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PAPER

Enantiomeric scaffolding of α-tetralone and related scaffolds by EKR (Enzymatic Kinetic Resolution) and stereoselective ketoreduction with ketoreductases†

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Stereochemically pure compounds containing an all carbon quaternary stereocenter based on 1-tetralone, 1-indanone and 4-chromanone scaffolds have been synthesized by employing Lipase PS (*Burkholderia cepacia*) catalyzed kinetic resolution. These scaffolds are further functionalized by microbial ketoreductase enzymes (*Geotrichum candidum*, *Candida parapsilosis* and *Aspergillus niger*) to access stereochemically pure diols which, on further synthetic manipulation, yield novel cyclic compounds.

Introduction

Natural products and their analogues provide the inspiration for an array of strategies used in the diversity oriented synthesis of novel small molecule libraries.[1] These libraries are generally focused on core scaffolds from individual natural products or specific substructures found across a class of natural products or altogether a new chemotype.[2] Increasing evidence supports the utility of these strategies for identifying new biologically active small organic molecules. These efforts also have led to noteworthy advances in several novel strategies in synthetic organic chemistry.[3] The introduction of chemical diversity in compound collection libraries according to different strategies of organic synthesis is essential for the identification of small organic molecules with diverse biological activities. The ongoing development of novel synthetic methodology, both on solid phase and in solution, enables the creation of small molecule libraries with well defined substituent, stereochemical and scaffold diversity to yield new lead molecules (after biological screening) from relatively small compound collections. Generation of carbon containing quaternary stereocenters is a challenging and daunting task in asymmetric organic synthesis. There exist many well-defined chemical strategies for creating a quaternary stereocenter in an organic molecule.[4] Still, the quest for newer methods for the above mentioned theme is ongoing. Though there exist many chemocatalyst based strategies for generation of quaternary stereocenters, very few efficient biocatalytic approaches have been known in the literature till today.[5] Enzymatic kinetic resolution (EKR), desymmetrization of *meso* or prochiral substrates (enantioselective enzymatic desymmetrization) are different approaches which can be used successfully to create all carbon quaternary stereocenters in small organic molecules.[6] We have earlier demonstrated an efficient method to generate all carbon quaternary stereocenters by EKR based on α-tetralone, α-indanone and chroman-4-one scaffolds.[7] The methodology has been successfully applied to the synthesis of 2,2-dialkylated tetralones and indanones in an asymmetric fashion. We have chosen chromanone, α-tetralone and α-indanone based scaffolds as there exist many natural products based on chromanone (flavonoids and homoisoflavonoids) and α-tetralone.[8] The generality of our method is well explored for many substrates. In the present work we intend to extend our strategies for further stereoselective biocatalytic functionalization on the existing scaffolds in a diverse way (Scheme 1).

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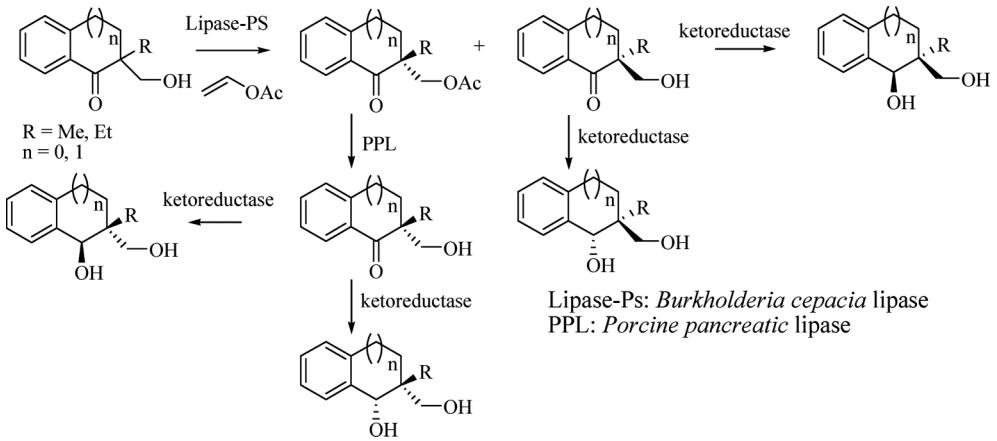
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra and HPLC chromatograms for all new compounds. The cif files for the two crystals reported in this article have been deposited with the Cambridge Crystallographic Data Centre. CCDC reference numbers 830577 and 830578. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob06545a

Results and discussion

Enzymatic kinetic resolution of tetralone/indanone and chromanone scaffolds

The initial EKR has been optimized in our lab by taking many substrates based on α-tetralone, α-indanone and chroman-4-one.[7b] The enantioselectivity and absolute configuration for the fast reacting acetate enantiomer and the slow reacting alcohol in the EKR reaction has been established by the Kazlauskas empirical rule. In our earlier article we did have minor problems using the deacetylation reaction from the acetate compounds (obtained from the fast reacting enantiomer) to access the stereochemically pure alcohols, mainly due to the fact that in some cases slight racemization is observed under the reaction conditions (K_2CO_3/MeOH). The problem of this racemization has been taken care of by performing an enzyme (lipase, *Porcine*



Scheme 1 Proposed biocatalytic functionalization of tetralone and indanone scaffolds.

pancreatic lipase) mediated deacetylation reaction. Though the enzyme-mediated (PPL) deacetylation is a little time consuming, the reaction is extremely efficient in terms of chemical yield as well as stereochemical purity of the obtained alcohols (as no racemization was observed during enzymatic deacetylation). So, by changing the deacetylation conditions we have access to both the enantiomeric hydroxymethylated compounds bearing all carbon quaternary stereocenters based on α-tetralones, α-indanones and chroman-4-one. The enantiomeric excess (ee) for the product acetates of **1–14** (Scheme 2) as well as the parent alcohols was determined by chiral-HPLC measurements. In all the cases we have synthesized racemic acetates of compounds **1–14** by means of chemical acylation and recorded their HPLC data, which allows us to assign the retention time for major and minor enantiomers respectively. The reaction was monitored by TLC and the reaction was stopped after an appreciable amount of conversion was achieved (as indicated by quantitative HPLC analysis; the presence of approximately 1 : 1 ratio of alcohol and acetate was indicated). The selectivity factor (*E*) for the EKR reaction is shown in Table 1 for all the substrates (**2–4** and **8–12**, data for substrates **1**, **5–7**, **13–14** was presented in our earlier article).[7b]

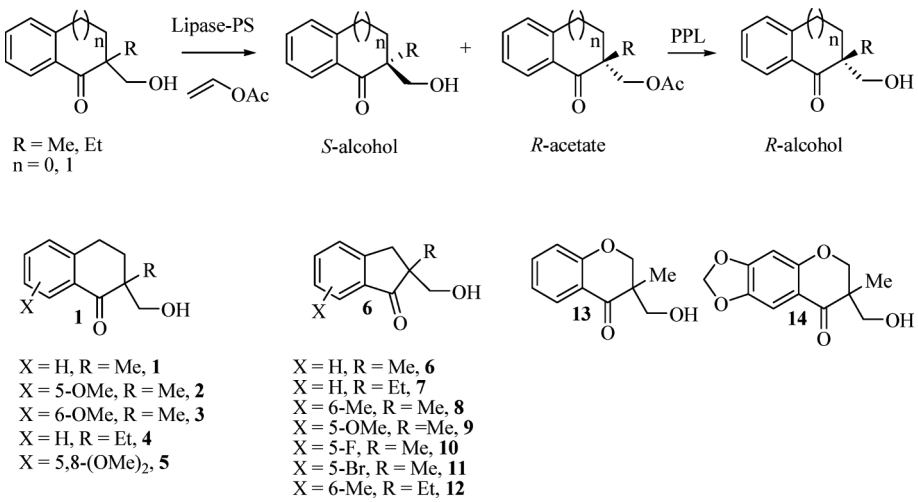
Table 1 Lipase-PS catalyzed transesterification of compounds **2–4** and **8–12**

Entry	Substrate	Conversion(c)	Ee_s[a] (%)	Ee_p[a] (%)	*E*[b]
1	2	49	97	99	> 200
2	3	49	96	98	> 200
3	4	49	96	98	> 200
4	8	49	94	97	> 200
5	9	49	96	99	> 200
6	10	49	94	99	> 200
7	11	49.9	93	94	110
8	12	49.9	94	95	139

[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/).

Microbial ketoreductase isolation and assay

Next we focused our attention on applying several ketoreductase classes of enzymes for the asymmetric reduction of the keto



Scheme 2 Monoalkylated hydroxymethylated tetralone, indanone and chromanone based scaffolds for EKR reaction.

functionality in compounds **1–14** (to both the enantiomers). Several microbial ketoreductases were screened for that purpose.[9] As the enantioselectivity of many of the ketoreductases was not known, we thought to develop an enantioselective assay based on chiral HPLC for all the ketoreductase enzymes employed in our work. α-Tetralone was taken as a model substrate as the corresponding reduced product 1,2,3,4-tetrahydro-naphthalen-1-ol is known in the literature,[10] and the HPLC retention times are also known for both the enantiomers (t_R = 7.55; t_S = 6.29; Chiral OJ-H column; hexane : *i*-PrOH = 9 : 1, flow rate: 1 ml min^{-1}; Fig. 1). We found that the ketoreductase enzyme isolated from *Geotrichum candidum* (NBRC 5767) reduces 1-tetralone in an *anti*-Prelog fashion to afford the corresponding alcohol (*R*-1,2,3,4-tetrahydro-napthalen-1-ol). Whereas ketoreductases from *Candida parapsilosis* (NBRC 1396) and *Aspergillus niger* (NBRC 4415) afford the corresponding alcohols in Prelog fashion for the reduction of 1-tetralone to yield (*S*)-1,2,3,4-tetrahydro-napthalen-1-ol (Scheme 3).

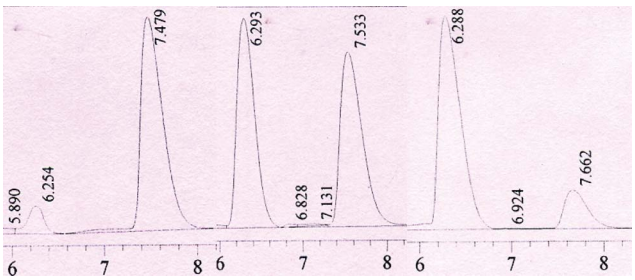
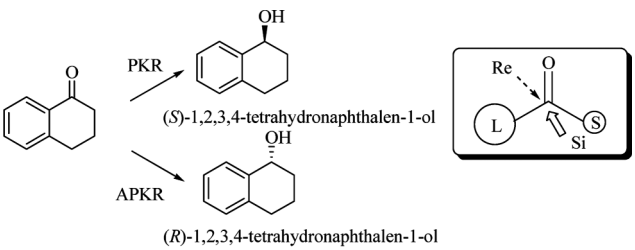


Fig. 1 HPLC chromatogram of (*R*)-enantiomer, racemic compound and (*S*)-enantiomer of 1,2,3,4-tetrahydro-naphthalen-1-ol (Chiral OJ-H; flow rate: 1 ml min^{-1}; mobile phase: hexane–*i*PrOH = 9 : 1).



PKR: Prelog ketoreductase; *Candida parapsilosis/Aspergilus niger*
APKR: Anti Prelog ketoreductase; *Geotrichum candidum*

Scheme 3 Enantioselective assay of microbial ketoreductase by using 1-tetralone as a substrate.

Biocatalytic reduction of both the enantiomers of 1–14 to access various stereochemically pure diols

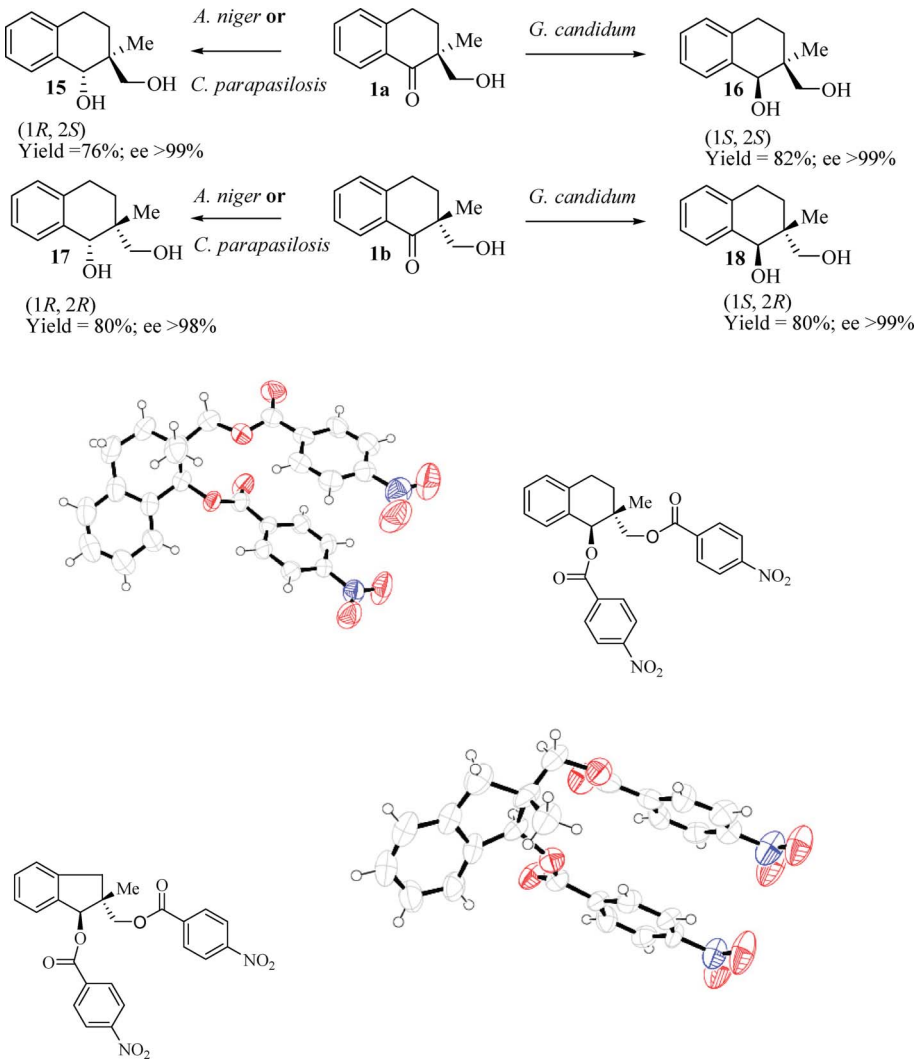
Next we focused our attention on applying the above microbial strains of the ketoreductase class of enzymes for the asymmetric reduction of the keto functionality in compounds **1–14**. Several microbial ketoreductases were employed for that purpose, and we found that the ketoreductase enzyme isolated from *Geotrichum candidum* (NBRC 5767) reduces the ketones in an *anti*-Prelog fashion to afford the corresponding alcohols. Whereas ketoreductases from *Candida parapsilosis* (NBRC 1396) and *Aspergillus niger* (NBRC 4415) affords the corresponding alcohols in Prelog fashion. Ketroreductase strains were obtained from NBRC, Osaka and stored in glycerol (50% v/v) at –20 °C. The cells were grown in specified medium (as mentioned in the manual) in 500 mL conical flasks for 24 h. Substrates (tetralones/indanones and chromanones) were directly added to the growing cells of ketoreductase solution. Reactions were monitored periodically by TLC analysis. It usually takes 2–3 days for quantitative conversion and after that the product alcohols can be extracted in organic solvents and purified by standard techniques. The stereochemistries of the final alcohols were confirmed by X-ray crystal analysis by preparing the corresponding PNBz (*para*-nitrobenzoate) derivatives (Scheme 4).† The chemical yield and enantiomeric purity of the reduction process of both the enantiomers of compound **1** are listed in Scheme 4. It was observed that the growing cells of the above mentioned microbial ketoreductase strains afford excellent enantioselection in the final alcohols, though the chemical yield is somewhat less in a few cases. It is also important to note that ketoreductases from *G. candidum* and *C. parapsilosis*/*A. niger* are stereocomplementary with respect to the product alcohols (as the hydride is transferred to *Re*- and *Si*- face subsequently). This methodology was successfully applied to all of the other compounds (**2–13**). In all the cases stereochemically pure diols were obtained in good yield. Therefore a series of stereochemically pure 1,3-diols have been prepared biocatalytically with PKR (*Candida parapsilosis*/*Aspergillus niger*) and APKR (*Geotrichum candidum*).

The structures of all the diols (**19–44**) are presented in Scheme 5. In general, good chemical yield and excellent diastereoselectivity were obtained for the synthesized diols by using those microbial ketoreductase strains. It is worth mentioning that, though ketoreductase from *G. candidum* has a wide application in synthetic biotransformation, ketoreductases from *A. niger* (NBRC 4415) and *C. parapsilosis* (NBRC 1396) are not explored well in synthetic biocatalysis.[11] Both of these ketoreductases follow the Prelog's rule for the hydride transfer to a prochiral carbonyl compound and provide excellent enantioselection for the synthesized diols.

Generation of stereochemically pure novel tricyclic scaffolds from biocatalytically derived diols

Next we focused our attention on creating further molecular complexity from the biocatalytically synthesized diols. We intended to create a dihydropyran ring from the two hydroxyl appendages by using a RCM (ring closing metathesis) reaction followed by an AD reaction (asymmetric dihydroxylation), to access stereochemically pure tricyclic diols. For that reason we have chosen diols **18** and **37**.

Diol **18** was monoprotected as its TBS ether (*tert*-butyldimethyl silyl) to yield compound **45** in 90% yield. The secondary hydroxyl group in **45** was protected as its PNBz (4-nitrobenzoate) ester on treatment with 4-nitrobenzoic acid with EDC·HCl–DMAP to afford **46** in 88% yield. Upon exposure to PPTS in methanol compound **46** furnished alcohol **47** with removal of the TBS group in 82% yield.[12] Oxidation of alcohol **47** under Swern conditions [13] afforded the aldehyde **48** in 90% yield. Wittig olefination of aldehyde **48** with methyltriphenylphosphonium iodide in the presence of LHMDS at –5 °C afforded compound **49** in 78% yield. Deprotection of the PNBz group in compound **49** was achieved



Scheme 4 Biocatalytic reduction of both the enantiomers of **1** for synthesis of all the possible stereoisomers of the diol, and ORTEP presentation of the bis-PNBz derivatives of diols **18** and **27**.

on treatment with 10% aq. NaOH [14] and afforded **50** in 86% yield. The secondary hydroxyl group in **50** was converted to its *O*-allyl ether upon treatment with allyl bromide and Ag_2O[15] to furnish compound **51** in 88% yield. Ring closing metathesis reaction (RCM) of compound **51** with Grubbs 1st generation catalyst [16] in DCM solvent at room temperature afforded compound **52** in 77% yield. Asymmetric dihydroxylation with AD mix-β [17] of compound **52** afforded the tricyclic diol **53** in 78% yield (overall yield = 21% from the diol **18**, Scheme 6). The same reaction sequence was performed with indanone based diol **37** to provide the tricyclic diol **62** as a single stereoisomer (overall yield = 19% from the diol **37**, Scheme 6). The synthesized tricyclic diol scaffold found in compounds **53** and **62** is unique, as these types of compounds have not been reported elsewhere, and can serve as a new chemotype.

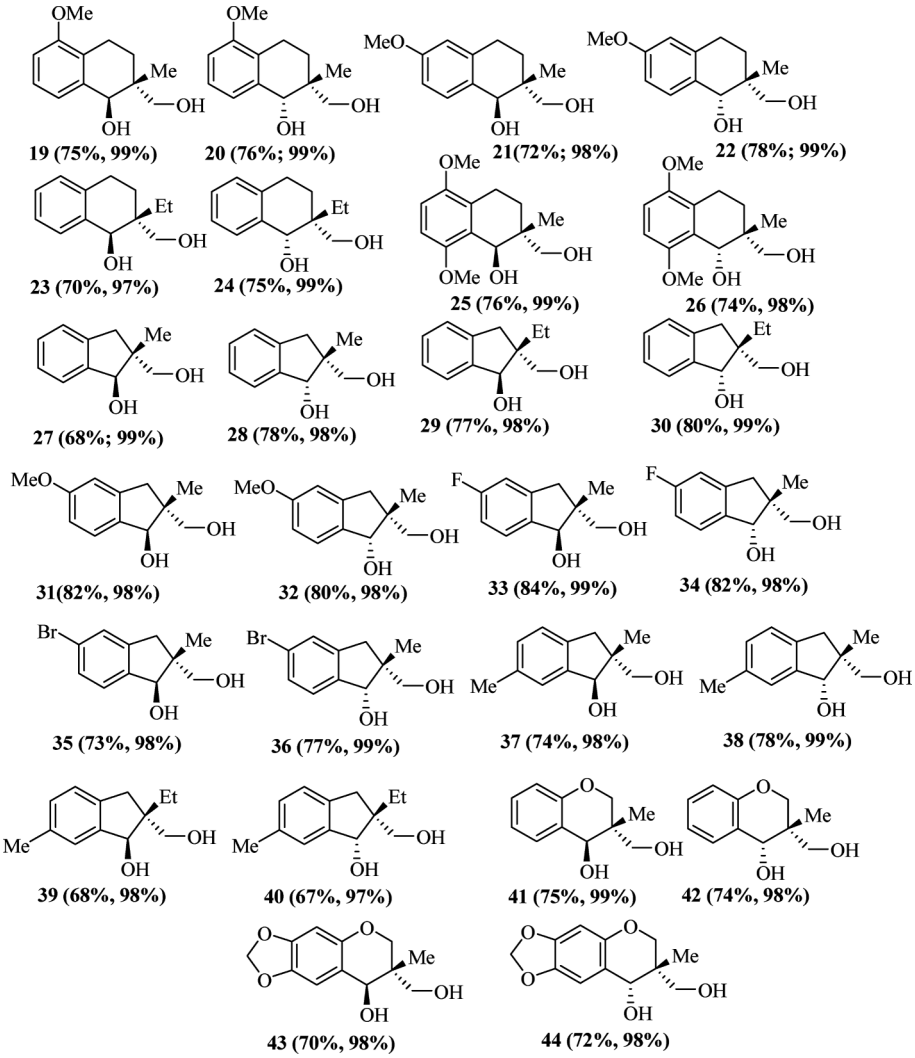
Conclusion

In conclusion we have described an efficient asymmetric synthetic strategy for a diverse set of diols based on α-tetralone, α-indanone and chroman-4-one scaffolds by employing two consecutive biocatalytic steps. The first one allows us to fix a quaternary stereocenter by lipase catalyzed EKR strategy whereas the second one involves a unique microbial carbonyl reductase induced alcohol synthesis with absolute stereocontrol. The synthesized diols can serve as potential chiral building blocks for novel tricyclic compounds as demonstrated by us in this article.

Experimental section

General information

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. Microbial ketoreductases strains *G. candidum* (NBRC 5767), *C. parapsilosis* (NBRC 1396) and *A. niger* (NBRC 4415) were obtained from NBRC, Japan and



Scheme 5 Biocatalytically synthesized diols (synthesis from one set of enantiomer is only shown) by applying PKR (*Candida parapsilosis*-NBRC 1396) and APKR (*Geotrichum candidum* NBRC 5767. Yields and enantiomeric purity are given under each compound.

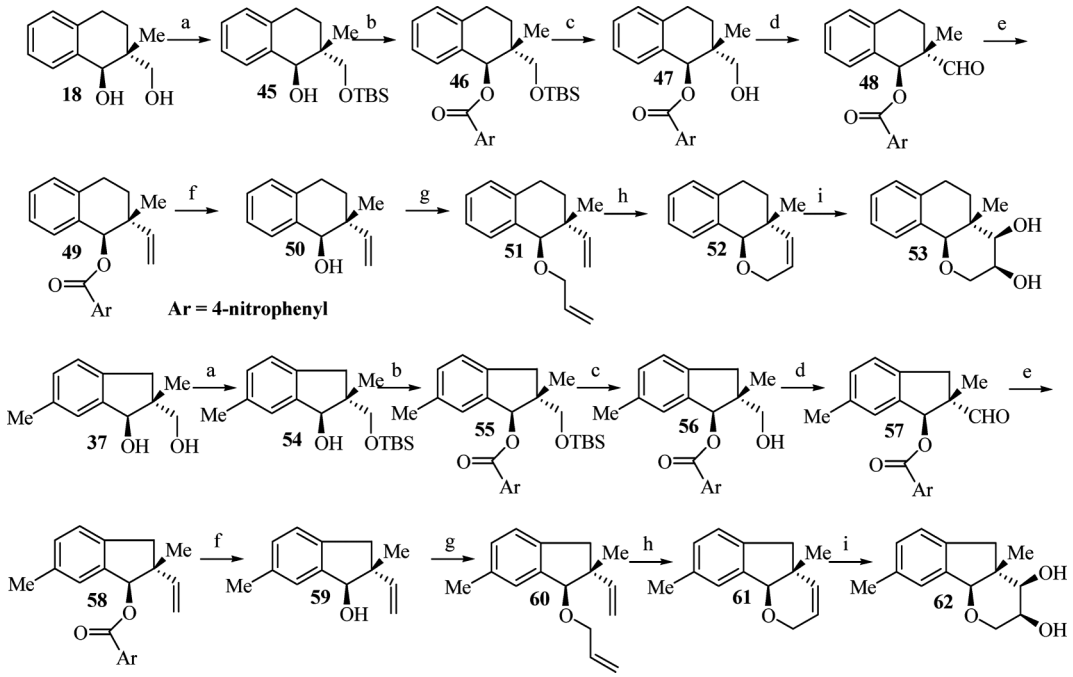
maintained in Petri dishes as well as in glycerol slants periodically. Bioreductions were performed in an incubator shaker at 35 °C. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (Merck) with UV light, ethanolic anisaldehyde and phosphomolybdic acid/heat 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 200 & 400 MHz spectrometers at 25 °C in $CDCl_3$ using TMS as the internal standard. Chemical shifts are shown in δ. ^{13}C NMR spectra were recorded with a complete proton decoupling environment. The chemical shift value is listed as δ_H and δ_C for ^1H and ^{13}C, respectively. Optical rotations were measured on a digital polarimeter. Chiral HPLC was performed using Chiral OJ-H, AS-H and OD-H column (0.46 × 25 cm) with LC-20AT chromatograph coupled with UV–vis detector (254 nm). Eluting solvent used was different ratios of hexane and 2-propanol. HRMS data are collected from University of Hyderabad, and IACS-Kolkata, India.

Growing conditions for microbial ketoreductases: *G. candidum* (NBRC 5767)

The dried cells obtained from the culture collection were moistened with the rehydration fluid (peptone 5 g, yeast extract 3 g, $MgSO_4 \cdot 7H_2O$ 1 g, distilled water 1 L, pH 7.0). It was streaked into several Petri dishes (Growth medium: PSA medium) and then incubated at 25 °C in an incubator for 24 h.

Recipe for PSA (potato sucrose agar) medium: potatoes were washed with tap water, peeled and cut into 1 cm small cubes. Then they were rinsed with tap water quickly and 200 g of potato cubes were boiled with 1 L of distilled water for 20 min. After that they were mashed and squeezed through a muslin bag. Finally agar was added to it and boiled till melted. Sucrose (20 g) was added to the solution and stirred well till dissolved. The final volume made was 1 L (pH = 5.6) and then it was autoclaved to sterilize it.

For the biotransformation purpose with NBRC 5767, PS liquid medium was prepared without agar, and then the grown cells of *G. candidum* were transferred to this medium through an inoculating



Scheme 6 Synthesis of stereochemically pure tricyclic diols from biocatalytically derived diols **18** and **37**. *Reagents and conditions*: a) TBS-Cl, imidazole, rt, 90%; b) 4-nitrobenzoic acid, EDC·HCl–DMAP, rt, 88%; c) PPTS, MeOH, rt, 82%; d) $(COCl)_2$, Me_2SO, Et_3N, −78 °C, 90%; e) $Ph_3P^+MeI^-$, LHMDS, −5 °C, 78%; f) 10% aq. NaOH, rt, 6h, 86%; g) $CH_2{=}CH{-}CH_2Br$, Ag_2O, rt, 48 h, 88%; h) Grubbs 1st generation catalyst, DCM, rt, 77%; i) AD mix-β, $MeSO_2NH_2$, *t*BuOH–H_2O (1 : 1), rt, 24 h, 78%.

loop. The content was incubated in an incubator shaker for 24 h, and after that substrates were directly added to the growing culture medium.

C. parapsilosis (NBRC 1396)

The dried cells obtained from the culture collection were moistened with the rehydration fluid (YM liquid medium: glucose 10 g, peptone 5 g, yeast extract 3 g, malt extract 3 g, distilled water 1 L, pH 7.0). It was streaked into several Petri dishes (growth medium: YM agar) and then incubated at 25 °C in an incubator for 24 h.

For the biotransformation purpose with NBRC 1396, YM liquid medium was prepared without agar, and then the grown cells of *C. parapsilosis* were transferred to this medium through an inoculating loop. The content was incubated in an incubator shaker for 24 h, and after that period substrates were directly added to the growing culture medium.

A. niger (NBRC 4415)

The dried cells obtained from the culture collection were moistened with the rehydration fluid (same as NBRC 5767). It was streaked into several Petri dishes (growth medium: PSA medium) and then incubated at 25 °C in an incubator for 24 h.

For the biotransformation purpose with NBRC 4415 similar procedures to those for NBRC 5767 were followed.

Experimental conditions for bioreductions

The strains of different microbial ketoreductases were grown on specific media as described earlier. Substrates (**1–14**, 100 mg) were dissolved in minimum amount of EtOH and added to the growing culture of ketoreductase medium. The reaction mixture was incubated with an incubator shaker at 30 °C. The reaction was monitored with periodical TLC analysis. After all the starting materials had been consumed (usually took 2–3 days) the reaction mixture was extracted several times with EtOAc, and the organic layer was dried (Na_2SO_4) followed by evaporation and purification by means of silica gel chromatography (SGC) affording the pure diols.

(1*R*,2*S*)-1,2,3,4-Tetrahydro-2-(hydroxymethyl)-2-methylnaphthalen-1-ol (15)

δ_H ($CDCl_3$, 400 MHz): 7.56 (d, J = 7.6 Hz, 1H), 7.23–7.08 (m, 3H), 4.76 (s, 1H), 3.65 (d, J = 10.4 Hz, 1H), 3.61 (d, J = 10.4 Hz, 1H), 2.90–2.76 (m, 2H), 1.59–1.51 (m, 2H), 0.98 (s, 3H).

δ_C ($CDCl_3$, 100 MHz): 138.6, 134.7, 127.3, 126.3, 125.6, 125.1, 72.3, 70.3, 37.5, 28.6, 24.6, 14.0.

$[\alpha]_D^{29}$ = +14.36 (c = 1, MeOH).

HRMS (ESI) Calcd for $C_{12}H_{16}O_2Na$ $[M + Na]^+$, 215.1047; Found, 215.1050.

(1*S*,2*S*)-1,2,3,4-Tetrahydro-2-(hydroxymethyl)-2-methylnaphthalen-1-ol (16)

δ_H ($CDCl_3$, 200 MHz): 7.42 (d, J = 7.6 Hz, 1H), 7.23–6.86 (m, 3H), 4.56 (s, 1H), 3.43 (d, J = 10.6 Hz, 1H), 3.3 (d, J = 10.6 Hz, 1H), 2.72–2.57 (m, 2H), 1.59–1.28 (m, 2H), 0.7 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 138.9, 135.2, 127.9, 126.6, 126.3, 125.8, 73.5, 71.6, 38.0, 29.2, 25.1, 14.2.

$[\alpha]_D^{29}$ = +4.36 (c = 0.5, MeOH).

HRMS (ESI) Calcd for $C_{12}H_{16}O_2Na[M + Na]^+$, 215.1047; Found, 215.1050.

(1*S*,2*R*)-1,2,3,4-Tetrahydro-2-(hydroxymethyl)-5-methoxy-2-methylnaphthalen-1-ol (19)

δ_H ($CDCl_3$, 400 MHz): 7.26–7.17 (m, 2H), 6.74 (d, J = 7.6 Hz, 1H), 4.73 (s, 1H), 3.82 (s, 3H), 3.6 (s, 2H), 2.77–2.57 (m, 2H), 1.57–1.54 (m, 2H), 0.96 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 156.9, 139.8, 127.0, 124.5, 118.8, 108.4, 75.2, 72.9, 55.5, 37.9, 28.8, 19.8, 14.2.

$[\alpha]_D^{29}$ −7.88 (*c* 0.8, MeOH).

HRMS (ESI) Calcd for $C_{13}H_{18}O_3Na[M + Na]^+$, 245.1153; Found, 245.1161.

(1*R*,2*R*)-1,2,3,4-Tetrahydro-2-(hydroxymethyl)-5-methoxy-2-methylnaphthalen-1-ol (20)

δ_H ($CDCl_3$, 400 MHz): 7.28–7.16 (m, 2H), 6.72 (d, J = 7.6 Hz, 1H), 4.76 (s, 1H), 3.80 (s, 3H), 3.6 (s, 2H), 2.77–2.52 (m, 2H), 1.57–1.54 (m, 2H), 0.92 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 156.8, 139.8, 127.2, 124.6, 118.9, 108.3, 75.2, 73.0, 55.4, 37.8, 28.7, 19.8, 14.2.

$[\alpha]_D^{29}$ −3.45 (*c* 0.6, MeOH).

HRMS (ESI) Calcd for $C_{13}H_{18}O_3Na[M + Na]^+$, 245.1153; Found, 245.1161.

(1*S*,2*R*)-1,2,3,4-Tetrahydro-2-(hydroxymethyl)-6-methoxy-2-methylnaphthalen-1-ol (21)

δ_H ($CDCl_3$, 200 MHz): 7.44 (d, J = 8.6 Hz, 1H), 6.78 (dd, J = 8.6, 2.6 Hz, 1H), 6.61 (d, J = 2.2 Hz, 1H), 4.68 (s, 1H), 3.78 (s, 3H), 3.64 (s, 2H), 2.97–2.63 (m, 2H), 1.68–1.45 (m, 2H), 1.0 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 158.4, 136.6, 130.5, 128.1, 113.2, 112.4, 74.7, 72.3, 55.4, 38.1, 29.2, 25.3, 14.3.

$[\alpha]_D^{29}$ = 0.88 (*c* = 1.0, MeOH).

HRMS (ESI) Calcd for $C_{13}H_{18}O_3Na[M + Na]^+$, 245.1153; Found, 245.1161.

(1*R*,2*R*)-1,2,3,4-Tetrahydro-2-(hydroxymethyl)-6-methoxy-2-methylnaphthalen-1-ol (22)

δ_H ($CDCl_3$, 200 MHz): 7.45 (d, J = 8.6 Hz, 1H), 6.78 (dd, J = 8.6, 2.6 Hz, 1H), 6.61 (d, J = 2.4 Hz, 1H), 4.69 (s, 1H), 3.78 (s, 3H), 3.6 (s, 2H), 2.93–2.63 (m, 2H), 1.62–1.52 (m, 2H), 0.98 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 158.6, 136.7, 130.6, 128.1, 113.0, 112.4, 74.6, 72.5, 55.2, 38.2, 29.1, 25.4, 14.3.

$[\alpha]_D^{29}$ = 11.2 (*c* = 1.0, MeOH).

HRMS (ESI) Calcd for $C_{13}H_{18}O_3Na[M + Na]^+$, 245.1153; Found, 245.1162.

(1*S*,2*R*)-2-Ethyl-1,2,3,4-tetrahydro-2-(hydroxymethyl)naphthalen-1-ol (23)

δ_H ($CDCl_3$, 200 MHz): 7.53 (d, J = 7.0 Hz, 1H), 7.26–7.07 (m, 3H), 4.81 (s, 1H), 3.75 (d, J = 10.8 Hz, 1H), 3.56 (d, J = 10.8 Hz, 1H), 2.83–2.66 (m, 2H), 1.83–1.6 (m, 2H), 1.5–1.22 (m, 2H), 1.15 (t, J = 7.4 Hz, 3H).

δ_C ($CDCl_3$, 50 MHz): 138.1, 135.6, 128.3, 126.9, 126.5, 126.3, 76.4, 68.9, 40.2, 25.2, 24.9, 17.6, 7.2.

$[\alpha]_D^{29}$ = 2.2 (*c* = 0.4, MeOH).

HRMS (ESI) Calcd for $C_{13}H_{18}O_2Na[M + Na]^+$, 229.1204; Found, 229.1197.

(1*R*,2*R*)-2-Ethyl-1,2,3,4-tetrahydro-2-(hydroxymethyl)naphthalen-1-ol (24)

δ_H ($CDCl_3$, 200 MHz): 7.52 (d, J = 6.4 Hz, 1H), 7.22–7.07 (m, 3H), 4.81 (s, 1H), 3.75 (d, J = 10.8 Hz, 1H), 3.56 (d, J = 10.8 Hz, 1H), 2.83–2.72 (m, 2H), 1.83–1.6 (m, 2H), 1.5–1.22 (m, 2H), 1.25 (t, J = 7.4 Hz, 3H).

δ_C ($CDCl_3$, 50 MHz): 138.1, 135.6, 128.3, 127.0, 126.6, 126.3, 76.5, 68.9, 40.2, 25.2, 24.9, 17.6, 7.2.

$[\alpha]_D^{29}$ −7.28 (*c* 0.8, MeOH).

HRMS (ESI) Calcd for $C_{13}H_{18}O_2Na[M + Na]^+$, 229.1204; Found, 229.1197.

(1*R*,2*R*)-1,2,3,4-Tetrahydro-2-(hydroxymethyl)-5,8-dimethoxy-2-methylnaphthalen-1-ol (25)

δ_H ($CDCl_3$, 200 MHz): 6.69 (s, 2H), 4.9 (s, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 3.56 (d, J = 10.6 Hz, 1H), 3.48 (d, J = 10.6 Hz, 1H), 2.65 (m, 2H), 1.65–1.38 (m, 2H), 1.15 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 152.4, 151.6, 127.8, 127.0, 108.5, 108.1, 72.2, 71.8, 55.9, 55.8, 37.7, 28.3, 20.3, 16.2.

$[\alpha]_D^{29}$ = 5.08 (*c* = 1.0, MeOH).

(1*S*,2*R*)-1,2,3,4-Tetrahydro-2-(hydroxymethyl)-5,8-dimethoxy-2-methylnaphthalen-1-ol (26)

δ_H ($CDCl_3$, 200 MHz): 6.66 (s, 2H), 4.87 (s, 1H), 3.8 (s, 3H), 3.75 (s, 3H), 3.53 (d, J = 10.4 Hz, 1H), 3.48 (d, J = 10.4 Hz, 1H), 2.62 (m, 2H), 1.59–1.38 (m, 2H), 1.06 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 152.4, 151.6, 127.9, 127.1, 108.6, 108.2, 72.2, 71.8, 55.9, 55.8, 37.7, 28.3, 20.3, 16.2.

$[\alpha]_D^{29}$ = 12.3 (*c* = 0.9, MeOH).

(1*S*, 2*R*)-2,3-Dihydro-2-(hydroxymethyl)-2-methyl-1*H*-inden-1-ol (27)

δ_H ($CDCl_3$, 200 MHz): 6.99 (s, 1H), 6.87–6.82 (m, 2H), 4.82 (s, 1H), 3.41 (s, 2H), 2.6 (d, J = 14.4 Hz, 1H), 2.34 (d, J = 14.4 Hz, 1H), 2.14 (s, 3H), 0.8 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 144.6, 137.4, 135.7, 128.1, 124.8, 124.5, 78.8, 69.0, 50.4, 39.7, 21.2, 17.1.

$[\alpha]_D^{29}$ −4.68 (*c* 1.0, MeOH).

HRMS (TOF) Calcd for $C_{11}H_{14}O_2Na$ $[M + Na]^+$,201.0892; Found, 201.0892.

(1*R*,2*R*)-2,3-Dihydro-2-(hydroxymethyl)-2-methyl-1*H*-inden-1-ol (28)

δ_H ($CDCl_3$, 200 MHz): 7.18 (s, 1H), 7.05 (m, 2H), 5.04 (s, 1H), 3.70 (s, 2H), 2.76 (d, J = 15.6 Hz, 1H), 2.57 (d, J = 15.6 Hz, 1H), 2.34 (s, 3H), 1.05 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 143.9, 137.3, 136.5, 128.8, 124.8, 124.7, 80.1, 70.3, 50.2, 39.9, 21.3, 16.9.

$[\alpha]_D^{29}$ −18.9 (*c* 1.0, MeOH).

HRMS (TOF) Calcd for $C_{11}H_{14}O_2Na$, 201.0892; Found, 201.0892.

(1*S*,2*R*)-2-Ethyl-2,3-dihydro-2-(hydroxymethyl)-1*H*-inden-1-ol (29)

δ_H ($CDCl_3$, 200 MHz): 7.38–7.34 (m, 1H), 7.25–7.14 (m, 3H), 5.1 (s, 1H), 3.72 (d, J = 10.6 Hz, 1H), 3.57 (d, J = 10.6 Hz, 1H), 2.78 (d, J = 15.8 Hz, 1H), 2.58 (d, J = 15.8 Hz, 1H), 1.83–1.69 (m, 1H), 1.55–1.4 (m, 1H), 0.89 (t, J = 7.4 Hz, 3H).

δ_C ($CDCl_3$, 50 MHz): 144.3, 141.0, 128.3, 126.9, 125.1, 124.4, 80.8, 67.2, 52.6, 37.4, 21.5, 8.9.

$[\alpha]_D^{29}$ −2.85 (*c* 1.0, MeOH).

HRMS (ESI) Calcd for $C_{12}H_{16}O_2Na[M + Na]^+$, 215.1047; Found, 215.1043.

(1*R*,2*R*)-2-Ethyl-2,3-dihydro-2-(hydroxymethyl)-1*H*-inden-1-ol (30)

δ_H ($CDCl_3$, 200 MHz): 7.38–7.34 (m, 1H), 7.25–7.14 (m, 3H), 5.1 (s, 1H), 3.71 (d, J = 10.6 Hz, 1H), 3.58 (d, J = 10.6 Hz, 1H), 2.77 (d, J = 15.8 Hz, 1H), 2.58 (d, J = 15.8 Hz, 1H), 1.83–1.69 (m, 1H), 1.55–1.4 (m, 1H), 0.89 (t, J = 7.4 Hz, 3H).

δ_C ($CDCl_3$, 50 MHz): 144.1, 140.8, 128.2, 126.8, 124.9, 124.2, 80.7, 67.1, 52.4, 37.2, 21.3, 8.8.

$[\alpha]_D^{29}$ −7.55 (*c* 0.75, MeOH).

HRMS (ESI) Calcd for $C_{12}H_{16}O_2Na[M + Na]^+$, 215.1047; Found, 215.1043.

(1*S*,2*R*)-2,3-Dihydro-2-(hydroxymethyl)-5-methoxy-2-methyl-1*H*-inden-1-ol (31)

δ_H ($CDCl_3$, 200 MHz): 7.24 (m, 1H), 6.75–6.69 (m, 2H), 4.95 (s, 1H), 3.79 (s, 3H), 3.57 (s, 2H), 2.77 (d, J = 15.8 Hz, 1H), 2.54 (d, J = 15.8 Hz, 1H), 1.05 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 159.9, 142.4, 136.1, 125.2, 126.7, 110.4, 78.9, 69.5, 55.4, 50.1, 40.4, 17.2.

$[\alpha]_D^{29}$ −8.45 (*c* 1.0, MeOH).

HRMS (ESI) Calcd for $C_{12}H_{16}O_3Na$ $[M + Na]^+$,231.0997; Found, 231.0991.

(1*R*,2*R*)-2,3-Dihydro-2-(hydroxymethyl)-5-methoxy-2-methyl-1*H*-inden-1-ol (32)

δ_H ($CDCl_3$, 200 MHz): 7.23 (m, 1H), 6.76–6.69 (m, 2H), 4.95 (s, 1H), 3.76 (s, 3H), 3.63 (s, 2H), 2.73 (d, J = 15.8 Hz, 1H), 2.57 (d, J = 15.8 Hz, 1H), 1.05 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 160.3, 142.6, 136.2, 125.4, 112.9, 110.7, 79.7, 70.3, 55.6, 50.3, 40.6, 17.3.

$[\alpha]_D^{29}$ −11.6 (*c* 1.0, MeOH).

HRMS(ESI) Calcd for $C_{12}H_{16}O_3Na[M + Na]^+$, 231.0997; Found, 231.0991.

(1*S*,2*R*)-5-Fluoro-2,3-dihydro-2-(hydroxymethyl)-2-methyl-1*H*-inden-1-ol (33)

δ_H ($CDCl_3$, 200 MHz): 7.27–7.2 (m, 1H), 6.86–6.77 (m, 2H), 4.95 (s, 1H), 3.57 (s, 2H), 2.77–2.46 (m, 2H), 0.96 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 162.82 (d, J = 242.5 Hz), 142.78 (d, J = 8.5 Hz), 139.73 (d, J = 2.0 Hz), 125.45 (d, J = 9.0 Hz), 113.46 (d, J = 22.5 Hz), 111.96 (d, J = 22.0 Hz), 78.7, 69.4, 50.6, 40.1, 17.0.

$[\alpha]_D^{29}$ −1.22 (*c* 0.5, MeOH).

(1*R*,2*R*)-5-Fluoro-2,3-dihydro-2-(hydroxymethyl)-2-methyl-1*H*-inden-1-ol (34)

δ_H ($CDCl_3$, 200 MHz): 7.34–7.27 (m, 1H), 6.95–6.85 (m, 2H), 5.03 (s, 1H), 3.68 (s, 2H), 2.79 (d, J = 15.8 Hz, 1H), 2.59 (d, J = 15.8 Hz, 1H), 1.05 (s, 3H).

δ_C ($CDCl_3$, 100 MHz): 162.9 (d, J = 243.2 Hz), 142.7 (d, J = 8.4 Hz), 139.24 (d, J = 2.2 Hz), 125.42 (d, J = 9.1 Hz), 113.73 (d, J = 22.5 Hz), 111.1 (d, J = 22.5 Hz), 79.1, 69.8, 50.3, 40.0, 29.6, 16.8.

$[\alpha]_D^{29}$ −4.43 (*c* 1.0, MeOH).

(1*S*,2*R*)-5-Bromo-2,3-dihydro-2-(hydroxymethyl)-2-methyl-1*H*-inden-1-ol (35)

δ_H ($CDCl_3$, 200 MHz): 7.26–7.12 (m, 3H), 4.93 (s, 1H), 3.55 (s, 2H), 2.72 (d, J = 15.8 Hz, 1H), 2.44 (d, J = 15.8 Hz, 1H), 0.91 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 143.5, 142.8, 129.5, 128.0, 125.8, 121.2, 78.0, 69.1, 50.6, 29.6, 16.9.

$[\alpha]_D^{29}$ −6.78 (*c* 0.9, MeOH).

HRMS (TOF) Calcd for $C_{11}H_{13}BrO_2Na$ $[M + Na]^+$, 278.9997; Found, 278.9672.

(1*R*,2*R*)-5-Bromo-2,3-dihydro-2-(hydroxymethyl)-2-methyl-1*H*-inden-1-ol (36)

δ_H ($CDCl_3$, 200 MHz): 7.26–7.12 (m, 3H), 4.93 (s, 1H), 3.55 (s, 2H), 2.72 (d, J = 15.8 Hz, 1H), 2.44 (d, J = 15.8 Hz, 1H), 0.91 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 143.4, 142.7, 129.5, 128.2, 125.6, 121.3, 78.3, 69.4, 50.8, 29.5, 16.7.

$[\alpha]_D^{29}$ −9.95 (*c* 0.8, MeOH).

HRMS (TOF) Calcd for $C_{11}H_{13}BrO_2Na$ $[M + Na]^+$, 278.9997; Found, 278.9672.

(1*S*,2*R*)-2,3-Dihydro-2-(hydroxymethyl)-2,6-dimethyl-1*H*-inden-1-ol (37)

δ_H ($CDCl_3$, 200 MHz): 6.99 (s, 1H), 6.87–6.82 (m, 2H), 4.82 (s, 1H), 3.41 (s, 2H), 2.59 (d, J = 15.6 Hz, 1H), 2.33 (d, J = 15.6 Hz, 1H), 2.14 (s, 3H), 0.81 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 144.6, 137.5, 135.7, 128.1, 124.8, 124.5, 78.8, 69.0, 50.4, 39.7, 21.2, 17.1.

$[\alpha]_D^{29}$ −16.7 (*c* 0.9, MeOH).

HRMS (TOF) Calcd for $C_{12}H_{16}O_2Na$ $[M + Na]^+$, 215.1048; Found, 215.1047.

(1*R*,2*R*)-2,3-Dihydro-2-(hydroxymethyl)-2,6-dimethyl-1*H*-inden-1-ol (38)

δ_H ($CDCl_3$, 200 MHz): 7.18 (s, 1H), 7.05 (m, 2H), 5.04 (s, 1H), 3.70 (s, 2H), 2.74 (d, J = 15.6 Hz, 1H), 2.57 (d, J = 15.6 Hz, 1H), 2.34 (s, 3H), 1.05 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 143.4, 137.3, 136.5, 128.9, 124.8, 124.7, 80.1, 70.3, 50.1, 39.9, 21.3, 16.9.

$[\alpha]_D^{29}$ −8.56 (*c* 0.66, MeOH).

HRMS (TOF) Calcd for $C_{12}H_{16}O_2Na$ $[M + Na]^+$, 215.1048; Found, 215.1047.

(1*S*,2*R*)-2-Ethyl-2,3-dihydro-2-(hydroxymethyl)-6-methyl-1*H*-inden-1-ol (39)

δ_H ($CDCl_3$, 200 MHz): 7.21–7.01 (m, 3H), 5.02 (s, 1H), 3.68 (d, J = 10.6 Hz, 1H), 3.54 (d, J = 10.6 Hz, 1H), 2.7 (d, J = 15.8 Hz, 1H), 2.5 (d, J = 15.8 Hz, 1H), 2.3 (s, 3H), 1.76–1.62 (m, 1H), 1.47–1.22 (m, 1H), 0.86 (t, J = 7.4 Hz, 3H).

δ_C ($CDCl_3$, 50 MHz): 144.2, 137.7, 136.4, 128.9, 124.7, 124.6, 80.6, 67.1, 52.6, 36.8, 21.3, 21.2, 8.7.

$[\alpha]_D^{29}$ −12.22 (*c* 1.1, MeOH).

HRMS (TOF) Calcd for $C_{13}H_{18}O_2Na$ $[M + Na]^+$, 229.1204; Found, 229.1205.

1*S*,2*R*)-2-Ethyl-2,3-dihydro-2-(hydroxymethyl)-6-methyl-1*H*-inden-1-ol (40)

δ_H ($CDCl_3$, 200 MHz): 7.20–7.01 (m, 3H), 5.04 (s, 1H), 3.66 (d, J = 10.6 Hz, 1H), 3.52 (d, J = 10.6 Hz, 1H), 2.74 (d, J = 15.8 Hz, 1H), 2.52 (d, J = 15.8 Hz, 1H), 2.3 (s, 3H), 1.76–1.65 (m, 1H), 1.47–1.22 (m, 1H), 0.88 (t, J = 7.4 Hz, 3H).

δ_C ($CDCl_3$, 50 MHz): 144.2, 137.8, 136.5, 128.9, 124.4, 124.2, 80.5, 67.1, 52.6, 36.8, 21.4, 21.2, 8.7.

$[\alpha]_D^{29}$ −9.8 (*c* 1.0, MeOH).

HRMS (TOF) Calcd for $C_{13}H_{18}O_2Na$ $[M + Na]^+$, 229.1204; Found, 229.1205.

(3*S*,4*R*)-3,4-Dihydro-3-(hydroxymethyl)-3-methyl-2*H*-chromen-4-ol (41)

δ_H ($CDCl_3$, 200 MHz): 7.43 (d, J = 7.2 Hz, 1H), 7.20 (m, 1H), 6.96 (m, 1H), 6.78 (d, J = 8.2 Hz, 1H), 4.72 (s, 1H), 4.0 (d, J = 11.2 Hz, 1H), 3.9 (d, J = 11.2 Hz, 1H), 3.59 (d, J = 11.0 Hz, 1H), 3.4 (d, J = 11.0 Hz, 1H), 1.0 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 153.6, 128.7, 124.6, 120.7, 116.0, 70.0, 68.1, 66.3, 37.9, 13.7.

$[\alpha]_D^{29}$ = +34.06 (*c* = 1.0, MeOH).

HRMS (ESI) Calcd for $C_{11}H_{14}O_3Na$ $[M + Na]^+$, 217.0841; Found, 217.0846.

(3*S*,4*S*)-3,4-Dihydro-3-(hydroxymethyl)-3-methyl-2*H*-chromen-4-ol (42)

δ_H ($CDCl_3$, 200 MHz): 7.38 (d, J = 7.4 Hz, 1H), 7.05 (m, 1H), 6.86 (m, 1H), 6.7 (d, J = 8.0 Hz, 1H), 4.64 (s, 1H), 3.95 (d, J = 11.0 Hz, 1H), 3.83 (d, J = 11.0 Hz, 1H), 3.5 (d, J = 11.2 Hz, 1H), 3.31 (d, J = 11.2 Hz, 1H), 0.91 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 153.6, 128.8, 128.5, 124.8, 120.5, 115.8, 70.1, 67.8, 66.1, 37.9, 13.7.

$[\alpha]_D^{29}$ = +24.3 (*c* = 0.8, MeOH).

HRMS (ESI) Calcd for $C_{11}H_{14}O_3Na$ $[M + Na]^+$, 217.0841; Found, 217.0846.

(7*S*,8*R*)-7,8-Dihydro-7-(hydroxymethyl)-7-methyl-6*H*-[1,3]dioxolo[4,5-*g*]chromen-8-ol (43)

δ_H (DMSO-d_6, 200 MHz): 6.73 (s, 1H), 6.3 (s, 1H), 5.85 (s, 2H), 4.2 (s, 1H), 3.75 (s, 2H), 3.25–3.1 (m, 2H), 0.77 (s, 3H).

δ_C (DMSO-d_6, 50 MHz): 148.5, 147.3, 141.3, 117.9, 108.7, 101.1, 97.6, 69.7, 60.3, 64.4, 39.1, 14.7.

$[\alpha]_D^{29}$ = +28.9 (*c* = 1.0, MeOH).

(7*R*,8*R*)-7,8-Dihydro-7-(hydroxymethyl)-7-methyl-6*H*-[1,3]dioxolo[4,5-*g*]chromen-8-ol (44)

δ_H (DMSO-d_6, 200 MHz): 6.74 (s, 1H), 6.32 (s, 1H), 5.83 (s, 2H), 4.24 (s, 1H), 3.78 (s, 2H), 3.25–3.16 (m, 2H), 0.77 (s, 3H).

δ_C (DMSO-d_6, 50 MHz): 148.6, 147.2, 141.4, 117.9, 108.8, 101.2, 97.6, 69.6, 60.4, 64.4, 39.1, 14.7.

$[\alpha]_D^{29}$ = +20.4 (*c* = 1.0, MeOH).

(1*S*,2*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-2-methyl-1,2,3,4-tetrahydronaphthalen-1-ol (45)

The diol **18** (480 mg, 2.5 mmol) was taken in anhydrous DCM (10 mL) and cooled to 0 °C. Imidazole (170 mg, 2.5 mmol) and DMAP (catalytic) were added to the reaction mixture followed by the addition of TBS-Cl (377 mg, 2.5 mmol). The reaction mixture was allowed to warm to room temperature for 1 h, after that time water was added to it and it was extracted with DCM, the organic layer was washed with brine and dried over Na_2SO_4. Evaporation and purification yielded the mono TBDMS-protected compound **45**, in 90% yield.

δ_H ($CDCl_3$, 200 MHz): 7.6 (d, J = 7.0 Hz, 1H), 7.22–7.06 (m, 3H), 4.78 (s, 1H), 3.62 (d, J = 9.4 Hz, 1H), 3.58 (d, J = 9.4 Hz, 1H), 2.96–2.66 (m, 2H), 1.66–1.42 (m, 2H), 0.95 (s, 12H), 0.1 (s, 6H).

δ_C ($CDCl_3$, 50 MHz): 138.4, 134.9, 128.1, 126.73, 126.6, 126.2, 75.0, 73.84, 38.0, 29.3, 25.91, 25.17, 18.2, 14.3, −5.5, −5.6.

$[\alpha]_D^{29}$ = +16.4 (*c* = 0.8, MeOH).

(1*S*,2*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-2-methyl-1,2,3,4-tetrahydronaphthalen-1-yl 4-nitrobenzoate (46)

4-Nitrobenzoic acid (131 mg, 0.784 mmol) was taken in dry DCM (5 mL). Dicyclohexylcarbodiimide (DCC, 162 mg, 0.784 mmol), DMAP (cat. amount) and compound **45** (160 mg, 0.523 mmol) were sequentially added to the reaction mixture. The reaction mixture was kept at room temperature for 3 h. After that time it was directly loaded into a silica gel column. The ester was purified by flash chromatography (40 : 1; hexane–EtOAc) to afford compound **46** in 88% yield.

δ_H ($CDCl_3$, 200 MHz): 8.28–8.17 (m, 4H), 7.24–7.1 (m, 4H), 6.26 (s, 1H), 3.56–3.3 (m, 2H), 2.98–2.72 (m, 2H), 1.91–1.77 (m, 2H), 1.04 (s, 3H), 0.87 (s, 9H), 0.06 (s, 6H).

δ_C ($CDCl_3$, 50 MHz): 164.3, 150.5, 136.6, 135.9, 134.0, 130.8, 129.0, 128.8, 127.9, 126.6, 123.5, 75.1, 67.7, 39.0, 28.4, 25.8, 25.5, 18.7, 18.2, −5.67.

$[\alpha]_D^{29}$ = +22.45 (*c* = 1.2, MeOH).

(1*S*,2*R*)-2-(Hydroxymethyl)-2-methyl-1,2,3,4-tetrahydronaphthalen-1-yl 4-nitrobenzoate (47)

The *para*-nitrobenzoate ester prepared in the previous step, **46** (240 mg, 0.528 mmol) was dissolved in absolute methanol (4 mL) and PPTS (70 mg, 0.3 mmol) was added in one portion. The reaction was stirred at rt for 2.5 h. After that time the solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. The crude residue was purified by flash column chromatography (1 : 10 EtOAc–Hexane) to afford the compound **47** (82%).

δ_H ($CDCl_3$, 200 MHz): 8.29 (m, 4H), 7.25–7.15 (m, 4H), 6.32 (s, 1H), 3.5 (d, J = 8.6 Hz, 1H), 3.42 (d, J = 8.6 Hz, 1H), 2.96–2.87 (m, 2H), 2.56 (br, 1H, -OH), 2.16–2.09 (m, 1H), 1.83–1.76 (m, 1H), 1.06 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 165.5, 150.7, 136.3, 135.2, 133.7, 131.0, 129.4, 128.9, 127.8, 126.2, 123.7, 74.8, 67.9, 39.0, 28.9, 25.3, 16.7.

$[\alpha]_D^{29}$ = +8.26 (c = 0.5, MeOH).

(1*S*,2*S*)-2-Formyl-2-methyl-1,2,3,4-tetrahydronaphthalen-1-yl 4-nitrobenzoate (48)

Oxalyl chloride (0.12 mL, 1.329 mmol) was taken in anhydrous DCM (5 mL). Then DMSO (0.19 mL, 2.66 mmol) was added to the solution and kept at −78 °C. After 15 min alcohol **47** (220 mg, 0.886 mmol) was added to it, and the solution was stirred at the same temperature for a further 45 min. After this time Et_3N (0.74 mL, 5.316 mmol) was added slowly to the reaction mixture at the same temperature. The reaction mixture was allowed to attain room temperature. Water was added to the solution, and the mixture was extracted with DCM. The organic extract was washed with water, $NaHCO_3$ solution and brine. The organic layer was dried (Na_2SO_4) and evaporated. Purification by silica gel chromatography yielded the aldehyde **48** in 90% yield.

δ_H ($CDCl_3$, 200 MHz): 9.57 (s, 1H), 8.27–8.14 (m, 4H), 7.33–7.11 (m, 4H), 6.57 (s, 1H), 3.07–2.87 (m, 2H), 2.24–1.91 (m, 2H), 1.19 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 202.1, 164.28, 150.7, 135.8, 135.1, 132.6, 131.2, 130.9, 129.0, 128.7, 126.6, 123.6, 72.9, 49.8, 26.7, 25.1, 16.2.

$[\alpha]_D^{29}$ = +32.0 (c = 1.5, MeOH).

(1*R*,2*R*)-2-Methyl-2-vinyl-1,2,3,4-tetrahydronaphthalen-1-yl 4-nitrobenzoate (49)

Wittig reaction of compound **48** was done by using KO*t*Bu as a base. To a suspension of freshly prepared KO*t*Bu (177 mg, 1.578 mmol) in 5 mL of diethyl ether was added methyltriphenylphosphonium iodide (709 mg, 1.752 mmol) in two portions. The bright yellow mixture was heated at reflux for 1 h. The yellow mixture was allowed to cool to room temperature. A solution of aldehyde **48** (180 mg, 0.796 mmol) in 5 mL of Et_2O was added to the reaction mixture. The solution was stirred at room temperature. After completion of the reaction, as indicated by TLC, the reaction was quenched with water and the layers were separated. The aqueous layer was extracted with 20 mL of Et_2O. The organic layers were combined, dried with Na_2SO_4, filtered, and the solvent was removed *in vacuo*. The crude residue was purified by flash column chromatography to afford the compound **49** (1 : 20 EtOAc–Hexane) in 78% yield.

δ_H ($CDCl_3$, 200 MHz): 8.31–8.19 (m, 4H), 7.34–7.12 (m, 4H), 6.22 (s, 1H), 5.84 (dd, J = 17.6, 10.6 Hz, 1H), 5.12–5.01 (m, 2H), 2.97–2.90 (m, 2H), 2.15–1.81 (m, 2H), 1.26 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 165.3, 150.5, 142.5, 136.6, 135.8, 133.7, 130.8, 129.3, 128.9, 128.2, 126.2, 123.5, 114.0, 76.4, 39.8, 30.8, 25.8, 21.5.

$[\alpha]_D^{29}$ = +20.8 (c = 1.1, MeOH).

(1*R*,2*R*)-2-Methyl-2-vinyl-1,2,3,4-tetrahydronaphthalen-1-ol (50)

A methanolic solution of 1% NaOH (212 mg, 5.313 mmol, 30 mL) was added to the olefinic compound **49** and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed *in vacuo* and the residue was dissolved in ethyl acetate. The organic layer was washed with brine and dried over Na_2SO_4. The crude residue was purified by flash column chromatography (1 : 10 EtOAc–Hexane) to afford the compound **50** (86%).

δ_H ($CDCl_3$, 200 MHz): 7.52 (m, 1H), 7.24–7.09 (m, 3H), 5.88 (dd, J = 17.6, 10.6 Hz, 1H), 5.15 (m, 2H), 4.5 (s, 1H), 2.88–2.8 (m, 2H), 1.89–1.71 (m, 2H), 1.09 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 145.2, 137.8, 135.6, 128.6, 128.1, 127.3, 126.2, 113.5, 74.4, 40.4, 31.0, 25.7, 18.2.

$[\alpha]_D^{29}$ = +12.66 (c = 0.5, MeOH).

HRMS (ESI) Calcd for $C_{13}H_{16}ONa[M + Na]^+$, 211.1098; Found, 211.1103.

(1*R*,2*R*)-1-(Allyloxy)-2-methyl-2-vinyl-1,2,3,4-tetrahydronaphthalene (51)

The compound **50** (25 mg, 0.133 mmol) was dissolved in 1 mL of dry DMF. Silver oxide (74 mg, 0.319 mmol) and allyl bromide (35 μL, 0.4 mmol) were added subsequently. The reaction mixture was stirred at room temperature for 4 days. After completion of the reaction, as indicated by TLC, the mixture was quenched with cold water (2 mL), and extracted with AcOEt. The combined organic layer was washed with brine and dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography of the residue over silica gel (Hexane–EtOAc, 20 : 1) afforded **51** (72% yield).

δ_H ($CDCl_3$, 200 MHz): 7.29–7.11 (m, 4H), 6.07–5.88 (m, 2H), 5.37–5.0 (m, 4H), 4.17–4.07 (m, 3H), 2.91–2.8 (m, 2H), 2.0 (m, 1H), 1.77–1.6 (m, 1H), 1.21 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 144.7, 136.4, 136.3, 135.4, 129.1, 128.9, 127.4, 125.3, 116.4, 112.6, 82.2, 71.7, 40.5, 30.2, 29.7, 21.7.

$[\alpha]_D^{29}$ = +18.45 (c = 0.6, MeOH).

HRMS (ESI) Calcd for $C_{16}H_{20}ONa[M + Na]^+$, 251.1412; Found, 251.1404.

(4a*R*,10b*R*)-4a-Methyl-4a,5,6,10b-tetrahydro-2*H*-benzo[*h*]chromene (52)

Compound **51** (15 mg, 0.0657 mmol) was taken in anhydrous degassed DCM (30 mL). Grubbs first generation metathesis catalyst (4 mg, 0.005 mmol) was then added and the solution was stirred at rt for 3 h. The solution was evaporated and the content of the flask was directly loaded onto a silica gel column. Flash chromatography with hexane : EtOAc (1 : 30) afforded the compound **52** in 77% yield.

δ_H ($CDCl_3$, 400 MHz): 7.51 (d, J = 6.8 Hz, 1H), 7.22–7.15 (m, 2H), 7.08 (d, J = 6.8 Hz, 1H), 5.79 (d, J = 9.6 Hz, 1H), 5.66 (td, J = 9.6, 2.4 Hz, 1H), 4.44–4.39 (m, 3H), 2.95–2.81 (m, 2H), 1.76–1.71 (m, 2H), 0.88 (s, 3H).

δ_C ($CDCl_3$, 100 MHz): 136.7, 136.3, 135.1, 128.1, 126.4, 125.7, 124.4, 124.3, 79.1, 67.3, 33.7, 31.7, 25.3, 17.6.

$[\alpha]_D^{29}$ = +28.6 (c = 0.33, MeOH).

HRMS (ESI) Calcd for $C_{14}H_{16}ONa[M + Na]^+$, 223.1099; Found, 223.1093.

(3*S*,4*R*,4a*R*,10b*S*)-4a-Methyl-3,4,4a,5,6,10b-hexahydro-2*H*-benzo[*h*]chromene-3,4-diol (53)

At first, *t*-BuOH (0.2 mL), H_2O (0.2 mL) and AD-mix-β (87 mg) were mixed and the mixture was stirred for 15 min. Methane

sulfonamide (9 mg) was then added and stirring was continued for a further 15 min. Compound **52** (12 mg, 0.06 mmol) was then added in one portion. The slurry was stirred vigorously at 20 °C for 24 h. After that time, sodium sulfite (96 mg) was added and stirring was continued for a further 1 h. The reaction mixture was extracted with EtOAc. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The diol was purified by flash chromatography (5 : 1; hexane : EtOAc) to afford diol **53** in 78% yield.

δ_H ($CDCl_3$, 400 MHz): 7.49 (m, 1H), 7.20–7.07 (m, 3H), 4.62 (s, 1H), 4.28 (m, 1H), 4.09 (m, 1H), 3.8–3.71 (m, 2H), 2.86–2.7 (m, 2H), 2.2 (m, 2H), 1.6 (m, 2H), 0.88 (s, 3H).

δ_C ($CDCl_3$, 100 MHz): 136.2, 134.5, 128.2, 126.5, 125.8, 125.4, 74.8, 74.4, 67.5, 64.9, 37.7, 29.6, 28.4, 22.6, 14.7.

$[\alpha]_D^{29}$ = +38.2 (c = 0.1, MeOH).

HRMS (ESI) Calcd for $C_{14}H_{18}O_3Na$ $[M+Na]^+$, 257.1153; Found, 257.1158.

(1*S*,2*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-2,3-dihydro-2,5-dimethyl-1*H*-inden-1-ol (54)

δ_H ($CDCl_3$, 200 MHz): 7.25–7.04 (3H), 5.06 (s, 1H), 3.6 (s, 2H), 2.81–2.54 (2H), 2.4 (s, 3H), 0.9 (s, 3H), 0.88 (s, 9H), 0.03 (s, 6H).

δ_C ($CDCl_3$, 50 MHz): 144.0, 137.5, 136.2, 128.5, 124.7, 80.0, 70.2, 50.5, 39.7, 25.9, 21.3, 18.3, 17.1, −5.48.

$[\alpha]_D^{29}$ = +8.62 (c = 0.5, MeOH).

(1*S*,2*R*)-2-((*tert*-Butyldimethylsilyloxy)methyl)-2,3-dihydro-2,5-dimethyl-1*H*-inden-1-yl 4-nitrobenzoate (55)

δ_H ($CDCl_3$, 200 MHz): 8.3–8.21 (m, 4H), 7.25–7.08 (m, 3H), 6.39 (s, 1H), 3.58 (d, J = 9.6 Hz, 1H), 3.5 (d, J = 9.6 Hz, 1H), 2.96 (d, J = 16.0 Hz, 1H), 2.8 (d, J = 16.0 Hz, 1H), 2.33 (s, 3H), 1.2 (s, 3H), 0.86 (s, 9H), 0.03 (s, 6H).

δ_C ($CDCl_3$, 50 MHz): 164.4, 150.5, 140.4, 139.8, 136.5, 136.0, 130.8, 129.9, 126.3, 124.8, 123.5, 81.8, 68.8, 49.6, 40.6, 25.8, 21.3, 18.5, 18.2, −5.5.

$[\alpha]_D^{29}$ = +13.9 (c = 0.5, MeOH).

(1*S*,2*R*)-2,3-Dihydro-2-(hydroxymethyl)-2,5-dimethyl-1*H*-inden-1-yl 4-nitrobenzoate (56)

δ_H ($CDCl_3$, 200 MHz): 8.26 (m, 4H), 7.15 (m, 3H), 6.38 (s, 1H), 3.6 (s, 2H), 2.98 (d, J = 16.0 Hz, 1H), 2.65 (d, J = 16.0 Hz, 1H), 2.32 (s, 3H), 1.2 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 165.3, 150.7, 139.8, 138.9, 136.8, 135.6, 130.9, 130.1, 126.0, 125.0, 123.7, 81.9, 68.6, 50.1, 40.8, 21.3, 18.3.

$[\alpha]_D^{29}$ = +2.45 (c = 0.2, MeOH).

(1*S*,2*S*)-2-Formyl-2,3-dihydro-2,5-dimethyl-1*H*-inden-1-yl 4-nitrobenzoate (57)

δ_H ($CDCl_3$, 200 MHz): 9.77 (s, 1H), 8.3–8.21 (m, 4H), 7.25–7.17 (m, 3H), 6.55 (s, 1H), 3.38 (d, J = 16.0 Hz, 1H), 2.89 (d, J = 16.0 Hz, 1H), 2.35 (s, 3H), 1.25 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 201.6, 164.5, 150.8, 138.8, 137.4, 136.2, 135.0, 130.9, 130.6, 126.0, 124.8, 123.7, 80.4, 58.7, 39.1, 21.3, 15.3.

$[\alpha]_D^{29}$ = +6.82 (c = 0.5, MeOH).

(2*R*,3*R*)-2,3-Dihydro-2,5-dimethyl-2-vinyl-1*H*-inden-3-yl 4-nitrobenzoate (58)

δ_H ($CDCl_3$, 200 MHz): 8.33–8.18 (m, 4H), 7.25–7.14 (m, 3H), 6.3 (s, 1H), 6.06 (dd, J = 16.0, 10.6 Hz, 1H), 5.17–5.03 (m, 2H), 3.0 (s, 2H), 2.34 (s, 3H), 1.33 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 164.4, 150.6, 144.0, 140.0, 136.7, 135.8, 130.8, 129.9, 126.2, 125.5, 124.7, 123.6, 113.16, 84.1, 50.2, 43.5, 21.3, 20.0.

$[\alpha]_D^{29}$ = +24.33 (c = 0.5, MeOH).

(1*R*,2*R*)-2,3-Dihydro-2,6-dimethyl-2-vinyl-1*H*-inden-1-ol (59)

δ_H ($CDCl_3$, 200 MHz): 7.26–7.06 (m, 3H), 6.09 (dd, J = 16.0, 10.6 Hz, 1H), 5.18–5.05 (m, 2H), 4.91 (s, 1H), 2.88 (d, J = 16.0 Hz, 1H), 2.7 (d, J = 16.0 Hz, 1H), 2.35 (s, 3H), 1.1 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 145.3, 143.7, 143.2, 137.8, 136.4, 128.8, 124.7, 112.7, 82.0, 51.5, 42.7, 21.3, 18.0.

$[\alpha]_D^{29}$ = +12.56 (c = 1.2, MeOH).

HRMS (ESI) Calcd for $C_{13}H_{16}ONa[M + Na]^+$, 211.1099; Found, 211.1104.

(1*R*,2*R*)-1-(Allyloxy)-2,3-dihydro-2,6-dimethyl-2-vinyl-1*H*-indene (60)

δ_H ($CDCl_3$, 400 MHz): 7.14 (s, 1H), 7.04 (m, 2H), 6.12 (dd, J = 160, 10.8 Hz, 1H), 6.01–5.94 (m, 1H), 5.32 (d, J = 17.2 Hz, 1H), 5.15 (m, 2H), 5.03 (d, J = 10.8 Hz, 1H), 4.66 (s, 1H), 4.24 (dd, J = 12.8, 5.2 Hz, 1H), 4.14 (dd, J = 12.8, 5.2 Hz, 1H), 2.84 (d, J = 16.0 Hz, 1H), 2.68 (d, J = 16.0 Hz, 1H), 2.33 (s, 3H), 1.14 (s, 3H).

δ_C ($CDCl_3$, 100 MHz): 146.5, 142.7, 137.8, 135.9, 135.0, 128.5, 125.2, 124.4, 116.6, 112.1, 88.4, 71.4, 51.3, 43.7, 21.2, 18.1.

$[\alpha]_D^{29}$ = +46.4 (c = 0.8, MeOH).

HRMS (ESI) Calcd for $C_{16}H_{20}ONa[M + Na]^+$, 251.1412; Found, 251.1404.

(4a*R*,9b*R*)-8-Dimethyl-2,4a,5,9b-tetrahydro-indeno[1,2-*b*]pyran (61)

δ_H ($CDCl_3$, 200 MHz): 7.11–6.96 (m, 3H), 6.26 (td, J = 10.0, 2.4 Hz, 1H), 5.58 (td, J = 10.0, 2.4 Hz, 1H), 4.79 (s, 1H), 4.52 (t, J = 2.2 Hz, 2H), 2.57 (s, 2H), 2.34 (s, 3H), 0.87 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 141.6, 137.7, 135.9, 134.8, 127.2, 125.4, 125.2, 122.5, 85.6, 68.3, 45.4, 38.2, 21.2, 20.6.

$[\alpha]_D^{29}$ = +18.2 (c = 0.4, MeOH).

HRMS (ESI) Calcd for $C_{14}H_{16}ONa[M + Na]^+$, 223.1099; Found, 223.1093.

(3*S*,4*R*,4a*R*,9b*R*)-8-Dimethyl-2,3,4,4a,5,9b-hexahydro-indeno[1,2-*b*]pyran-3,4-diol (62)

δ_H ($CDCl_3$, 400 MHz): 7.07 (2H), 6.97 (d, J = 7.6 Hz, 1H), 5.01 (s, 1H), 4.24 (m, 1H), 4.05 (m, 2H), 3.62 (t, J = 10.8 Hz, 1H), 2.94 (d, J = 14.0 Hz, 1H), 2.36 (d, J = 14.0 Hz, 1H), 2.32 (s, 3H), 1.6 (br, 2H, -OH), 0.88 (s, 3H).

δ_C ($CDCl_3$, 100 MHz): 140.8, 137.1, 136.4, 127.8, 125.9, 123.4, 80.6, 73.4, 69.3, 64.9, 50.7, 36.3, 21.6, 17.6.

$[\alpha]_D^{29}$ = +23.96 (c = 0.13, MeOH).

HRMS (ESI) Calcd for $C_{14}H_{18}O_3Na$ $[M+Na]^+$, 257.1154; Found, 257.1158.

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References

1 (*a*) R. A. Bauer, J. M. Wurst and D. S. Tan, *Curr. Opin. Chem. Biol.*, 2010, **14**, 308–314; (*b*) M. E. Welsch, S. A. Snyder and B. R. Stockwell, *Curr. Opin. Chem. Biol.*, 2010, **14**, 347–361; (*c*) S. Shang and D. Tan, *Curr. Opin. Chem. Biol.*, 2002, **6**, 161–167; (*d*) A. Reayi and P. Arya, *Curr. Opin. Chem. Biol.*, 2005, **9**, 240–247; (*e*) R. Breinbauer, I. R. Vetter and H. Waldmann, *Angew. Chem., Int. Ed*, 2002, **41**, 2879–2890; (*f*) D J. Ecker and S, T. Crooke, *Biotechnology*, 1995, **13**, 351–60; (*g*) P. Arya, R. Joseph, Z. Gan and B. Rakic, *Chemistry & Biology*, 2005, **12**, 163–180; (*h*) S. Shang and D. S. Tan, *Curr. Opin. Chem. Biol.*, 2005, **9**, 248–258; (*i*) D. S. Tan, *Nat. Chem. Biol.*, 2005, **1**, 74–84; (*j*) M. Oikawa, M. Ikoma and M. Sasaki, *Tetrahedron Lett.*, 2005, **46**, 5863–5866; (*k*) L. Weber, *Methods in Molecular Biology*, 2005, **310**, 11–24; (*l*) D. E. G. Shuker, Annual Reports on the Progress of Chemistry, Section B:, *Organic Chemistry*, 2005, **101**, 137–147; (*m*) S. Hotha, *Chemical Industry Digest*, 2006, **19**, 51–56; (*n*) D. S. Tan, Eds by S. L. Schreiber, T. M. Kapoor and G. Wess, *Chemical Biology: From Small Molecules to Systems Biology and Drug Design*, Wiley-VCH, 2007, Vol 2, 483-518.

2 (*a*) G. Klebe, *Drug Discovery Today*, 2006, **11**, 580–594; (*b*) J. C. Hermann, R. Marti-Arbona, A. A. Fedorov, E. Fedorov, S. C. Almo, B. K. Shoichet and F. M. Raushel, *Nature*, 2007, **448**, 775–779; (*c*) P. Willet, *Drug Discovery Today*, 2006, **11**, 1046–1053; (*d*) J. Rosen, J. Gottfries, S. Muresan, A. Backlund and T. I. Opera, *J. Med. Chem.*, 2009, **52**, 1953–1962; (*e*) D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2007, **70**, 461–477; (*f*) M. A. Koch, A. Schuffenhauer, M. Scheck, S. Wetzel, M. Casaulta, A. Odermatt, P. Ertl and H. Waldmann, *Proc. Natl. Acad. Sci. U. S. A.*, 2005, **102**, 17272–17277; (*g*) S. Wetzel, A. Schuffenhauer, S. Roggo, P. Ertl and H. Waldmann, *Chimia*, 2007, **61**, 355–360; (*h*) C. M. Dobson, *Nature*, 2004, **431**, 931–945; (*i*) C. Lipinski and A. Hopkins, *Nature*, 2004, **432**, 855–861.

3 (*a*) S. Dandapani and L. A. Marcaurelle, *Curr. Opin. Chem. Biol.*, 2010, **14**, 362–370; (*b*) J. E. Biggs-Houck, A. Younai and J. T. Shaw, *Curr. Opin. Chem. Biol.*, 2010, **14**, 371–382; (*c*) M. Vendrell, J. S. Lee and Y. T. Chang, *Curr. Opin. Chem. Biol.*, 2010, **14**, 383–389; (*d*) S. Goldman, *Curr. Opin. Chem. Biol.*, 2010, **14**, 390–395; (*e*) B. Lepenies, J. Yin and P. H. Seeberger, *Curr. Opin. Chem. Biol.*, 2010, **14**, 404–411; (*f*) I. R. J. Correa, A. Noren-Muller, H.-D. Ambrosi, S. Jakupovic, K. Saxena, H. Schwalbe, M. Kaiser and H. Waldmann, *Chem.–Asian. J.*, 2007, **2**, 1109–1126; (*g*) C. Rosenbaum, P. Baumhot, R. Mazitschek, O. Muller, A. Giannis and H. Waldmann, *Angew. Chem., Int. Ed.*, 2004, **43**, 224–228; (*h*) F. Wehner, A. Noren-Muller, O. Muller, I. Jr. Reis-Correa, A. Giannis and H. Waldmann, *ChemBioChem*, 2008, **9**, 401–405; (*i*) A. Noren-Muller, W. Wilk, K. Saxena, H. Schwalbe, M. Kaiser and H. Waldmann, *Angew. Chem., Int. Ed.*, 2008, **47**, 5973–5977; (*j*) W. Wilk, A. Noren-Muller, M. Kaiser and H. Waldmann, *Chem.–Eur. J.*, 2009, **15**, 11976–11984; (*k*) M. A. Koch, L.-O. Wittenberg, S. Basu, D. A. Jeyaraj, E. Gourzoulidou, K. Reinecke, A. Odermatt and H. Waldmann, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 16271–16276; (*l*) M. Scheck, M. A. Koch and H. Waldmann, *Tetrahedron*, 2008, **64**, 4792–4802; (*m*) S. Wetzel, K. Klein, S. Renner, D. Rauh, T. I. Oprea, P. Mutzel and H. Waldmann, *Nat. Chem. Biol.*, 2009, **5**, 581–583; (*n*) S. Renner, W. A. van Otterlo, M. Dominguez Seoana, S. Mocklinghoff, B. Hofmann, S. Wetzel, A. Schuffenhauer, P. Ertl, T. I. Oprea, D. Steinhilber, L. Brunsveld, D. Rauh and H. Waldmann, *Nat. Chem. Biol.*, 2009, **5**, 585–592; (*o*) K. Kumar and H. Waldmann, *Angew. Chem., Int. Ed.*, 2009, **48**, 3224–3242; (*p*) J. P. Nandy, M. Prakesch, S. Khadem, P. T. Reddy, U. Sharma and P. Arya, *Chem. Rev.*, 2009, **109**, 1990–2060; (*q*) T. E. Nielsen and S. L. Schreiber, *Angew. Chem., Int. Ed.*, 2008, **47**, 48–56; (*r*) H. Waldmann, M. Kuhn, W. Lui and K. Kumar, *Chem. Commun.*, 2008, **10**, 1211–1213; (*s*) A. Ulaczyk-Lesanko and D. G. Hall, *Curr. Opin. Chem. Biol.*, 2005, **9**, 266–276; (*t*) O. Ramstrom and J. M. Lehn, *Nat. Rev. Drug Discovery*, 2002, **1**, 26–36; (*u*) R A. Goodnow, W. Guba and W. Haap, *Comb. Chem. High Throughput. Screen.*, 2003, **6**, 649–90.

4 *New frontiers in asymmetric catalysis*, Ed by K. Mikami and M. Lautens, Wiley-Interscience, New Jersey, 2007.

5 *Enzyme catalysis in organic synthesis* (Vol 1-3)., Ed by K. Drauz and H. Waldmann, Wiley-VCH, Weinheim, 2002.

6 E. Garcia-Urdiales, I. Alfonso and V. Gotor, *Chem. Rev.*, 2005, **105**, 313–354.

7 (*a*) T. Mahapatra, T. Das and S. Nanda, *Tetrahedron: Asymmetry*, 2008, **19**, 2497–2507; (*b*) T. Mahapatra, N. Jana and S. Nanda, *Tetrahedron: Asymmetry*, 2008, **19**, 1224–1232; (*c*) T. Mahapatra, N. Jana and S. Nanda, *Adv. Synth. Catal.*, 2011, **353**, 2152–2168.

8 (*a*) S. Kesavan, J. S. Panek and J. A. Jr. Porko, *Org. Lett.*, 2007, **9**, 5203–5206; (*b*) W. Gu, H. M. Ge, Y. C. Song, H. Ding, H. L. Zhu, X. A. Zhao and R. X. Tan, *J. Nat. Prod.*, 2007, **70**(1), 114–117; (*c*) Rene Beugelmans, Jacqueline Chastanet, Helene Ginsburg, Leticia Quintero-Cortes and Georges Roussi, *J. Org. Chem.*, 1985, **50**, 4933–4938.

9 (*a*) D. C. Demirjian, P. C. Shah and F. Moris-Varas, *In Biocatalysis From Discovery to Application*, (Ed: W. D Fessner), Springer-Verlag, Berlin, 2000, pp. 1–29; (*b*) Y. Yasohara, N. Kizaki, J. Hasegawa, M. Takahashi, M. Wada, M. Kataoka and S. Shimizu, *Appl. Microbiol. Biotechnol.*, 1999, **51**, 847–851; (*c*) S. Shimizu, H. Hata and H. Yamada, *Agric. Biol. Chem.*, 1984, **48**, 2285–2291; (*d*) M. Kataoka, S. Shimizu, Y. Doi, K. Sakamoto and H. Yamada, *Biotechnol. Lett.*, 1990, **12**, 357–360; (*e*) H. Miya, M. Kawada and Y. Sugiyama, *Biosci., Biotechnol., Biochem.*, 1996, **60**, 95–98; (*f*) A. Shafiee, H. Motamedi and A. King, *Appl. Microbiol. Biotechnol.*, 1998, **49**, 709–717; (*g*) M. Wada, M. Kataoka, H. Kawabata, Y. Yasohara, N. Kizaki, J. Hasegawa and S. Shimizu, *Biosci., Biotechnol., Biochem.*, 1998, **62**, 280–285; (*h*) M. Wada, H. Kawabata, A. Yoshizumi, M. Kataoka, S. Nakamori, Y. Yasohara, N. Kizaki, J. Hasegawa and S. Shimizu, *J. Biosci. Bioeng.*, 1999, **87**, 144–148.

10 Y. N. Niu, Z. Y. Yan, G. Q. Li, H. L. Wei, G. L. Gao, L. Y. Wu and Y. M. Liang, *Tetrahedron: Asymmetry*, 2008, **19**, 912–920.

11 (*a*) K Nakamura, R Yamanaka, T Matsuda and T Harada, *Tetrahedron: Asymmetry*, 2003, **14**, 2659–2681; (*b*) K. Nakamura and T. Matsuda, *J. Org. Chem.*, 1998, **63**, 8957–8964; (*c*) K. Nakamura, K. Kitano, T. Matsuda and A. Ohno, *Tetrahedron Lett.*, 1996, **37**, 1629–1632; (*d*) D. Buisson, R. Azerad, C. Sanner and M. Larcheveque, *Biocatalysis.*, 1992, **5**, 249–265; (*e*) D. Buisson, R. Azerad, C. Sanner and M. Larcheveque, *Tetrahedron: Asymmetry*, 1991, **2**, 987–988; (*f*) D. Buisson, R. Azerad, C. Sanner and M. Larcheveque, *Biocatalysis.*, 1990, **3**, 85–93; (*g*) K. Nakamura, Y. Inoue, T. Matsuda and I. Misawa, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2397–2402; (*h*) K. Nakamura, M. Fujii and Y. Ida, *J. Chem. Soc., Perkin Trans 1.*, 1997, 2375; (*i*) K. Nakamura, S. Takano and A. Ohno, *Tetrahedron Lett.*, 1993, **34**, 6087–6090; (*j*) K. Nakamura, *J. Mol. Catal B: Enzymatic.*, 1998, **5**, 129–132; (*k*) Z. L. Wie, G. Q. Lin and Z. Y. Li, *Bioorg. Med. Chem.*, 2000, **8**, 1129–1137; (*l*) R. N. Patel, C. G. Mcnamee, A. Banerje, J. M. Howell, R. S. Robison and L. Szarka, *J. Enzyme Microb. Technol.*, 1992, **14**, 731–738; (*m*) T. Kitayama, *Tetrahedron: Asymmetry*, 1997, **8**, 3765–3774; (*n*) R. Azerad and D. Buisson, In: *Microbial Reagents in Organic Synthesis*, (Ed: S. Servi), Kluwer Academic Publishers, Netherlands, 1992, pp. 421–440; (*o*) K. Nakamura, T. Matsuda, T. Itoh and A. Ohno, *Tetrahedron Lett.*, 1996, **37**, 5727–5730; (*p*) T. Matsuda, T. Harada, N. Nakajima, T. Itoh and K. Nakamura, *J. Org. Chem.*, 2000, **65**, 157–163; (*q*) A. Arnone, R. Bernardi, F. Blasco, R. Cardillo, R. Resnati, I. I. Gerus and V. P. Kukhar, *Tetrahedron*, 1998, **54**, 2809–2818; (*r*) T. Kitazume and T. Kobayashi, *Synthesis*, 1987, 187–188; (*s*) T. Kitazume and Y. Nakayama, *J. Org. Chem.*, 1986, **51**, 2795–2799; (*t*) T. Kitazume and T. Sato, *J. Fluorine Chem.*, 1985, **30**, 189–202; (*u*) T. Fujisawa, K. Ichikawa and M. Shimizu, *Tetrahedron: Asymmetry*, 1993, **4**, 1237–1240; (*v*) T. Fujisawa, T. Sugimoto and M. Shimizu, *Tetrahedron: Asymmetry*, 1994, **5**, 1095–1098; (*w*) T. Fujisawa, Y. Onogawa, A. Sato, T. Mitsuya and M. Shimizu, *Tetrahedron*, 1998, **54**, 4267–4276; (*x*) K. Nakamura, T. Matsuda, M. Shimizu and T. Fujisawa, *Tetrahedron*, 1998, **54**, 8393–8402; (*y*) Y. Ohtsuka, O. Katoh, T. Sugai and H. Ohta, *Bull. Chem. Soc. Jpn.*, 1997, **70**, 483–491; (*z*) A. Sakai, M. Bakke, H. Ohta, H. Kosugi and T. Sugai, *Chem. Lett.*, 1999, 1255–1256.

12 C. Prakash, S. Saleh and A. I. Blair, *Tetrahedron Lett.*, 1989, **30**, 19.

13 A. J. Mancuso, D. S. Brownfain and D. Swern, *J. Org. Chem.*, 1979, **44**, 4148.

14 K. Mashimo and Y. Sato, *Tetrahedron*, 1970, **26**, 803.

15 L. Van Hijfte and R. D. Little, *J. Org. Chem.*, 1985, **50**, 3940.

16 P. Schwab, R. H. Grubbs and J. W. Ziller, *J. Am. Chem. Soc.*, 1996, **118**, 100.

17 L. F. Tietze, T. Eicher, U. Diederichsen and A. Speicher, In *Reactions and Syntheses*, Wiley-VCH, Weinheim, 2007, pp. 211.