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Synthesis of Enantiomerically Pure Stereomers of Rosaprostol

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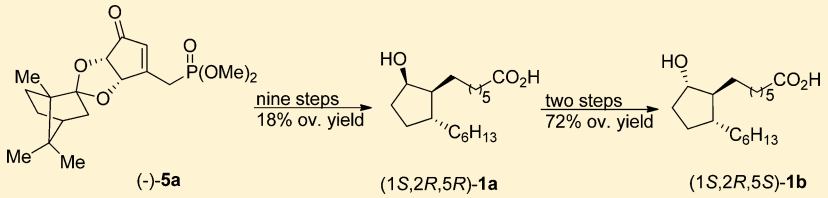
Supporting Information



(-)-**5a** (1*S*,2*R*,5*R*)-**1a** (1*S*,2*R*,5*S*)-**1b**

ABSTRACT: Enantiopure stereomers of rosaprostol **1**, an antiulcer drug, were synthesized from diastereomeric building blocks (−)-**5a** and (+)-**5b**. Conversion of (−)-**5a** into rosaprostol stereomer (−)-(1*S*,2*R*,5*R*)-**1a** was accomplished in nine steps in 18% overall yield. In this sequence, fully diastereoselective hydrogenation of the endocyclic carbon double bond in the cyclopentenone ring was key, generating a new stereogenic center (C-2 in **1a**). C-5 epimeric rosaprostol (−)-(1*S*,2*R*,5*S*)-**1b** was obtained from (−)-**1a** in 72% yield by a two-reaction sequence involving methylation and one-pot Mitsunobu esterification−hydrolysis.

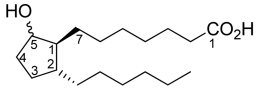
Prostaglandins are part of a rich family of naturally occurring biologically active compounds that regulate a great number of physiological processes in animals and humans. Their chemically more stable structural analogues also exhibit a broad range of biological activities, and some of them have found commercial application as medicines.[1] A good example of the use of prostanoids in a health care is rosaprostol **1** (Scheme 1).

Rosaprostol belongs to a series of 19,20-bisnorprostanoic acid derivatives, and the sodium salt of racemic rosaprostol **1** [a mixture of racemic 1,2-*trans*-1,5-*cis* and 1,2-*trans*-1,5-*trans* diastereomers] is used for the treatment of gastric and duodenal ulcers under the market name Rosal.[2] As with many naturally occurring prostaglandins, rosaprostol **1** shows gastric antisecretory activity and cytoprotective action; however, it is devoid of their undesirable side effects, including diarrhea, hypotension, and uterine stimulation.[3] At the end of the last century, racemic rosaprostol **1** became an interesting target of biological and synthetic studies. As a result, various synthetic approaches to (±)-**1** have been reported,[4] including two of them developed by our group.[4f,g]

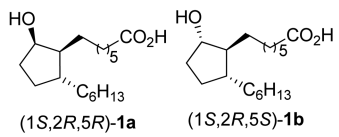
Recently, in the context of our research program aimed at the development of new methods for the synthesis of bioactive prostanoids and investigation of stereostructure−activity relationships in this class of compounds, we have reported the synthesis and cytotoxicity of enantiomeric 13,14-dihydro-15-deoxy-Δ^7-PGA$_1$ methyl esters (**2**) (TEI-9826)[5] and structurally related NEPP-11 **3** and its J-type analogue **4**[6] (Scheme 2).

As part of the execution of this program and extension of our earlier work on rosaprostol **1**, we report herein the first synthesis and characterization of the unknown enantiopure

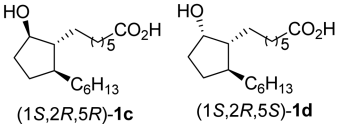
Scheme 1. Structure, Numbering System, and Four Optically Active Stereomers of Rosaprostol



(±)-7-[2-hexyl-5-hydroxycyclopentyl]heptanoic acid **1**

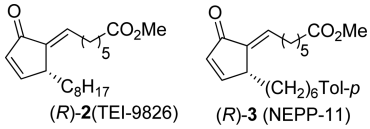


(1*S*,2*R*,5*R*)-**1a** (1*S*,2*R*,5*S*)-**1b**

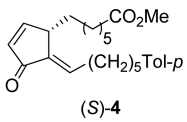


(1*S*,2*R*,5*R*)-**1c** (1*S*,2*R*,5*S*)-**1d**

Scheme 2. Structures of Cross-Conjugated Cyclopentenones



(*R*)-**2**(TEI-9826) (*R*)-**3** (NEPP-11)



(*S*)-**4**

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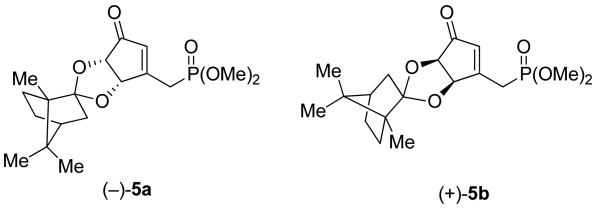
stereomers of **1** that will be used in the next step for determination of their biological activity. Although there are three stereogenic centers in the structure of rosaprostol **1** (at C-1, C-2, and C-5), it can exist in the form of only four stereomers, **1a**–**d** (Scheme 1), because of the *trans* arrangement of substituents at C-1 and C-2. To date, only one paper related to the subject of our work has been reported. In 2007, Csaky and his group[7] described a short and efficient asymmetric synthesis of two stereomeric rosaprostol methyl esters. However, the esters obtained were not hydrolyzed to the corresponding stereomeric rosaprostols **1** and, as we found in the present work (see below), were not enantiopure.

The synthesis of enantiopure rosaprostol stereomers was accomplished according to the recently elaborated strategy for the synthesis of cross-conjugated cyclopentenone prostaglandins **2**–**4**, where the diastereomerically pure camphor protected 3-[(dimethoxyphosphoryl)methyl]-4,5-dihydroxycyclopent-2-enones **5** (Scheme 3) were used as starting reagents. Thus, the ω side chain was first installed by the Horner olefination reaction of **5** with a proper aldehyde, whereas the α side chain was introduced at a later stage of synthesis, after generation of a stereogenic center at C-2. The latter process is the most important one from the viewpoint of configurational assignment and preparation of enantiopure target compounds required for studies of the stereostructure–bioactivity relationship.

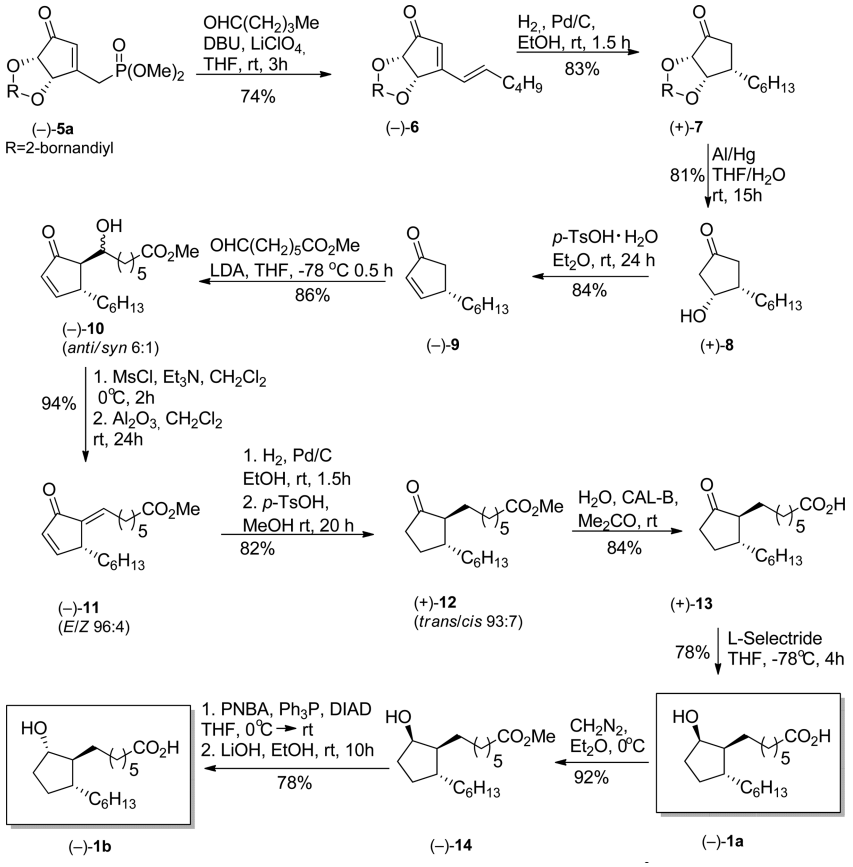
Scheme 3. Structures of Building Blocks 5a and 5b



The reaction sequence leading to stereomeric rosaprostols **1a** and **1b** and some experimental details are depicted in Scheme 4 and briefly discussed below. In the first step, the reaction of cyclopentenone phosphonate (−)-**5a** with commercially available *n*-pentanal was carried out at room temperature using DBU/$LiClO_4$ as a basic system. It afforded the corresponding olefination product (−)-**6** with a clean *E* geometry of the exocyclic carbon–carbon double bond, as evidenced by a large coupling constant value ($^3J_{H-H}$ = 15.7 Hz) of the olefinic protons in the ^{1}H NMR spectrum. Then, dienone (−)-**6** was hydrogenated in the presence of 10% Pd/C to give cyclopentanone (+)-7, which was formed as a single diastereomer.

In this crucial reaction, a new streogenic center at C-4 was generated under steric control of the bulky camphor protected *cis*-diol moiety. As the absorption of the palladium catalyst and addition of hydrogen to the endocyclic double bond in (−)-**6** take place exclusively from the less hindered side of the cyclopentenone ring, i.e., opposite a chiral diol moiety, diastereomer (+)-7 thus obtained has an (*S*) configuration at C-4. Transformation of (+)-7 into enantiopure 4-hexylcyclopent-2-enone (−)-**9** was effected in two steps. First, Johnson

Scheme 4. Synthesis of Stereomeric Rosaprostols 1a and 1b



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selective deoxygenation[8] of (+)-**7** with aluminum amalgam furnished 3-hydroxycyclopentanone (+)-**8**, which was subsequently converted into 4-hexylcyclopent-2-enone (−)-**9** under acidic conditions.

Having synthesized enantiopure cyclopentenone (−)-**9** as a key intermediate, we could begin installation of the methyl heptanoate group at the α-position of the cyclopentenone ring (C-5 in **9**). Thus, aldol condensation of (−)-**9** with methyl 6-formylhexanoate gave a mixture of *anti*- and *syn*-aldols **10** in a ratio of approximately 6:1 and in 86% total yield. The *anti*/*syn* ratio was determined by integration of the hydroxy group protons showing different chemical shifts in the ^{1}H NMR spectrum (δ_{OH} = 3.85 and 4.02 ppm for *anti*- and *syn*-**10**, respectively). The major isomer was separated by column chromatography and characterized. Its *anti* configuration at C-7 was assigned based on the coupling constant value ($^3J_{H-H}$ = 8.2 Hz) between protons at C-7 and C-1 of the five-membered ring. Aldols **10** were then subjected to mesylation and subsequent elimination to produce, in excellent yield (94%), the cross-conjugated dienone *E*-(−)-**11** contaminated with small amounts (4%) of the *Z* isomer. Interestingly, the same stereochemical outcome of elimination of the mesyloxy group from *anti*-**10** and *syn*-**10** can be explained in terms of the *syn* elimination (E1cB) and *anti* elimination (E2), respectively, as proposed by Kobayashi.[9] The product of the above reaction was hydrogenated on 10% Pd/C, and cyclopentanone (+)-**12** was obtained as a mixture of 1,2-*cis* and 1,2-*trans* isomers in a ratio 55:45, as revealed by ^{13}C NMR spectra displaying two carbonyl resonances at δ = 220.7 (*cis*) and 221.5 (*trans*) ppm. Therefore, the crude hydrogenation product was treated with *p*-toluenesulfonic acid in methanol. Under these epimerization conditions, the isomeric ratio was changed to 93:7 in favor of the thermodynamically more stable *trans*-**12**. Hydrolysis of the methyl ester moiety in (+)-**12** was achieved under very mild conditions using *Candida antarctica* lipase B (CAL-B) as a biocatalyst. Corresponding acid (+)-**13** thus obtained in 84% isolated yield contained only 2% of the *cis* isomer. Finally, treatment of (+)-**13** with L-Selectride under optimized conditions (THF, −78 °C, 4 h) gave the desired enantiopure rosaprostol stereomer, (−)-(1*S*,2*R*,5*R*)-**1a**. In spite of requiring nine steps to convert starting (−)-**5a** into rosaprostol (−)-**1a**, its synthesis was completed in a reasonable 18% overall yield.

According to our strategy, rosaprostol stereomer **1b** was to be prepared from (−)-**1a** by inversion of configuration of the C-5 stereocenter by a Mitsunobu reaction.[10] However, before this reaction was carried out, (−)-**1a** was treated with diazomethane to give corresponding methyl ester (−)-**14** with optical rotation $[\alpha]_D^{20}$ = −60.0 (*c* 0.7, $CHCl_3$). As mentioned above, both enantiomeric methyl esters, (−)- and (+)-**14**, were also prepared by Csaky et al.;[7] however, the optical rotations were much lower [(+)-**14**, $[\alpha]_D^{25}$ = +13 (*c* 0.6, $CHCl_3$)]. Hence, they were not enantiomerically pure. To complete the synthesis of **1b**, (−)-**14** was subjected to Mitsunobu reaction under standard conditions [*p*-nitrobenzoic acid (PNBA), triphenylphosphine (Ph_3P), diisopropyl azidodicarboxylate (DIAD), THF, rt], and the *p*-nitrobenzoate ester transiently formed was subsequently hydrolyzed under basic conditions. This one-pot procedure provided the C-5 epimeric rosaprostol (−)-(1*S*,2*R*,5*S*)-**1b** in 78% yield.

In summary, we have devised the first and experimentally simple synthesis of four enantiomerically pure stereomeric rosaprostols **1** from chiral diastereomeric 3-(phosphorylmethyl)cyclopent-2-enones (−)-**5a** and (+)-**5b** as building blocks. Thus, starting from (−)-**5a**, stereomer (−)-(1*S*,2*R*,5*S*)-**1a** was obtained in a nine-step sequence. The latter was converted into epimeric rosaprostol (−)-(1*S*,2*R*,5*S*)-**1b** by inversion of configuration at the C-5 center by a Mitsunobu reaction. It is obvious that the remaining two stereomers, **1c** and **1d**, could be prepared from (+)-**5b** according to the same protocol. Moreover, our synthesis is modular and can be applied for the preparation of enantiopure rosaprostol analogues.

EXPERIMENTAL SECTION

General Experimental Details. Unless stated otherwise, all air- and water-sensitive reactions were carried out under an argon atmosphere using freshly distilled dry solvents. Glassware was dried prior to use by heating under vacuum. Commercial grade reagents and solvents were used without further purification except as indicated below. THF and diethyl ether were distilled over Na/benzophenone prior to use. Dichloromethane, triethylamine, and diisopropylamine were distilled from CaH_2. Column chromatography was performed using silica gel (70−230 mesh). ^{1}H NMR spectra were recorded on a 600 or 500 MHz NMR spectrometer. Assignment of the chemical shift of the specific carbon and hydrogen atoms was based on HMQC, HMBC, and COSY experiments. Chemical shifts are quoted in parts per million (ppm) and reported relative to the residual proton resonance in the deuterated solvents. The mass spectra and HRMS were measured using a double-focusing (BE geometry) mass spectrometer utilizing a chemical ionization (CI), with isobutane as an ionizating agent, or electron ionization (EI) technique. Optical rotations were measured using a photopolarimeter. Melting points are uncorrected. Starting reagents (−)-**5a** and (+)-**5b** were prepared according to ref 11.

(+)-Camphor Protected (*E*)-3-(Hex-1-enyl)-4,5-dihydroxycyclopent-2-enone ((−)-6). (+)-Camphor protected 3-[(dimethoxyphosphoryl)methyl]-4,5-dihydroxycyclopent-2-enone (−)-**5a** ($[\alpha]_D^{22}$ −20.2 (*c* 4, acetone)) (2.0 g, 5.73 mmol) and lithium perchlorate (0.59 g, 5.56 mmol) were dissolved in THF (12 mL) and cooled to 0 °C. 1,8-Diazobicyclo[5.4.0]undec-7-ene (DBU) (0.85 g, 5.56 mmol) was added, and the mixture was stirred for 15 min. Pentanal (0.49 g, 5.72 mmol) was slowly added, the ice bath was removed, and the resulting mixture was stirred at room temperature for 3 h. After evaporation of THF under reduced pressure, the residue was subjected to column chromatography (petroleum ether/acetone 30:1), affording dienone (−)-**6** (1.31 g, 74%) as a light yellow oil; $[\alpha]_D^{20}$ −141.4 (*c* 2.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.62 (dt, *J* = 15.7, 7.1 Hz, 1H, CH═C*H*−CH_2), 6.43 (d, *J* = 15.7 Hz, 1H, C*H*═CH−CH_2), 5.79 (s, 1H, C(O)C*H*═C), 5.28 (d, *J* = 5.8 Hz, 1H, C(O)−C*H*−O), 4.33 (d, *J* = 5.7 Hz, 1H, C(O)−CH−C*H*−O), 2.31−2.21 (m, 2H, CH═CH−CH_2), 2.07 (ddd, *J* = 13.1, 4.4, 3.0 Hz, 1H), 1.92 (ddd, *J* = 13.1, 9.4, 3.9 Hz, 1H), 1.74 (t, *J* = 4.3 Hz, 1H, C*H* (camphor)), 1.69−1.62 (m, 1H), 1.51 (d, *J* = 13.1 Hz, 1H), 1.49−1.42 (m, 2H), 1.39−1.28 (m, 3H), 1.21−1.15 (m, 1H), 0.95 (s, 3H, CH_3 (camphor)), 0.91 (t, *J* = 7.3 Hz, 3H, CH_3CH$_2$), 0.81 (s, 3H, CH_3 (camphor)), 0.60 (s, *J* = 3.0 Hz, 3H, CH_3 (camphor)); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 201.4, 169.0, 146.4, 126.8, 124.8, 124.2, 78.2, 76.4, 51.7, 48.0, 45.3, 44.7, 33.5, 30.8, 29.5, 27.0, 22.3, 20.4, 20.4, 14.04, 9.5. Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.01; H, 9.06.

(+)-Camphor Protected (*S*)-4-Hexyl-2,3-dihydroxycyclopentanone ((+)-7). A mixture of (−)-**6** (1.33 g, 4.02 mmol) and 10% Pd/C (0.53 g) in ethanol (25 mL) was vigorously stirred at room temperature under a hydrogen atmosphere for 1.5 h. After filtration through a pad of Celite and evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography (petroleum ether/acetone 30:1) to yield (+)-7 (0.98 g, 72%) as a colorless solid; mp 67.0−67.5 °C; $[\alpha]_D^{20}$ +120.9 (*c* 2.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.64 (t, *J* = 3.5 Hz, 1H, C(O)−CH−C*H*−O), 4.03 (d, *J* = 5.2 Hz, 1H, C(O)−C*H*−O), 2.31−2.11 (m, 3H), 2.02−1.91 (m, 2H), 1.73 (t, *J* = 4.6 Hz, 1H, C*H* (camphor)), 1.72−1.61 (m, 2H), 1.60−1.49 (m, 1H), 1.44 (d, *J* = 12.9 Hz, 1H), 1.42−

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1.15 (m, 10H, CH_2), 0.98 (s, 3H, CH_3 (camphor)), 0.89 (t, J = 6.9 Hz, 3H, CH_3CH_2), 0.84 (s, 3H, CH_3 (camphor)), 0.71 (s, 3H, CH_3 (camphor)); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 214.7, 120.1, 78.9, 78.3, 51.9, 48.0, 45.4, 43.9, 40.3, 35.7, 31.9, 30.4, 29.7, 29.6, 27.6, 27.2, 22.8, 20.5, 20.5, 14.3, 9.4. Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.46; H, 10.27.

(+)-(3*R*,4*S*)-3-Hydroxy-4-hexylcyclopentanone (8). The freshly prepared aluminum amalgam from granular aluminum (0.5 g) and the saturated solution of mercuric chloride (10 mL) were added to a solution of (+)-**7** (0.160 g, 0.478 mmol) in 8:1 THF/H_2O (2 mL). Additional portions of aluminum amalgam were added after 3 and 15 h. After being stirred for an additional 4 h, the mixture was filtered through a pad of Celite, and the solvent was evaporated under reduced pressure. The residue was subjected to column chromatography (petroleum ether/acetone 10:1) affording (+)-**8** (71 mg, 81%) as a colorless liquid; $[\alpha]_D^{22}$ +139.9 (c 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.47 (br s, 1H, C*H*−OH), 2.43−2.24 (m, 3H, C*H*$_2$−C(O)−C*H*$_2$−C*H*−C*H*$_2$), 2.20−2.05 (m, 2H, C(O)−C*H*$_2$−CH−C*H*$_2$), 1.68 (s, 1H, CH−O*H*), 1.62−1.23 (m, 10H, CH_2), 0.88 (t, J = 6.9 Hz, 3H, CH_3CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 217.7, 70.9, 48.7, 42.3, 40.9, 31.7, 29.4 (2C), 27.7, 22.6, 14.0. Anal. Calcd for $C_{11}H_{20}O_2$: C,71.70; H, 10.94; Found: C, 71.53; H, 10.91.

(−)-(*S*)-4-Hexylcyclopent-2-enone (9). A solution of (+)-**8** (89 mg, 0.488 mmol) and *p*-toluenesulfonic acid hydrate (14 mg, 0.072 mmol) in Et_2O (3 mL) was stirred at room temperature for 24 h. The mixture was neutralized with a saturated aqueous solution of $NaHCO_3$ and extracted with $CHCl_3$ (4 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated, and the crude product was purified by flash column chromatography (petroleum ether/acetone 8:1) to yield (−)-**9** (68 mg, 84%) as a colorless liquid; $[\alpha]_D^{22}$ −160.6 (c 2.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.59 (dd, J = 5.6, 2.5 Hz, 1H, C(O)−CH=C*H*), 6.08 (dd, J = 5.6, 2.0 Hz, 1H, C(O)−C*H*=CH), 2.95−2.81 (m, 1H, CH=CH−C*H*), 2.47 (dd, J = 18.8, 6.3 Hz, 1H, C(O)−C*H*$_A$H$_B$), 1.94 (dd, J = 18.8, 2.1 Hz, 1H, C(O)−CH$_A$*H*$_B$), 1.58−1.17 (m, 10H, CH_2), 0.83 (t, J = 6.9 Hz, 3H, CH_3CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 207.0, 168.6, 133.4, 41.3, 40.9, 34.6, 31.5, 29.1, 27.4, 22.4, 13.9. Anal. Calcd for $C_{11}H_{18}O$: C,79.46; H, 10.91. Found: C, 79.34; H, 10.87.

Methyl (*R*)-7-Hydroxy-[(1*R*,2*R*)-2-hexyl-5-oxocyclopent-3-enyl]heptanoate ((−)-10). To a stirred solution of *i*-Pr_2NH (0.134 g, 1.32 mmol) in THF (12 mL) was added *n*-BuLi (0.48 mL, 2.2 M in THF, 1.06 mmol) at −30 °C under an argon atmosphere. After 15 min, the mixture was allowed to warm to 0 °C, and then the resulting solution of LDA was cooled to −78 °C. A solution of (−)-**9** (0.146 g, 0.881 mmol) in THF (2 mL) was slowly added, and the mixture was stirred for 15 min. Methyl 6-formylhexanoate (0.174 g, 1.10 mmol) was then added. After 0.5 h, the mixture was quenched with saturated aqueous NH_4Cl and warmed to room temperature. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (4 × 50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography (petroleum ether/acetone 5:1) to yield **10** (246 mg, 86%, *anti*/*syn*, 6:1) as a colorless liquid. For analytical purposes, pure *anti*-**10** was isolated from the mixture by column chromatography; *anti*-**10**: $[\alpha]_D^{20}$ −106.0 (c 2.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72−7.61 (m, 1H, C(O)−CH=C*H*), 6.12 (d, J = 4.6 Hz, 1H, C(O)−C*H*=CH), 3.85 (s, 1H, O*H*), 3.65 (s, 3H, CH_3O), 2.63 (br s, 1H, C*H*−OH), 2.33−2.23 (m, 2H, CH_3−CO_2−C*H*$_2$), 1.99 (d, J = 8.2 Hz, 1H, C(O)−C*H*−CH), 1.74−1.15 (m, 19H, CH_2, C(O)−CH−C*H*), 0.92−0.80 (m, 3H, CH_3CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 213.0, 174.2, 168.6, 132.8, 72.1, 55.9, 51.4, 44.9, 35.3, 33.9, 33.8, 31.6, 29.3, 29.0, 26.8, 25.0, 24.8, 22.5, 14.0. Anal. Calcd for $C_{19}H_{32}O_4$: C,70.33; H, 9.94. Found: C, 70.19; H, 9.98.

Methyl 7-[(2*R*)-2-Hexyl-5-oxocyclopent-3-enyl]heptenoate ((−)-11). To a solution of a mixture of *anti*- and *syn*-aldols **10** prepared as above (0.21 g, 0.65 mmol) and Et_3N (0.658 g, 6.50 mmol) in dry CH_2Cl_2 (6 mL) was added methanesulfonyl chloride (0.521 g, 4.55 mmol) at 0 °C under an argon atmosphere. Stirring was continued for 2 h, and saturated aqueous $NaHCO_3$ was slowly added. The mixture was extracted with $CHCl_3$ (4 × 25 mL), and the combined organic layers were dried over Na_2SO_4. After concentration in vacuo, the residue was filtered throught a tin pad of silica gel. To a solution of the crude mesylate in dry CH_2Cl_2 (8 mL) was added the neutral aluminum oxide (1.5 g). The suspension was stirred for 24 h at room temperature. Additional portions of aluminum oxide were added after 3 and 16 h. The mixture was filtered through a pad of Celite and concentrated, and the residue was purified by column chromatography (petroleum ether/acetone 5:1) to afford **11** (*E*/*Z*, 96:4) (194 mg, 94%) as a colorless oil; $[\alpha]_D^{20}$ −162.6 (c 2.1, CH_2Cl_2). *E*-(−)-**11**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.53 (dd, J = 5.9, 2.0 Hz, 1H, C(O)−CH=C*H*), 6.51 (t, J = 7.7 Hz, 1H, C=C*H*−CH$_2$), 6.31 (dd, J = 6.0, 1.8 Hz, 1H, C(O)−C*H*=CH), 3.66 (s, 3H, CH_3O), 2.30 (t, J = 7.5 Hz, 2H, $CH_3CO_2CH_2$), 2.28−2.19 (m, 2H, C=CH−C*H*$_2$), 1.85−1.75 (m, 1H, C(O)−C−C*H*), 1.70−1.59 (m, 2H), 1.50 (dt, J = 15.2, 7.4 Hz, 3H), 1.41−1.33 (m, 2H), 1.33−1.19 (m, 9H), 0.86 (t, J = 6.9 Hz, 3H, CH_3CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 197.0, 174.0, 162.0, 138.0, 135.2, 134.7, 51.5, 43.3, 33.9, 32.4, 31.6, 29.4, 28.9 (2C), 28.3, 25.8, 24.7, 22.5, 14.0. Anal. Calcd for $C_{19}H_{30}O_3$: C,74.47; H, 9.87. Found: C, 74.14; H, 9.99.

Methyl 7-[(1*S*,2*R*)-2-Hexyl-5-oxocyclopentyl]heptanoate ((+)-12). A mixture of *E*- and *Z*-**11** (0.127 g, 0.414 mmol) and 10% Pd/C (0.41 g) in ethanol (4.5 mL) was vigorously stirred at room temperature under a hydrogen atmosphere for 1.5 h. After filtration through a pad of Celite and evaporation of ethanol under reduced pressure, a crude mixture of *trans* and *cis* isomers of **12** was dissolved in MeOH (2 mL) and treated with *p*-toluenesulfonic acid (5 mg). The reaction mixture was stirred for 20 h and neutralized by saturated aqueous $NaHCO_3$. The product was purified by column chromatography (petroleum ether/acetone 25:1), affording **12** (*trans*/*cis*, 93:7) (0.106 g, 82%) as a colorless liquid; $[\alpha]_D^{20}$ +22.8 (c 2.0, CH_2Cl_2). (+)-*trans*-**12**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.64 (s, 3H, CH_3O), 2.27 (t, J = 7.5 Hz, 2H, $CH_3CO_2CH_2$), 2.15−1.99 (m, 2H, CH_2 (ring)), 1.83−1.74 (m, 1H, C*H* (ring)), 1.69−1.55 (m, 4H), 1.50 (dd, J = 13.8, 7.3 Hz, 2H), 1.43−1.15 (m, 17H), 0.87 (t, J = 6.8 Hz, 3H, CH_3CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 221.5, 174.2, 55.0, 51.4, 41.5, 37.8, 34.7, 34.00, 31.8, 29.5, 29.4, 28.9, 27.9, 27.0, 27.0, 26.6, 24.8, 22.6, 14.0. HRMS (EI): calcd for $C_{19}H_{34}O_3$, 310.2495; found, 310.2507.

(+)-7-[(1*S*,2*R*)-2-Hexyl-5-oxocyclopentyl]heptanoic Acid (13). A solution of **12** (a *trans*/*cis* mixture) (103 mg, 0.332 mmol) and CAL-B (21 mg) in acetone (2 mL) and phosphate buffer solution (1 mL, pH 7.2) was stirred at room temperature for 24 h. The reaction mixture was acidified by addition of 5% aqueous HCl and filtrated through a pad of Celite. After evaporation of the solvent under reduced pressure, the residue was extracted with $CHCl_3$ (4 × 25 mL). The combined organic layers were dried over Na_2SO_4. After concentration in vacuo, the residue was subjected to column chromatography (petroleum ether/acetone 5:1), affording ketoacid (+)-**13** (*trans*/*cis*, 98:2) (83 mg, 84%) as a colorless liquid; $[\alpha]_D^{20}$ +27.3 (c 1.9, $CHCl_3$). *trans*-**13**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.33 (t, J = 7.5 Hz, 3H, CH_2CO_2H), 2.29 (d, J = 8.9 Hz, 1H), 2.20−2.01 (m, 2H, CH_2 (ring)), 1.86−1.75 (m, 1H, C*H* (ring)), 1.73−1.56 (m, 4H), 1.52 (dd, J = 13.9, 7.2 Hz, 2H), 1.45−1.18 (m, 16H), 0.88 (t, J = 6.7 Hz, 3H, CH_3CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 221.8, 179.9, 55.0, 41.5, 37.9, 34.7, 34.0, 31.8, 29.5, 29.5, 28.8, 27.9, 27.0, 27.0, 26.6, 24.6, 22.6, 14.1. HRMS (EI): calcd for $C_{18}H_{32}O_3$, 296.2351; found, 296.2352.

(−)-7-[(1*S*,2*R*,5*R*)-2-Hexyl-5-hydroxycyclopentyl]heptanoic Acid (1a). To a solution of (+)-**13** (74 mg, 0.249 mmol) in THF (5 mL) was added L-Selectride (600 μL, 1 M in THF, 0.599 mmol) dropwise at −78 °C under an argon atmosphere. After 4 h, a saturated aqueous solution of NH_4Cl was added at −78 °C, and the resulting mixture was extracted $CHCl_3$ (4 × 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduce pressure, and the crude product was purified by column chromatography (petroleum ether/acetone 5:1) to yield **1a** (57 mg, 78%) as colorless crystals; mp 41.0−42.0 °C; $[\alpha]_D^{20}$ −60.2 (c 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.22 6.22 (br s, 1H, CO_2H), 4.20 (s, 1H, C*H*−OH), 2.33 (t, J = 7.4 Hz, 2H, CH_2CO_2H), 2.02−1.90 (m, 1H), 1.88−1.76 (m, 1H, C*H* (ring)), 1.66−1.56 (m, 4H), 1.55−1.11 (m,

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20H), 1.08−0.97 (m, 1H), 0.88 (t, J = 6.8 Hz, 3H, CH_3CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.5, 74.5, 51.4, 41.8, 35.1, 34.0, 33.4, 31.9, 29.6 (2 C), 29.0, 28.9, 28.3, 28.1, 27.6, 24.6, 22.7, 14.1. HRMS (EI): calcd for $C_{18}H_{34}O_3$, 297.2429; found, 297.2436.

Methyl 7-[(1*S*,2*R*,5*R*)-2-Hexyl-5-hydroxycyclopentyl]-heptanoate ((−)-14). To a solution of (−)-**1a** (25 mg, 0.084 mmol) in dry Et_2O (1 mL) was added dropwise a cooled ethereal solution of diazomethane at the moment that a durable yellow color of the solution appeared at 0 °C. After 5 min, the solvent was evaporated, and the residue was subjected to column chromatography (petroleum ether/acetone 10:1), giving (−)-**14** (24 mg, 92%) as a colorless liquid; $[\alpha]_D^{20}$ −60.0 (c 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 4.19 (s, 1H, C*H*−OH), 3.66 (s, 3H, CH_3CO_2), 2.30 (t, J = 7.5 Hz, 2H, $CH_2CO_2CH_3$), 2.00−1.92 (m, 1H), 1.87−1.75 (m, 1H, C*H* (ring)), 1.66−1.55 (m, 4H), 1.52−1.12 (m, 20H), 1.05−0.97 (m, 1H), 0.87 (t, J = 6.7 Hz, 3H, CH_3CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.3, 74.4, 51.5, 51.4, 41.8, 35.1, 34.0, 33.5, 31.8, 29.6, 29.6, 29.1, 29.0, 28.3, 28.2, 27.6, 24.8, 22.7, 14.1. HRMS (EI) (M − H_2O): calcd for $C_{19}H_{36}O_3$, 294.2551; found, 294.2559.

(−)-7-[(1*S*,2*R*,5*S*)-2-Hexyl-5-hydroxycyclopentyl]heptanoic Acid (1b). A stirred solution of (−)-**14** (211 mg, 0.676 mmol), Ph_3P (230 mg, 0.878 mmol), and *p*-nitrobenzoic acid (PNBA) (124 mg, 0.743 mmol) in THF (10 mL) was placed in an ice-water bath for 15 min. Diisopropyl azodicarboxylate (DIAD) (163 mg, 0.810 mmol) was added dropwise. The yellow homogeneous mixture was stirred at 0 °C for 0.5 h and then overnight at room temperature. The solvent was removed in vacuo, and the crude product was dissolved in EtOH (7 mL). 1 M aqueous LiOH (6 mL) was added, and the mixture was stirred for 16 h at room temperature. The solvent was evaporated in vacuo, and the residue was acidified by addition of 5% aqueous HCl and extracted with $CHCl_3$ (3 × 20 mL). The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure, and the crude product was purified by column chromatography (petroleum ether/acetone 2:1) to yield **1b** (157 mg, 78%) as colorless crystals; mp 28.0−30.0 °C; $[\alpha]_D^{20}$ −24.7 (c 1.7, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) δ 6.75 (s, 1H, CO_2H), 3.92−3.80 (m, 1H, C*H*−OH), 2.32 (t, J = 7.5 Hz, 2H, CH_2CO_2H), 1.78−1.68 (m, 2H), 1.64−1.54 (m, 3H), 1.50−1.40 (m, 1H), 1.40−1.13 (m, 21H), 0.86 (t, J = 6.9 Hz, 3H, CH_3CH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.3, 79.2, 54.3, 44.6, 35.9, 34.1, 34.0, 33.5, 31.9, 29.6, 29.5, 29.3, 29.0, 28.2, 27.6, 24.6, 22.6, 14.1. HRMS (EI): calcd for $C_{18}H_{34}O_3$, 297.2429; found, 297.2436.

■ ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via Internet at The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01749.

^1H and ^{13}C NMR spectra of the products and intermediates (PDF).

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Notes

The authors declare no competing financial interest.

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