz), 7.20-8.20 (m, 4H, aromatic H). ¹³C NMR: δC 15.30 (OCH₂CH₃), 33.71 (CH₂), 65.35 (CH-OCH₂CH₃), 101.14 (CH-OCH₂CH₃), 125.04, 127.70, 128.34, 129.97 (aromatic), 134.12, 136.68 (quaternary aromatic), 164.22 (C=O). MS (EI): m/z 192(M+). Anal. Calcd for C₁₁H₁₂O₃: C, 68.74; H, 6.29. Found: C, 68.76; H, 6.23.

**3,4-Dihydro-3-propoxyisochroman-1-one (46b)**

Light yellow liquid, IR (ν_{max}, cm⁻¹): 2964, 2933, 2879, 1728, 1610, 1462, 1379, 1271, 1016, 910, 731; ¹H NMR: δH 0.88 (t, 3H, OCH₂CH₂CH₃, \( J = 7.2 \) Hz), 1.60 (m, 2H, OCH₂CH₂CH₃), 3.12 (dd, 1H, CH₂, \( J_1 = 16.3 \) Hz, \( J_2 = 4.4 \) Hz), 3.31 (dd, 1H, CH₂, \( J_1 = 16.6 \) Hz, \( J_2 = 4.6 \) Hz), 3.59 (m, 1H, OCH₂CH₂CH₃), 3.91 (m, 1H, OCH₂CH₂CH₃), 5.57 (t, 1H, CH–OCH₂CH₂CH₃, \( J = 4.4 \) Hz), 7.20-8.20 (m, 4H, aromatic H). ¹³C NMR: δC 15.30 (OCH₂CH₂CH₃), 22.62, 33.41 (CH₂), 71.17 (CH-OCH₂CH₂CH₃), 101.06 (CH-OCH₂CH₂CH₃), 124.93, 127.57, 128.15, 129.90 (aromatic), 133.97, 136.51 (quaternary aromatic), 164.23 (C=O). MS (EI): m/z 206(M+). Anal. Calcd for C₁₂H₁₄O₃: C, 69.88; H, 6.84. Found: C, 69.79; H, 6.88.
3-Butoxy-3,4-dihydroisochroman-1-one (46c)

Light yellow liquid, IR (ν<sub>max</sub>, cm<sup>-1</sup>): 2958, 2935, 2874, 1728, 1610, 1460, 1379, 1271, 1128, 1053, 732, 692. <sup>1</sup>H NMR: δ<sub>H</sub> 0.89 (t, 3H, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, J = 7.2 Hz), 1.30 (m, 2H, OCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.60 (m, 2H, OCH₂CH₂CH₂CH₃), 3.11 (dd, 1H, CH₂, J₁ = 18.2 Hz, J₂ = 4.4 Hz), 3.30 (dd, 1H, CH₂, J₁ = 18.6 Hz, J₂ = 4.6 Hz), 3.62 (m, 1H, OCH₂CH₂CH₂CH₃), 3.97 (m, 1H, OCH₂CH₂CH₂CH₃), 5.56 (t, 1H, CH–OCH₂CH₂CH₂CH₃, J = 4.1 Hz), 7.20-8.20 (m, 4H, aromatic H). <sup>13</sup>C NMR: δ<sub>C</sub> 13.78 (OCH₂CH₂CH₂CH₃), 19.09, 31.36, 33.44 (CH₂), 69.39 (CH-OCH₂CH₂CH₂CH₃), 101.06 (CH-OCH₂CH₂CH₂CH₃), 124.96, 127.58, 128.13, 129.95 (aromatic), 133.95, 136.49 (quaternary aromatic), 164.21 (C=O). MS (EI): m/z 220(M<sup>+</sup>). Anal. Calcd for C₁₅H₁₈O₃: C, 70.89; H, 7.32. Found: C, 70.81; H, 7.26.

3,4-Dihydro-3-(pentyl(tert-butoxy))isochroman-1-one (46d)

Light yellow liquid, IR (ν<sub>max</sub>, cm<sup>-1</sup>): 2956, 2933, 2872, 1732, 1620, 1460, 1383, 1271, 1136, 1072, 732. <sup>1</sup>H NMR: δ<sub>H</sub> 0.86 (t, 3H, OCH₂(CH₂)₅CH₃, J = 6.4 Hz), 1.28 (m, 4H, OCH₂CH₂(CH₂)₅CH₃), 1.56 (m, 2H, OCH₂CH₂(CH₂)₅CH₃), 3.10 (dd, 1H, CH₂, J₁ = 17.4 Hz, J₂ = 4.4 Hz), 3.29 (dd, 1H, CH₂, J₁ = 17.1 Hz, J₂ = 4.2 Hz), 3.60 (m, 1H, OCH₂(CH₂)₅CH₃), 3.94 (m, 1H, OCH₂(CH₂)₅CH₃), 5.55 (t, 1H, CH–OCH₂(CH₂)₅CH₃, J = 4 Hz), 7.20-8.20 (m, 4H, aromatic H). <sup>13</sup>C NMR: δ<sub>C</sub> 12.37 (OCH₂(CH₂)₅CH₃), 22.50, 27.91, 29.00, 34.21 (CH₂), 69.65 (CH-OCH₂(CH₂)₅CH₃), 101.05 (CH-OCH₂(CH₂)₅CH₃), 123.43, 127.57, 128.14, 129.91 (aromatic), 133.95, 136.51 (quaternary aromatic), 164.21 (C=O). MS (EI): m/z 234(M<sup>+</sup>). Anal. Calcd for C₁₄H₁₈O₃: C, 71.77; H, 7.74. Found: C, 71.68; H, 7.71.

3,4-Dihydro-3-(octyl)isochroman-1-one (46e)

Light yellow liquid, IR (ν<sub>max</sub>, cm<sup>-1</sup>): 3018, 2928, 1723, 1612, 1464, 1320, 1244, 1045, 794, 689. <sup>1</sup>H NMR: δ<sub>H</sub> 0.86 (t, 3H, OCH₂(CH₂)₆CH₃, J = 6.4 Hz), 1.25 (m, 10H, OCH₂CH₂(CH₂)₆CH₃), 1.55 (m, 2H, OCH₂CH₂(CH₂)₆CH₃), 3.09 (dd, 1H, CH₂, J₁ = 17.1 Hz, J₂ = 4.4 Hz), 3.28 (dd, 1H, CH₂, J₁= 17.4 Hz, J₂= 4.6 Hz), 3.59 (m, 1H, OCH₂(CH₂)₆CH₃), 3.93 (m, 1H, OCH₂(CH₂)₆CH₃), 5.54 (t, 1H, CH–OCH₂(CH₂)₆CH₃, J = 3.6 Hz), 7.20-8.20 (m, 4H, aromatic H). <sup>13</sup>C NMR: δ<sub>C</sub> 14.08 (OCH₂(CH₂)₆CH₃), 22.60, 25.85, 29.15, 29.29, 31.73, 33.41 (CH₂), 69.61 (CH-OCH₂(CH₂)₆CH₃), 101.02 (CH-OCH₂(CH₂)₆CH₃), 124.98, 127.50, 128.12, 129.85
(aromatic), 133.88, 136.52 (quaternary aromatic), 164.07 (C=O). Anal. Calcd for C₁₇H₂₄O₂: C, 73.88; H, 8.75. Found: C, 73.82; H, 8.78.

3-(Dodecyloxy)-3,4-dihydroisochroman-1-one (46f)

Light yellow liquid, IR (ν_max, cm⁻¹): 2968, 2931, 2868, 1728, 1637, 1487, 1251, 1045, 792, 688. ¹H NMR: δ_H 0.89 (t, 3H, OCH₂(CH₂)₁₀CH₃, J = 6.8 Hz), 1.26 (m, 18H, OCH₂(CH₂)₀(CH₃), 1.60 (m, 2H, OCH₂CH₂(CH₂)₉CH₃), 3.12 (dd, 1H, CH₂, J₁ = 16.6 Hz, J₂ = 4.8 Hz), 3.31 (dd, 1H, CH₂, J₁ = 16.6 Hz, J₂ = 4.6 Hz), 3.62 (m, 1H, OCH₃(CH₂)₀(CH₃), 3.96 (m, 1H, OCH₂(CH₂)₁₀CH₃), 5.56 (t, 1H, CH-OCH₂(CH₂)₁₀CH₃, J = 4 Hz), 7.20-8.20 (m, 4H, aromatic H). ¹³C NMR: δ_C 14.13 (OCH₂(CH₂)₁₀CH₃), 22.67, 25.76, 29.33, 29.44, 29.59, 29.61, 29.65, 31.89, 32.77 (CH₂), 62.91 (CH-OCH₂(CH₂)₁₀CH₃), 107.04 (CH-OCH₂(CH₂)₁₀CH₃), 125.58, 128.56, 129.52, 134.81 (aromatic), 136.43, 144.66 (quaternary aromatic), 162.25 (C=O). MS (EI): m/z 332(M⁺). Anal. Calcd for C₂₁H₃₂O₃: C, 75.86; H, 9.70. Found: C, 75.78; H, 9.66.

3,4-Dihydro-3-(tetradecyloxy)isochroman-1-one (46g)

White crystalline solid, IR (ν_max, cm⁻¹): 3020, 2938, 1720, 1637, 1487, 1330, 1251, 1045, 794, 688. ¹H NMR: δ_H 0.89 (t, 3H, OCH₂(CH₂)₁₂CH₃, J = 6.8 Hz), 1.28 (m, 22H, OCH₂CH₂(CH₂)₁₁CH₃), 1.58 (m, 2H, OCH₂CH₂(CH₂)₁₁CH₃), 3.12 (dd, 1H, CH₂, J₁ = 16.6 Hz, J₂ = 4.4 Hz), 3.31 (dd, 1H, CH₂, J₁ = 16.6 Hz, J₂ = 4.5 Hz), 3.62 (m, 1H, OCH₂(CH₂)₁₂CH₃), 3.95 (m, 1H, OCH₂(CH₂)₁₂CH₃), 5.56 (t, 1H, CH-OCH₂(CH₂)₁₂CH₃, J = 4.4 Hz), 7.20-8.20 (m, 4H, aromatic H). ¹³C NMR: δ_C 14.17 (OCH₂(CH₂)₁₂CH₃), 22.72, 25.89, 29.31, 29.39, 29.55, 29.58, 29.68, 29.69, 29.71, 31.95, 33.46 (CH₂), 69.70 (CH-OCH₂(CH₂)₁₂CH₃), 101.02 (CH-OCH₂(CH₂)₁₂CH₃), 124.99, 127.58, 128.12, 129.97 (aromatic), 133.93, 136.49 (quaternary aromatic), 164.19 (C=O). MS (EI): m/z 360(M⁺). Anal. Calcd for C₂₃H₃₆O₃: C, 76.62; H, 10.06. Found: C, 76.58; H, 10.10.

3-(Hexadecyloxy)-3,4-dihydroisochroman-1-one (46h)

White crystalline solid, IR (ν_max, cm⁻¹): 3090, 2941, 2837, 1720, 1637, 1487, 1251, 1045, 794, 688. ¹H NMR: δ_H 0.89 (t, 3H, OCH₂(CH₂)₁₄CH₃, J = 6.9 Hz), 1.26 (m, 26H, OCH₂CH₂(CH₂)₁₃CH₃), 1.57 (m, 2H, OCH₂CH₂(CH₂)₁₃CH₃), 3.11 (dd, 1H, CH₂, J₁ = 16.6 Hz, J₂ = 4.4 Hz), 3.30 (dd, 1H, CH₂, J₁ = 16.6 Hz, J₂ = 4.2 Hz), 3.61 (m, 1H,
OCH₂(CH₂)₁₄CH₃), 3.96 (m, 1H, OCH₂(CH₂)₁₄CH₃), 5.56 (t, 1H, CH–OCH₂(CH₂)₁₄CH₃, J = 4 Hz), 7.20-8.20 (m, 4H, aromatic H). ¹³C NMR: δC 14.16 (OCH₂(CH₂)₁₄CH₃), 22.72, 25.75, 25.89, 29.31, 29.39, 29.46, 29.55, 29.58, 29.64, 29.69, 29.72, 31.95, 32.81, 33.46 (CH₂), 69.70 (CH–OCH₂(CH₂)₁₄CH₃), 101.03 (CH–OCH₂(CH₂)₁₄CH₃), 124.99, 127.58, 128.13, 129.96 (aromatic), 133.94, 136.50 (quaternary aromatic), 164.19 (C=O). MS (EI): m/z 388(M⁺). Anal. Calcd for C₂₅H₄₀O₃: C, 77.27; H, 10.38. Found: C, 77.22; H, 10.30.

**IH-isochromen-1-one (47)**

White crystalline solid, mp. 46 °C; IR (ν max, cm⁻¹): 2962, 1732, 1610, 1462, 1246, 1008, 731. ¹H NMR: δH 6.52 (d, 1H, CH=CH-O, J = 5.6 Hz), 7.28 (d, 1H, CH=CH-O, J = 5.2 Hz), 7.20-8.30 (m, 4H, aromatic H). ¹³C NMR: δC 107.04, 121.89 (olefinic), 125.56, 128.63, 129.72, 134.83 (aromatic), 136.48, 144.71 (quaternary aromatic), 162.29 (C=O).

**1.5 Conclusion**

First one-pot synthesis of 3,4-dihydro-3-hydroxyisochroman-1-one (lactol) 20 from indene 19 is reported. A probable steps of its formation is also proposed by various experimental studies. Various acetal derivatives of lactol (57a-h) were prepared by acid catalyzed reaction with different aliphatic alcohols. It was further found that similar reaction with phenols resulted in the dehydration of 20 to 47.
1.6 Spectra
Figure 1.4: $^1$H NMR of 2,3-dihydro-1H-indan-trans-1,2-diol (11)
Figure 1.5: $^1$H NMR with D$_2$O exchange of 2,3-dihydro-1H-indan-trans,trans-1,2-diol (II)
Figure 1.6. $^{13}$C NMR of 2,3-dihydro-1H-indan-trans-1,2-diol (11)
Figure 1.7: Mass Spectrum of 2,3-dihydro-1H-indan-trans-1,2-diol (11)
Figure 1.8: $^1$H NMR of 3,4-Dihydro-3-hydroxyisochroman-1-one (20)
Figure 1.9: $^1$H NMR with D$_2$O exchange of 3,4-Dihydro-3-hydroxyisochroman-1-one (20)
Figure 1.10: $^{13}$C NMR of 3,4-Dihydro-3-hydroxyisochroman-1-one (20)
Figure 1.11: Mass Spectrum of 3,4-Dihydro-3-hydroxyisochroman-1-one (20)
Figure 1.12: $^1$H NMR of 3-ethoxy-3,4-dihydroisochroman-1-one (46a)
Figure 1.13: $^{13}$C NMR of 3-ethoxy-3,4-dihydroisochroman-1-one (46a)
Figure 1.14: Mass Spectrum of 3-ethoxy-3,4-dihydroisochroman-1-one (46a)
Figure 1.15: $^1$H NMR of 3,4-dihydro-3-propoxyisochroman-1-one (46b)
Figure 1.16. $^{13}$C NMR of 3,4-dihydro-3-propoxyisochroman-1-one (46b)
Figure 1.17: Mass Spectrum of 3,4-dihydro-3-propoxyisochroman-1-one (46b)
Figure 1.18: \( ^1\text{H} \) NMR of 3-butoxy-3,4-dihydroisochroman-1-one (46c)
Figure 1.19: $^{13}$C NMR of 3-butoxy-3,4-dihydroisochroman-1-one (46c)
Figure 1.20: Mass Spectrum of 3-butoxy-3,4-dihydroisochroman-1-one (46c)
H NMR of 3,4-dihydro-3-(pentyloxy)isochroman-1-one (46d)
Figure 1.22. $^{13}$C NMR of 3,4-dihydro-3-(pent-4-en-1-yl)isochroman-1-one (46d)
Figure 1.23: Mass Spectrum of 3,4-dihydro-3-(pentyloxy)isochroman-1-one (46d)
Figure 1.24: $^1$H NMR of 3,4-dihydro-3-(octyloxy)isochroman-1-one (46e)
Figure 1.25. $^{13}$C NMR of 3,4-dihydro-3-(octyloxy)isochroman-1-one (46e)
Figure 1.26: Mass Spectrum of 3,4-dihydro-3-(octyloxy)isochroman-1-one (46e)
Figure 1.27: $^1$H NMR of 3-(dodecyloxy)-3,4-dihydroisochroman-1-one (46f)
Figure 1.28: $^{13}$C NMR of 3-(dodecyloxy)-3,4-dihydroisochroman-1-one (46f)
**Figure 1.29:** Mass Spectrum of 3-(dodecyloxy)-3,4-dihydroisochroman-1-one (46f)
Figure 1.30: \(^1\)H NMR of 3,4-dihydro-3-(tetradecyloxy)isochroman-1-one (46g)
Figure 1.31: $^{13}$C NMR of 3,4-dihydro-3-(tetradecyloxy)isochroman-1-one (46g).
Figure 1.32 - Mass Spectrum of 3,4-dihydro-3-(tetradecyloxy)isochroman-1-one (46g)
Figure 1.33: 1H NMR of 3-(hexadecyloxy)-3,4-dihydroisochroman-1-one (46h)
Figure 1.34: $^{13}$C NMR of 3-(hexadecyloxy)-3,4-dihydroisochroman-1-one (46b)
Figure 1.3.5: Mass Spectrum of 3-(hexadecyloxy)-3,4-dihydroisochroman-1-one (46h)
Figure 1.36: $^1$H NMR of 1H-isochromen-1-one (47)
Figure 1.37: $^{13}$C NMR of 1H-isochromen-1-one (47)
Figure 1.38: Mass spectrum of 1H-isochromen-1-one (47)
1.7 References


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