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# Chemoenzymatic synthesis and resolution of compounds containing a quaternary stereocenters adjacent to a carbonyl group

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ABSTRACT

Racemic compounds containing a quaternary stereocenter (having hydroxymethyl and alkyl group adjacent to keto functionality) based on chromanone, α-tetralone, and indalone scaffolds have been synthesized. An enzymatic irreversible transesterification approach has been applied to generate the pure enantiomers in a stereocontrolled fashion. The pure enantiomers of some α,α-dialkylated carbonyl compounds have been synthesized by this method.



## 1. Introduction

The generation of carbon containing a quaternary stereocenter is a challenging task. There exist many well-defined chemical strategies for creating a quaternary stereocenter in a molecule.[1] However, the search for newer methods for the abovementioned theme still remains. Although there exist many chemical catalyst based strategies for the generation of quaternary stereocenters, very few biocatalytic approaches have been known in the literature.[2] Enzymatic kinetic resolution and desymmetrization of meso or prochiral substrates (EED: enantioselective enzymatic desymmetrization) are different approaches which can be used successfully to create quaternary stereocenters.[3] Natural products provide the inspiration for a variety of strategies used in the diversity oriented synthesis (DOS) of novel small molecule libraries.[4] These libraries are mainly based on core scaffolds from individual natural products or specific substructures found across a class of natural products or a new chemotype altogether. An increasing body of evidence supports the effectiveness of these strategies for identifying new biologically active small organic molecules. These efforts also have led to significant advances in novel strategies in synthetic organic chemistry.[5]

In our combinatorial biocatalysis project, we needed to design and synthesize various small molecular multifunctional scaffolds which would lead us to a natural product like library after biocatalytic modification. We chose chromanone, α-tetralone, and α-indanone based scaffolds as there exist many natural products based on chromanone (flavonoids and homoisoflavonoids) and α-tetralone.[6] The asymmetric alkylation of a carbonyl compound is a well-known strategy for making a new C–C bond, where the enolates generated from the carbonyl compound and a suitable base were reacted with an external electrophile (alkyl halide). Treatment of the enolate with two different electrophiles in an asymmetric fashion leads to the generation of new quaternary stereocenters. The efficiency of this reaction depends on the use of expensive chiral bases and chiral catalysts.[7] We planned to generate an asymmetric quaternary center via an enzymatic approach. Although hydroxymethylation of enolates with formaldehyde provides an efficient method to introduce a functional group at the α-position of carbonyl groups, there have been few, successful examples of catalytic asymmetric hydroxymethylation that satisfy the synthetic utility in terms of both yield and selectivity for a wide range of substrates.[8] In our case the installation of an alkyl group followed by a hydroxymethyl group on the carbonyl compounds (chromanones, α-tetralones, and α-indanone) was first achieved to generate the racemic quaternary stereocenter. The introduction of hydroxymethyl functionality served a dual purpose, firstly it allows us to adopt enzymatic transesterification reaction to fix the quaternary stereocenter and secondly it opens up the possibility to convert it to other alkyl groups different from the alkyl group which was introduced in the initial step (Scheme 1).

## 2. Results and discussion

Commercially available substituted α-tetralones and α-indalones are used whereas different substituted chromanones are prepared as reported elsewhere. When these carbonyl compounds are treated with LDA and the proper alkyl iodide (1.1 equiv) at −78 °C, monoalkylated compounds were obtained in good yield.[9] In the major cases, the first alkyl group introduced was either methyl or ethyl. The monoalkylation reaction seems to be problematic for different chromanone substrates as base induced ring opening of chromanones has been reported in the literature.[10] However, the chemical yields of the monoalkylated chromanones were good enough (50–60%) to carry out the subsequent steps.

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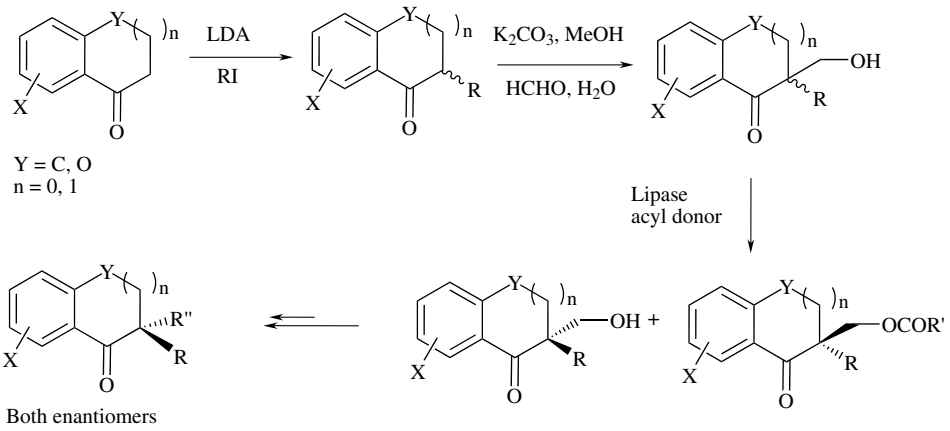



**Scheme 1.** Enzymatic approach for the generation of dialkylated carbonyl compounds.

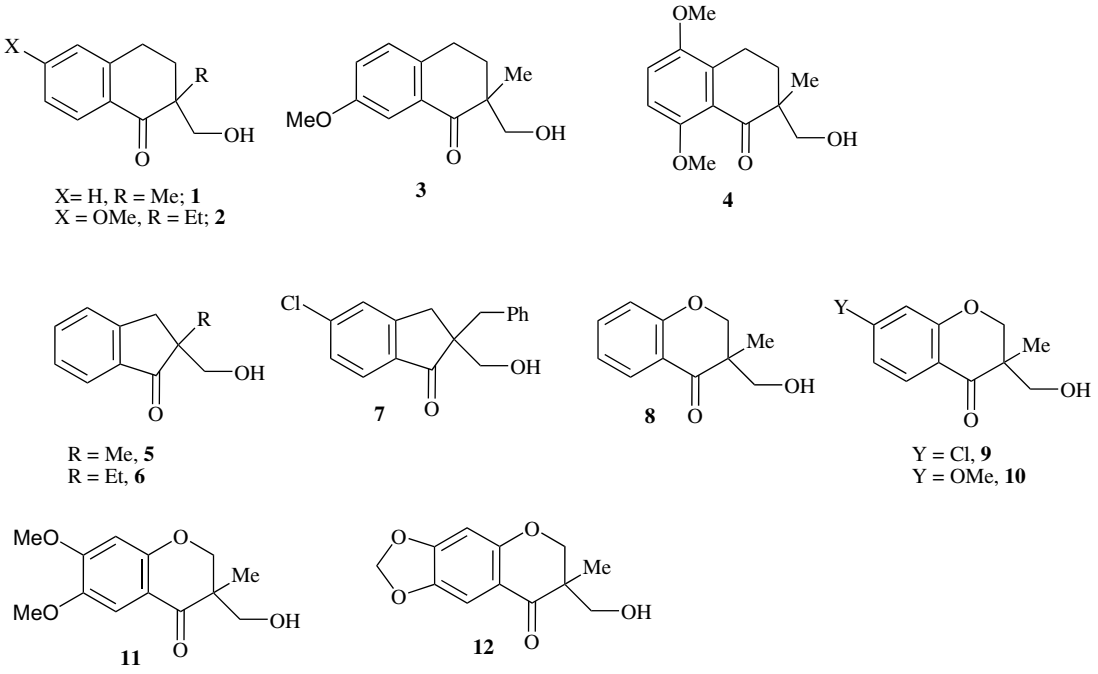
The hydroxymethyl group was successfully installed by treating the monoalkylated carbonyl compounds with formalin in mild basic medium ($K_2CO_3$/MeOH).[11] By applying the above strategy we have synthesized 12 carbonyl compounds containing alkyl groups and hydroxymethyl functionality (Scheme 2). All the monoalkylhydroxymethylated compounds **1**–**12** are well characterized by standard spectroscopic techniques. We also recorded the HPLC data for the racemic compounds **1**–**12** to obtain a clear idea of the retention time for the individual enantiomers.

### 2.1. Enzymatic kinetic resolution of compounds 1–12

After completion of the successful synthesis of compounds **1**–**12**, the next task was to generate the quaternary stereocenter by an irreversible enzymatic acylation (transesterification) reaction. We initially chose substrate **8** for enzyme screening to check the feasibility and efficiency of the reaction (in terms of enantiomeric excess) with different lipases in organic solvents with vinyl acetate as an acyl donor. For this purpose 50 mg of compound **8** was taken in anhydrous diisopropyl ether (DIPE, 5 mL), followed by the addition of 50 mg of the required lipase and 8 equiv of vinyl acetate. The reaction was monitored periodically with TLC. The results are summarized in Table 1.

It was noticed (from Table 1) that Lipase-PS (Amano) gave the best result in terms of selectivity ($E = 159$) with substrate **8**. Although Lipase-AK (Amano) and lipozyme also provided good enantioselectivities, we applied Lipase-PS for the transesterification reaction of compounds **1**–**7** and **9**–**12** under similar reaction conditions. The results are summarized in Table 2.

From Table 2, it was observed that after enzymatic transesterification the product esters obtained from compounds **1**–**12** provide very good enantioselectivities (94–99%), whereas the slow reacting enantiomeric alcohols **1**–**12** are not so enantiopure (37–53%). The enantioselectivities for the product acetates of **1**–**12** as well as the parent alcohols are determined by Chiral-HPLC measurement. In all cases, we synthesized racemic acetates of compounds **1**–**12** by means of a chemical acylation method and recorded their HPLC data, which allowed us to assign the retention time for the major and minor enantiomers. The reaction was monitored by TLC and was stopped after an appreciable amount of conversion was achieved (as indicated by TLC; presence of approximately 1:1 ratio of alcohol and acetate was indicated).




**Scheme 2.** Monoalkylated hydroxymethyl carbonyl compounds.

**Table 1**
Lipase catalyzed transesterification of compound **8**

| Entry | Lipase | Conversion (c) | $ee_s$[a] (%) | $ee_p$[a] (%) | $E$[b] |
|---|---|---|---|---|---|
| 1 | Lipase AK-Amano | 37 | 55 | 94 | 57 |
| 2 | Lipase PS-Amano | 34 | 50 | 98 | 159 |
| 3 | Lipase A (Aamno-6) | 36.5 | 46 | 80 | 15.5 |
| 4 | Lipase F (AP 15) | 26.8 | 22 | 60 | 4.8 |
| 5 | Lipase PS-D | 25 | 20 | 60 | 4 |
| 6 | Novozyme-435 | 38 | 33 | 54 | 4.6 |
| 7 | Lipozyme | 35 | 52 | 96 | 92 |
| 8 | *Rhizopus arrhizus* | 31.2 | 10 | 22 | 1.7 |
| 9 | *Candida lipolytica* | 39.6 | 21 | 32 | 2.4 |

[a] Ees were calculated by chiral HPLC (Diacel, Chiral OD-H, and OJ-H column, hexane/isopropanol, 9/1).
[b] Enantioselectivities of the reactions ($E$) were determined from the following equation: $E = \ln[1 - c(1 + ee_p)]/\ln[1 - c(1 - ee_p)]$, where $ee_p$ = product ee, $ee_s$ = substrate ee; $c = ee_s/(ee_s + ee_p)$%. Enantioselectivities of the reaction ($E$) were determined using the 'SELECTIVITY' program developed by K. Faber, H. Hönig, and A. Kleewein (http://www.cis.TUGraz.at/orgc/).

**Table 2**
Lipase-PS catalyzed transesterification of compounds **1**–**7** and **9**–**12**

| Entry | Substrate | Conversion (c) | $ee_s$[a] (%) | $ee_p$[a] (%) | $E$[b] |
|---|---|---|---|---|---|
| 1 | **1** | 32.2 | 47 | 99 | 316 |
| 2 | **2** | 28.9 | 40 | 98 | 146 |
| 3 | **3** | 33.3 | 49 | 98 | 161 |
| 4 | **4** | 34.8 | 52 | 97 | 110 |
| 5 | **5** | 31.7 | 46 | 99 | 314 |
| 6 | **6** | 30.7 | 44 | 99 | 307 |
| 7 | **7** | 35.1 | 51 | 94 | 54 |
| 8 | **9** | 28 | 37 | 95 | 57 |
| 9 | **10** | 30 | 42 | 98 | 150 |
| 10 | **11** | 35 | 53 | 98 | 168 |
| 11 | **12** | 31.4 | 44 | 96 | 75.6 |

[a] Ees were calculated by chiral HPLC (Diacel, Chiral OD-H, and OJ-H column, hexane/isopropanol, 9/1).
[b] Enantioselectivities of the reactions ($E$) were determined from the following equation: $E = \ln[1 - c(1 + ee_p)]/\ln[1 - c(1 - ee_p)]$, where $ee_p$ = product ee, $ee_s$ = substrate ee; $c = ee_s/(ee_s + ee_p)$%. Enantioselectivities of the reaction ($E$) were determined using the 'SELECTIVITY' program developed by K. Faber, H. Hönig, and A. Kleewein (http://www.cis.TUGraz.at/orgc/).

### 2.2. Determination of the absolute configuration of product acetate

An empirical rule as predicted by Weissfloch and Kazlauskas[12] was applied to determine the enantiopreference of lipases from *Pseudomonas* species toward primary alcohols. The rule is based on the size of the substituents at the stereocenter (Scheme 3). Substrates **1**–**12** follow this empirical model perfectly and in each case, the (*R*)-enantiomer was acylated faster with the enzyme, whereas the (*S*)-enantiomer was the slow reacting enantiomer remaining unreacted in the mixture. We assumed that an alkyl group (e.g., Me, Et) attached to the quaternary stereocenter would be the medium group (M) as depicted in the model, whereas the compact ring structure of α-tetralone, α-indalone, and 4-chromanone would be the large group (L). In the case of substrate **7**, a little ambiguity may arise as the stereocenter contains a benzyl group (–$CH_2$Ph) and the cyclic ring structure of α-indalone (with a Cl atom in the 5 position). Although their steric nature seems to be similar mainly due to the similar size of both the groups, we assume that the compactness of the rigid α-indalone ring as well as presence of an extra 'Cl' group made the rigid indalone ring the large group (L). It was also noticed that substrate **7** provided a little less enantioselection To gain further proof for the enantiopreference of Lipase-PS with our substrates **1**–**12**, we deacetylated the enantiopure (*R*)-acetate obtained from substrates **1** and **5** with $K_2CO_3$/MeOH. The specific rotations for enantiopure (*R*)-alcohol **1** and **5** were recorded {for (*R*)-**1**; $[\alpha]_D^{28} = +1.8$ (*c* 2.04, MeOH) and for (*R*)-**5** $[\alpha]_D^{28} = +4.1$ (*c* 0.5, MeOH)} and compared with those of known compounds[13] {reported value for (*S*)-**1**; $[\alpha]_D^{24} = -1.4$ (*c* 1.3, $CHCl_3$) and for (*R*)-**5** $[\alpha]_D^{21} = +1.6$ (*c* 0.95, $CHCl_3$)} and satisfactory results were found which further established the usefulness of such an empirical model in the lipase catalyzed transesterification reaction. A simplified and modified version of the above rule has already been proposed by two different research groups[14] to predict the enantiopreference of lipases from *Pseudomonas fluorescens* toward primary alcohols having quaternary stereocenters. Our substrates **1**–**12** fit perfectly in that model too. It was also observed in the HPLC chromatogram that (*R*)-acetates **13**–**24** were eluted first compared to their corresponding (*S*)-isomers. A similar trend was observed in a previous report[13] for an enantiomeric mixture of compounds **1** and **5** in HPLC chromatogram.

### 2.3. Asymmetric synthesis of dialkylated carbonyl compounds

After successful installation of the quaternary stereocenters adjacent to the carbonyl groups of compounds **1**–**12**, we extended our synthetic strategy to the general synthesis of α,α-dialkylated carbonyl compounds. We chose compounds **3** and **6** for this method. After successful enzymatic transesterification of compounds **3** and **6** with lipase PS followed by deacetylation with $K_2CO_3$/MeOH yielded the corresponding (*S*) alcohols. The carbonyl group was protected with ethyleneglycol as the corresponding ketals. The free alcohol group was converted to respective methanesulfonate ester. Reductive deoxygenation of mesylates with LAH in refluxing THF followed by acid induced deketalyzation afforded the dialkylated compound in good yield (Scheme 4).

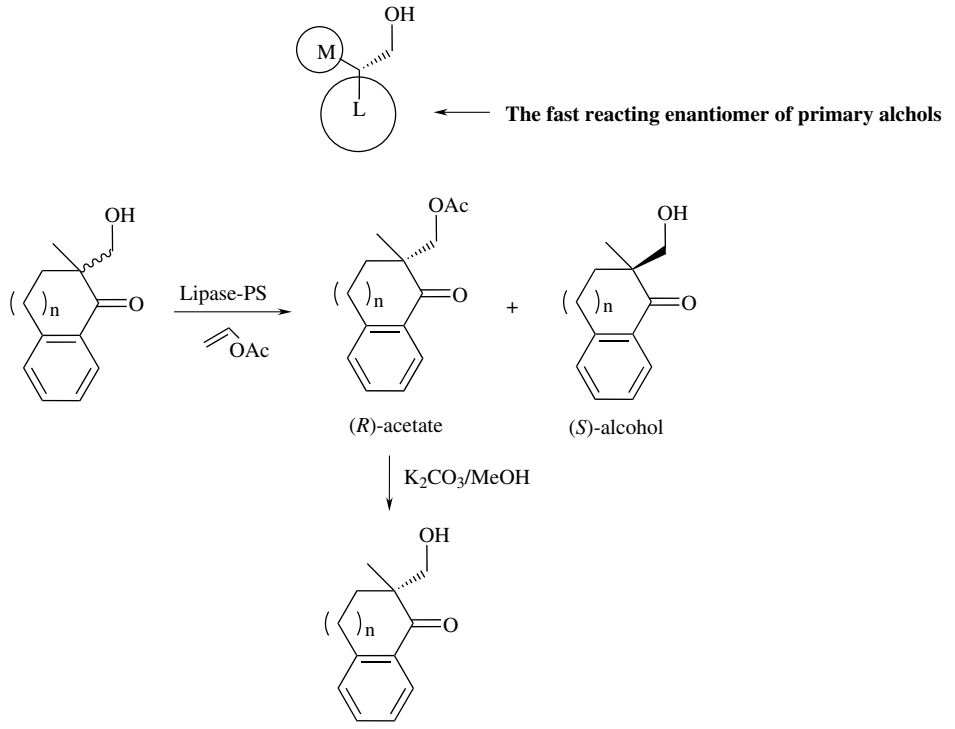
## 3. Conclusion

In conclusion, we have developed an efficient, chemoenzymatic strategy for the synthesis of several alcohols having quaternary stereocenters based on 4-chromanone, α-tetralone, and α-indanone scaffolds. Further synthetic manipulation of the enantiopure alcohols yielded dialkylated carbonyl compounds in good overall yields with high enantioselectivities. Elaboration of the above synthetic strategy is currently ongoing in our laboratory to access enantiopure novel chemical intermediates based on multifunctional scaffolds.

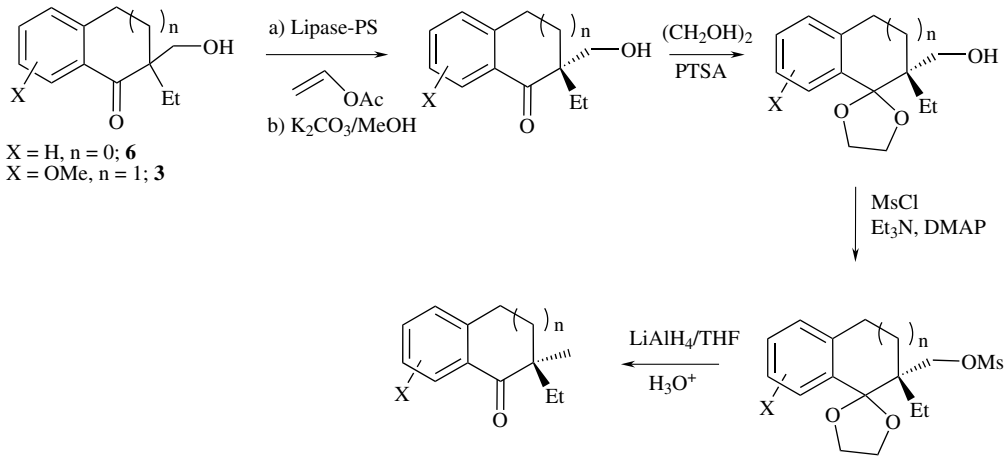
## 4. Experimental

### 4.1. General

Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. THF and diethylether were distilled from sodiumbenzophenone ketyl. Dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were distilled from calcium hydride. Lipase AK (*P. fluorescens*), LipasePS (*Burkholderia cepacia*), Lipase A (*Aspergillus niger*), and Lipase F (*Rhizopus oryzae*) were purchased from AMANO, Japan. Novozyme-435, Lipozyme and other lipases (*Porcine pancreatic*, *Mucor javanicus*, *Rhizopus arrhizus*, *Candida lipolytica*, *Penicillum roqueforti*) were purchased from FLUKA, USA. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (Merck) with UV light, ethanolic anisaldehyde, and phosphomolybdic acid/heat as developing agents. Silicagel 100–200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. NMR spectra were recorded on Bruker 400 MHz spectrometers at 25 °C in $CDCl_3$ using TMS as the internal standard. Chemical shifts are shown in $\delta$. $^{13}$C NMR spectra were recorded with a complete proton decoupling environment.




**Scheme 3.** Emperical rule showing the enantiopreference of lipase toward the primary alcohol (no 'O' at stereocenter).




**Scheme 4.** Asymmetric synthesis of dialkylated carbonyl compounds.

The chemical shift values are listed as $\delta_H$ and $\delta_C$ for $^1H$ and $^{13}C$, respectively. Optical rotations were measured on a JASCO Dip 360 digital polarimeter. Chiral HPLC was performed using Chiral OJ-H and OD-H column (0.46 × 25 cm, Daicel industries) with Shimadzu Prominence LC-20AT chromatograph coupled with UV–vis detector (254 nm). Eluting solvent used was different ratio of hexane and 2-propanol. Mass spectra were recorded at CRF (Central Research Facility), IIT, Kharagpur.

### 4.2. General method for chroman-4-one synthesis

#### 4.2.1. Coupling of substituted phenols with 3-bromopropionic acid

To a mixture of sodium hydride (1 equiv) in DMF (15 mL/g) was added 3-methoxyphenol (1 equiv) in DMF (10 mL) at 10–15 °C and the mixture was stirred at rt for 1 h. A solution of 3-bromo propionic acid (1 equiv) in DMF was added and the mixture was then stirred for 14 h. The reaction mixture was diluted with methanol (10 mL), acidified with dilute HCl, and extracted with ethyl acetate (2 × 100 mL). The combined ethyl acetate layer was washed with water (50 mL) and brine (30 mL), and dried over sodium sulfate. The residue obtained after evaporation of the solvent was chromatographed over a silica gel column using a mixture of petroleum ether and ethyl acetate (75:25) as eluent to give the coupled acids in 35–40% yield in all cases.

#### 4.2.2. Intramolecular Friedel–Crafts acylation reaction for substituted chromanone synthesis

A catalytic amount of dry DMF was added to a suspension of different 3-aryloxy-propionic acid (0.5 g, 1 equiv) in 50 mL of dry benzene. Oxalyl chloride (2 equiv) was then added, and the resulting solution was stirred at rt for 4 h. The organic solvent was

removed under reduced pressure, and the resulting oil was dissolved in 30 mL of dry DCM. After the solution was cooled to 0 °C, $SnCl_4$ (1.4 equiv) was added and the solution was stirred for further 1 h while allowing it to attain rt. Next the reaction mixture was poured into ice (20 g) and after dilution with water (30 mL), the aqueous layer was extracted with DCM. The organic extracts were dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was chromatographed over silica gel column using mixture of petroleum ether and ethyl acetate (80:20) as eluent to give the chromanones in 90% yield in all the cases.

**4.2.2.1. 7-Chloro-chroman-4-one.** $\delta_H$: 7.7 (d, *J* = 8.8 Hz, 1H), 7.0 (m, 2H), 4.5 (t, *J* = 6.0 Hz, 2H), 2.8 (t, *J* = 6.0 Hz, 2H).

**4.2.2.2. 7-Methoxy-chroman-4-one.** $\delta_H$: 7.8 (d, *J* = 8.8 Hz, 1H), 6.6 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.4 (d, *J* = 2.4 Hz, 1H), 4.5 (t, *J* = 6.2 Hz, 2H), 3.8 (s, 3H), 2.75 (t, *J* = 6.2 Hz, 2H).

**4.2.2.3. 6,7-Dimethoxy-chroman-4-one.** $\delta_H$: 7.4 (s, 1H), 6.4 (s, 1H), 4.5 (t, *J* = 6.2 Hz, 2H), 3.9 (s, 3H), 3.87 (s, 3H), 2.7 (t, *J* = 6.2 Hz, 2H).

**4.2.2.4. 6,7-Dihydro-[1,3]dioxolo[4,5-g]chromen-8-one.** $\delta_H$: 7.4 (s, 1H), 6.45 (s, 1H), 6.0 (s, 2H), 4.5 (t, *J* = 6.2 Hz, 2H), 2.75 (t, *J* = 6.2 Hz, 2H).

### 4.3. Monomethylation of substituted chromanones

Substituted chromanones (0.5 g) were slowly added to a stirred solution of LDA (1 equiv, 1.5 M in THF) in THF (8 mL) at −78 °C and stirred for 20 min. Methyliodide (1 equiv) was then added and this solution was stirred for 6 h at room temperature. A solution of saturated $NH_4Cl$ (2 mL) was added and mixture was extracted with ether. The combined organic layers were dried over $Na_2SO_4$ and the solvents were evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether/ethyl acetate (10:1) to give the desired product in 70% yield.

### 4.4. Monomethylation of 1-tetralone and 1-indalones

Substituted 1-tetralone/1-indalone (2.0 g) was slowly added dropwise to a stirred solution of LDA (1.2 equiv, 1.5 M in THF) at −78 °C and stirred for 20 min. Methyliodide (1.2 equiv) was then added and this solution was stirred for 14 h. A solution of saturated $NH_4Cl$ (10 mL) was added and the mixture was extracted with ether ($3 \times 50$). The combined organic layers were dried over $Na_2SO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with light petroleum ether/ethyl acetate (7:1) to give the desired 2-methyl 1-tetralone/1-indalones in 65% yield.

### 4.5. Hydroxymethylation of 2-methyl-1-tetralone/1-indanone and substituted 3-methyl-chroman-4-one

A mixture of 2-methyl 1-tetralone/1-indanone/chroman-4-one (0.25 g), and $K_2CO_3$ (0.5 equiv)/in 40 mL of water/ethanol (10:1) was stirred vigorously at 40 °C while formaldehyde (19 mL, 0.230 mmol, 1.9 equiv, 37% aqueous solution) was added for 0.5 h. Stirring was continued for 1 h at the same temperature, the reaction mixture was cooled and extracted with ether, and the organic layer was dried over $Na_2SO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel eluting with light petroleum ether/ethyl acetate (3:1) to give 2-(hydroxymethyl)-2-methyl-1-tetralone/1-indanone and the chromanones in 80% yield in almost all cases.

### 4.6. 2-Hydroxymethyl-2-methyl-3,4-dihydro-2*H*-naphthalen-1-one 1

$\delta_H$: 8.0 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.5 (t, *J* = 8.0 Hz, 1H, Ar*H*), 7.32 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.24 (d, *J* = 8.0 Hz, 1H, Ar*H*), 3.73 (d, *J* = 10.8 Hz, 1H, –C*H*$_2$OH), 3.65 (d, *J* = 10.8 Hz, 1H, –C*H*$_2$OH), 3.18 (dt, *J* = 16.0, 5.2 Hz, 1H, –C–C*H*$_2$), 2.95 (td, *J* = 16.0, 4.0 Hz, 1H, –C–C*H*$_2$), 2.25 (dt, *J* = 16.0, 5.2 Hz, 1H, –CH$_2$–C*H*$_2$), 1.75 (td, *J* = 16.0, 4.0 Hz, 1H, –CH$_2$–C*H*$_2$), 1.24 (s, 3H, –*Me*). $\delta_C$: 204.04 (*C*=O), 143.41, 133.61, 131.36, 128.74, 127.66, 126.67, 68.96 (–CH$_2$O), 46.25 (–*C*2), 31.3 (–*C*4), 24.9 (–*C*3), 18.2 (–CH$_3$). IR (neat): 3442, 1657 cm$^{-1}$. ES$^+$MS (TOF): 191 (M+1). HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 0.75 mL/min) $t_R$ = 11.87 min (major, assumed *R*), $t_R$ = 13.24 min (minor, assumed *S*).

### 4.7. 2-Ethyl-2-hydroxymethyl-6-methoxy-3,4-dihydro-2*H*-naphthalen-1-one 2

$\delta_H$: 7.96 (d, *J* = 8.8 Hz, 1H, Ar*H*), 6.82 (dd, *J* = 8.8, 1.6 Hz, 1H, Ar*H*), 6.65 (d, *J* = 1.6 Hz, 1H, Ar*H*), 3.84 (s, 3H, –O*Me*), 3.72 (d, *J* = 12.0 Hz, 1H, –C*H*$_2$OH), 3.62 (d, *J* = 12.0 Hz, 1H, –C*H*$_2$OH), 3.1 (m, 1H, -C–C*H*$_2$), 2.85 (m, 1H, –C–C*H*$_2$), 2.03 (m, 1H, –CH$_2$–C*H*$_2$), 1.98 (m, 1H, –CH$_2$–C*H*$_2$), 1.75 (m, 1H, –C*H*$_2$–Me), 1.55 (m, 1H, –C*H*$_2$–Me), 0.93 (t, *J* = 7.6 Hz, 3H, –*Me*). $\delta_C$: 203.5 (*C*=O), 163.73, 145.94, 130.1, 125.05, 113.37, 112.32, 66.5 (–*C*H$_2$O), 55.4 (–O*Me*), 48.59 (–*C*2), 28.6 (–*C*4), 25.43 (–*C*3), 22.67 (–*C*H$_2$–Me), 8.1 (–CH$_2$–*Me*). IR (neat): 3448, 1635, 1456, 1250 cm$^{-1}$. ES$^+$MS (TOF): 235 (M+1). HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 0.5 mL/min) $t_R$ = 28.97 min (major, assumed *R*), $t_R$ = 38.18 min (minor, assumed *S*).

### 4.8. 2-Hydroxymethyl-7-methoxy-2-methyl-3,4-dihydro-2*H*-naphthalen-1-one 3

$\delta_H$: 7.45 (d, *J* = 2.8 Hz, 1H, Ar*H*), 7.2 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.0 (dd, *J* = 8.0, 2.8 Hz, 1H, Ar*H*), 3.8 (s, 3H, –O*Me*), 3.72 (d, *J* = 11.2 Hz, 1H, –C*H*$_2$OH), 3.62 (d, *J* = 11.2 Hz, 1H, –C*H*$_2$OH), 3.05 (m, 1H, –C–C*H*$_2$), 2.88 (m, 1H, –C–C*H*$_2$), 2.2 (m, 1H, –CH$_2$–C*H*$_2$), 1.75 (m, 1H, –CH$_2$–C*H*$_2$), 1.12 (s, 3H, –*Me*). $\delta_C$: 203.9 (*C*=O), 158.3, 136.1, 132.09, 129.94, 122.08, 109.6, 68.94 (–*C*H$_2$O), 55.4 (–O*Me*), 46.1 (–*C*2), 31.7 (–*C*4), 24.38 (–*C*3), 19.4 (–*Me*). IR (neat): 3445, 1634, 1460, 1250 cm$^{-1}$. ES$^+$MS (TOF): 221 (M+1). HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min) $t_R$ = 16.72 min (major, assumed *R*), $t_R$ = 21.06 min (minor, assumed *S*).

### 4.9. 2-Hydroxymethyl-5,8-dimethoxy-2-methyl-3,4-dihydro-2*H*-naphthalen-1-one 4

$\delta_H$: 7.0 (d, *J* = 8.8 Hz, 1H, Ar*H*), 6.8 (d, *J* = 8.8 Hz, 1H, Ar*H*), 3.85 (s, 3H, –O*Me*), 3.82 (s, 3H, O*Me*), 3.67 (s, 2H, –C*H*$_2$OH), 3.1 (m, 1H, –C–C*H*$_2$), 2.8 (m, 1H, –C–C*H*$_2$), 2.15 (m, 1H, –CH$_2$–C*H*$_2$), 1.75 (m, 1H, –CH$_2$–C*H*$_2$), 1.2 (s, 3H, –*Me*). $\delta_C$: 204.4 (*C*=O), 154.42, 150.06, 134.08, 121.49, 115.38, 109.88, 69.28 (–*C*H$_2$O), 56.2 (–O*Me*), 55.84 (–O*Me*), 46.95 (–*C*2), 30.23 (–*C*4), 19.54 (–*C*3), 18.04 (–*Me*). IR (neat): 3442, 1630, 1461, 1254 cm$^{-1}$. ES$^+$MS (TOF): 251 (M+1). HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min) $t_R$ = 22.92 min (major, assumed *R*), $t_R$ = 34.06 min (minor, assumed *S*).

### 4.10. 2-Hydroxymethyl-2-methyl-indan-1-one 5

$\delta_H$: 7.72 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.6 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.4 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.33 (d, *J* = 7.6 Hz, 1H, Ar*H*), 3.85 (d, *J* = 10.8 Hz, 1H, –C*H*$_2$OH), 3.6 (d, *J* = 10.8 Hz, 1H, –C*H*$_2$OH), 3.25 (d, *J* = 17.2 Hz, 1H, –C–C*H*$_2$), 2.88 (d, *J* = 17.2 Hz, 1H, –C–C*H*$_2$), 1.23 (s, 3H, –*Me*). $\delta_C$: 211.17 (*C*=O), 153.3, 135.72, 135.15, 127.43,

126.63, 124.15, 67.7 (–$CH_2O$), 50.85 (–*C*2), 37.88 (–*C*3), 20.6 (–*Me*). IR (neat): 3440, 1668 $cm^{-1}$. $ES^+MS$ (TOF): 177 (M+1). HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min) $t_R$ = 8.64 min (major, assumed *R*), $t_R$ = 9.43 min (minor, assumed *S*).

### 4.11. 2-Hydroxymethyl-2-ethyl-indan-1-one 6

$\delta_H$: 7.72 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.6 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.4 (d, *J* = 7.6 Hz, 1H, Ar*H*), 7.33 (d, *J* = 7.6 Hz, 1H, Ar*H*), 3.85 (d, *J* = 10.8 Hz, 1H, –C$H_2$OH), 3.6 (d, *J* = 10.8 Hz, 1H, –C$H_2$OH), 3.0 (s, 2H, –C–C$H_2$), 1.75 (m, 2H, –C$H_2$–Me), 0.84 (t, *J* = 7.6 Hz, 3H, –*Me*). $\delta_C$: 211.56 (*C*=O), 153.91, 136.76, 130.83, 127.15, 126.72, 124.16, 67.23 (–$CH_2O$), 54.83 (–*C*2), 34.24 (–*C*3), 25.6 (–$CH_2$–Me), 10.1 (–*Me*). IR (neat): 3444, 1664 $cm^{-1}$. $ES^+MS$ (TOF): 191 (M+1). HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 0.8 mL/min) $t_R$ = 10.41 min (major, assumed *R*), $t_R$ = 13.59 min (minor, assumed *S*).

### 4.12. 2-Benzyl-5-chloro-2-hydroxymethyl-indan-1-one 7

$\delta_H$: 7.62 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.33 (s, 1H, Ar*H*), 7.27 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.17–7.12 (m, 5H, Ar*H*), 3.85 (d, *J* = 11.2 Hz, 1H, –C$H_2$OH), 3.62 (d, *J* = 11.2 Hz, 1H, –C$H_2$OH), 3.1 (d, *J* = 17.6 Hz, 1H, –C–C$H_2$), 3.0 (d, *J* = 3.6 Hz, 2H, –C$H_2$Ph), 2.84 (d, *J* = 17.6 Hz, 1H, –C–C$H_2$). $\delta_C$: 209.51 (*C*=O), 154.98, 141.71, 136.28, 134.65, 130.04, 129.96, 128.24, 127.9, 126.46, 124.87, 66.58 (–$CH_2O$), 55.65 (–*C*2), 39.85 (–$CH_2$–Ph), 34.18 (–*C*3). IR (neat): 3448, 1674 $cm^{-1}$. $ES^+MS$ (TOF): 287 (M+1). HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min) $t_R$ = 16.77 min (major, assumed *R*), $t_R$ = 25.61 min (minor, assumed *S*).

### 4.13. 3-Hydroxymethyl-3-methyl-chroman-4-one 8

$\delta_H$: 7.87 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.5 (t, *J* = 8.0 Hz, 1H, Ar*H*), 7.05 (d, *J* = 8.0 Hz, 1H, Ar*H*), 6.9 (d, *J* = 8.0 Hz, 1H, Ar*H*), 4.5 (d, *J* = 12.0 Hz, 1H, –O–C$H_2$–), 4.16 (d, *J* = 12.0 Hz, 1H, –O–C$H_2$–), 3.92 (d, *J* = 11.6 Hz, 1H, –C$H_2$OH), 3.57 (d, *J* = 11.6 Hz, 1H, –C$H_2$OH), 1.2 (s, 3H, –*Me*). $\delta_C$: 197.15 (*C*=O), 161.25, 136.08, 127.64, 121.46, 119.8, 117.75, 73.37 (–O–$CH_2$), 64.6 (–$CH_2O$), 46.98 (–*C*3), 16.35 (–*Me*). IR (neat): 3436, 1620, 1462 $cm^{-1}$. $ES^+MS$ (TOF): 193 (M+1). HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min) $t_R$ = 4.73 min (major, assumed *R*), $t_R$ = 5.4 min (minor, assumed *S*).

### 4.14. 7-Chloro-3-hydroxymethyl-3-methyl-chroman-4-one 9

$\delta_H$: 7.7 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.0 (m, 2H, Ar*H*), 4.5 (d, *J* = 12.0 Hz, 1H, –O–C$H_2$–), 4.2 (d, *J* = 12.0 Hz, 1H, –O–C$H_2$–), 3.88 (d, *J* = 11.6 Hz, 1H, –C$H_2$OH), 3.65 (d, *J* = 11.6 Hz, 1H, –C$H_2$OH), 1.2 (s, 3H, –*Me*). $\delta_C$: 193.8 (*C*=O), 161.86, 142.2, 134.94, 128.52, 122.35, 117.9, 72.31 (–O–$CH_2$), 65.3 (–$CH_2O$), 48.72 (–*C*3), 15.32 (–*Me*). IR (neat): 3439, 1622, 1460 $cm^{-1}$. $ES^+MS$ (TOF): 227 (M+1). HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min) $t_R$ = 7.55 min (major, assumed *R*), $t_R$ = 9.25 min (minor, assumed *S*).

### 4.15. 7-Methoxy-3-hydroxymethyl-3-methyl-chroman-4-one 10

$\delta_H$: 7.81 (d, *J* = 8.8 Hz, 1H, Ar*H*), 6.58 (dd, *J* = 2.4 Hz, 8.8 Hz, 1H, Ar*H*), 6.4 (d, *J* = 2.0 Hz, 1H, Ar*H*), 4.5 (d, *J* = 11.2 Hz, 1H, –O–C$H_2$–), 4.15 (d, *J* = 11.2 Hz, 1H, –O–C$H_2$–), 3.88 (d, *J* = 11.2 Hz, 1H, –C$H_2$OH), 3.83 (s, 3H, –O*Me*), 3.57 (d, *J* = 11.2 Hz, 1H, –C$H_2$OH), 1.2 (s, 3H, –*Me*). $\delta_C$: 208.3 (*C*=O), 166.22, 163.25, 129.16, 113.62, 110.53, 100.25, 73.64 (–O-$CH_2$), 64.87 (–$CH_2O$), 55.6 (–O*Me*), 46.44 (–*C*3), 16.64 (–*Me*). IR (neat): 3428, 1624, 1462, 1265 $cm^{-1}$. $ES^+MS$ (TOF): 223 (M+1). HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min) $t_R$ = 7.21 min (major, assumed *R*), $t_R$ = 8.75 min (minor, assumed *S*).

### 4.16. 3-Hydroxymethyl-6,7-dimethoxy-3-methyl-chroman-4-one 11

$\delta_H$: 7.22 (s, 1H, Ar*H*), 6.4 (s, 1H, Ar*H*), 4.36 (d, *J* = 11.2 Hz, 1H, –O–C$H_2$–), 4.1 (d, *J* = 11.2 Hz, 1H, –O–C$H_2$–), 3.88 (s, 3H, –O*Me*), 3.85 (d, *J* = 11.6 Hz, 1H, –C$H_2$OH), 3.83 (s, 3H, –O*Me*), 3.54 (d, *J* = 11.6 Hz, 1H, –C$H_2$OH), 1.18 (s, 3H, –*Me*). $\delta_C$: 195.85 (*C*=O), 157.8, 156.26, 144.6, 111.98, 106.83, 99.79, 73.82 (–O–$CH_2$), 64.83 (–$CH_2O$), 56.2 (–O*Me*), 56.0 (–O*Me*), 46.36 (–*C*3), 16.58 (–*Me*). IR (neat): 3438, 1631, 1460, 1262 $cm^{-1}$. $ES^+MS$ (TOF): 253 (M+1). HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min) $t_R$ = 11.01 min (major, assumed *R*), $t_R$ = 12.91 min (minor, assumed *S*).

### 4.17. 7-Hydroxymethyl-7-methyl-6,7-dihydro-[1,3]dioxolo[4,5-*g*]-chromen-8-one 12

$\delta_H$: 7.24 (s, 1H, Ar*H*), 6.41 (s, 1H, Ar*H*), 5.98 (s, 2H, –O–C$H_2$–O–), 4.44 (d, *J* = 11.2 Hz, 1H, –O–C$H_2$–), 4.1 (d, *J* = 11.2 Hz, 1H, –O–C$H_2$–), 3.8 (d, *J* = 10.0 Hz, 1H, –C$H_2$OH), 3.56 (d, *J* = 10.0 Hz, 1H, –C$H_2$OH), 1.19 (s, 3H, –*Me*). $\delta_C$: 195.61 (*C*=O), 159.38, 154.45, 143.23, 113.33, 104.45, 102.0, 98.1 (–O–$CH_2$–O), 73.8 (–O–$CH_2$), 64.8 (–$CH_2O$), 46.22 (–*C*3), 16.63 (–*Me*). IR (KBr): 3449, 1620, 1480, 1258 $cm^{-1}$. $ES^+MS$ (TOF): 237 (M+1). HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 19/1, flow rate = 0.5 mL/min) $t_R$ = 31.67 min (major, assumed *R*), $t_R$ = 33.9 min (minor, assumed *S*).

### 4.18. Enzymatic transesterification of Compounds 1–12

In a typical resolution experiment, a solution of **1**–**12** (50 mg) in anhydrous diisopropylether (5 mL) was stirred with vinyl acetate (8 equiv) and powdered molecular sieves (25 mg, 4 Å) followed by the addition of Lipase (50 mg). The reaction mixture was stirred in an orbit shaker (250 rpm) at room temperature for 12 h. After 50% conversion (by TLC analysis) the reaction mixture was filtered through a pad of Celite and evaporated to dryness. The alcohols **1**–**12** and their acetates were isolated by flash chromatography.

### 4.19. Acetic acid 2-methyl-1-oxo-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl ester 13

$\delta_H$: 8.0 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.5 (t, *J* = 8.0 Hz, 1H, Ar*H*), 7.32 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.24 (d, *J* = 8.0 Hz, 1H, Ar*H*), 4.47 (d, *J* = 10.8 Hz, 1H, –C$H_2$OAc), 4.11 (d, *J* = 10.8 Hz, 1H, –C$H_2$OAc), 3.18 (dt, *J* = 16.0, 5.2 Hz, 1H, –C–C$H_2$), 2.95 (td, *J* = 16.0, 4.0 Hz, 1H, –C–C$H_2$), 2.25 (dt, *J* = 16.0, 5.2 Hz, 1H, –$CH_2$–C$H_2$), 2.0 (s, 3H, –OCOC$H_3$), 1.75 (td, *J* = 16.0, 4.0 Hz, 1H, –$CH_2$–C$H_2$), 1.24 (s, 3H, –*Me*). $\delta_C$: 199.55 (*C*=O), 170.89 (–O*C*OMe), 143.41, 133.61, 131.36, 128.74, 127.66, 126.67, 68.56 (–$CH_2$OAc), 45.25 (–*C*2), 31.3 (–*C*4), 24.9 (–*C*3), 20.78 (–OCO*C*$H_3$), 19.08 (–*Me*). $[\alpha]_D^{28} = -11.1$ (*c* 1.0, MeOH). $ES^+MS$ (TOF): 233 (M+1). HRMS *m*/*z* $[M+H]^+$ found 233.1178 calculated 233.1173 for $C_{14}H_{17}O_3$. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min) $t_R$ = 9.5 min (major, assumed *R*), $t_R$ = 9.9 min (minor, assumed *S*).

### 4.20. Acetic acid 2-ethyl-6-methoxy-1-oxo-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl ester 14

$\delta_H$: 7.96 (d, *J* = 8.8 Hz, 1H, Ar*H*), 6.82 (dd, *J* = 8.8, 1.6 Hz, 1H, Ar*H*), 6.65 (d, *J* = 1.6 Hz, 1H, Ar*H*), 4.5 (d, *J* = 12.0 Hz, 1H, –C$H_2$OAc),

4.12 (d, $J$ = 12.0 Hz, 1H, –C$H_2$OAc), 3.84 (s, 3H, –O*Me*), 3.1 (m, 1H, –C–C$H_2$), 2.85 (m, 1H, –C–C$H_2$), 2.1 (s, 3H, –OCOC$H_3$), 2.03 (m, 1H, –C$H_2$–C$H_2$), 1.98 (m, 1H, –C$H_2$–C$H_2$), 1.75–1.55 (m, 2H, –C$H_2$–Me), 0.93 (t, $J$ = 7.6 Hz, 3H, –*Me*). $\delta_C$: 201.5 (*C*=O), 172.25 (–O*C*OMe), 163.73, 145.94, 130.1, 125.05, 113.37, 112.32, 68.5 (–*C*H$_2$OAc), 55.4 (–O*Me*), 48.59 (–*C*2), 28.6 (–*C*4), 25.43 (–*C*3), 22.67 (–OCO*CH*3), 20.48 (–*C*H$_2$–Me), 8.1 (–*Me*). $[\alpha]_D^{28} = -18.5$ (*c* 0.7, MeOH) ES$^+$MS (TOF): 277 (M+1). HRMS *m*/*z* [M+H]$^+$ found 277.1429 calculated 277.1434 for $C_{16}H_{21}O_4$. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min) $t_R$ = 14.55 min (major, assumed *R*), $t_R$ = 17.25 min (minor, assumed *S*).

### 4.21. Acetic acid 7-methoxy-2-methyl-1-oxo-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl ester 15

$\delta_H$: 7.55 (d, $J$ = 2.8 Hz, 1H, Ar*H*), 7.2 (d, $J$ = 8.0 Hz, 1H, Ar*H*), 7.0 (dd, $J$ = 8.0, 2.8 Hz, 1H, Ar*H*), 4.52 (d, $J$ = 11.2 Hz, 1H, –C*H*$_2$OAc), 4.13 (d, $J$ = 11.2 Hz, 1H, –C*H*$_2$OAc), 3.8 (s, 3H, –O*Me*), 3.05 (m, 1H, –C–C$H_2$), 2.88 (m, 1H, –C–C$H_2$), 2.2 (m, 1H, –CH$_2$–C$H_2$), 2.1 (s, 3H, –OCOC$H_3$), 1.75 (m, 1H, –CH$_2$–C$H_2$), 1.12 (s, 3H, –*Me*). $\delta_C$: 199.65 (*C*=O), 171.05 (–O*C*OMe), 158.3, 136.1, 132.09, 129.94, 122.08, 109.6, 68.64 (–*C*H$_2$OAc), 55.4 (–O*Me*), 45.1 (–*C*2), 31.7 (–*C*4), 24.38 (–*C*3), 20.89 (–OCO*CH*3), 19.4 (–*Me*). $[\alpha]_D^{28} = -7.6$ (*c* 0.9, MeOH). ES$^+$MS (TOF): 263 (M+1). HRMS *m*/*z* [M+H]$^+$ found 263.1285 calculated 263.1278 for $C_{15}H_{19}O_4$. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min) $t_R$ = 13.27 min (major, assumed *R*), $t_R$ = 15.98 min (minor, assumed *S*).

### 4.22. Acetic acid 5,8-dimethoxy-2-methyl-1-oxo-1,2,3,4-tetrahydro-naphthalen-2-ylmethyl ester 16

$\delta_H$: 7.0 (d, $J$ = 8.8 Hz, 1Hm Ar*H*), 6.8 (d, $J$ = 8.8 Hz, 1H, Ar*H*), 4.45 (d, $J$ = 11.2 Hz, 1H, –C*H*$_2$OAc), 4.15 (d, $J$ = 11.2 Hz, 1H, –C*H*$_2$OAc), 3.85 (s, 3H, –O*Me*), 3.82 (s, 3H, –O*Me*), 3.1 (m, 1H, –C–C$H_2$), 2.8 (m, 1H, –C–C$H_2$), 2.15 (m, 1H, –CH$_2$–C$H_2$), 2.1 (s, 3H, –OCOC$H_3$), 1.75 (m, 1H, –CH$_2$–C$H_2$), 1.2 (s, 3H, –*Me*). $\delta_C$: 200.4 (*C*=O), 172.38 (–O*C*OMe), 154.42, 150.06, 134.08, 121.49, 115.38, 109.88, 68.28 (–*C*H$_2$OAc), 56.2 (–O*Me*), 55.84 (–O*Me*), 46.95 (–*C*2), 31.23 (–*C*4), 20.98 (–*C*3), 19.24 (–OCOCH3), 18.04 (–*Me*). $[\alpha]_D^{28} = -2.3$ (*c* 0.4, MeOH). ES$^+$MS (TOF): 293 (M+1). HRMS *m*/*z* [M+H]$^+$ found 293.1376 calculated 293.1383 for $C_{16}H_{21}O_5$. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min) $t_R$ = 25.85 min (major, assumed *R*), $t_R$ = 31.24 min (minor, assumed *S*).

### 4.23. Acetic acid 2-methyl-1-oxo-indan-2-ylmethyl ester 17

$\delta_H$: 7.72 (d, $J$ = 7.6 Hz, 1H, Ar*H*), 7.6 (d, $J$ = 7.6 Hz, 1H, Ar*H*), 7.4 (d, $J$ = 7.6 Hz, 1H, Ar*H*), 7.33 (d, $J$ = 7.6 Hz, 1H, Ar*H*), 4.21 (s, 2H, –C$H_2$OAc), 3.31 (d, $J$ = 17.2 Hz, 1H, –C–C$H_2$–), 2.95 (d, $J$ = 17.2 Hz, 1H, C–C$H_2$–), 1.91 (s, 3H, –OCOC$H_3$), 1.23 (s, 3H, –Me). $\delta_C$: 204.17 (*C*=O), 178.92 (–O*C*OMe), 153.3, 135.72, 135.15, 127.43, 126.63, 124.15, 67.7 (–*C*H$_2$OAc), 50.85 (–*C*2), 37.88 (–*C*3), 22.52 (–OCOCH$_3$), 20.6 (–*Me*). $[\alpha]_D^{28} = -5.6$ (*c* 1.1, MeOH). ES$^+$MS (TOF): 219 (M+1). HRMS *m*/*z* [M+H]$^+$ found 219.1024 calculated 219.1017 for $C_{13}H_{15}O_3$. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min) $t_R$ = 9.7 min (major, assumed *R*), $t_R$ = 10.25 min (minor, assumed *S*).

### 4.24. Acetic acid 2-ethyl-1-oxo-indan-2-ylmethyl ester 18

$\delta_H$: 7.72 (d, $J$ = 7.6 Hz, 1H, Ar*H*), 7.6 (d, $J$ = 7.6 Hz, 1H, Ar*H*), 7.4 (d, $J$ = 7.6 Hz, 1H, Ar*H*), 7.33 (d, $J$ = 7.6 Hz, 1H, Ar*H*), 4.24 (s, 2H, –C$H_2$OAc), 3.20 (d, $J$ = 17.4, 1H, C–C$H_2$–), 3.06 (d, $J$ = 17.4, 1H, C–C$H_2$–), 1.96 (s, 3H, –OCOC$H_3$), 1.75 (m, 2H, –C$H_2$–Me), 0.84 (t, $J$ = 7.6 Hz, 3H, –*Me*). $\delta_C$: 203.56 (*C*=O), 174.32 (–O*C*OMe), 153.91, 136.76, 130.83, 127.15, 126.72, 124.16, 67.23 (–*C*H$_2$OAc), 54.83 (–*C*2), 34.24 (–*C*3), 25.6 (–*C*H$_2$–Me), 21.25 (–OCOCH$_3$), 10.1 (–*Me*). $[\alpha]_D^{28} = -18.8$ (*c* 0.6, MeOH). ES$^+$MS (TOF): 233 (M+1). HRMS *m*/*z* [M+H]$^+$ found 233.0658 calculated 233.0663 for $C_{14}H_{17}O_3$. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min) $t_R$ = 8.3 min (major, assumed *R*), $t_R$ = 9.4 min (minor, assumed *S*).

### 4.25. Acetic acid 2-benzyl-5-chloro-1-oxo-indan-2-ylmethyl ester 19

$\delta_H$: 7.62 (d, $J$ = 8.0 Hz, 1H, Ar*H*), 7.33 (s, 1H, Ar*H*), 7.27 (d, $J$ = 8.0 Hz, 1H, Ar*H*), 7.17–7.12 (m, 5H, Ar*H*), 4.27 (d, J = 5.2 Hz, 2H, –C$H_2$OAc), 3.1 (d, $J$ = 17.6 Hz, 1H, C–C$H_2$–), 3.0 (d, $J$ = 3.6 Hz, 2H, –C$H_2$Ph), 2.84 (d, $J$ = 17.6 Hz, 1H, C–C$H_2$–), 1.94 (s, 3H, –OCOC$H_3$). $\delta_C$: 201.34 (*C*=O), 173.24 (–O*C*OMe), 154.98, 141.71, 136.28, 134.65, 130.04, 129.96, 128.24, 127.9, 126.46, 124.87, 66.58 (–*C*H$_2$OAc), 55.65 (–*C*2), 39.85 (–*C*H$_2$Ph), 34.18 (–*C*3), 22.54 (–OCOCH$_3$). $[\alpha]_D^{28} = -12.6$(*c* 0.5, MeOH). ES$^+$MS (TOF): 329 (M+1). HRMS *m*/*z* [M+H]$^+$ found 329.5769 calculated 329.5778 for $C_{19}H_{18}ClO_3$. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min) $t_R$ = 17.42 min (major, assumed *R*), $t_R$ = 19.2 min (minor, assumed *S*).

### 4.26. Acetic acid 3-methyl-4-oxo-chroman-3-ylmethyl ester 20

$\delta_H$: 7.87 (d, $J$ = 8.0 Hz, 1H, Ar*H*), 7.5 (t, $J$ = 8.0 Hz, 1H, Ar*H*), 7.05 (d, $J$ = 8.0 Hz, 1H, Ar*H*), 6.9 (d, $J$ = 8.0 Hz, 1H, Ar*H*), 4.5 (d, $J$ = 12.0 Hz, 2H, –O–C$H_2$–), 4.36 (d, $J$ = 12.0 Hz, 1H, –C*H*$_2$OAc), 4.18 (d, $J$ = 12.0 Hz, 1H, –C*H*$_2$OAc), 2.0 (s, 3H, –OCOC$H_3$), 1.2 (s, 3H, –*Me*). $\delta_C$: 193.45 (*C*=O), 170.98 (–O*C*OMe), 161.25, 136.08, 127.64, 121.46, 119.8, 117.75, 73.37 (–OCH$_2$), 64.6 (–CH$_2$OAc), 46.98 (–*C*3), 20.67 (–OCOCH$_3$), 16.35 (–*Me*). $[\alpha]_D^{28} = -2.0$ (*c* 0.5, MeOH). ES$^+$MS (TOF): 235 (M+1); HRMS *m*/*z* [M+H]$^+$ found 235.0958 calculated 235.0966 for $C_{13}H_{15}O_4$. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min) $t_R$ = 11.1 min (major, assumed *R*), $t_R$ = 12.88 min (minor, assumed *S*).

### 4.27. Acetic acid 7-chloro-3-methyl-4-oxo-chroman-3-ylmethyl ester 21

$\delta_H$: 7.7 (d, $J$ = 8.0 Hz, 1H, Ar*H*), 7.0 (m, 2H, Ar*H*), 4.5 (d, $J$ = 12.0 Hz, 2H, –O–C$H_2$–), 4.4 (d, $J$ = 11.6 Hz, 1H, –C*H*$_2$OAc), 4.28 (d, $J$ = 11.6 Hz, 1H, –C*H*$_2$OAc), 1.98 (s, 3H, –OCOC$H_3$), 1.2 (s, 3H, –*Me*). $\delta_C$: 193.48 (*C*=O), 171.23 (–O*C*OMe), 161.86, 142.26, 134.94, 128.82, 122.38, 117.9, 72.31 (–OCH$_2$), 65.3 (–CH$_2$OAc), 48.72 (–*C*3), 21.46 (–OCOCH$_3$), 15.62 (–*Me*). $[\alpha]_D^{28} = -17.5$ (*c* 1.0, MeOH). ES$^+$MS (TOF): 269 (M+1). HRMS *m*/*z* [M+H]$^+$ found 269.5422 calculated 269.5415 for $C_{13}H_{14}ClO_4$. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min) $t_R$ = 19.55 min (major, assumed *R*), $t_R$ = 22.25 min (minor, assumed *S*).

### 4.28. Acetic acid 7-methoxy-3-methyl-4-oxo-chroman-3-ylmethyl ester 22

$\delta_H$: 7.81 (d, $J$ = 8.8 Hz, 1H, Ar*H*), 6.58 (dd, $J$ = 2.4 Hz, 8.8 Hz, 1H, Ar*H*), 6.4 (d, $J$ = 2.0 Hz, 1H, Ar*H*), 4.5 (d, $J$ = 11.2 Hz, 2H, –O–C$H_2$–), 4.35 (d, $J$ = 11.2 Hz, 1H, –C*H*$_2$OAc), 4.12 (d, $J$ = 11.2 Hz, 1H, –C*H*$_2$OAc), 3.83 (s, 3H, –O*Me*), 2.0 (s, 3H, –OCOC$H_3$), 1.2 (s, 3H, –*Me*). $\delta_C$: 204.53 (*C*=O), 172.25 (–O*C*OMe), 166.28, 163.46, 129.34, 113.62, 110.53, 100.25, 73.64 (–OCH$_2$), 64.57 (–CH$_2$OAc), 55.6 (–O*Me*), 46.44 (–*C*3), 22.45 (–OCOCH$_3$), 16.64 (–*Me*). $[\alpha]_D^{28} = -7.1$ (*c* 0.5, MeOH). ES$^+$MS (TOF): 265 (M+1). HRMS *m*/*z* [M+H]$^+$ found 265.1078 calculated 265.1071 for $C_{14}H_{17}O_5$. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min) $t_R$ = 21.81 min (major, assumed *R*), $t_R$ = 25.3 min (minor, assumed *S*).

### 4.29. Acetic acid 6,7-dimethoxy-3-methyl-4-oxo-chroman-3-ylmethyl ester 23

$\delta_H$: 7.28 (s, 1H, Ar*H*), 6.4 (s, 1H, Ar*H*), 4.44 (d, *J* = 6.2 Hz, 1H, –O–C*H*$_2$–), 4.38 (d, *J* = 6.2 Hz, 1H, –O–C*H*$_2$–), 4.19 (d, *J* = 4.4 Hz, 1H, –C*H*$_2$OAc), 4.12 (d, *J* = 4.4 Hz, 1H, –C*H*$_2$OAc), 3.91 (s, 3H, –O*Me*), 3.87 (s, 3H, –O*Me*), 2.0 (s, 3H, –OCOC*H*$_3$), 1.18 (s, 3H, –*Me*). $\delta_C$: 194.50 (*C*=O), 171.26 (–O*C*OMe), 157.8, 156.26, 144.6, 111.98, 106.83, 99.79, 73.82 (–O*C*H$_2$), 64.53 (–*C*H$_2$OAc), 56.2 (–O*Me*), 56.0 (–O*Me*), 46.67 (–*C*3), 23.14 (–OCO*C*H$_3$), 16.78 (–*Me*). $[\alpha]_D^{28} = -4.27$ (*c* 0.6, MeOH). ES$^+$MS (TOF): 295 (M+1). HRMS *m*/*z* [M+H]$^+$ found 295.1169 calculated 295.1176 for $C_{15}H_{19}O_6$. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min) $t_R$ = 55.0 min (major, assumed *R*), $t_R$ = 60.2 min (minor, assumed *S*).

### 4.30. Acetic acid 7-methyl-8-oxo-7,8-dihydro-6*H*-[1,3]dioxolo[4,5-*g*]chromen-7-ylmethyl ester 24

$\delta_H$: 7.25 (s, 1H, Ar*H*), 6.42 (s, 1H, Ar*H*), 5.99 (s, 2H, –O–*H*$_2$–O), 4.40 (d, *J* = 7.4 Hz, 1H, –O–C*H*$_2$–), 4.35 (d, *J* = 7.4 Hz, 1H, –O–C*H*$_2$–), 4.15 (d, *J* = 11.2 Hz, 2H, –C*H*$_2$OAc), 2.1 (s, 3H, –OCOC*H*$_3$), 1.19 (s, 3H, –*Me*). $\delta_C$: 194.87 (*C*=O), 172.68 (–O*C*OMe), 159.38, 154.45, 143.23, 113.33, 104.45, 102.67, 98.16 (–O–*C*H$_2$–O), 73.48 (–O*C*H$_2$), 64.85 (–*C*H$_2$OAc), 46.22 (–*C*3), 21.67 (–OCO*C*H$_3$), 16.63 (–*Me*). $[\alpha]_D^{28} = -7.3$ (*c* 0.8, MeOH). ES$^+$MS (TOF): 279 (M+1). HRMS *m*/*z* [M+H]$^+$ found 279.0868 calculated 279.0864 for $C_{14}H_{15}O_6$. HPLC (Daicel Chiralcel OJ-H, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min) $t_R$ = 22.8 min (major, assumed *R*), $t_R$ = 29.4 min (minor, assumed *S*).

### 4.31. (*R*)-3,4-Dihydrospiro[1,3-dioxolane-2-ethyl-2-hydroxymethyl-6-methoxy-1′(2*H*)-napthalene] 25

(*R*)-2-Hydroxymethyl-2-methyl-3,4-dihydro-2*H*-naphthalen-1-one (100 mg, 0.42 mmol) was taken in 5 mL benzene. Ethyleneglycol (200 mg, 2.5 mmol) was then added followed by the addition of catalytic PPTS. The reaction mixture was refluxed in a Dean–Stark apparatus for 2 days. Next benzene was evaporated and the mixture purified by flash chromatography to give the required compound in 60% yield. $\delta_H$: 7.16 (d, *J* = 8.8 Hz, 1H, Ar*H*), 6.62 (dd, *J* = 8.8, 1.6 Hz, 1H, Ar*H*), 6.45 (d, *J* = 1.6 Hz, 1H, Ar*H*), 3.88–3.8 (m, 4H, –O–C*H*$_2$–C*H*$_2$–O–), 3.85 (s, 3H, –O*Me*), 3.72 (d, *J* = 12.0 Hz, 1H, –C*H*$_2$OH), 3.65 (d, *J* = 12.0 Hz, 1H, –C*H*$_2$OH), 3.1–2.85 (m, 2H, –C–C*H*$_2$), 2.06–1.9 (m, 2H, –CH$_2$–C*H*$_2$–), 1.75–1.60 (m, 2H, –C*H*$_2$–Me), 0.93 (t, *J* = 7.6 Hz, 3H, –*Me*). $\delta_C$: 162.76 (*C*=O), 144.24, 132.35, 124.16, 116.45, 113.87, 111.32, 72.45 (–O–*C*H$_2$–CH$_2$–O–), 71.68 (–O–CH$_2$–*C*H$_2$–O–), 66.56 (–*C*H$_2$OH), 56.47 (–O*Me*), 48.79 (–*C*2), 28.66 (–*C*4), 25.43 (–*C*3), 22.67 (–*C*H$_2$–Me), 9.32 (–*Me*). ES$^+$MS (TOF): 279 (M+1).

### 4.32. (*R*)-Methanesulfonic acid-3,4-dihydrospiro[1,3-dioxolane-2-ethyl-6-methoxy-1′(2*H*)-napthalene]-2-ylmethylester 26

The compound obtained in the previous step was dissolved in anhydrous DCM (64 mg, 0.23 mmol) at 0 °C. Triethylamine (45 mg, 0.46 mmol) was added to it at the same temperature, followed by the dropwise addition of methanesulfonyl chloride (39 mg, 35 mmol). The reaction mixture was allowed to attain room temperature and stirred overnight. Next it was quenched with water, washed successively with 5% $NaHCO_3$ and brine. Evaporation of the organic layer followed by chromatographic separation provided the desired methanesulfonate ester in 65% yield. $\delta_H$: 7.19 (d, *J* = 8.8 Hz, 1H, Ar*H*), 6.68 (dd, *J* = 8.8, 1.6 Hz, 1H, Ar*H*), 6.51 (d, *J* = 1.6 Hz, 1H, Ar*H*), 3.88–3.8 (m, 4H, –O–C*H*$_2$–C*H*$_2$–O–), 3.85 (s, 3H, –O*Me*), 3.56 (d, *J* = 12.0 Hz, 1H, –C*H*$_2$–O–SO$_2$–Me), 3.44 (d, *J* = 12.0 Hz, 1H, –C*H*$_2$–O–SO$_2$–Me), 3.1–2.9 (m, 2H, –C–C*H*$_2$), 2.85 (s, 3H, –CH$_2$–O–SO$_2$–*Me*), 2.1–1.9 (m, 2H, –CH$_2$–C*H*$_2$–), 1.76–1.64 (m, 2H, –C*H*$_2$–Me), 0.92 (t, *J* = 7.6 Hz, 3H, –*Me*). $\delta_C$: 164.66, 146.46, 131.85, 123.96, 117.75, 112.87, 111.88, 73.41, 72.65, 60.46, 55.86, 48.89 (–*C*2), 39.46 (–CH$_2$–O–SO$_2$–*Me*), 27.22 (–*C*4), 24.86 (–*C*3), 20.97 (*C*H$_2$–Me), 10.42 (–CH$_2$–*Me*). ES$^+$MS (TOF): 357 (M+1).

### 4.33. (*R*)-2-Ethyl-6-methoxy-2-methyl-3,4-dihydro-2*H*-naphthalen-1-one 27

The mesylate ester (60 mg, 0.17 mmol) obtained in the previous step was taken in THF followed by addition of $LiAlH_4$ (15 mg, 0.34 mmol). The reaction mixture was refluxed for 8 h, after which time TLC indicates presence of no starting material. The reaction mixture was quenched with careful addition of saturated aqueous $Na_2SO_4$ solution at 0 °C. The reaction mixture was filtered upon a pad of Celite, and the filtrate was evaporated. The crude demesylated product (30 mg) was dissolved in THF/1M HCl (2 mL) and stirred for 24 h at room temperature. The solvent was evaporated in vacuo and the product purified by flash chromatography to afford (12 mg) the parent keto compound in 60% yield. $\delta_H$: 8.0 (d, *J* = 8.8 Hz, 1H, Ar*H*), 6.81 (dd, *J* = 8.8, 2.6 Hz, 1H, Ar*H*), 6.64 (d, *J* = 2.6 Hz, 1H, Ar*H*), 3.84 (s, 3H, O*Me*), 3.0 (m, 2H, –C–C*H*$_2$), 2.0 (m, 2H, –CH$_2$–C*H*$_2$–), 1.6 (m, 2H, –C*H*$_2$–Me), 1.2 (s, 3H, –*Me*), 0.85 (t, *J* = 7.4 Hz, 3H, C*H*$_2$–*Me*). $\delta_C$: 201.59 (*C*=O), 163.24, 145.72, 130.36, 125.47, 113.16, 112.31, 55.39 (–O*Me*), 44.52 (–*C*2), 33.29 (–*C*4), 29.71 (–*C*3), 25.84 (–*C*H$_2$–Me), 21.78 (–*Me*), 8.36 (–CH$_2$–*Me*). $[\alpha]_D^{28} = -21.1$ (*c* 1.2, MeOH). ES$^+$MS (TOF): 219 (M+1).

### 4.34. (*R*)-2-Ethyl-2-methyl-indan-1-one 28

$\delta_H$: 7.6 (d, *J* = 6.2 Hz, 1H, Ar*H*), 7.45 (m, 1H, Ar*H*), 7.40 (m, 2H, Ar*H*), 3.1 (d, *J* = 17.4 Hz, 1H, –C–C*H*$_2$), 2.85 (d, *J* = 17.4 Hz, 1H, –C–C*H*$_2$), 1.65 (m, 2H, –C*H*$_2$–Me), 1.60 (s, 3H,-CH$_2$–*Me*), 0.85 (t, *J* = 7.4 Hz, 3H, –*Me*). $\delta_C$: 211.66 (*C*=O), 152.84, 136.27, 134.76, 127.35, 126.54, 124.16, 49.72 (–*C*2), 31.28 (–*C*3), 25.8 (–*C*H$_2$–Me), 21.78 (–*Me*), 8.46 (–CH$_2$–*Me*). $[\alpha]_D^{28} = -10.4$ (*c* 1.0, MeOH). ES$^+$MS (TOF): 175 (M+1).

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