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Chemoenzymatic route to optically active dihydroxy cyclopenta[*b*]naphthalenones; precursors for decalin-based bioactive natural products

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ABSTRACT

The development of an efficient chemoenzymatic route for the synthesis of optically active dihydroxy cyclopenta[*b*]naphthalenones; (+)-1,4a-dihydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1*H*-cyclopenta[*b*]naphthalen-2(4*H*)-one (+)-**10** and (+)-1,8a-dihydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1*H*-cyclopenta[*b*]naphthalen-2(4*H*)-one (+)-**11** is described. Different lipases and esterases were tested in the enzymatic hydrolysis of the corresponding acetates (±)-4a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1*H*-cyclopenta[*b*]naphthalen-1-yl acetate (±)-**8**, (±)-8a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1*H*-cyclopenta[*b*]naphthalen-1-yl acetate (±)-**9**, CRL (*Candida Rugosa Lipase*) and PLE (*Pig Liver Esterase*) were found to be the most effectual enzymes; for (−)-**8** by 47% ee with the corresponding dihydroxy; (+)-**10** by 98% ee in the presence of CRL; whereas, (−)-**8** was obtained with 40% ee with the corresponding dihydroxy, (+)-**10** with 58% ee in the PLE hydrolysis. It was concluded that CRL was the best biocatalyst for the substrate (±)-**8**. Moreover, enzymatic resolution in the presence of CRL yields, (−)-**9** with 46% ee with the corresponding dihydroxy derivative; (+)-**11** with 98% ee; however, in the presence of PLE, yields (−)-**9** with 36% ee as well as the related dihydroxy derivative; (+)-**11** with 49% ee respectively. The study concluded that CRL is the best biocatalyst for compounds (±)-**8** and (±)-**9**.

1. Introduction

Optically active decalin-based compounds are valuable substructures of many biologically active natural products.[1] In particular, hydroxy substituted ones are the main units of the C_2-symmetric metabolite HMPY-1 (Fig. 1) and messengers of hibarimicins.[2] Huberamicin, and huberamicinone have been reported as tyrosine kinase blockers as well as having cytotoxicity against human colon carcinoma cells, thus make the AB decalin framework valuable, although it is difficult to construct.

(+)-Fusarisetin A (Fig. 2), which has remarkable blocking activity on the metastasis of breast cancer cells, is one of the most important biologically active natural products, possessing decalin subunits, the synthesis of which requires a useful level of regio- and stereoselectivity. As well as occurring as an acinar morphogenesis inhibitor,[1] it also blocks cell migration and invasion without significant cytotoxicity, which makes the establishment of this unique pentacyclic ring system more attractive for many groups.[3–5] The development of the cyclopentanaphthalenone framework is the crucial point of its total synthesis in order to achieve great stereoselectivity and high chemical yield with a short route. The introduction of the cyclopentenone ring to the decalin unit in a fused manner of the cyclopentanaphthalenone moiety with the desired selectivity either via Pauson–Khand reaction,[3] or any other multistep reaction pathways, successfully where each step requires high selectivity, requires much effort to be achieved, i.e., the oxidative radical reactions where there is stability of the radicals with irreversible routes is the main challange.[5,6]

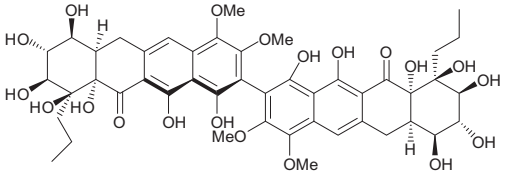

Figure 1. Structure of HMPY-1.

It is known that Mn-(III)-acetate is an effective single-electron oxidant for enolizable carbonyl compounds. The construction of C and D rings of (+)-Fusarisetin A with high diastereoselectivity

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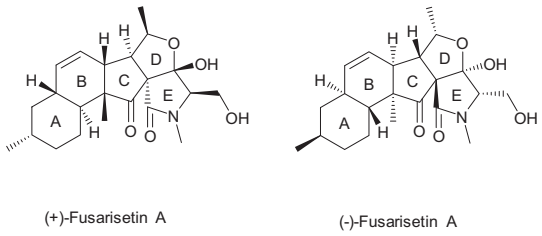

Figure 2. The structure of enantiomeric pair of (±)-Fusarisetin A.

and chemical yield via Mn(III)-based oxidative radical cyclization is difficult to achieve.[4]

From this point of view, the current work provides the corresponding acetates; (±)-**8** and (±)-**9** of octahydrocyclopenta[*b*]naphthalenone framework, fused tricyclic skeletons via intramolecular Pauson–Khand reaction, builds the cyclopentanaphthalenone framework in one pot, followed by regioselective Mn(III)-acetate oxidation of the α′-position, which offers the corresponding acetates (±)-**8** and (±)-**9** subjected to the enzymatic hydrolysis in the presence of hydrolase type enzyme, i.e., PLE and CRL produce enantiomerically enriched ones with the corresponding diols, to create a new stereogenic center, which is a critical point for further processes, especially in the development of antitumor reagents, natural products with a cyclopentanaphthalenone framework, and inhibiting biological activities, i.e., (+)-Fusarisetin-A and its related natural analogues such as, chaetochalasin A, phomopsichalasin and diaporthichalasin[5] (Fig. 3) with its precursors such as, equisetin, maklamicin, superstolide, chlorotricolide, tetrodecamycin (Fig. 4) can be obtained with high enantioselectivity and acceptable diastereoselectivity in high chemical yield via a short route.[3]

Herein the chiral hydroxy-octahydrocyclopenta[*b*]naphthalen-yl-acetates (−)-**8**, (−)-**9** and the corresponding diols (+)-**10**, (+)-**11** via *Pig Liver Esterase* and *Candida Rugosa Lipase* have been obtained via mediated hydrolysis; 6,6,5 fused tricyclic skeleton has the advantage of requiring a short synthetic strategy and can achieve good dia- and regio-selectivities with high chemical yields and enantioselectivities (Scheme 1).

2. Results and discussion

For the construction of dihydroxy-cyclopenta[*b*]naphthalenone scaffolds; hydroxy-octahydrocyclopenta[*b*]naphthalen-yl acetates *rac*-**8** and *rac*-**9** to the parent enyne templates 1-allyl-2-(prop-2-yn-1yl)cyclohexanol 4, 2-allyl-1(prop-2-yn-1yl)cyclohexanol **5**, were used as building blocks, synthesized from 1-(cyclohex-1-en-1yl)pyrrolidine[7] **1** obtained as a colorless oil with 95% chemical yield after reflux of cyclohexanone with pyrrolidine in toluene followed by vacuum distillation subjected to alkylation reactions with the corresponding alkyl halides; allylbromide and propargylbromide in 1,4-dioxane. Hydrolysis with 1% HCl provided 2-allylcyclohexanone **3**[8a,8b] and 2-(prop-2yn-1-yl)cyclohexanone **2**[9] in 95% and 82% chemical yield respectively, as the only products with the expected selectivity.

Herein, the corresponding tertiary homopropargyl alcohol, 2-allyl-1(prop-2-yn-1yl)cyclohexanol **5** and homoallyl alcohol, 1-allyl-2-(prop-2-yn-1yl)cyclohexanol **4** intermadiates,[10] required for the octahydrocyclopenta[*b*]naphthalenone frameworks were synthesized by the addition of propargyl bromide (80% wt in toluene) to the carbonyl group using Zn-Cu couple as described in our previous work[11] in 78% chemical yield with acceptable diastereoselectivity and via indium-mediated Barbier type

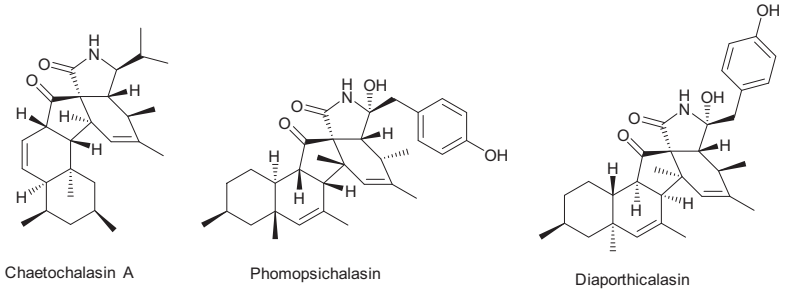

Figure 3. (+)-Fusarisetin-A related natural analougous.

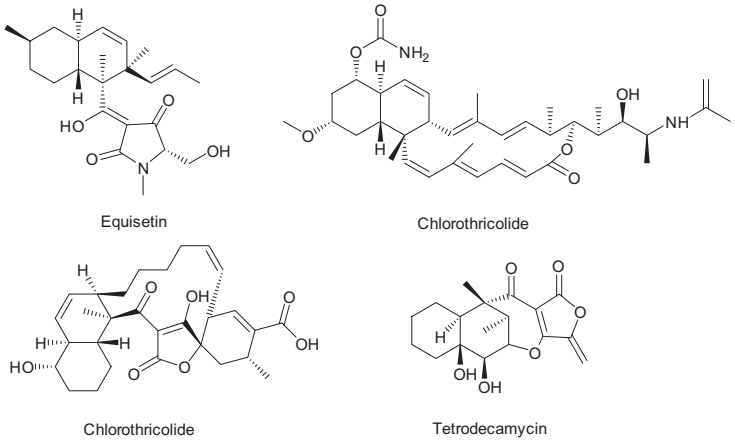

Figure 4. (+)-Fusarisetin-A precursors.

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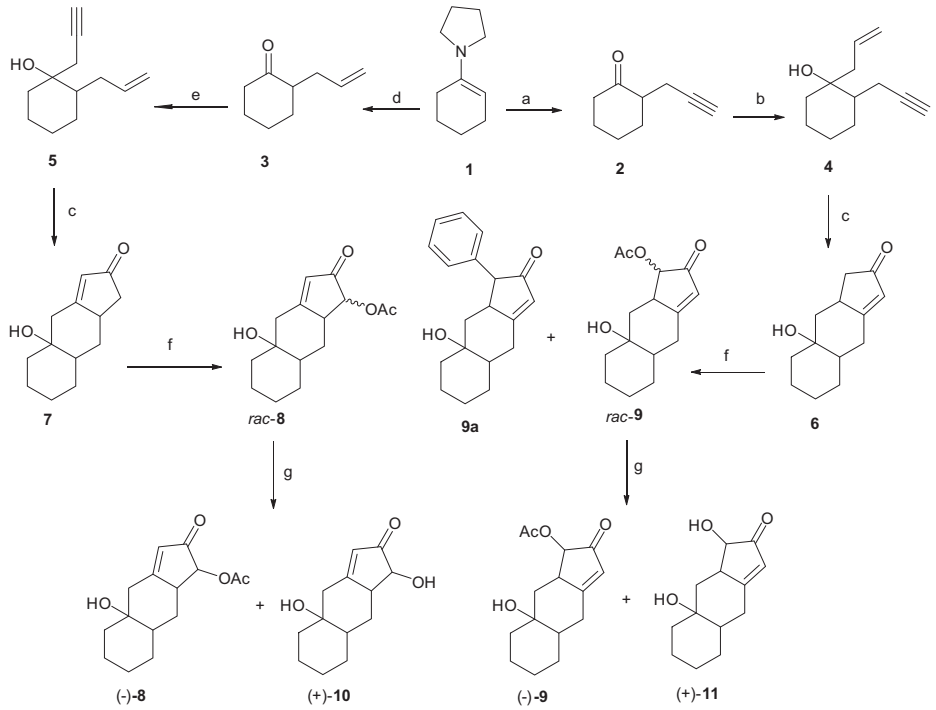

Scheme 1. Reagents and conditions: (a) propargyl bromide, 1,4-dioxane, reflux, HCl (1%); (b) indium powder, allylbromide, DMF, room temperature; (c) Co_2CO_8, NMO, DCM; (d) allylbromide, 1,4-dioxane, reflux, HCl (1%); (e) Zn-Cu, THF, propargylbromide, reflux; (f) Co_2CO_8, NMO, DCM (g) KH_2PO_4, $KHPO_4$ pH = 7 buffer solution, enzyme.

allylation in DMF, in 81% chemical yield with complete diastereoselectivity.

The Pauson–Khand reaction is commonly used for creating cyclopentenone frameworks, by cobalt-mediated reactions performed by joining alkyne, olefin and carbon monoxide. The intramolecular version has become more popular in recent years since building cyclopentanone-fused ring systems requires great efforts. The optimal reaction conditions, metal catalyst, additive, solvent and temperature are critical parameters to achieve complete diastereoselectivity[3,4] in the construction of the cyclopentanaphthalenone subunit of (+)-Fusarisetin A[3] as stated above. To the best of our knowledge, the intramolecular Pauson–Khand reaction version is not preferred for the construction of the related frameworks. Tanyeli et al. have recently reported that the intramolecular Pauson–Khand reaction gave enantiomerically enriched cyclopentenone-pyrans with spirocyclic motifs as single diastereomers in good chemical yields and with excellent diastereoselectivities.[12a] With this in mind, we investigated the applicability of intramolecular Pauson–Khand reaction to enyne templates **4** and **5**, to obtain octahydrocyclopenta[*b*]naphthalenone frameworks 8a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1*H*-cyclopenta[*b*]-naphthalen-2(4*H*)-one **6**, 4a-hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1*H*-cyclopenta[*b*]naphthalen-2(4*H*)-one **7**. For this purpose, the corresponding enynes **4** and **5** were constructed on tertiary cyclohexanol moiety and then subjected to an intramolecular Pauson–Khand reaction. In this protocol, cobalt-alkyne complexes were prepared using enyne/dicobalt octacarbonyl in a molar ratio of 1.0/1.7 in DCM after which *N*-methyl-morpholine-*N*-oxide monohydrate was added as a promotor. Compound **4** was isolated as single diastereomer in 81% chemical yield, leading to cyclopentanaphthalenone skeleton, **6** by 80% chemical yield, whereas compound **5** was isolated as diastereomeric mixtures with d.r 2.33:1 as established by ^{1}H NMR spectroscopy with the corresponding cyclopentanaphthalenone framework **7** in 78% and 85% chemical yield, respectively. The addition of allylic and propargylic nucleophiles to carbonyl groups is one of the efficient methods to obtain homopropargylic and homoallylic alcohols; in this respect, enyne systems were constructed from α′-allyl and α′-propargyl cyclohexanones by the addition of propargylic and allylic nucleophiles. Compounds **5** and **4** were then subjected to an intramolecular Pauson–Khand reaction, as indicated above, to yield diastereomers **7** and **6** in 85% and 80% chemical yield respectively, which were then isolated as single diastereomers due to the more favored chair conformation of the cyclohexane ring. As mentioned, the control of stereoselectivity in the construction of cyclopentanaphthalene ring during the synthesis of bioactive compounds is a great challenge in the enyne systems; for instance, **4** requires protection of the OH group as well as temperature control, these problems were solved and the corresponding cyclopentanaphthalenone derivatives **7** and **6** were isolated as single diastereomers (established by ^{1}H NMR spectroscopy) as indicated above in 85% and 80% chemical yield respectively.

The importance of decalin-based bioactive compounds prompted us to use the regioselective α′-oxidation of the hydroxy-cyclopentanaphthalenone framework by a single-electron oxidant; Mn(III)-acetate is efficacious in the oxidation of enones, which we have experienced in the various α′- and α-substituted α,β-unsaturated cyclic aromatic ketones,[12b] to afford the corresponding hydroxy cyclopenta[*b*]naphthalenylacetates, (±)-**8** and (±)-**9**. We also tested Pb (IV)-acetate to compare the yields of the regioselective α′-oxidation reaction; Mn-(III)-acetate was established as the more promising one. The most important part is the enzymatic resolution of the α′-acetoxylated compounds (±)-**8** and (±)-**9** for the construction of decalin-based bioactive natural products. From this point of view, the corresponding oxidated hydroxy-cyclopenta[*b*]naphthalenones **6** and **7** were used to obtain hydroxy-cyclopentanaphthalenyl acetate frameworks (±)-**8** and (±)-**9**, which were subjected to enzymatic hydrolysis by using various hydrolase-type enzymes, CAL-A (*Candida Antarctica Lipase A*), CAL-B (*Candida Antarctica Lipase B*) CRL, PLE, HLE (*Horse Liver Esterase*), PPL (*Porcine Pancreatic Lipase*), by changing substrate:enzyme ratio from 1:0.25 to 1:1,

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Table 1
The results of the enzymatic resolution of (±)-4a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1*H*-cyclopenta[*b*]naphthalen-1-yl acetate (±)-**7** and (±)-8a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1*H*-cyclopenta[*b*]naphthalen-1-yl acetate (±)-**6**

Entry	Substrate	Enzyme	Temperature (°C)	Time (h)	c[a] (%)	ee_p[b] (%)	ee_s (%)	*E*[c]
1	*rac*-**8**	CRL	26	15	52	98	47	163
2	*rac*-**8**	PLE	22	5	56	58	40	5
3	*rac*-**9**	CRL	20	27	60	98	46	124
4	*rac*-**9**	PLE	20	2.5	65	49	36	5

[a] $c = ee_s/ee_s + ee_p$.
[b] Enantiomeric excesses were determined by Daicel Chiralcel OD-H and OJ-H column HPLC analysis.
[c] $E = \ln[(1 - c)(1 - ee_s)]/\ln[(1 - c)(1 + ee_s)]$.[13]

screening the temperature from 19 °C to 30 °C where CRL and PLE provided the most promising results.

The most important step is the enantiomeric resolution of hydroxy cyclopenta[*b*]naphthalenylacetates (±)-**8** and (±)-**9** to produce enantiomerically enriched ones with corresponding optically active dihydroxy compounds (+)-**10** and (+)-**11** that could serve as noteworthy templates for the construction of decalin based bioactive natural products. All of the enantiomeric resolution reactions were performed using different hydrolase-type enzymes with different substrates: enzyme ratio at different temperatures as mentioned above. CRL and PLE provided the most promising results among the hydrolase-type enzymes. The results are summarized in Table 1.

Enzymatic resolution of hydroxy-cyclopenta[*b*]naphthalenyl acetate *rac*-**8** by HLE gave 14% conversion after 62 h of shaking at 29 °C; PPL yielded 17% conversion value after 45 hr at the same temperature. Low conversion values prompted us to examine other enzymes; CRL presented the most promising results, with the conditions of 1:1 (w/w) substrate:enzyme ratio at 26 °C to give 52% conversion with 98.0% ee and 47.0% ee after shaking for 15 h, (+)-1,4a-dihydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1*H*-cyclopenta[naphthalen-2(4*H*)-one (+)-**10** with the corresponding acetate, (−)-4a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1*H*-cyclopenta[*b*]naphthalen-1-yl acetate (−)-**8** respectively. In the case of 50 μL PLE application at 22 °C with pH = 7 phosphate buffer solution, afford (+)-**10** was obtained with 58% ee with (−)-**8** with 40% ee in 56% conversion after shaking for 5 h. PLE and CRL were next examined. Initially, CRL was tested at 20 °C, using (+)-1,8a-dihydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1*H*-cyclopenta [naphthalen-2(4*H*)-one (+)-**11** with (−)-8a-hydroxy-2-oxo-2,4, 4a,5,6,7,8,8a,9,9a-decahydro-1*H*-cyclopenta[*b*]naphthalen-1-yl acetate (−)-**9** by 46% conversion after 20 h of shaking; 60% conversion was reached with shaking at 27 h in 98% ee and 46% ee respectively. Finally, PLE-catalyzed hydrolysis of (±)-**9** with 50 μL at 20 °C gave 42% conversion after 4 h of shaking. When the reaction time was extended to 12 h, 65% conversion was achieved with 49% ee of corresponding diol (+)-**11** with (−)-**9** with 36% ee.

3. Conclusion

Herein, we have reported the first chemoenzymatic route to optically active dihydroxy cyclopenta[*b*]naphthalenones; (+)-1,4a-dihydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1*H*-cyclopenta [*b*]naphthalen-2(4*H*)-one (+)-**10,** (+)-1,8a-dihydroxy-4a,5,6, 7,8,8a,9,9a-octahydro-1*H*-cyclopenta[*b*]napthalen-2-(4*H*)-one (+)-**11**; precursors of decalin-based bioactive natural products by hydrolase type enzymes CRL and PLE. Enzyme CRL was found to be the best biocatalyst and gave (−)-4a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1*H*-cyclopenta[*b*]naphthalen-1-yl acetate (−)-**8** with 47% ee and the corresponding diol (+)-**10** with 98% ee together with (−)-8a-hydroxy-2-oxo-2,4,4a,5,6,7,8,8a, 9,9a-decahydro-1*H*-cyclopenta[*b*]naphthalen-1-yl acetate (−)-**9** with 46% ee and the corresponding diol, (+)-1,8a-dihydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1*H*-cyclopenta[*b*]napthalen-2-(4*H*)-one (+)-**11** with 98% ee. We have also demonstrated the first short synthetic pathway to **6** and **7** via a Pauson–Khand cycloaddition applied to enyne templates **4** and **5**, which in turn were isolated as single diastereomers with 80% and 85% chemical yield respectively, as single diastereomers due to the more favored chair conformation of the cyclohexane ring.

4. Experimental

4.1. General

All experiments were carried out in pre-dried glassware (1 h, 150 °C) under an inert atmosphere of Argon. The following reaction solvents were distilled from the indicated drying agents: dichloromethane (P_2O_5), tetrahydrofuran (sodium, benzophenone), ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker Spectrospin Avance DPX-400 spectrometer. ^1H (400 MHz) and ^{13}C NMR were recorded in $CDCl_3$ and the chemical shift as are expressed in ppm relative to $CDCl_3$ (δ 7.26 and 77.0 for ^1H and ^{13}C NMR, respectively) as the internal standard. Standard COSY, HETCOR and DEPT experiments were performed to establish NMR assignments. Infrared spectra were recorded on a Thermo Nicolet IS10 ATR-FT-IR spectrophotometer**.** HRMS spectra were detected on an Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS at National Nanotechnology Research Center of Bilkent University (UNAM). Optical rotations were measured employing a Rudolph research analytical, autopol III automatic polarimeter. Flash column chromatography was performed by using thick-walled glass columns with a flash grade (Merc Silica Gel 60). Reactions were monitored by thin layer chromatography using precoated silica gel plates (Merc Silica Gel PF-254),visualized by UV-light and polymolybden phosphoric acid in ethanol as appropriate. All extracts were dried over anhydrous magnesium sulfate and solutions were concentrated under vacuum by using rotary evaporator.

Although many attempts were made to determine the absolute configuration of all hydroxy-octahydrocyclopenta[*b*]naphthalen-yl acetates (−)-**8** and (−)-**9** and the corresponding diols (+)-**10** and (+)-**11** by anchoring chiral units such as, 1*S*-(+)-10-camphorsulfonyl chloride and (*S*)-(+)-mandelic acid, unfortunately, we could not obtain any feasible crystalline structure suitable for X-ray.

4.2. Synthesis of 1-(cyclohex-1-en-1-yl) pyrrolidine 1

Cyclohexanone (20.0 g, 0.200 mol) was dissolved in cyclohexane (250 mL) after which anhydrous magnesium sulfate (120 g) was added in one portion under a nitrogen atmosphere. The mixture was then cooled to 0 °C with an ice bath and pyrrolidine (84.0 ml, 1.00 mol) was added dropwise over a 0.5 h period. After the reaction mixture had been stirred for an additional 30 min at 0 °C, the ice bath was removed and the reaction mixture was stirred overnight at room temperature. Magnesium sulfate was removed by filtration and rinsed throughly with dry cyclohexane

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(3 × 50 mL). The combined filtrates were concentrated under reduced pressure to give the crude product as an orange oil, then distilled under reduced pressure (69 °C /1 mmHg), to give a colorless oil (13.36 g, 84% yield).

4.2.1. 1-(Cyclohex-1-en-1-yl) pyrrolidine 1

Colorless oil, (20.79 g, 95% yield). IR ν_{max} (neat, cm^{-1}): 1652, 1255, 820 ^1H NMR ($CDCl_3$, 400 MHz): δ 4.22 (s, 1H), 2.93 (m, 1H), 2.85 (t, J = 4.0 Hz, 1H), 2.27 (t, J = 7.0 Hz, 1H), 2.12 (m, 2H), 2.03 (m, 3H), 1.71–1.86 (m, 3H), 1.58–1.68 (m, 2H), 1.45–1.52 (m, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 143.3, 93.5, 47.4, 27.5, 25.4, 25.2, 25.0, 24.5, 23.2, 23.0. HRMS (ESI-TOF) for $C_7H_{12}O$ $[M+H]^+$ was calculated as 152.1362 and found to be 152.1371.

4.3. Synthesis of α′-allyl 3 and α′-propargyl 2 cyclohexanones

To a stirred solution of anhydrous 1,4-dioxane (20 ml) and 1-(cyclohex-1-en-1-yl) pyrrolidine **1** (5 g, 33 mmol) at 0 °C equipped with a reflux condenser was added dropwise a mixture of allylbromide (2.855 ml, 33 mmol) or propargylbromide (3.68 ml, 33 mmol) in anhydrous dioxane (20 mL). The resultant mixture was stirred for 4 h at reflux followed by the addition of HCl solution (1%, 12 ml) and then by an additional 3 h reflux by removing 1,4-dioxane. The reaction mixture was washed with diethyl ether (3 × 50 mL). The combined organic phase was washed with brine (50 mL) dried over $MgSO_4$ and vaporated in vacuo. The crude products were purified by flash column chromatography with a mixture of ethylacetate and hexane in suitable ratios.

4.3.1. 2-Allylcyclohexanone 3

Colorless oil, (18.05 g, 95% yield). IR ν_{max} (neat, cm^{-1}): 1715, 1651, 925. ^1H NMR ($CDCl_3$, 400 MHz): δ 5.72–5.83 (m, 1H), 5.04 (d, J = 1.0 Hz, 1H), 4.98–5.01 (m, 1H), 2.50–2.57 (m, 1H), 2.24–2.42 (m, 2H), 2.09–2.16 (m, 2H), 1.94–2.08 (m, 1H), 1.81–1.88 (m, 1H), 1.60–1.73 (m, 2H), 1.53 (d, J = 7.0 Hz, 1H), 1.35 (dq, J = 12.0 and 3.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 212.4, 136.5, 116.2, 50.3, 42.0, 33.8, 33.4, 27.9, 24.9 HRMS (ESI-TOF) for $C_9H_{14}O$ $[M]^+$, was calculated as 138.1045 and found to be 138.1054.

4.3.2. 2-(Prop-2yn-1yl)cyclohexanone 2

Colorless oil, (15.35 g, 82% yield). IR ν_{max} (neat, cm^{-1}): 3379, 2137, 1707, 695. ^1H NMR ($CDCl_3$, 400 MHz): δ 2.62 (ddd, J = 2.7, 4.5 and 17.0 Hz, 1H), 2.47–2.54 (m, 1H), 2.40–2.46 (m, 1H), 2.35 (t, J = 2.6 Hz, 1H), 2.20–2.35 (m, 1H), 2.16–2.23 (m, 1H), 2.09–2.13 (m, 1H), 1.96 (t, J = 2.6 Hz, 1H), 1.80–1.95 (m, 1H), 1.65–1.75 (m, 1H), 1.59–1.65 (m, 1H), 1.37–1.48 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 210.4, 82.4, 69.3, 49.4, 41.9, 33.0, 26.9, 24.9, 18.7. HRMS (ESI-TOF) for $C_9H_{12}O$ $[M]^+$ was calculated as 136.0888 and found to be 136.0894.

4.3.3. Synthesis of homopropargyl alcohol (isolated as diastereomeric mixture) 5

Initially, Zn-Cu couple preparation is required to be carried out in an oxygen-free environment. Zinc dust (9.54 g, 74 mmol) was suspended in distilled water (10 mL), after which an acidic cupric chloride solution (0.15 M in 5% hydrochloric acid, 22 mL) was added with vigorous magnetic stirring. When the evolution of the gas ceased, the suspension was filtered and the black solid was washed with water until the wash gave a negative test with 6% silver nitrate solution.[14]

To a stirred mixture of the corresponding ketone **3** (10.23 g) (74 mmol) and freshly prepared Zn-Cu couple (10.32 g, 80 mmol) in THF (30 mL), propargyl bromide (11.90 g, 80 mmol, 80 wt % in toluene) was added dropwise at 0 °C. The mixture was reflux for 5 h by monitoring with TLC. The resulting mixture was hydrolyzed with 1 M HCl (7 mL) and extracted with diethyl ether (3 × 30 mL), dried over $MgSO_4$, and evaporated in vacuo. The crude product was purified by flash column chromatography using a mixture of ethylacetate and hexane in suitable ratios.

4.3.4. 2-Allyl-1-(prop-2yn-1yl)cyclohexanol (diastereomeric mixture) 5

Yellow oil, (18.16 g, 78% yield). IR ν_{max} (neat, cm^{-1}): 3612, 3271, 2124, 1643, 942, 615. Diastereomeric ratio (d.r, 2.33:1 determined by the integration of ^1H NMR signal: δ 2.31 d (major), 2.29 d (minor). ^1H NMR ($CDCl_3$, 400 MHz): δ 5.66–5.80 (m, 2H), 5.01 (t, J = 6.9 Hz, 2H), 4.94 (d, J = 9.6 Hz, 2H), 2.35–2.49 (m, 4H), 2.31 (d, J = 2.45 Hz, 1H), 2.29 (d, J = 2.40 Hz, 1H) 1.99 (t, J = 2.6 Hz, 2H), 1.84–1.92 (m, 2H), 1.65–1.74 (m, 2H), 1.52–1.62 (m, 4H), 1.47–1.52 (m, 4H) 1.13–1.28 (m, 6H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 137.9, 137.8, 115.9, 115.7, 80.8, 80.5, 72.9, 72.8, 71.8, 70.2, 42.6, 42.5, 35.7, 35.5, 33.9, 33.7, 31.3, 31.2, 27.5, 27.3, 25.2, 25.1, 21.7, 21.6. HRMS (ESI-TOF) for $C_{12}H_{18}O$ $[M]^+$ was calculated as 178.1358 and found to be 178.1394.

4.3.5. Synthesis of homoallyl alcohol (isolated as single diastereomer) 4

To a stirred solution of Mg turnings (15 mmol) and iodine (2 pieces) in dry diethyl ether (15 mL) at room temperature equipped with a reflux condenser, a mixture of allylbromide (11 mmol) was added dropwise in anhydrous diethyl ether (7 mL). The mixture was allowed to reflux for 25 min, Then cooled down to 0 °C followed by the addition of the corresponding ketone (2-(prop-2-yn-1yl)cyclohexanone) (10 mmol) in dry diethyl ether (5 mL), in a dropwise manner. The resultant mixture was stirred for 4 h. The reaction mixture was hydrolyzed with saturated ammonium chloride solution (20 mL) and then with HCl (3 mL). The resultant mixture was extracted with diethyl ether (3 × 30 mL). The combined organic phase was washed with brine (20 mL), dried over $MgSO_4$ and evaporated in vacuo. The crude products were purified by flash column chromatography with a mixture of ethylacetate and hexane in suitable ratios.

4.3.5.1. 1-Allyl-2-(prop-2-yn-1-yl)cyclohexanol (isolated as single diastereomer) 4. Yellow oil, (16.28 g, 81% yield). IR ν_{max} (neat, cm^{-1}): 3629, 3284, 2131, 957, 621. ^1H NMR ($CDCl_3$, 400 MHz): δ 5.69–5.89 (m, 1H), 5.04–5.08 (m, 1H), 5.02 (d, J = 1.2 Hz, 1H), 2.38 (td, J = 4.5 and 12.0 Hz, 1H), 2.29 (m, 3H), 2.16 (qd, J = 2.0 and 5.4 Hz, 1H), 1.94 (t, J = 2.7 Hz, 1H), 1.66–1.78 (m, 2H), 1.56–1.66 (m, 1H), 1.62 (bs, 1H), 1.36–1.56 (m, 3H), 1.22–1.40 (m, 1H), 1.10–1.22 (m, 1H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 134.6, 118.5, 83.8, 72.3, 67.7, 44.6, 43.1, 36.9, 27.7, 25.4, 21.5, 18.5. HRMS (ESI-TOF) for $C_{12}H_{18}O$ $[M]^+$ was calculated as 178.1358 and found to be 178.1385.

4.4. General procedure for the Pauson–Khand reaction

To a solution of **4** or **5** (1.13 mmol) in DCM (15 mL) $Co_2(CO)_8$ (0.683 g, 2 mmol) was added and stirred for 2 h with TLC monitoring. Next, NMO (1.32 g, 11.3 mmol) was added and stirred for 24 h. The crude products were purified by flash column chromatography using EtOAc/hexane as the eluent.

4.4.1. 4a-Hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1*H*-cyclopenta-[*b*]naphthalen-2(4*H*)-one 7

White solid, (17.86 g, 85% yield), melting point range: 80.2–80.9 °C. IR ν_{max} (neat, cm^{-1}): 3605, 3375, 1669, 1645 ^1H NMR ($CDCl_3$, 400 MHz): δ 5.84 (s, 1H), 2.70 (d, J = 9.0 Hz, 2H), 2.48 (dd, J = 9.0 and 17.6 Hz, 1H), 2.21 (d, J = 14.0 Hz, 1H), 1.95 (dd, J = 2.0 and 17.2 Hz, 1H), 1.74–1.84 (m, 2H), 1.63–1.74(m, 2H), 1.37–1.55 (m, 3H), 1.21–1.32 (m, 2H), 1.20–1.26 (m, 1H), 1.05–1.26 (m,

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2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 208.5, 181.3, 128.7, 71.3, 43.9, 42.1, 41.3, 40.6, 38.6, 35.6, 27.0, 24.8, 20.2. HRMS (ESI-TOF) for $C_{13}H_{18}O_2$ $[M]^+$, was calculated as 206.1307 and found to be 206.1335.

4.4.2. 8a-Hydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1*H*-cyclopenta-[*b*]naphthalen-2(4*H*)-one 6

White solid, (15.0735 g, 80% yield), melting point range: 76.6–77.3 °C. IR ν_{max} (neat, cm^{-1}): 3594, 3345, 1665, 1642 ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.77 (s, 1H), 3.13 (bs, 1H), 2.51 (dd, J = 5.3 and 18.5 Hz, 1H), 2.32–2.45 (m, 2H), 2.00 (dd, J = 5.4 and 12.0 Hz, 1H), 1.90 (d, 14.0 Hz, 1H), 1.71 (d, J = 12.0 Hz, 1H), 1.45–1.65 (m, 3H), 1.35–1.45 (m, 2H), 1.22–1.29 (m, 2H), 1.03–1.22 (m, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 209.2, 184.3, 126.8, 70.1, 47.6, 44.6, 42.0, 39.1, 37.4, 33.4, 28.7, 25.7, 21.2. HRMS (ESI-TOF) for $C_{13}H_{18}O_2$ $[M]^+$ was calculated as 206.1307 and found to be 206.1343.

4.5. General procedure for the $Mn(OAc)_3$ oxidation of *rac*-4a-(7)- or *rac*-8a-(6)-hydroxy-octahydro-1*H*-cyclopenta[*b*]naphthalenones

A mixture of $Mn(OAc)_3$ (2.41 g, 9.0 mmol) in cyclohexane (100 mL) was refluxed for 45 min under a Dean–Stark trap, then cooled to room temperature. Next, *rac*-**4a** or *rac*-**8a**-hydroxy-octahydro-1*H*-cyclopenta[*b*]naphthalenones: *rac*-**4a-7** or *rac*-**8a-6** was gradually added and the mixture was allowed to reflux until the dark brown color disappeared (TLC monitoring). The reaction mixture was diluted with ethyl acetate (100 mL) and the organic phase was washed with 1 M HCl (100 mL), saturated $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude product was separated by flash column chromatography using ethyl acetate/hexane as eluent to obtain the product.

4.5.1. (±)-4a-Hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1*H*-cyclopenta[*b*]naphthalen-1-yl acetate *rac*-8

Colorless oil, (17.16 g, 75% yield). IR ν_{max} (neat, cm^{-1}): 3612, 3389, 1749, 1685, 1153, 1102 ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.94 (s, 1H), 4.76 (d, J = 1.6 Hz, 1H), 2.72 (d, J = 10.8 Hz, 1H), 2.64 (bs, 1H), 2.26–2.33 (m, 1H), 2.04 (s, 3H), 2.00 (d, J = 1.0 Hz, 1H), 1.93–2.03 (m, 1H), 1.65–1.70 (m, 2H), 1.52–1.59 (m, 2H), 1.37–1.48 (m, 2H), 1.30–1.37 (m, 1H), 1.15–1.26 (m, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 201.2, 177.7, 169.7, 126.6, 77.6, 71.0, 46.8, 44.5, 41.7, 38.2, 32.7, 26.7, 24.7, 19.8. 19.6. HRMS (ESI-TOF) for $C_{15}H_{20}O_4$ $[M]^+$ was calculated as 264.1356 and found to be 264.1372.

4.5.2. (±)-8a-Hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1*H*-cyclopenta[*b*]naphthalen-1-yl acetate *rac*-9

Colorless oil, (15.26 g, 79% yield). IR ν_{max} (neat, cm^{-1}): 3585, 3215, 3075, 1743, 1672, 1147, 1100. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.84 (s, 1H), 4.74 (d, J = 3.0 Hz, 1H), 2.37–2.47 (m, 2H), 2.26 (dd, J = 6.0 and 14.0 Hz, 1H), 2.08 (s, 3H), 2.05 (bs, 1H), 1.61–1.74 (m, 3H), 1.53–1.59 (m, 3H), 1.42–1.47 (m, 2H), 1.26 (d, J = 6.0 Hz, 1H), 1.15–1.24 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 200.9, 180.0, 170.4, 123.6, 77.3, 68.2, 44.2, 43.0, 42.3, 38.8, 32.7, 27.6, 24.6, 19.6. HRMS (ESI-TOF) for $C_{15}H_{20}O_4$ $[M]^+$ was calculated as 264.1356 and found to be 264.1393.

4.5.2.1. 8a-Hydroxy-1-phenyl-4a,5,6,7,8,9,9a-octahydro-1*H*-cyclopenta[*b*]naphthalen-2(4*H*)-one 9a.

Colorless oil, (2.68 g, 13% yield). IR ν_{max} (neat, cm^{-1}): 3612, 3364, 3071, 1674. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.21–7.36 (m, 3H), 7.11 (d, J = 7.0 Hz, 2H), 5.92 (s, 1H), 3.19 (dd, J = 3.0 and 12.0 Hz, 1H), 3.11 (d, J = 2.0 Hz, 1H), 2.60 (dd, J = 3.0 and 14.0 Hz, 1H), 2.47–2.56 (m, 1H), 2.16 (dd, J = 6.0 and 14.0 Hz, 1H), 1.79 (d, J = 17.0 Hz, 1H), 1.58–1.66 (m, 3H), 1.49 (dd, J = 4.0 and 14.0 Hz, 1H), 1.47–1.50 (m, 2H), 1.42 (d, J = 10.0 Hz, 1H), 1.38 (d, J = 17.0 Hz, 1H), 1.22–1.31 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 208.1, 182.6, 139.2, 128.7, 128.1, 126.9, 125.8, 70.1, 59.8, 47.5, 46.8, 44.7, 39.2, 33.4, 28.7, 25.7, 21.2. HRMS (ESI-TOF) for $C_{19}H_{22}O_2$ $[M+H]^+$ was calculated as 283.1692 and found to be 283.1685.

4.5.3. General procedure for CRL (*Candida Rugosa Lipase*) hydrolysis of *rac*-8 and *rac*-9

To a stirred solution of 100 mg of substrate in phosphate buffer (0.1 M, pH 7.00, 20 mL), 100 mg of CRL were added in one portion and shaken at suitable temperature. The conversion was monitored by TLC. The reaction mixture was extracted with ethyl acetate, dried over $MgSO_4$, and concentrated under reduced pressure. Followed by flash-column chromatography which purified the crude mixture using suitable ethylacetate/hexane as an eluent.

4.5.4. General procedure for PLE (*Pig Liver Esterase*) hydrolysis of *rac*-8 and *rac*-9

To a stirred solution of 500 mg of *rac*-**8** or *rac*-**9** in 50 mL of pH 7.00 phosphate buffer, 50 μL of *PLE* was added in one portion and the reaction mixture was stirred at suitable temperature (TLC monitoring). The reaction mixture was extracted with ethyl acetate, dried over $MgSO_4$ and concentrated under reduced pressure. This was followed by flash-column chromatography which purified the crude mixture using suitable ethylacetate/hexane as an eluent.

4.5.4.1. (−)-8a-Hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1*H*-cyclopenta[*b*]naphthalen-1-yl acetate (−)-9 at the end of CRL hydrolysis.

Colorless oil (37 mg, 37% yield). $[\alpha]_D^{26} = -3.2$ (c 1.00, $CHCl_3$), 46% ee. The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralcel OD-H, λ = 230 nm, n-hexane/2-propanol 98:2, 0.5 mL/min), t_1 = 3.1 min (major) and t_2 = 3.7 min (minor). HRMS (ESI-TOF) for $C_{15}H_{20}O_4$ $[M+H]^+$ was calculated as 265.1434 and found to be 265.1447.

4.5.4.2. (+)-1,8a-Dihydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1*H*-cyclopenta[*b*]napthalen-2-(4*H*)-one (+)-11 at the end of CRL hydrolysis.

Yellow oil (55 mg, 55% yield). $[\alpha]_D^{26} = +9.2$ (c 1.0, $CHCl_3$), 98% ee. IR ν_{max} (neat, cm^{-1}): 3605, 3612, 3364, 3352, 1671, 1644 ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.79 (s, 1H), 3.74 (d, J = 2.0 Hz, 1H), 2.99–3.03 (m, 1H), 2.34–2.48 (m, 2H), 2.20 (dd, J = 6.0 and 13.0 Hz, 1H), 1.71 (dd, J = 4.0 and 17.0 Hz, 1H), 1.52–1.62 (m, 2H), 1.31–1.43 (m, 4H), 1.29–1.34 (m, 2H), 1.24 (d, J = 17.0 Hz, 1H), 1.13–1.21 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 206.4, 179.3, 122.4, 78.0, 68.8, 43.9, 43.3, 42.2, 32.3, 38.2, 27.5, 24.6, 20.0. HPLC conditions: (Daicel Chiralcel OD-H, λ = 230 nm, n–hexane/2-propanol 98:2, 0.5 mL/min), t_1 = 5.5 min (minor) and t_2 = 5.9 min (major). HRMS (ESI-TOF) for $C_{13}H_{18}O_3$ $[M+H]^+$, was calculated as 223.1329, and found to be 223.1345.

4.5.4.3. (−)-8a-Hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1*H*-cyclopenta[*b*]naphthalen-1-yl acetate-(−)-9 at the end of PLE hydrolysis.

Colorless oil (32 mg, 32% yield). $[\alpha]_D^{26} = -3.8$ (c 1.00, $CHCl_3$), 36% ee. HRMS (ESI-TOF) for $C_{15}H_{20}O_4$ $[M+H]^+$, was calculated as 265.1434 and found to be 265.1447.

4.5.4.4. (+)-1,8a-Dihydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1*H*-cyclopenta[*b*]napthalen-2-(4*H*)-one (+)-11 at the end of PLE hydrolysis.

Yellow oil (59 mg, 59% yield). $[\alpha]_D^{26} = +8.9$ (c 1.0, $CHCl_3$), 49% ee. IR ν_{max} (neat, cm^{-1}): 3605, 3612, 3364, 3352, 1671, 1644 ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.79 (s, 1H), 3.74 (d, J = 2.0 Hz, 1H), 2.99–3.03 (m, 1H), 2.34–2.48 (m, 2H), 2.20 (dd, J = 6.0 and 13.0 Hz, 1H), 1.71 (dd, J = 4.0 and 17.0 Hz, 1H),

1.52–1.62 (m, 2H), 1.31–1.43 (m, 4H), 1.29–1.34 (m, 2H), 1.24 (d, J = 17.0 Hz, 1H), 1.13–1.21 (m, 2H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 206.4, 179.3, 122.4, 78.0, 68.8, 43.9, 43.3, 42.2, 32.3, 38.2, 27.5, 24.6, 20.0. HRMS (ESI-TOF) for $C_{13}H_{18}O_3$ $[M+H]^+$ was calculated as 223.1329 and found to be 223.1345.

4.5.4.5. (−)-4a-Hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1*H*-cyclopenta[*b*]naphthalen-1-yl acetate (−)-8 at the end of CRL hydrolysis. Colorless oil (42 mg, 42% yield). $[\alpha]_D^{26}$ = −1.9 (c 1.00, $CHCl_3$), 47% ee. The enantiomeric excess of the product was determined by HPLC analysis (Daicel Chiralcel OD-H, λ = 230 nm, n-hexane/2-propanol 98:2, 0.5 mL/min), t_1 = 4.6 min (major) and t_2 = 5.1 min (minor). HRMS (ESI-TOF) for $C_{15}H_{20}O_4$ $[M]^+$, was calculated as 264.1356 and found to be 264.1372.

4.5.4.6. (+)-1,4a-Dihydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1*H*-cyclopenta[*b*]naphthalen-2(4*H*)-one-(+)-10 at the end of CRL hydrolysis. Dark yellow oil (40 mg, 40% yield). $[\alpha]_D^{26}$ = +5.9 (c 1.0, $CHCl_3$), 98.0% ee. IR ν_{max} (neat, cm^{-1}): 3642, 3617, 3371, 3369, 1679, 1648 ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.95 (s, 1H), 3.89 (d, J = 2.0 Hz, 1H), 2.82 (d, J = 14.0 Hz, 1H), 2.63–2.76 (m, 2H), 2.35 (dd, J = 4.0 and 14.0 Hz, 1H), 2.00–2.10 (m, 2H), 1.72–1.78 (m, 2H), 1.53 (d, J = 3.0 Hz,1H), 1.59 (d, J = 3.0 Hz, 1H), 1.35–1.51 (m, 3H), 1.21–1.32 (m, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 207.6, 178.4, 125.8, 79.1, 71.8, 48.7, 45.6, 43.1, 39.5, 33.8, 28.2, 25.7, 21.2. HPLC conditions: (Daicel Chiralcel OD-H, λ = 230 nm, n-hexane/2-propanol 98:2, 0.5 mL/min), t_1 = 6.8 min. (minor) and t_2 = 8.1 min. (major). HRMS (ESI-TOF) for $C_{13}H_{18}O_3$ $[M+H]^+$ was calculated as 223.1329 and found to be 223.1353.

4.5.4.7. (−)-4a-Hydroxy-2-oxo-2,4,4a,5,6,7,8,8a,9,9a-decahydro-1*H*-cyclopenta[*b*]naphthalen-1-yl acetate (−)-8 at the end of PLE hydrolysis. Colorless oil (32 mg, 32% yield). $[\alpha]_D^{26}$ = −1.8 (c 1.00, $CHCl_3$), 40% ee. HRMS (ESI-TOF) for $C_{15}H_{20}O_4$ $[M]^+$ was calculated as 264.1356 and found to be 264.1372.

4.5.4.8. (+)-1,4a-Dihydroxy-4a,5,6,7,8,8a,9,9a-octahydro-1*H*-cyclopenta[*b*]naphthalen-2(4*H*)-one (+)-10 at the end of PLE hydrolysis. Dark yellow oil (35 mg, 35% yield). $[\alpha]_D^{26}$ = +3.5 (c 1.00, $CHCl_3$), 58% ee. HRMS (ESI-TOF) for $C_{13}H_{18}O_3$ $[M+H]^+$ was calculated as 223.1329 and found to be 223.1353.

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