DOI: 10.1002/ejoc.200900713

Total Synthesis of (–)-13-Acetoxymodhephene and (+)-14-Acetoxymodhephene

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Keywords: Total synthesis / Epoxidation / Enantioselectivity / Polycycles / Radical reactions

Stereoselective epoxidation of [4.3.3]propellane **16** set the stage for the Lewis acid catalyzed stereospecific ring contraction to an oxygenated modhephene structure and eventually led to the total synthesis of (–)-13-acetoxymodhephene and (+)-14-acetoxymodhephene.

Introduction

Propellanes are tricyclic compounds conjoined by a C–C single bond. Propellanes appear to be highly congested and are considered to be unstable. Contrary to their appearance, however, propellanes with cyclopentanes or larger rings are rather stable and have been the subject of theoretical chemistry as well as synthetic chemistry.[1] The unexpected stability of propellane was also observed in nature, as several classes of propellane natural products were identified.[2] Among them, modhephene with a [3.3.3]propellane structure was isolated from the rayless goldenrod plant (*Isocoma wrightii*) in 1978 with toxicity to sheep and cattle.[3] Subsequently, oxygenated derivatives of modhephene, 9-acetoxymodhephene,[4] 15-acetoxymodhephene,[5] 13-acetoxymodhephene,[6] and 14-acetoxymodhephene[7] were isolated. Recently, taxane derivatives containing an embedded [3.3.3]propellane structure were isolated (Figure 1).[8]

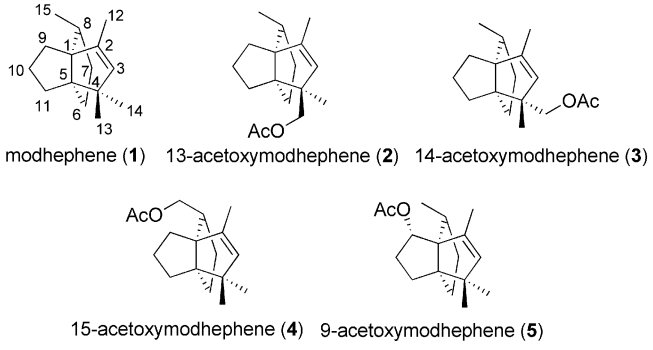

Figure 1. [3.3.3]Propellane natural products.

These natural products drew attention from the synthetic organic chemistry community for their unique structural features and biological activities. As a result, various synthetic strategies to propellanes have been developed and applied to the total synthesis of modhephene.[9] Although some of the total syntheses were elegant and highly efficient,[10] none were applied to the total synthesis of functionalized modhephenes, probably due to the fact that selective introduction of an acetoxy group would require modification of the synthetic strategies or development of new ones.

Results and Discussion

Herein, we report the first total synthesis of (–)-13-acetoxymodhephene and (+)-14-acetoxymodhephene in a stereoselective manner from the common intermediate obtained through a tandem radical cyclization reaction. Our synthetic strategy of acetoxymodhephenes focused on regioselective introduction of the acetoxy group to modhephene. Because the [3.3.4]propellane ring structure could be readily constructed from a cyclopentane precursor through a tandem radical cyclization reaction,[9a] oxygenated modhephenes could be obtained from [3.3.4]propellane **8** through stereospecific ring contraction of the corresponding epoxides **6** and **7**[11] (Scheme 1).

Because introduction of all stereocenters of acetoxymodhephenes would be controlled by the single quaternary carbon center at the C-5 position of the modhephene structure, enantioselective introduction of the quaternary carbon center was required. To create the quaternary carbon center, diastereoselective alkylation of a chiral enamine was explored. Guingant reported[12] that the reaction of 2-methoxycarbonylcyclopentanone with the enamine of (*R*)-phenylethanamine produced alkylated compound in 41% yield with 87%*ee* when alkylated with acrylonitrile. When we repeated the reaction, we were able to obtain a better yield but a lower enantiomeric excess (Table 1, Entry 1). When

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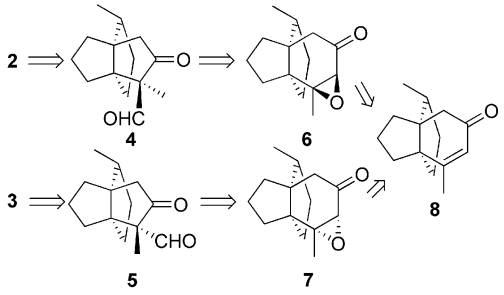
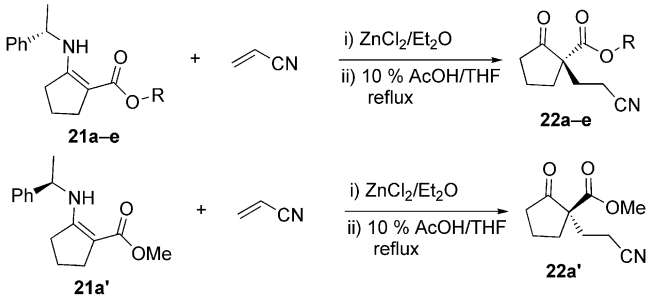
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900713.



Scheme 1. Synthetic analysis of (–)-13-acetoxymodhephene (**2**) and (+)-14-acetoxymodhephene (**3**).

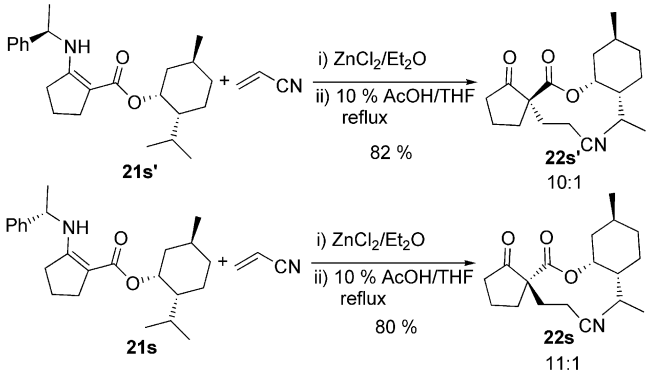
the methyl ester was replaced with a menthol ester in hope to improve the selectivity of the alkylation, the product showed improved selectivity with 82%*ee* When the enamine of (*S*)-phenylethanamine with menthol ester was used to find out which one was the better matched pair of isomers, to our surprise the opposite isomer was obtained with same selectivity (82%*ee*; Scheme 2).

Table 1. Asymmetric alkylation of chiral enamine esters.



Substrate	R	% Yield	Ratio[a]	$[\alpha]_D$[b]
21a	Me	85	6:1	+18.22
21b	*i*Pr	70	9:1	+10.50
21c	*i*Bu	67	10.5:1	+9.41
21d	*t*Bu	60	12:1	+4.81
21e	Ph_2CH	65	12.5:1	–
21a′	Me	95	4:1	–15.73

[a] Determined by GC analysis. [b] Measured in EtOH with c = 3.05 (**22a**), 2.05 (**22b**), 6.00 (**22c**), 2.93 (**22d**), 1.2 (**22a′**).

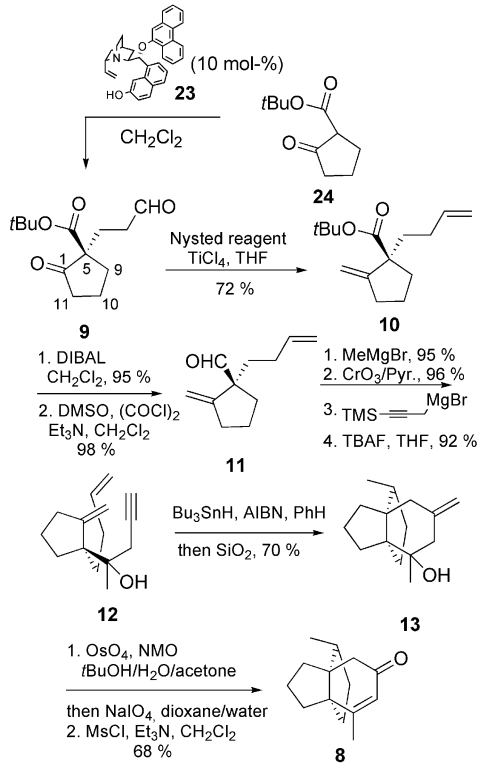


Scheme 2. Alkylation of two diastereomeric enaminyl esters.

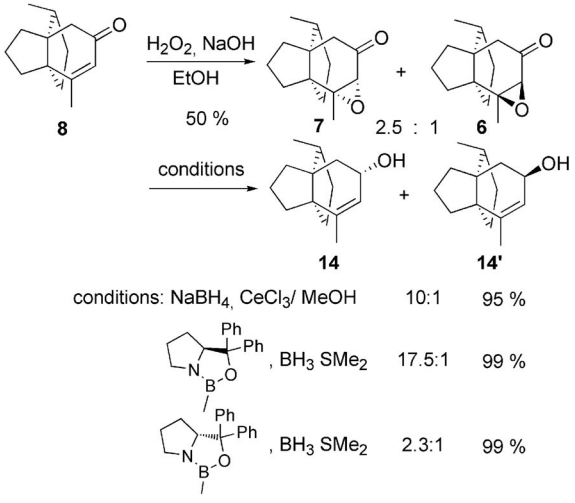
This result strongly suggested that the bulkiness rather than the stereostructure of menthol might be responsible for the improvement in the selectivity. This explanation was supported by the results obtained with various esters (Table 1). As the bulkiness increased, the selectivity increased from a ratio of 6:1 to 12.5:1 (85%*ee*) without a decrease in the yield of the reaction. Another noteworthy observation was that the enantioselectivity decreased with an increase in product yield.

The total synthesis of hydroxymodhephenes started with the introduction of the C-5 quaternary center enantioselectively by asymmetric alkylation of **21a′**. Though the ratio of selective alkylation improved with increasing bulkiness of the ester, the optical purity of the product did not exceed 85%*ee*. Therefore, **21a′** was used for asymmetric induction and the optical purity was further improved by eliminating undesired enantiomer **22a′** through the formation of chiral sulfoximine of **22a′**.[16] An alternative route to introduce the C-5 quaternary center was also explored, as the cinchona alkaloid catalyzed alkylation of **24** was reported to produce **9** with high enantioselectivity. The enantioselective conjugate addition reaction of *tert*-butyl 2-oxocyclopentane carboxylate (**24**) to acrolein by using quinidine-based organocatalyst **23** provided **9** with 93%*ee*.[13] Both carbonyl groups of **9** were treated with Nysted reagent[14] to install the two alkene groups needed for tandem radical cyclization reaction. The remaining appendage for the tandem radical cyclization was introduced in a five-step sequence starting from **10** in the same manner as the previously reported total synthesis of modhephene.[9a] The ester of **10** was converted into aldehyde **11** through a reduction–oxidation sequence and sequential introduction of the methyl group and the propargyl group furnished all the appendages for the tandem radical cyclization reaction. The tin hydride mediated tandem radical cyclization of **12** produced [4.3.3]-propellane **13** stereoselectively (10:1 ratio) as an inseparable mixture of diastereomers at the C-8 position bearing the methyl group. This diastereomeric mixture of propellane products was converted into enone **8** through oxidative cleavage of the exocyclic olefin followed by a dehydration reaction[15] (Scheme 3).

At this stage, purity of enone **8** was further enhanced through chiral sulfoximine adduct formation. The sulfoximine adduct of **8** was separable from other diastereomers, and hydrolysis of the sulfoximine regenerated pure **8**.[16] Stereoselective functionalization of enone **8** to epoxyketones **6** and **7** was one of the crucial steps in the total synthesis. However, an earlier observation from the total synthesis of modhephene from racemic **8** was not promising, as the cyanide addition reaction proceeded with low selectivity, resulting in a 2.5:1 diastereomeric ratio of the 1,4-addition products. Direct epoxidation of enone **8** showed a similar selectivity of 2.5:1 for epoxyketones **7** and **6**, as expected (Scheme 4). These outcomes were not surprising, as the only possible discrimination of the two faces of the enone ring is the existence of the methyl group on one of the two five-membered rings. Even the methyl group is positioned at the opposite side of the cyclohexenone ring to provide no immediate facial discrimination.



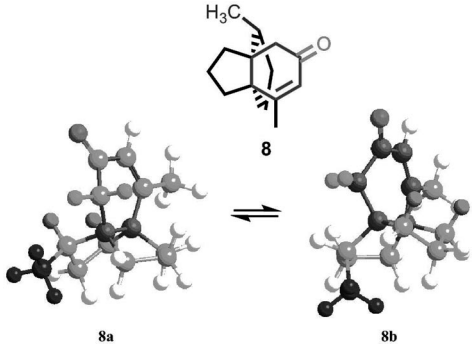
Scheme 3. Asymmetric synthesis of **8**.



Scheme 4. Stereoselective functionalization of **8**.

If allylic alcohols **14** and **14′** could be obtained selectively, they could be converted into **7** and **6**, respectively, as the alcohol stereochemistry of **14** and **14′** can direct the epoxidation reaction. Reagent-controlled diastereoselective reduction of ketone **8** by using Corey–Bakshi–Shibata (CBS) reduction[17] could be applied to produce allylic alcohols **14** and **14′** selectively. When (*S*)-2-methyl-CBS-oxazaborolidine was used as the catalyst for asymmetric borane reduction of ketone **8**, as anticipated, allylic alcohol **14** was obtained with 17.5:1 ratio of two epimers. When (*R*)-2-methyl-CBS-oxazaborolidine was used as the catalyst for alcohol **14′**, contrary to expectation, allylic alcohol **14** was obtained as the major product with 2.3:1 ratio of two epimers. This result was quite surprising, because the facial discrimination of enone **8** was not expected to be large enough to override the stereoselectivity of the CBS reagents. Luche reduction[18] of ketone **8** confirmed this intrinsic facial discrimination by hydride addition, as allylic alcohol **14** was obtained with 10:1 ratio.

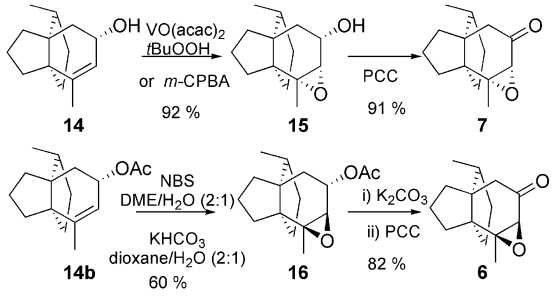
Careful analysis of the structure of **8** indicated that the cyclohexenone ring of **8** is not planar and two five-membered rings of **8** could not adopt the same conformation like the five-membered rings of modhephenes (the modhephene skeleton showed symmetric nature through the plane of the five-membered ring containing the double bond as shown in the X-ray crystallographic structure of 14-hydroxymodhephene[19]). On the basis of MM2 calculations (Scheme 5),[20] the cyclohexenone ring of compound **8** adopts two half-chair conformations **8a** and **8b**, in which the carbonyl group bends towards the methyl-substituted and unsubstituted cyclopentane ring, respectively, thus exposing either the β-face or α-face to the reducing agent. From the calculations, conformer **8a** was found to be far more stable than **8b**, as the latter displays a pseudoaxial orientation for the methyl group. Hence, the more stable conformer **8a** provides better accessibility from the β-face.



Scheme 5. Two conformers of **8**.

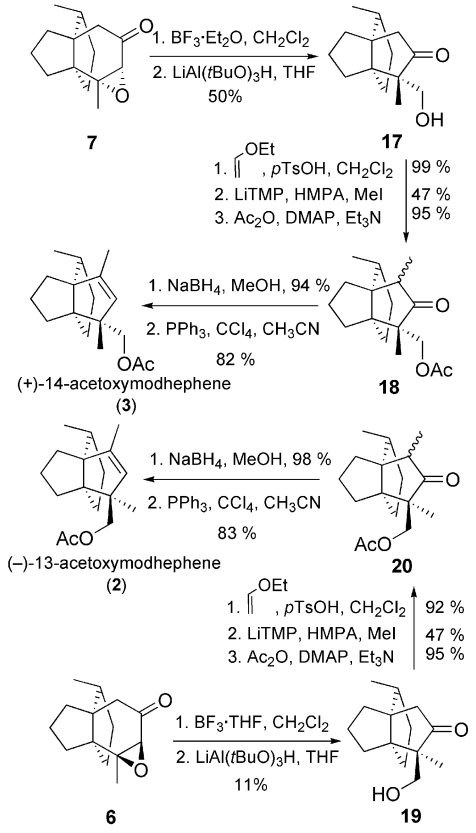
For the synthesis of **7**, hydroxy group directed epoxidation of allylic alcohol **14** through a Sharpless protocol[21] was used to produce epoxy alcohol **15** with no detectable amount of the other diastereomer. When the alcohol of **14** was protected and the olefin was oxidized with *m*-CPBA in hope to obtain the opposite epoxide as the major product,[22] the same selectivity as the alcohol-directed epoxidation reaction was observed. This result indicated that the intrinsic facial selectivity of the allylic alcohol is even better than enone **8**. Though this result hampered our original plan to obtain epoxide **6** through **14′**, we could use this unexpected facial selectivity of allyl alcohol **14**.[23] The epoxide with opposite stereochemistry **16** was obtained stereoselectively through bromohydrin formation followed by epoxide formation. Because the facial selectivity of initial bromonium ion formation should be similar to *m*-CPBA oxidation, hydroxide would add from the opposite side of the bromonium ion and subsequent base treatment would yield epoxide **16** selectively. When acetate-protected allyl alcohol **14b** was treated with NBS in water/DME, ep-

oxide **16** was obtained after $KHCO_3$ treatment. Hydrolysis of the acetate followed by PCC oxidation produced epoxy ketone **6**. Epoxy alcohol **15** was also oxidized with PCC to provide **7** (Scheme 6).



Scheme 6. Stereoselective synthesis of epoxy ketones **6** and **7**.

With the two desired epoxy ketones **6** and **7** in hand, the total synthesis of (–)-13-acetoxymodhephene and (+)-14-acetoxymodhephene was accomplished starting with the crucial epoxide rearrangement to form the modhephene skeleton stereospecifically. When epoxy ketone **7** was subjected to $BF_3{\cdot}Et_2O$-mediated rearrangement, the desired ketoaldehyde was obtained as the major product and the aldehyde was reduced selectively by using $LiAl(tBuO)_3H$[9b] to produce **17** in 50% yield over two steps. The alcohol of **17** was temporarily protected as ethoxyethyl ether to introduce a methyl group next to the ketone.[24] After the ethoxyethyl ether was replaced by the acetate group, $NaBH_4$ reduction of the ketone followed by dehydration reaction[25] produced (+)-14-acetoxymodhephene (Scheme 7). The total synthesis of (–)-13-acetoxymodhephene was accomplished in the same way as the total synthesis of (+)-14-acetoxymodhephene. Lewis acid catalyzed rearrangement of **6** produced desired hydroxy ketone **19** after selective reduction, though the yield was not as high as in the rearrangement of **7**. Presumably, the conformational difference that discriminated the faces of **8** played a similar role, and thus the migrating aptitude of the desired C–C bond of **6** was not as favorable as that of **7**. Efficiency of the rearrangement for the ring contraction did not change much by using various Lewis acids[26] and $BF_3{\cdot}THF$ provided the best result for the rearrangement of **6**. Hydroxy ketone **20** was converted into (–)-13-acetoxymodhephene through the same four-step sequence as that used for the synthesis of (+)-14-acetoxymodhephene. The ^{13}C -NMR spectroscopic data of synthetic acetoxymodhephenes were identical to the data reported for natural acetoxymodhephenes, and the ^1H NMR spectroscopic data of the synthetic ones had all the data reported for the natural ones.



Scheme 7. Total synthesis of (+)-14-acetoxymodhephene and (–)-13-acetoxymodhephene.

Conclusions

In summary, the stereoselective total synthesis of (–)-13-acetoxymodhephene and (+)-14-acetoxymodhephene was achieved from the common propellane intermediate **8** readily obtained through a tandem radical cyclization reaction. This work also demonstrated that a remote stereocenter could provide enough bias to distinguish between the two faces of the electrophilic sites of a cyclohexenone system.

Experimental Section

General Information: NMR spectra were recorded with a Bruker DPX400 spectrometer (400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR) and measured in $CDCl_3$. Chemical shifts were recorded in ppm relative to the internal standard $CDCl_3$. High-resolution mass spectra were recorded with VG Autospec Ultima and JMS-700 spectrometers. The enantioselectivities were determined by HPLC. HPLC measurements were done with a DIONEX model equipped with P580G pump, UV 525 detector (Thermo Science, Waltham, MA) measured at 254 nm, and chiral column DAICEL AD-H. Eluting solvent was a mixture of 2-propanol and hexane. All reactions were carried out in oven-dried glassware under a N_2 atmosphere. All solvents were distilled from the indicated drying reagents right before use: Et_2O and THF (Na, benzophenone), CH_2Cl_2 (P_2O_5), and MeCN, 1,4-dioxane, and DMF (CaH_2). The normal workup included extraction, drying over Na_2SO_4, and evaporation of volatile materials in vacuo. Purification by column chromatography was performed using Merck (Darmstadt, Germany) silica gel 60 (230–400 mesh).

Methyl 2-{[(*R*)-1-Phenylethyl]amino}cyclopent-1-ene-1-carboxylate (21a′): To a stirred solution of methyl 2-oxocyclopentanecarboxylate (10.0 g, 70.3 mmol) and 4 Å molecular sieves in CH_2Cl_2 (100 mL) was added (*R*)-(+)-phenylethanamine (10.9 mL, 84.6 mmol). The reaction mixture was stirred under reflux for 1 d. The mixture was filtered, and the resulting solution was concen-

trated in vacuo. The organic residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:20) to afford 15.9 g (64.8 mmol, 92%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.81 (br. s, 1 H), 7.31–7.27 (m, 2 H), 7.23–7.18 (m, 3 H), 4.55–4.48 (m, 1 H), 3.68 (s, 3 H), 2.53–2.43 (m, 3 H), 2.23–2.15 (m, 1 H), 1.676–1.62 (m, 2 H), 1.48 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 164.4, 145.0, 128.6, 126.9, 125.3, 93.0, 54.2, 50.0, 32.1, 28.7, 24.8, 20.9 ppm. IR (neat): $\tilde{\nu}$ = 2956, 1752, 1724, 1641, 1456, 1408, 1389, 1369, 1179, 1023 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{19}NO_2$ 245.1416; found 245.1412

Methyl (*R*)-1-(2-Cyanoethyl)-2-oxocyclopentanecarboxylate (22a′): To a solution of zinc chloride in Et_2O (1 M, 46.5 mL, 46.5 mmol) and acrylonitrile (4.6 mL, 70.7 mmol) in Et_2O (400 mL) was added dropwise an ethereal solution (50 mL) of compound **21a′** (11.4 g, 46.5 mmol) at 0 °C. Vigorous stirring was continued for 2 h. The solvent was replaced with THF (500 mL) and then 10% aqueous acetic acid (150 mL) was added to the mixture. The resulting solution was heated at 60 °C for 12 h. The reaction mixture was cooled to room temperature and neutralized with saturated $NaHCO_3$ solution and extracted with Et_2O (3 × 300 mL). The combined extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the organic residue (EtOAc/hexane, 1:3) afforded 8.6 g (44.2 mmol, 95%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.63 (s, 3 H), 2.53–2.32 (m, 4 H), 2.27–2.18 (m, 1 H), 2.15–2.08 (m, 1 H), 2.01–1.80 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.4, 170.5, 119.0, 58.4, 52.6, 37.5, 33.5, 29.1, 19.3, 12.8 ppm. IR (neat): $\tilde{\nu}$ = 2959, 2248, 1750, 1727, 1451, 1264, 1237, 1166, 530 cm^{-1}. HRMS (EI): calcd. for $C_{10}H_{13}NO_3$ 195.0895; found 195.0895. $[a]_D^{28}$ = –15.73 (c = 1.2, EtOH)

***tert*-Butyl (*R*)-1-(But-3-enyl)-2-methylenecyclopentanecarboxylate (10):** A solution of $TiCl_4$ (1 M in CH_2Cl_2, 30 mL, 30 mmol) was added by syringe to a solution of Nysted's reagent (57 mL, 30 mmol) in THF (200 mL) at 0 °C, followed by a solution of compound **9** (1.0 g, 4.27 mmol). The cooling bath was removed, and the mixture was heated at reflux for 4 h. After cooling to room temperature, the reaction mixture was quenched with 10% HCl (200 mL) and transferred to a separatory funnel. The product was extracted into ether (3 × 300 mL), and the combined organic phase was dried with anhydrous $MgSO_4$ and concentrated to leave a residue (726 mg, 72%) that was purified by flash chromatography (4% Et_2O/pentane). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.84–5.74 (m, 1 H), 5.04–5.03 (m, 1 H), 5.01–4.95 (m, 2 H), 4.93–4.88 (m, 1 H), 2.37–2.30 (m, 3 H), 2.02–1.98 (m, 3 H), 1.64–1.46 (m, 4 H), 1.41 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 155.5, 138.7, 114.2, 106.9, 79.9, 56.7, 38.4, 34.9, 33.8, 30.1, 27.8, 24.1 ppm.

(*R*)-[1-(But-3-enyl)-2-methylenecylcopentyl]methanol: Compound **10** (726 mg, 3.1 mmol), dissolved in CH_2Cl_2 (30 mL), was cooled to –15 °C and a solution of DIBAL (1 M in CH_2Cl_2, 9.2 mL, 9.2 mmol) was added dropwise. After stirring for 4 h at –15 °C, the excess amount of hydride was destroyed by the addition of EtOAc (10 mL). H_2O (10 mL) and 1 N HCl (10 mL) were added. The resulting solution was extracted with EtOAc (3 × 30 mL), and the combined organic extract was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to afford 482 mg (2.9 mmol, 95%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83–5.73 (m, 1 H), 5.04–5.03 (m, 1 H), 5.00–4.96 (m, 1 H), 4.91–4.88 (m, 1 H), 4.75–4.74 (m, 1 H), 3.42 (d, J = 10.9 Hz, 1 H), 3.31 (d, J = 10.9 Hz, 1 H), 2.38–2.33 (m, 2 H), 2.03–1.95 (m, 2 H), 1.65–1.53 (m, 6 H), 1.48–1.40 (1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.7, 139.2, 114.1, 105.8, 68.0, 50.5, 35.6, 34.6, 34.2, 28.8, 23.0 ppm. IR (neat): $\tilde{\nu}$ = 3378, 3074, 2952, 1642, 1454, 1022, 909, 885 cm^{-1}. HRMS (EI): calcd. for $C_{11}H_{18}O$ 166.1358; found 166.1350. $[a]_D^{20}$ = –35.78 (c = 1.5, $CHCl_3$)

(*R*)-1-(But-3-enyl)-2-methylenecylcopentanecarbaldehyde (11): A dry-ice cooled, magnetically stirred solution of oxalyl chloride (5.3 mL, 60.2 mmol) in CH_2Cl_2 (50 mL) was treated with DMSO (8.5 mL, 120.3 mmol) and stirred for 30 min. A solution of alcohol (5.0 g, 30.1 mmol) in CH_2Cl_2 (10 mL) was introduced dropwise, followed by Et_3N (20 mL, 150.3 mmol) 1 h later. The reaction mixture was poured into saturated aqueous NH_4Cl (70 mL), and the aqueous layer was extracted with EtOAc (3 × 50 mL). After the combined organic extract was dried with anhydrous $MgSO_4$ and concentrated, flash chromatography of the organic residue on silica gel (Et_2O/pentane, 1:30) produced 4.8 g (29.2 mmol, 97%) of aldehyde **11** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.25 (s, 1 H), 5.80–5.74 (m, 1 H),5.19–5.18 (m, 1 H), 5.02–4.97 (m, 1 H), 4.95–4.92 (m, 1 H), 4.87–4.86 (m, 1 H), 2.38–2.34 (m, 2 H), 2.28–2.22 (m, 1 H), 2.00–1.91 (m, 2 H), 1.88–1.81 (m, 1 H), 1.73–1.66 (m, 1 H), 1.62–1.16 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 200.7, 152. 1, 138.1, 114.8, 109.4, 61.1, 34.3, 33.9, 31.3, 29.0, 23.6 ppm. IR (neat): $\tilde{\nu}$ = 3077, 2958, 1723, 1643, 1452, 994, 911 cm^{-1}. HRMS (EI): calcd. for $C_{11}H_{16}O$ 164.1201; found 164.1201. $[a]_D^{20}$ = + 197.05 (c = 1.5, $CHCl_3$)

(*R*)-1-(1-But-3-enyl)-2-methylenecylcopentylethanol: To a stirred solution of aldehyde **11** (4.8 g, 29.2 mmol) in Et_2O (30 mL) was added dropwise a solution of methylmagnesium bromide (3 M in ether, 20 mL, 58.6 mmol) at 0 °C. After stirring for 30 min, the solution was quenched with saturated aqueous NH_4Cl (40 mL) and extracted with EtOAc (3 × 25 mL). The organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography on silica gel (Et_2O/pentane, 1:5) produced 5.02 g (27.8 mmol, 95%) of the title compound as a colorless oil.

(*R*)-1-(1-But-3-enyl)-2-methylenecylcopentylethanone: To a solution of chromium oxide (16.7 g, 167 mmol) in CH_2Cl_2 (50 mL) was added pyridine (24.7 mL, 306 mmol) at 0 °C. The reaction mixture was stirred for 10 min. To the reaction mixture was added alcohol (5.0 g, 27.8 mmol), and then the reaction mixture was stirred for 6 h. The mixture was filtered, and the resulting solution was concentrated in vacuo. The organic residue was purified by column chromatography on silica gel (Et_2O/pentane, 1:20) to afford 4.8 g (26.7 mmol, 96%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.83–5.73 (m, 1 H), 5.08–5.07 (m, 1 H), 5.01–4.96 (m, 1 H), 4.93–4.89 (m, 2 H), 2.41–2.36 (m, 2 H), 2.32–2.26 (m, 1 H), 2.10 (s, 3 H), 1.99–1.88 (m, 3 H), 1.73–1.65 (m, 2 H), 1.59–1.52 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.5, 154.7, 138.5, 114.5, 108.3, 63.1, 36.6, 34.2, 33.7, 29.6, 25.3, 23.5 ppm. IR (neat): $\tilde{\nu}$ = 3077, 2956, 1703, 1643, 1435, 1353, 1136, 910 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{18}O$ 178.1358; found 178.1363. $[a]_D^{21}$ = + 127.29 (c = 1.4, $CHCl_3$)

2-[(*R*)-1-(But-3-enyl)-2-methylenecyclopentyl]pent-4-yn-2-ol (12): To a stirred solution of ketone (4 g, 26.7 mmol) in Et_2O (40 mL) was added dropwise 3-(trimethylsilyl)-1-propynylmagnesium bromide [prepared from 3-bromo-1-(trimethylsilyl)-1-propyne and Mg] at 0 °C. After stirring for 30 min, the solution was quenched with saturated aqueous NH_4Cl (60 mL) and extracted with EtOAc (3 × 40 mL). The organic extracts were dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexane, 1:40) produced 7.1 g (24.6 mmol, 92%) as a colorless oil. TMS–dienyne **12** (7.1 g, 24.6 mmol) was dissolved in THF (20 mL) and treated with TBAF (1 M in THF, 27.1 mL). After stirring for 10 min, the reaction mixture was

poured into saturated aqueous NH_4Cl (40 mL) and extracted with EtOAc (3 × 25 mL). After the combined organic extract was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo, the organic residue was purified by flash chromatography on silica gel (EtOAc/hexane, 1:20) to yield 4.9 g (22.6 mmol, 92%) of dienyne **12** as a colorless oil. NMR spectroscopic data of the major diastereoisomer was extracted from the data of the diastereoisomeric mixtures obtained above. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.82–5.72 (m, 1 H), 5.143–5.142 (m, 1 H), 4.99–4.95 (m, 1 H), 4.91–4.88 (m, 1 H), 4.84–4.80 (m, 1 H), 2.70 (dd, J = 16.2, 2.8 Hz, 1 H), 2.34–2.30 (m, 3 H), 2.06–2.03 (m, 1 H), 2.01–1.89 (m, 3 H), 1.75–1.53 (m, 4 H), 1.44–1.36 (m, 1 H), 1.32 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 139.4, 113.9, 108.2, 81.5, 75.7, 71.3, 54.9, 37.6, 35.1, 34.2, 29.6, 28.1, 24.0, 23.0 ppm. IR (neat): $\tilde{\nu}$ = 3568, 3306, 3075, 2952, 2117, 1641, 1455, 1099, 909, 637 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{22}O$ 218.1671; found 218.1666. $[\alpha]_D^{15}$ = + 50.02 (c = 1.0, $CHCl_3$)

(1*R*,6*S*)-2,7-Dimethyl-4-methylenetricyclo[4.3.3.0]dodecan-2-ol (13): A mixture of dienyne **12** (0.40 g, 1.83 mmol), Bu_3SnH (0.59 mL, 2.2 mmol), and AIBN (82 mg, 0.5 mmol) in benzene (220 mL) was heated for 3 h at 80 °C. The reaction mixture was cooled to room temperature. Silica gel was added to the reaction mixture, which was then stirred for 24 h. The reaction mixture was filtered and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexane, 1:20) afforded 282 mg (1.28 mmol, 70%) of **13** as a colorless oil. NMR spectroscopic data of the major diastereoisomer was extracted from the data of the diastereoisomeric mixtures obtained above. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.78–4.77 (m, 1 H), 4.74–4.73 (m, 1 H), 2.51–2.43 (m, 2 H), 2.24–2.11 (m, 3 H), 1.58–1.40 (m, 6 H), 1.32–1.22 (m, 4 H), 1.14 (s, 3 H), 0.82 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.7, 110.7, 75.3, 58.1, 54.5, 40.9, 40.0, 38.6, 37.6, 37.5, 35.7, 30.9, 26.7, 25.6, 13.2 ppm. IR (neat): $\tilde{\nu}$ = 3473, 3067, 2951, 1640, 1455, 1375, 1089, 874 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{24}O$ 220.1827; found 220.1823. $[\alpha]_D^{15}$ = + 16.82 (c = 1.0, $CHCl_3$)

(1*R*,6*S*)-2,7-Dimethyl-2-hydroxytricyclo[4.3.3.0]dodecan-4-one: To a stirred solution of **13** (700 mg, 3.18 mmol) in tBuOH/H_2O/acetone (3:20:12 mL) was added osmium tetraoxide (2.2 mL, 2.5 wt.-% in 2-methyl-2-propanol, 0.17 mmol) and 4-methylmorpholine N-oxide (NMO; 447 mg, 3.81 mmol) at room temperature. The resulting mixture was stirred for 12 h. The reaction mixture was poured into H_2O (20 mL), and the aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic extract was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. To the resulting triol in 1,4-dioxane/H_2O (16:6 mL) was added sodium periodate (1.06 g, 4.96 mmol) at room temperature. The resulting mixture was stirred for 2 h. The reaction mixture was poured into H_2O (20 mL), and the aqueous layer was extracted with EtOAc (3 × 15 mL), and the combined organic extract was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexane, 1:3) afforded 552 mg (2.48 mmol, 78%) of the title compound as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.66 (d, J = 16.4 Hz, 1 H), 2.45 (d, J = 18.5 Hz, 1 H), 2.35 (d, J = 16.4 Hz, 1 H), 2.28–2.26 (m, 1 H), 2.22 (d, J = 18.5 Hz, 1 H), 1.63–1.38 (m, 4 H), 1.31–1.24 (m, 6 H), 1.23 (s, 3 H), 0.86 (d, J = 6.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.1, 75.7, 58.3, 54.8, 48.3, 47.1, 44.0, 37.8, 37.6, 35.4, 30.6, 26.5, 25.5, 12.9 ppm. IR (neat): $\tilde{\nu}$ = 3465, 2951, 1703, 1456, 1377, 1456, 1377, 1085 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{22}O_2$ 222.1620; found 222.1617. $[\alpha]_D^{15}$ = + 65.80 (c = 1.4, $CHCl_3$)

(1*R*,6*S*)-2,7-Dimethyltricyclo[4.3.3.0]dodec-2-en-4-one (8): (1*R*,6*S*)-2,7-Dimethyl-2-hydroxytricyclo[4.3.3.0]dodecan-4-one (552 mg, 2.48 mmol) was dissolved in CH_2Cl_2 (5 mL) and treated with methanesulfonyl chloride (0.96 mL, 12.4 mmol) and Et_3N (3.46 mL, 24.8 mmol) at 0 °C. After stirring overnight at room temperature, the resulting mixture was poured into H_2O (10 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extract was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue on silica gel (EtOAc/hexane, 1:10) afforded 441 mg (2.16 mmol, 87%) of **8** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.68 (s, 1 H), 2.43 (d, J = 16.1 Hz, 1 H), 2.23 (d, J = 16.1 Hz, 1 H), 2.00–1.93 (m, 1 H), 1.91 (s, 3 H), 1.75–1.60 (m, 8 H), 1.39–1.28 (m, 1 H), 1.25–1.19 (m, 1 H), 0.91 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.4, 166.5, 123.3, 57.5, 55.0, 45.1, 41.7, 39.2, 39.0, 34.3, 31.1, 23.9, 21.2, 13.6 ppm. IR (neat): $\tilde{\nu}$ = 2952, 1670, 1622, 1455, 1378, 1273 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{20}O$ 204.1514; found 204.1521. $[\alpha]_D^{19}$ = +24.32 (c = 1.0, $CHCl_3$)

Kinetic Resolution: To a solution of (+)-(*S*)-*N*,*S*-dimethyl-*S*-phenylsulfoximine (439 mg, 2.59 mmol) in THF (7 mL) was added nBuLi (2.4 M in hexane, 1.08 mL, 2.59 mmol) at 0 °C. After stirring for 30 min, enone (441 mg, 2.16 mmol) was added to the resulting anion solution at –78 °C and stirred for 3 h. The cold mixture was quenched with NH_4Cl (aq.), extracted with EtOAc, and concentrated in vacuo. Flash chromatography of the residue on silica gel (EtOAc/hexane, 1:5) afforded 565 mg (1.51 mmol, 70%) of the sulfoximine derivative. The sulfoximine derivative (565 mg, 1.51 mmol) was heated in toluene under reflux for 4 h. The reaction mixture was concentrated and purified by silica gel column chromatography (EtOAc/hexane, 1:10) to give 287 mg (1.40 mmol, 93%) of enone **8** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.68 (s, 1 H), 2.43 (d, J = 16.1 Hz, 1 H), 2.23 (d, J = 16.1 Hz, 1 H), 2.00–1.93 (m, 1 H), 1.91 (s, 3 H), 1.75–1.60 (m, 8 H), 1.39–1.28 (m, 1 H), 1.25–1.19 (m, 1 H), 0.91 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 199.4, 166.5, 123.3, 57.5, 55.0, 45.1, 41.7, 39.2, 39.0, 34.3, 31.1, 23.9, 21.2, 13.6 ppm. IR (neat): $\tilde{\nu}$ = 2952, 1670, 1622, 1455, 1378, 1273 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{20}O$ 204.1514; found 204.1521. $[\alpha]_D^{19}$ = +24.32 (c = 1.0, $CHCl_3$)

(1*R*,6*S*,4*S*)-2,10-Dimethyl-4-hydroxytricyclo[4.3.3.0]dodec-2-ene (14): To a solution of (*S*)-2-methyl-CBS-oxazaborolidine and BH_3·Me_2S in THF (5 mL) was added enone **8** (287 mg, 1.40 mmol) at 0 °C. The reaction mixture was allowed to stir for 1 h at 0 °C. H_2O (10 mL) was added to the reaction mixture, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined extract was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography on silica gel (EtOAc/hexane, 1:5) of the residue produced 286 mg (1.39 mmol, 99%) of **14**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.26–5.25 (m, 1 H), 4.10–4.06 (m, 1 H), 2.03 (dd, J = 11.2, 5.2 Hz, 1 H), 1.87–1.82 (m, 1 H), 1.69 (s, 3 H), 1.67–1.46 (m, 7 H), 1.41–1.33 (m, 1 H), 1.28–1.19 (m, 1 H), 1.13–1.08 (m, 2 H), 0.91 (d, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6, 124.1, 65.7, 55.8, 54.0, 40.6, 40.0, 39.5, 39.2, 34.6, 31.1, 24.2, 20.3, 13.8 ppm. IR (neat): $\tilde{\nu}$ = 3320, 2945, 1659, 1449, 1376, 1014 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{22}O$ 206.1671; found 206.1665. $[\alpha]_D^{24}$ = –17.18 (c = 0.77, $CHCl_3$)

(1*R*,2*R*,3*S*,4*S*,6*S*)-2,7-Dimethyl-2,3-epoxytricyclo[4.3.3.0]dodecan-4-ol (15): To a stirred solution of **14** (286 mg, 1.39 mmol) in CH_2Cl_2 (4 mL) was added m-CPBA (80% in purified, 358 mg, 166 mmol) at 0 °C. After stirring for 1 h, saturated aqueous $NaHCO_3$ (5 mL) was added to the reaction mixture and extracted with EtOAc (3 × 5 mL). The combined organic extract was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected on flash chromatography (EtOAc/hexane, 1:3) to give 284 mg (1.28 mmol, 92%) of epoxy alcohol **15**. ^{1}H NMR

(400 MHz, $CDCl_3$): δ = 4.00 (dd, J = 11.4, 4.9 Hz, 1 H), 3.02 (s, 1 H), 2.28–2.22 (m, 1 H), 1.71 (dd, J = 12.5, 4.8 Hz, 1 H), 1.56–1.43 (m, 5 H), 1.40–1.32 (m, 3 H), 1.30 (s, 3 H), 1.26–1.18 (m, 2 H), 1.14–1.08 (m, 1 H), 0.85 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 66.3, 66.1, 63.6, 55.2, 52.7, 41.3, 38.7, 38.6, 36.6, 35.9, 30.7, 25.1, 20.8, 13.2 ppm. IR (neat): $\tilde{\nu}$ = 3398, 2952, 1460, 1379, 1252, 1089, 1012, 883 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{22}O_2$ 222.1620; found 222.1620. $[\alpha]_D^{22}$ = + 10.45 (c = 0.7, $CHCl_3$)

(1*R*,2*R*,3*S*,6*S*)-2,10-Dimethyl-2-oxotricyclo[4.3.3.0]dodecan-4-one (7): To a solution of epoxy alcohol **15** (284 mg, 1.28 mmol) dissolved in CH_2Cl_2 (4 mL) was added PCC (414 mg, 1.92 mmol) and Celite. The reaction mixture was allowed to stir for 4 h at room temperature. The mixture was filtered, and the resulting solution was concentrated in vacuo. The organic residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:20) to afford 257 mg (1.16 mmol, 91%) of **7**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.99 (d, J = 0.9 Hz, 1 H), 2.75 (d, J = 12.4 Hz, 1 H), 2.43–2.37 (m, 1 H), 2.03 (d, J = 12.4 Hz, 1 H), 1.80–1.69 (m, 1 H), 1.66–1.59 (m, 1 H), 1.56–1.50 (m, 2 H), 1.49–1.41 (m, 3 H), 1.38 (s, 3 H), 1.37–1.31 (m, 1 H), 1.26–1.20 (m, 2 H), 0.83 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.9, 72.8, 62.7, 60.6, 54.5, 43.7, 42.5, 38.9, 38.4, 36.3, 30.3, 25.4, 20.8, 12.7 ppm. IR (neat): $\tilde{\nu}$ = 2962, 1709, 1460, 1391, 1299, 1233, 1071, 862 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{20}O_2$ 220.1463; found 220.1458. $[\alpha]_D^{19}$ = + 16.80 (c = 0.7, $CHCl_3$)

(1*R*,6*S*,4*S*)-2,7-Dimethyltricyclo[4.3.3.0]dodec-2-en-4-yl Acetate (14b): To a solution of alcohol **14** (1.18 g, 5.72 mmol) dissolved in CH_2Cl_2 (20 mL) was added Et_3N (0.93 mL, 11.44 mmol) and Ac_2O (0.81 mL, 8.58 mmol) at 0 °C, and the reaction mixture was allowed to stir for 4 h at room temperature. The mixture was poured into H_2O (10 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined extract was dried with $MgSO_4$ and concentrated in vacuo. Flash chromatography of the residue on silica gel (EtOAc/hexane, 1:20) afforded 1.34 g (5.38 mmol, 94%) of **14b**. NMR spectroscopic data of the major diastereoisomer was deduced from the data of the diastereoisomeric mixtures obtained above. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.19–5.15 (m, 2 H), 2.03 (s, 3 H), 2.01–1.97 (m, 1 H), 1.89–1.83 (m, 1 H), 1.78–1.72 (m, 1 H), 1.69 (m, 3 H), 1.65–1.48 (m, 6 H), 1.43–1.35 (m, 1 H), 1.30–1.20 (m, 2 H), 1.13–1.08 (m, 1 H), 0.91 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 145.2, 119.8, 69.3, 55.8, 53.6, 39.8, 39.6, 39.2, 35.6, 34.6, 31.1, 24.2, 21.4, 20.3, 13.8 ppm. $[\alpha]_D^{23}$ = + 6.64 (c = 1.0, $CHCl_3$)

(1*R*,2*S*,3*R*,4*S*,6*S*)-2,7-Dimethyl-2,3-epoxotricyclo[4.3.3.0]dodec-4-yl Acetate (16): To a stirred solution of **14b** (1.34 g, 5.38 mmol) in DME/H_2O (10:5 mL) was added *N*-bromosuccinimide (1.15 g, 6.46 mmol) at 0 °C. After stirring for 4 h at that temperature, the mixture was poured into H_2O (20 mL), and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined extract was dried with $MgSO_4$ and concentrated in vacuo. Flash chromatography of the residue on silica gel (EtOAc/hexane, 1:10) afforded 1.3 g (3.77 mmol, 70%). To a stirred solution of bromohydrin (1.3 g, 3.77 mmol) in 1,4-dioxane/H_2O (10:5 mL) was added potassium bicarbonate (754 mg, 7.54 mmol) at room temperature. After stirring for 12 h, the mixture was poured into H_2O (15 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined extract was dried and concentrated in vacuo. Flash chromatography of the residue on silica gel (EtOAc/hexane, 1:15) afforded 0.85 g (3.2 mmol, 85%) of **16**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.22–5.19 (m, 1 H), 3.03 (d, J = 2.0 Hz, 1 H), 2.05 (s, 3 H), 2.01–1.95 (m, 1 H), 1.89–1.51 (m, 9 H), 1.49–1.41 (m, 1 H), 1.29 (s, 3 H), 1.26–1.12 (m, 2 H), 0.85 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3, 69.3, 64.7, 61.7, 54.4, 52.1, 45.4, 39.7, 35.7, 35.5, 35.1, 32.6, 24.2, 21.2, 20.6, 14.6 ppm. IR (neat): $\tilde{\nu}$ = 3456, 2954, 1661, 1473, 1112, 1058, 887 cm^{-1}.

(1*R*,2*S*,3*R*,4*S*,6*S*)-2,7-Dimethyl-2,3-epoxytricyclo[4.3.3.0]dodecan-4-ol: To a stirred solution of **16** (0.85 g, 3.2 mmol) in MeOH (6 mL) was added potassium carbonate (885 mg, 6.4 mmol) at room temperature. After stirring for 4 h, the mixture was poured into H_2O (7 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined extract was dried with $MgSO_4$ and concentrated in vacuo. Flash chromatography of the residue on silica gel (EtOAc/hexane, 1:3) afforded 662 mg (2.98 mmol, 93%) of the title compound as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.14–4.10 (m, 1 H), 3.00 (s, 1 H), 2.21 (br. s, 1 H), 1.99–1.91 (m, 1 H), 1.85–1.57 (m, 7 H), 1.53–1.41 (m, 2 H), 1.34–1.29 (m, 1 H), 1.27 (s, 3 H), 1.24–1.11 (m, 2 H), 0.81 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 66.0, 65.6, 65.4, 54.3, 52.9, 42.6, 38.7, 38.4, 34.7, 34.5, 32.3, 23.3, 20.9, 14.6 ppm. $[\alpha]_D^{25}$ = –7.74 (c = 2.6, $CHCl_3$)

(1*R*,2*S*,3*R*,6*S*)-2,7-Dimethyl-2,3-epoxytricyclo[4.3.3.0]dodecan-4-one (6): To the epoxy alcohol (33 mg, 0.1484 mmol) dissolved in CH_2Cl_2 (2 mL) was added PCC (64 mg, 0.2969 mmol) and Celite. The reaction mixture was allowed to stir for 1 h at room temperature. The mixture was filtered, and the resulting solution was concentrated in vacuo. The organic residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:20) to afford 28.7 mg (0.13 mmol, 88%) of **6**. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.09 (s, 1 H), 2.71 (d, J = 12.4 Hz, 1 H), 2.10–2.00 (m, 2 H), 1.96–1.88 (m, 1 H), 1.81–1.64 (m, 4 H), 1.60–1.54 (m, 1 H), 1.43–1.33 (m, 5 H), 1.28–1.15 (m, 2 H), 0.87 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 211.1, 72.1, 64.0, 59.5, 55.7, 49.1, 48.6, 41.1, 37.0, 36.5, 33.6, 25.2, 20.5, 14.1 ppm. $[\alpha]_D^{25}$ = –41.89 (c = 1.1, $CHCl_3$)

(1*R*,2*S*,6*S*)-2-Hydroxymethyl-2,6-dimethyltricyclo[3.3.3.0]undecan-3-one (17): To a solution of epoxy ketone **7** (50 mg, 0.23 mmol) in CH_2Cl_2 (1 mL) was added $BF_3{\cdot}Et_2O$ (0.014 mL, 0.11 mmol) at room temperature. The reaction mixture was stirred for 10 min. The mixture was poured into saturated aqueous $NaHCO_3$ (2 mL), and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic layer was dried with anhydrous $MgSO_4$. The mixture was concentrated in vacuo. The crude product was dissolved in THF (1 mL) and treated with a solution of $LiAl(OtBu)_3H$ (1 M in THF, 0.23 mL, 0.23 mmol) at –78 °C. After stirring for 1 h, the mixture was poured into H_2O (1 mL), and the aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic layer was dried with anhydrous $MgSO_4$ and concentrated. The residue was purified by flash chromatography on silica gel (EtOAc/hexane, 1:3) to afford 25.6 mg (0.115 mmol, 50%) of **17**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.75 (d, J = 11.2 Hz, 1 H), 3.52 (d, J = 11.2 Hz, 1 H), 2.29 (s, 2 H), 2.08–2.03 (m, 1 H), 1.97 (br. s, 1 H, OH) 1.71–1.53 (m, 5 H), 1.43–1.20 (m, 5 H), 1.15 (s, 3 H), 0.96 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 223.7, 67.1, 62.1, 57.1, 55.5, 49.7, 46.1, 38.1, 35.3, 34.3, 32.7, 27.0, 18.3, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 3459, 2955, 1731, 1456, 1040 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{22}O_2$ 222.1620; found 222.1608. $[\alpha]_D^{26}$ = –4.67 (c = 1.2, $CHCl_3$)

(1*R*,2*S*,6*S*)-2-[(1-Ethoxyethoxy)methyl]-2,6-dimethyltricyclo[3.3.3.0]-undecan-3-one: To a solution of alcohol **17** (25.6 mg, 0.115 mmol) in CH_2Cl_2 (1 mL) was added ethyl vinyl ether (EVE) and *p*TosOH at room temperature. After stirring for 1 h, the mixture was poured into H_2O (2 mL), and the aqueous layer was extracted with EtOAc (3 × 3 mL). The organic extract was dried with $MgSO_4$ and concen-

trated. The residue was purified by flash chromatography (EtOAc/hexane, 1:20) to give 32 mg (0.114 mmol, quant.) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.61–4.54 (m, 1 H), 3.61–3.50 (m, 2 H), 3.43–3.30 (m, 2 H), 2.34 (dd, J = 17.6, 4.8 Hz, 1 H), 2.19 (dd, J = 17.6, 2.4 Hz, 1 H), 2.06–1.99 (m, 1 H), 1.77–1.56 (m, 5 H), 1.44–1.13 (m, 11 H), 1.07 (s, 3 H), 0.95 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 221.8, 99.9, 70.6, 70.1, 62.3, 61.0, 56.6, 54.9, 50.7, 46.1, 38.8, 36.0, 34.6, 33.0, 26.5, 19.5, 18.5, 15.2, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2953, 1734, 1458, 1377, 1136, 1058 cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{30}O_3$ 294.2195; found 294.2181. $[\alpha]_D^{23}$ = –8.51 (c = 1.5, $CHCl_3$)

(1*R*,2*S*,6*R*)-2-Hydroxymethyl-2,4,6-trimethyltricyclo[3.3.3.0]undecan-3-one: To a solution of ketone (32 mg, 0.114 mmol) in THF (1 mL) was added lithium 2,2,6,6-tetramethylpiperidide(LiTMP; 2 M in THF, 0.57 mL, 1.14 mmol) [prepared from 2,2,6,6-tetramethylpiperidine and *n*BuLi in THF at 0 °C] at 0 °C. After stirring for 30 min, CH_3I (0.07 mL, 1.14 mmol) and HMPA (0.1 mL, 0.57 mmol) were added to the reaction mixture. Stirring was continued for 2 h at 0 °C. The mixture was poured into H_2O (2 mL), and the aqueous layer was extracted with EtOAc (3 × 3 mL). The mixture was concentrated in vacuo. The crude product was dissolved in THF (1 mL) and 1 N HCl was added to the reaction mixture at room temperature. After stirring for 1 h, the mixture was poured into H_2O (2 mL), and the aqueous layer was extracted with EtOAc (3 × 4 mL). The combined organic layer was dried with anhydrous $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (EtOAc/hexane, 1:5) produced 12.7 mg (0.054 mmol, 47%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (d, J = 11.5 Hz, 1 H), 3.51 (d, J = 11.5 Hz, 1 H), 2.42 (q, J = 6.9 Hz, 1 H), 2.30 (br. s, 1 H, OH), 2.13–2.09 (m, 1 H), 1.82–1.78 (m, 1 H), 1.70–1.47 (m, 6 H), 1.45–1.40 (m, 1 H), 1.36–1.31 (m, 1 H), 1.25–1.22 (m, 1 H), 1.21 (s, 3 H), 1.02 (d, J = 6.9 Hz, 3 H), 0.94 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 224.2, 66.5, 60.4, 60.0, 52.9, 49.3, 39.6, 37.2, 34.3, 32.9, 32.5, 27.3, 20.2, 15.2, 8.73 ppm. IR (neat): $\tilde{\nu}$ = 3500, 2953, 1728, 1463, 1380, 1048, 989 cm^{-1}. HRMS (EI): calcd. for $C_{15}H_{24}O_2$ 236.1776; found 236.1769. $[\alpha]_D^{22}$ = + 8.26 (c = 0.9, $CHCl_3$)

(1*R*,2*S*,3*S*,6*R*)-3-Hydroxy-2,4,6-trimethyltricyclo[3.3.3.0]undec-3-ylmethyl Acetate: To a solution of (1*R*,2*S*,6*R*)-2-hydroxymethyl-2,4,6-trimethyltricyclo[3.3.3.0]undecan-3-one (12.7 mg, 0.054 mmol) dissolved in CH_2Cl_2 (1 mL) was added Et_3N (0.017 mL, 0.12 mmol) and Ac_2O (0.01 mL, 0.11 mmol) at 0°C, and the mixture was allowed to stir for 4 h at room temperature. The mixture was poured into H_2O (2 mL), and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined extract was dried and concentrated in vacuo. Flash chromatography of the residue on silica gel (EtOAc/hexane, 1:15) afforded 14.3 mg (0.051 mmol, 95%) of the title compound as a colorless oil. To a stirred solution of acetate (14.3 mg, 0.051 mmol) in methanol (1 mL) was added $NaBH_4$ (2.2 mg, 0.056 mmol) at 0 °C. After stirring for 20 min, H_2O (2 mL) was added to the reaction mixture and extracted with EtOAc (3 × 2 mL). The combined organic extract was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to flash chromatography (EtOAc/hexane, 1:5) to give 13.4 mg (0.048 mmol, 94%) of the products [3.2 mg of the (1*R*,2*S*,3*R*,6*R*)-product and 10.2 mg of the (1*R*,2*S*,3*S*,6*R*)-product]. Data for the (1*R*,2*S*,3*R*,6*R*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.56 (d, J = 11.2 Hz, 1 H), 3.93 (d, J = 11.2 Hz, 1 H), 3.54 (d, J = 3.8 Hz, 1 H), 2.56 (br. s, 1 H, OH), 2.32–2.26 (m, 1 H), 2.06 (s, 3 H), 1.99–1.94 (m, 1 H), 1.89–1.75 (m, 2 H), 1.64–.1.51 (m, 2 H), 1.43–1.29 (m, 4 H), 1.18–1.10 (m, 2 H), 1.07 (d, J = 7.2 Hz, 3 H), 0.96 (s, 3 H), 0.87 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3, 86.4, 68.1, 66.8, 65.7, 49.0, 44.5, 39.4, 38.0, 35.1, 33.7, 32.7, 27.3, 21.0, 19.4, 15.2, 10.5 ppm. IR (neat): $\tilde{\nu}$ = 3444, 2957, 1742, 1471, 1385, 1259, 1068, 1033, 987 cm^{-1}. HRMS (EI): calcd. for $C_{17}H_{28}O_3$ 280.2038; found 280.2025. $[\alpha]_D^{22}$ = –39.88 (c = 0.8, $CHCl_3$). Data for the (1*R*,2*S*,3*S*,6*R*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.15 (d, J = 11.0 Hz, 1 H), 4.04 (d, J = 11.0 Hz, 1 H), 3.38 (d, J = 11.0 Hz, 1 H), 2.04 (s, 3 H), 2.03–1.94 (m, 1 H), 1.64–1.49 (m, 4 H), 1.45–1.37 (m, 2 H), 1.34–1.21 (m, 3 H), 1.13–1.08 (m, 1 H), 1.02 (d, J = 7.6 Hz, 3 H), 0.99 (s, 3 H), 0.92 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 80.2, 72.1, 63.0, 60.7, 46.7, 45.9, 39.6, 37.6, 35.7, 32.5, 32.3, 27.2, 20.9, 15.2, 13.7, 11.9 ppm. $[\alpha]_D^{20}$ = –5.04 (c = 0.7, $CHCl_3$).

(+)-14-Acetoxymodhephene (3): To a stirred solution of acetate (13.4 mg, 0.048 mmol) in CH_3CN (2 mL) was added triphenylphosphane (50.4 mg, 0.192 mmol) and carbon tetrachloride (18.5 μL, 0.192 mmol) at room temperature. The mixture was stirred under reflux for 2 h. The reaction mixture was cooled to room temperature. The mixture was concentrated under the reduced pressure. Flash chromatography of the residue (EtOAc/hexane, 1:40) afforded 10.3 mg (0.039 mmol, 82%) of **3** as a colorless oil. ^{1}H NMR (400 MHz, C_6D_6): δ = 4.71 (q, J = 1.4 Hz, 1 H), 4.11 (d, J = 10.8 Hz, 1 H), 3.90 (d, J = 10.8 Hz, 1 H), 2.09–2.02 (m, 1 H), 1.70 (s, 3 H), 1.60–1.45 (m, 2 H), 1.52 (d, J = 1.4 Hz, 3 H), 1.42–1.19 (m, 7 H), 1.06 (s, 3 H), 1.03–0.96 (m, 1 H), 0.92 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 144.7, 129.6, 73.4, 71.8, 65.3, 49.4, 43.4, 39.0, 35.0, 34.1, 29.9, 26.9, 21.0, 15.3, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 2950, 1741, 1656, 1462, 1376, 1241 cm^{-1}. HRMS (EI): calcd. for $C_{17}H_{26}O_2$ 262.1933; found 262.1937. $[\alpha]_D^{23}$ = + 17.60 (c = 0.5, $CHCl_3$).

(1*R*,2*R*,6*S*)-2-Hydroxymethyl-2,6-dimethyltricyclo[3.3.3.0]undecan-3-one (19): To a solution of epoxy ketone **6** (70 mg, 0.32 mmol) in CH_2Cl_2 (1 mL) was added BF_3·THF (0.070 mL, 0.64 mmol) at room temperature. The reaction mixture was stirred for 10 min. The mixture was poured into saturated aqueous $NaHCO_3$ (2 mL), and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic layer was dried with anhydrous $MgSO_4$. The mixture was concentrated in vacuo. The crude product was dissolved in THF (1 mL), and a solution of $LiAl(OtBu)_3H$ (1 M in THF, 0.35 mL, 0.35 mmol) was added to the reaction mixture at –78 °C. After stirring for 1 h, the mixture was poured into H_2O (2 mL), and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic layer was dried with anhydrous $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (EtOAc/hexane, 1:3) produced 8 mg (0.036 mmol, 11%) of **19**. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (d, J = 11.2 Hz, 1 H), 3.49 (d, J = 11.2 Hz, 1 H), 2.55 (d, J = 18.3 Hz, 1 H), 2.09 (d, J = 18.3 Hz, 1 H), 1.91–1.82 (m, 2 H), 1.80–1.70 (m, 3 H), 1.64–1.58 (m, 1 H), 1.40–1.29 (m, 5 H), 1.17 (s, 3 H), 0.98 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 224.4, 66.2, 62.6, 57.6, 55.5, 50.3, 47.2, 38.0, 35.9, 34.0, 33.7, 26.3, 20.8, 14.4 ppm. $[\alpha]_D^{25}$ = –13.61 (c = 1.2, $CHCl_3$).

(1*R*,2*R*,6*S*)-2-[(1-Ethoxyethoxy)methyl]-2,6-dimethyltricyclo[3.3.3.0]-undecan-3-one: To a solution of alcohol **19** (34 mg, 0.153 mmol) in CH_2Cl_2 (1 mL) was added ethyl vinyl ether (EVE; 0.03 mL, 0.306 mmol) and *p*TosOH at room temperature. After stirring for 1 h, the mixture was poured into H_2O (2 mL), and the aqueous layer was extracted with EtOAc (3 × 3 mL). After the organic extract was dried and concentrated. Flash chromatography (EtOAc/hexane, 1:20) of the residue gave 39.3 mg (0.141 mmol, 92%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.61–4.54 (m, 1 H), 3.61–3.50 (m, 2 H), 3.43–3.30 (m, 2 H), 2.34 (dd, J = 17.6, 4.8 Hz, 1 H), 2.19 (dd, J = 17.6, 2.4 Hz, 1 H), 2.06–1.99 (m, 1 H),

1.77–1.56 (m, 5 H), 1.44–1.13 (m, 11 H), 1.07 (s, 3 H), 0.95 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 221.8, 99.9, 70.3, 62.3, 61.0, 56.6, 54.9, 50.7, 46.1, 38.8, 36.0, 34.6, 33.0, 26.5, 19.5, 18.5, 15.2, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 2953, 1734, 1458, 1377, 1136, 1058 cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{30}O_3$ 294.2195; found 294.2181.

(1*R*,2*R*,6*R*)-2-Hydroxymethyl-2,4,6-trimethyltricyclo[3.3.3.0]undecan-3-one: To a solution of ketone (5 mg, 0.018 mmol) in THF (1 mL) was added LiTMP (0.53 M in THF, 0.340 mL, 0.18 mmol) [prepared from 2,2,6,6-tetramethylpiperidine and *n*BuLi in THF at 0 °C] at 0 °C. After stirring for 30 min, CH_3I (0.012 mL, 0.18 mmol) and HMPA (0.006 mL, 0.036 mmol) were added to the reaction mixture. Stirring was continued for 2 h at 0 °C. The mixture was poured into H_2O (2 mL), and the aqueous layer was extracted with EtOAc (3 × 3 mL). The mixture was concentrated in vacuo. The crude product was dissolved in THF (1 mL) and 1 N HCl was added to the reaction mixture at room temperature. After stirring for 1 h, the mixture was poured into H_2O (2 mL), and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined organic layer was dried with anhydrous $MgSO_4$ and concentrated. Flash chromatography of the residue on silica gel (EtOAc/hexane, 1:5) produced 2 mg (0.008 mmol, 47%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.81 (d, J = 11.4 Hz, 1 H), 3.47 (d, J = 11.4 Hz, 1 H), 2.52 (q, J = 7.0 Hz, 1 H), 2.36 (br. s, 1 H), 1.95–1.87 (m, 2 H), 1.84–1.73 (m, 2 H), 1.55–1.40 (m, 4 H), 1.36–1.28 (m, 2 H), 1.26–1.19 (m, 4 H), 1.00 (d, J = 6.0 Hz, 3 H), 0.98 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 225.8, 65.9, 61.0, 60.6, 52.9, 49.9, 49.8, 38.2, 34.5, 33.2, 29.1, 26.0, 23.1, 14.9, 10.1 ppm. $[\alpha]_D^{20}$ = –21.78 (c = 0.7, $CHCl_3$).

(1*R*,2*R*,3*R*,6*R*)-(3-Hydroxy-2,4,6-trimethyltricyclo[3.3.3.0]undec-2-yl)methyl Acetate: To a solution of (1*R*,2*R*,6*R*)-2-hydroxymethyl-2,4,6-trimethyltricyclo[3.3.3.0]undecan-3-one (7 mg, 0.030 mmol) dissolved in CH_2Cl_2 (1 mL) was added Et_3N (0.01 mL, 0.12 mmol) and Ac_2O (0.006 mL, 0.06 mmol) at 0 °C, and the mixture was allowed to stir for 4 h at room temperature. The mixture was poured into H_2O (2 mL), and the aqueous layer was extracted with EtOAc (3 × 3 mL). The combined extract was dried and concentrated in vacuo. Flash chromatography of the residue on silica gel (EtOAc/hexane, 1:15) afforded 7.8 mg (0.028 mmol, 95%) of the acetate as a colorless oil. To a stirred solution of acetate (7.8 mg, 0.028 mmol) in methanol (1 mL) was added $NaBH_4$ (1.21 mg, 0.031 mmol) at 0 °C. After stirring for 20 min, H_2O (1 mL) was added to the reaction mixture, which was then extracted with EtOAc (3 × 2 mL). The combined organic extract was dried with anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was subjected to flash chromatography (EtOAc/hexane, 1:5) to give 7.2 mg (0.026 mmol, 92%) of the products [3.7 mg of the (1*R*,2*R*,3*R*,6*R*)-product and 3.4 mg of the (1*R*,2*R*,3*S*,6*R*)-product]. Data for the (1*R*,2*R*,3*R*,6*R*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.53 (d, J = 11.1 Hz, 1 H), 3.93 (d, J = 11.1 Hz, 1 H), 3.70 (d, J = 4.4 Hz, 1 H), 2.47 (br. s, 1 H), 2.25–2.18 (m, 1 H), 2.05 (s, 3 H), 2.04–1.95 (m, 2 H), 1.83–1.75 (m, 2 H), 1.73–1.61 (m, 2 H), 1.46–1.30 (m, 4 H), 1.18–1.12 (m, 1 H), 1.01 (s, 3 H), 0.99 (d, J = 7.2 Hz, 3 H), 0.93 (d, J = 6.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 87.7, 68.3, 68.2, 67.0, 50.2, 48.9, 46.5, 39.2, 38.5, 35.5, 29.1, 27.6, 22.3, 21.0, 16.2, 11.1 ppm. $[\alpha]_D^{25}$ = + 28.38 (c = 0.8, $CHCl_3$). Data for the (1*R*,2*R*,3*S*,6*R*)-isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.07 (d, J = 11.0 Hz, 1 H), 4.00 (d, J = 11.0 Hz, 1 H), 3.44 (d, J = 11.0 Hz, 1 H), 2.04 (s, 3 H), 2.00–1.94 (m, 1 H), 1.80–1.69 (m, 4 H), 1.47–1.42 (m, 3 H), 1.39–1.31 (m, 3 H), 1.20–1.14 (m, 1 H), 1.01 (s, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 0.92 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 84.0, 71.3, 64.7, 62.0, 49.4, 48.2, 47.0, 39.6, 36.8, 35.0, 28.7, 27.3, 21.0, 16.3, 15.5, 13.8 ppm. $[\alpha]_D^{25}$ = –12.88 (c = 0.8, $CHCl_3$).

(–)-13-Acetoxymodhephene (2): To a stirred solution of acetate (1.3 mg, 0.0046 mmol) in CH_3CN (1 mL) was added triphenylphosphane (4.83 mg, 0.0184 mmol) and carbon tetrachloride (1.8 μL, 0.192 mmol) at room temperature. The mixture was stirred under reflux for 2 h. The reaction mixture was cooled to room temperature. The mixture was concentrated under the reduced pressure. Flash chromatography of the residue (EtOAc/hexane, 1:40) afforded 1 mg (0.0038 mmol, 83%) of 13-acetoxymodhephene as a colorless oil. ^{1}H NMR (400 MHz, C_6D_6): δ = 4.77 (q, J = 1.3 Hz, 1 H), 4.10 (d, J = 10.9 Hz, 1 H), 4.06 (d, J = 10.9 Hz, 1 H), 2.07–2.01 (m, 1 H), 1.83–1.77 (m, 1 H), 1.70 (s, 3 H), 1.64–1.57 (m, 2 H), 1.52 (d, J = 1.2 Hz, 3 H), 1.50–1.45 (m, 1 H), 1.37–1.19 (m, 5 H), 1.08 (s, 3 H), 1.06–1.02 (m, 1 H), 0.92 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 144.3, 129.7, 73.6, 70.5, 65.5, 49.6, 43.8, 38.3, 35.7, 34.5, 29.2, 27.0, 24.4, 21.0, 15.5, 14.0 ppm. HRMS (EI): calcd. for $C_{17}H_{26}O_2$ 262.1933; found 262.1937. $[\alpha]_D^{24}$ = –14.15 (c = 0.5, $CHCl_3$).

Supporting Information (see footnote on the first page of this article): ^{1}H NMR and ^{13}C NMR of the intermediates and synthetic acetoxymodhephenes.

Acknowledgments

This work was supported by the Korea Research Foundation (grant KRF-2006-312-C00587).

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Received: June 27, 2009
Published Online: September 2, 2009

