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Synthesis of the BCDE Molecular Fragment of Azadiradione Mediated by Titanocene(III)

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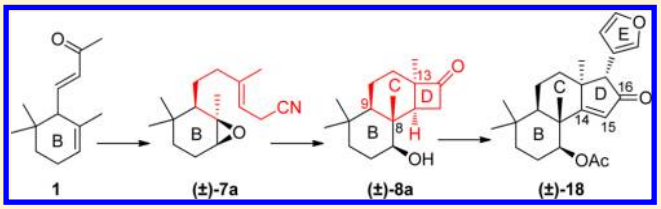
Supporting Information

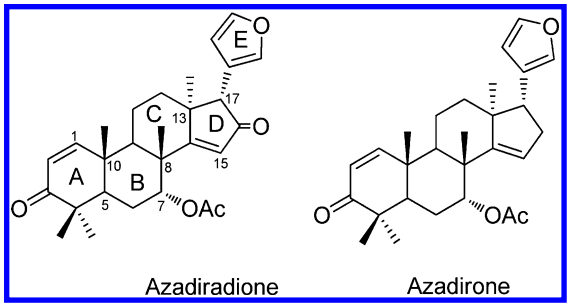
ABSTRACT: A practical, short, and diastereoselective synthesis of the azadiradione BCDE fragment from a readily available starting material is described. The key step was the titanocene(III)-promoted tandem cyclization of unsaturated epoxy nitrile.



INTRODUCTION

Limonoids are degraded triterpenoids occurring in the Meliaceae plant family, and they are used in popular medicine owing to their wide range of biological properties, such as antifeedant and growth-regulating activities on insects as well as antibacterial, antifungal, anticancer and antiviral activities and a number of pharmacological activities in humans.[1]

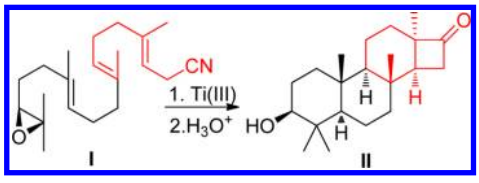
The azadiradione and other limonoids isolated from the Neem tree, *Azadirachta indica* (A. Juss), are known for their insect antifeedant activity.[2] They are currently displacing traditional insecticides in integrated pest control, being biodegradable, bioselective, and very effective at low concentration.[1,2] Recent studies have revealed that there is some interest in the azadirone, a limonoid with cytotoxic activity against cancer cells.[3]



Despite their significant bioactivity, little synthetic effort has been invested in these natural products.[4] Our research group has developed a broad range of synthetic methods of "limonoid structural fragments" constituted by the CDE[5] and BCDE[6] rings and limonoid analogues.[7] Numerous compounds synthesized by us have shown high insect antifeedant activity, particularly the fragment consisting of epoxyazadiradione CDE rings, which has also been found to be active against the AIDS virus when tested "in vitro".[8]

RESULTS AND DISCUSSION

Following with our previous studies, we have designed a new approach with a view to confirming the viability of a cascade radical cyclization titanocene(III)-based procedure.[9] Our strategy was based on a stereoselective cascade radical cyclization from an unsaturated epoxy nitrile to a bicyclic hydroxyketone,[10] induced by titanocene chloride. In general, our cascade started with the known homolytic cleavage of the oxirane with titanocene chloride, followed by a radical 6-*endo* cyclization onto C=C and finishing on a nitrile group. The novelty of this cascade is the termination step. Although radical cyclization onto nitrile has been considered a slow process, we have demonstrated the reliability of epoxy nitrile cyclizations with titanocene chloride by synthesizing cycloalkanones in good yields.[9c] The stereochemistry of the adducts is consistent with the notion of the cyclizations proceeding via a chairlike transition state. As an outstanding example we have reported a stereocyclization mode represented by the quadruple cyclization of **I**, which is consistent via three 6-*endo* chairlike transition-state processes and a further 4-*exo* cyclization onto nitrile, providing in good yield (50%) the single diastereoisomer **II**.[10]



Scheme 1 shows the graphical synthetic sequence of the target azadiradione BCDE fragment, which consists of five general steps.

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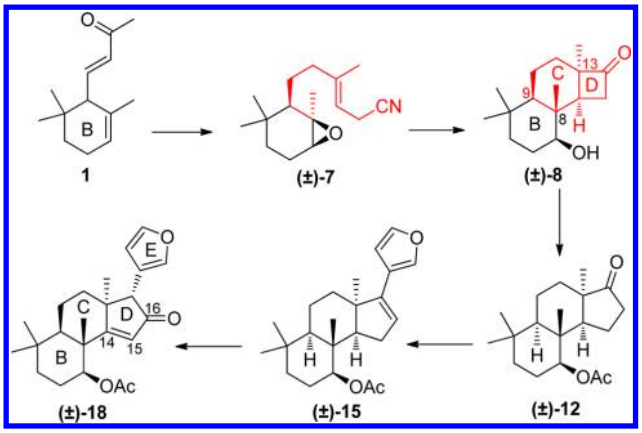
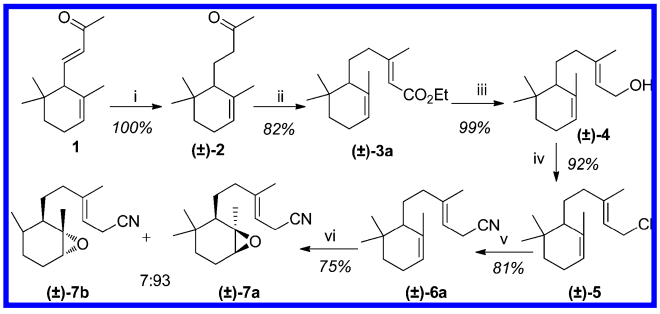
Scheme 1. General Synthetic Sequence of the Azadiradione BCDE Fragment



As starting material we chose the ready available α-ionone **1**, whose cyclohexane ring was to constitute the B ring in our azadiradione BCDE fragment. The carbonyl function in the chain of **1** allows adequate elongation and functionalization, and the endocyclic double bond is located in the best position to introduce the oxygen atom of the oxirane, which will be the starting point of the radical cascade cyclization, establishing the hydroxyl group at C-7. If the cyclization pattern occurs according to the stereochemical 6-*endo*/4-*exo* pattern of our previous studies, we expect a *trans* fusion for the first two rings and a *cis* fusion for the others. Thus, the relative configuration of the stereocenters C-8, C-9 and C-13 would be identical to those of natural limonoids. To complete the synthesis, it would be necessary to expand and properly functionalize the D ring, and introduce the E ring.

The first general step leading to epoxy nitrile (±)-7 commenced with α-ionone **1**, which was converted to dihydro-α-ionone (±)-**2** by a chemoselective hydrogenation (Scheme 2).[11] Subsequent olefination of (±)-**2** by the

Scheme 2. Preparation of Epoxy Nitriles (±)-7a/7b from α-Ionone[a]

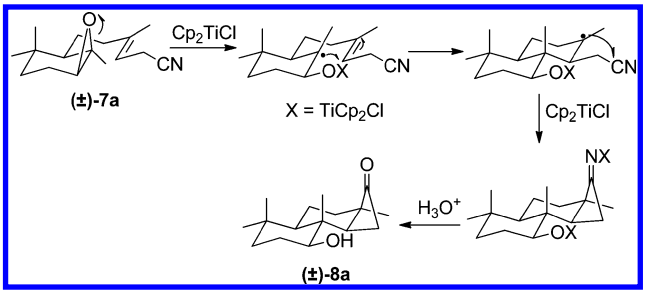


[a]Key: (i) H_2, Pd/C, Et_2NH, EtOAc, 25°C; (ii) $EtOOCCH_2P(O)(OEt)_2$, NaH, $PhCH_3$, 0 → 25 °C; (iii) DIBAH, $PhCH_3$, −20°C; (iv) CCl_4, PPh_3, 80 °C; (v) NaCN, DMSO, 25 °C; (vi) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, −20 °C.

Wadsworth−Emmons method[12] furnished the unsaturated ketoesters (±)-**3a** (*E*) and (±)-**3b** (*Z*) in a ratio of 91:9. Reduction of (±)-**3a** with DIBAH at −20 °C gave rise to the alcohol (±)-**4**, which after hydroxyl substitution afforded the allylic chloride (±)-**5**. This compound was transformed into the unsaturated nitrile (±)-**6a** by nucleophilic displacement with sodium cyanide in DMSO. Treatment of the diunsaturated nitrile (±)-**6a** with *m*-CPBA produced the epoxy nitrile (±)-**7a** chemo and stereoselectively with a small quantity of the isomer (±)-**7b**. The relative configuration of (±)-**7a** and (±)-**7b** was assigned by analogy with similar epoxyesters, reported by us elsewhere,[5d] and from X-ray diffraction of product (±)-**12**, to be explored further below.

The second step was to address the construction of the CD rings by cyclization of epoxy nitrile (±)-**7a**. The tandem radical cyclization was carried out by reaction of (±)-**7a** with 2 equiv of titanocene chloride, generated in situ in THF at room temperature.[10] The hydroxy ketone (±)-**8a** was obtained as the only product in 82% yield. The cyclization mechanism is depicted in Scheme 3: it starts with the homolytic cleavage of

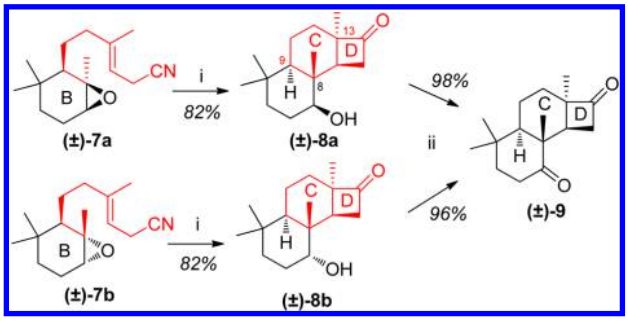
Scheme 3. Mechanism for the Formation of (±)-8a



the oxirane with titanocene chloride, which is followed by a radical 6-*endo* cyclization onto C═C, and it finishes with a 4-*exo* cyclization on the nitrile group.

In the same way, treatment of the epoxy nitrile (±)-**7b** with titanocene afforded (±)-**8b** in 82% yield, as a result of the radical cyclization (Scheme 4). In both radical cyclizations,

Scheme 4. Cyclization of Epoxy Nitriles (±)-7a and (±)-7b with Cp_2TiCl[a]



[a]Key: (i) Cp_2TiCl_2, Zn, THF, 25 °C; (ii) PCC, CH_2Cl_2, 25 °C.

three stereocenters are created with complete control of diastereoselectivity according to the model compound **I**: *trans* for the BC ring fusion and *cis* for the CD ring fusion, such that the relative configuration of the carbons C8, C9, and C13 is identical to the configuration of these carbons in the azadiradione and other limonoids. The relative configuration of (±)-**8a** and (±)-**8b** was assigned by its chemical correlation with product (±)-**12** (see below). The hydroxy ketones (±)-**8a** and (±)-**8b** only differ in the orientation of the hydroxyl group, as demonstrated by their oxidation to the same diketone (±)-**9**.

Regarding these cyclizations, we wished to test the homologous epoxy nitrile (±)-**7c** in order to determine its pattern of cyclization (Scheme 5). If it was the same as with compounds (±)-**7a** and (±)-**7b**, we would be able to dispense

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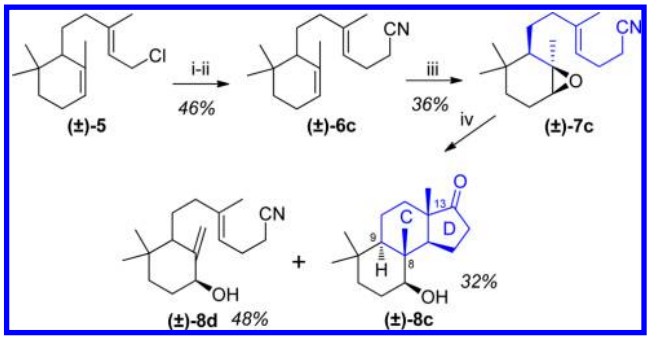
Scheme 5. Preparation and Cyclization of Epoxy Nitrile (±)-7c[a]



[a]Key: (i) $NCCH_2CO_2Me$, NaH, DMF, 25 °C; (ii) H_2O, DMSO, 180 °C; (iii) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, −20 °C; (iv) Cp_2TiCl_2, Zn, THF, 25 °C.

with the ring-expansion step (Scheme 1). The nitrile (±)-**7c** was obtained from chloride (±)-**5** in three steps: side-chain elongation to (±)-**6b** using methyl cyanoacetate anion followed by desmethoxycarbonylation by the Krapcho method[13] to (±)-**6c** and epoxidation with *m*-CPBA.

The cyclization of (±)-**7c** carried out with titanocene chloride gave the tricyclic hydroxy ketone (±)-**8c** together with the unsaturated hydroxy nitrile (±)-**8d** in 32% and 48% yield, respectively. It is worth noting the yield difference between the synthesis of tricyclic products (±)-**8a** (82%) and (±)-**8c** (32%) in the radical reaction induced by titanocene from epoxides (±)-**7a** and (±)-**7c** and also the difference in the cyclization pattern. Thus, whereas in (±)-**8a** the CD ring fusion was *cis*, in (±)-**8c** the CD ring fusion was *trans*. The structure of (±)-**8c** was initially assigned on the basis of its spectroscopic data as a compound with the BCD ring fusion *trans-anti-trans*, and this structure was subsequently confirmed by X-ray diffraction analysis (Figure 1). Thus, these results prevented us of using the epoxy nitrile (±)-**7c** in the synthesis and led us back to our initial synthesis plan.

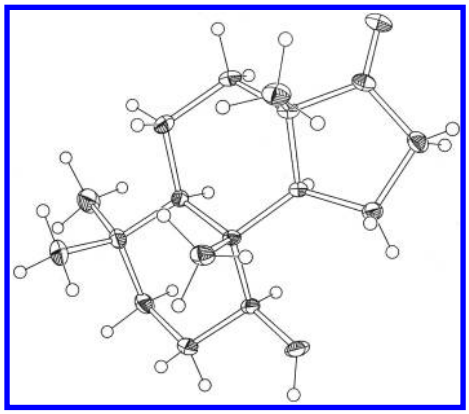
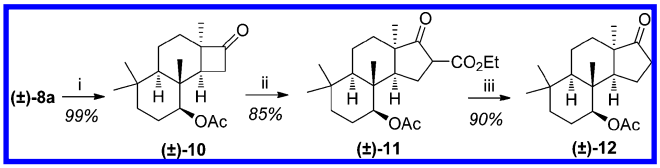


Figure 1. X-ray structure of (±)-**8c**.

The third step in the synthetic sequence to the azadiradione BCDE fragment consisted of D ring expansion (Scheme 6). This was accomplished by reacting acetate (±)-**10** with ethyl diazoacetate,[14] followed by desethoxycarbonylation of the intermediate (±)-**11** to give (±)-**12** in 77% overall yield. Attempts to achieve the cyclobutanone ring expansion of (±)-**10** with (trimethylsilyl)diazomethane gave a mixture of products and low yields.

Scheme 6. Expansion of the D Ring[a]



[a]Key: (i) Ac_2O, pyr, DMAP, CH_2Cl_2; (ii) $N_2{=}CHCO_2Et$, $BF_3{\cdot}Et_2O$, THF; (iii) H_2O, DMSO, 180 °C.

The structure of (±)-**12**, initially assigned on the basis of its spectroscopic data as a compound with the BCD ring fusion *trans-anti-cis*, was subsequently confirmed by X-ray diffraction analysis (Figure 2).

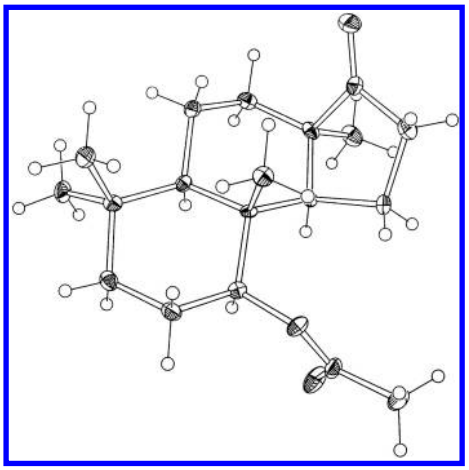
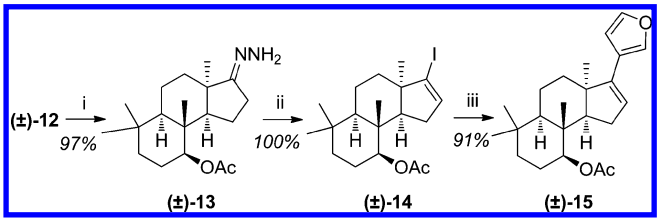


Figure 2. X-ray structure of (±)-**12**.

The target of the fourth main step was the introduction of the E ring, constituted by the furan ring (Scheme 7). This step

Scheme 7. Introduction of the E Ring[a]



[a]Key: (i) $NH_2NH_2{\cdot}H_2O$, EtOH, reflux; (ii) I_2, Et_3N, THF, 25 °C; (iii) (3-fur)$SnBu_3$, Pd $(PPh_3)_4$, LiCl, DMSO, 60 °C.

was achieved by a Stille coupling, developed by our group for similar compounds,[15] between vinyl iodide (±)-**14**, obtained from ketone (±)-**12** through hydrazone (±)-**13**, and 3-furyltributylstannane.

The last target in our approach to the synthesis of the azadiradione BCDE fragment was the ketoacetate (±)-**18**. The structural features of this final main stage include the transformation of the unsaturated D ring into an enone system, which has been accomplished in three steps (Scheme 8).[15] Treatment of the furylketone (±)-**15** with 3 equiv of *m*-CPBA at −40 °C to avoid the oxidation of the furan afforded, after attempts of purification through silicagel, an epimeric mixture of ketones (±)-**17a** and (±)-**17b**, at a 6:4 ratio respectively. Their formation was easily explained in terms of the relief of the

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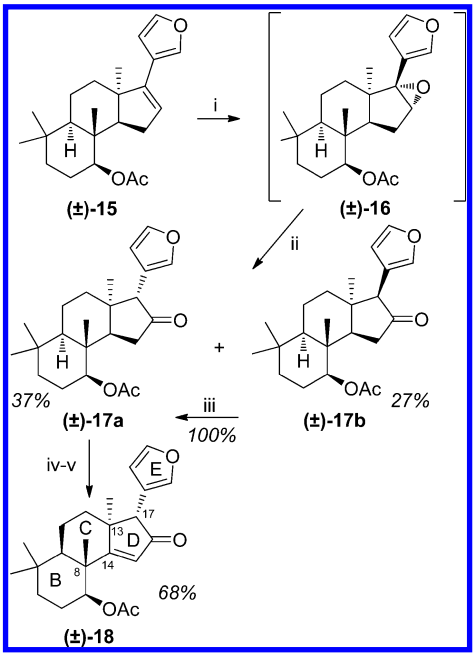
Scheme 8. Elaboration of D Ring[a]



[a]Key: (i) *m*-CPBA, CH_2Cl_2, −40 °C; (ii) SiO_2; (iii) Et_3N, CH_3CN; (iv) TMSOTf, Et_3N, −30 °C; (v) PhSeCl, CH_2Cl_2, −78 °C; (vi) *m*-CPBA, CH_2Cl_2, −78 °C.

strong interaction between the methyl group in C-8 position and the furan after the regioselective heterolytic cleavage of the oxirane and the migration of the hydrogen from C-16 to C-17. Isomerization of (±)-**17b** to (±)-**17a** was achieved at 100% yield by triethylamine treatment. The *cis* relationship between the furan and C-13 methyl group was seen in the diamagnetic shielding effect caused in the methyl group by the furan ring, as has been observed for related compounds. The structure of (±)-**17a** was unambiguously confirmed by X-ray crystallographic analyses (see Supporting Information).

Dehydrogenation of (±)-**17a** to the target azadiradione BCDE fragment (±)-**18** was accomplished by the known sequence of selenylation, oxidation, and selenoxide elimination.

CONCLUSION

The stereocontrolled total synthesis of the azadiradione BCDE fragment (±)-**18** has been accomplished from α-ionone. The key feature includes the stereoselective construction of the CD rings core by titanocene(III)-catalyzed tandem cyclization of unsaturated epoxy nitrile (±)-**7a** by a *6-endo*/*4-exo* pattern, which allows the relative configuration of the C-8, C-9, and C-13 stereocenters of the hydroxy ketone (±)-**8a** to be identical to that of natural limonoids. It is also worth noting the introduction of the E ring by Stille coupling and the stereoselective functionalization of the D ring. The procedure reported here could also allow the enantiospecific synthesis of azadiradione, diverse molecular fragments, and analogues to be achieved.

EXPERIMENTAL SECTION

General Methods. Melting points are uncorrected. ^{1}H NMR spectra were measured at either 200 or 400 MHz, and ^{13}C NMR were measured at 50 or 100 MHz in $CDCl_3$ and referenced to TMS (^{1}H) or solvent (^{13}C). HRMS mass spectrometry data were acquired in a hybrid quadrupole time-of-flight mass spectromer. Samples were dissolved in methanol, and electrospray was used for ionization. When required, all solvents and reagents were purified by standard techniques: tetrahydrofuran (THF) was purified by distillation from sodium and benzophenone and degassed before use. All air- or moisture-sensitive reactions were conducted under a positive pressure of argon, utilizing standard benchtop techniques for the handling of air-sensitive materials. Chromatographic separations were carried out under pressure on silica gel using flash column techniques on Merck silica gel 60 (0.040−0.063 mm). Yields reported are for chromatographically pure isolated products unless otherwise mentioned.

Compound (±)-2. A 10% solution of Pd/C (10.0 g), Et_2NH (35.0 mL) and EtOAc (150.0 mL) was stirred under H_2 atmosphere for 15 min. After this time, α-ionone **1** (35.0 g, 182.0 mmol) in EtOAc (200.0 mL) was added, and the mixture was stirred at room temperature. The reaction completion was checked by NMR. After 3 h, the mixture was filtered through a fritted glass funnel, washed with $CHCl_3$, and concentrated under reduced pressure. Purification of the residue by flash chromatography over silica gel with a mixture hexane/Et_2O 9:1 as eluent afforded (±)-**2** (colorless oil) (35.9 g, 100%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.83 (s, 3H), 0.88 (s, 3H), 1.1−1.9 (m, 7H), 1.63 (br s, 3H), 2.09 (s, 3H), 2.43 (m, 2H), 5.32 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 22.9 (CH_2), 23.4 (CH_3), 24.3 (CH_2), 27.5 (CH_3), 27.6 (CH_3), 29.8 (CH_3), 31.5 (CH_2), 32.5 (C), 43.7 (CH_2), 48.4 (CH), 120.9 (CH), 135.5 (C), 209.1 (C) ppm; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{22}NaO$ 217.1568, found 217.1556.

Compounds (±)-3a and (±)-3b. Triethylphosphonoacetate (22.4 mL, 113.0 mmol) was slowly added to a suspension of 60% NaH (4.1 g, 102.0 mmol) in toluene (34.0 mL) under argon atmosphere and at 0 °C, and the mixture was stirred at the same temperature until the complete formation of the anion (ca. 30 min). Ketone (±)-**2** (20.0 g, 102.9 mmol) was then added dropwise and the new mixture stirred at room temperature for 15 h, when it was diluted with Et_2O and quenched with water. The aqueous layer was extracted with Et_2O, the mixture of organic extracts was washed with brine and dried over anhydrous Na_2SO_4, and the solvent removed under reduced pressure. Purification of the residue by flash chromatography over silica gel with a mixture hexane/Et_2O 98:2 as eluent afforded (±)-**3b** (colorless oil) (2.2 g, 8%) followed by (±)-**3a** (colorless oil) (22.5 g, 82%).

*Data for cis isomer (±)-**3b**:* 1H NMR ($CDCl_3$, 200 MHz) δ 0.85 (s, 3H), 0.96 (s, 3H), 1.0−2.0 (m, 7H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.70 (s, 3H), 1.85 (s, 3H), 2.48 (m, 1H), 2.76 (m, 1H), 4.11 (q, *J* = 7.0 Hz, 2H), 5.28 (br s, 1H), 5.59 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.3 (CH_3), 22.9 (CH_2), 23.3 (CH_3), 25.1 (CH_3), 27.4 (CH_3), 27.5 (CH_3), 29.2 (CH_2), 31.5 (CH_2), 32.5 (C), 33.8 (CH_2), 49.4 (CH), 59.3 (CH_2), 115.8 (CH), 120.2 (CH), 136.2 (C), 160.4 (C), 166.1 (C) ppm.

*Data for trans isomer (±)-**3a**:* ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.86 (s, 3H), 0.91 (s, 3H), 1.0−2.1 (m, 9H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.66 (s, 3H), 2.15 (s, 3H), 4.15 (q, *J* = 7.2 Hz, 2H), 5.30 (br s, 1H), 5.65 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.3 (CH_3), 18.8 (CH_3), 22.9 (CH_3), 23.3 (CH_3), 27.4 (CH_3), 27.5 (CH_3), 29.1 (CH_2), 31.6 (CH_2), 32.5 (C), 41.5 (CH_2), 48.9 (CH), 59.3 (CH_2), 115.4 (CH), 120.6 (CH), 135.7 (C), 160.3 (C), 166.7 (C) ppm; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{28}NaO_2$ 287.1987, found 287.1969.

Compound (±)-4. A solution of (±)-**3a** (5.0 g, 18.9 mmol) in toluene (189 mL) under argon atmosphere was stirred at −20 °C while a 1.5 M solution of DIBAH in toluene was added dropwise. The reaction was stirred at this temperature for 30 min when 37.0 mL of water was added and the mixture allowed to reach room temperature. The reaction was then filtered through a fritted glass funnel, the solid washed with Et_2O, and the filtrate dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue obtained was identified as (±)-**4** (colorless oil) (4.19 g, 99%) and was used in the next reaction without further purification: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.83 (s, 3H), 0.90 (s, 3H), 1.20 (m, 1H), 1.3−1.6 (m, 4H), 1.66 (s, 6H), 1.93 (m, 2H), 2.05 (m, 2H), 4.10 (d, *J* = 7.0 Hz, 2H), 5.27 (br s, 1H), 5.38 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 15.9 (CH_3), 22.9 (CH_2), 23.4 (CH_3), 27.4 (CH_3), 27.5 (CH_3), 29.4

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(CH_2), 31.5 (CH_2), 32.5 (C), 40.3 (CH_2), 48.9 (CH), 59.3 (CH_2), 120.0 (CH), 123.1 (CH), 136.4 (C), 140.3 (C) ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{15}H_{26}NaO$ 245.1881, found 245.1890.

Compound (±)-5. Triphenylphosphine (3.54 g, 13.5 mmol) was added to a solution of (±)-**4** (2.00 g, 9.01 mmol) in CCl_4 (12.9 mL), and the resulting mixture was heated at 80 °C for 150 min. After this time, the reaction was allowed to cool to room temperature, pentane was added, and the mixture kept at −18 °C until all the triphenylphosphine oxide had precipitated (ca. 30 min). The mixture was then filtered over a fritted glass funnel and the solid washed with pentane. The filtrate was concentrated under reduced pressure and the residue obtained identified as (±)-**5** (colorless oil) (1.98 g, 92%) and used in the next reaction without further purification: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (s, 3H), 0.92 (s, 3H), 1.16 (m, 1H), 1.3−1.6 (m, 4H), 1.66 (s, 3H), 1.72 (s, 3H), 1.94 (m, 2H), 2.07 (m, 2H), 4.01 (d, J = 8.4 Hz, 2H), 5.29 (br s, 1H), 5.53 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 16.0 (CH_3), 22.9 (CH_2), 23.5 (CH_3), 27.5 (2CH_3), 29.2 (CH_2), 31.5 (CH_2), 32.5 (C), 40.2 (CH_2), 44.1 (CH_2), 48.8 (CH), 120.2 (CH), 120.3 (CH), 136.3 (C), 144.4 (C) ppm, HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{15}H_{25}ClNa$ 263.1542, found 263.1569.

Compound (±)-6a. Over a stirred solution of (±)-**5** (2.94 g, 12.25 mmol) in 41.0 mL of DMSO was added powdered NaCN (900 mg, 18.38 mmol), and the mixture was stirred at room temperature for 5 h. After this time, the reaction was diluted in Et_2O and quenched with water. The aqueous layer was extracted with Et_2O, the combined organic extracts were washed abundantly with water and brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography over silica gel with a mixture hexane/Et_2O 9:1 as eluent to afford (±)-**6a** (yellow oil) (1.61 g, 81%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (s, 3H), 0.91 (s, 3H), 1.13 (m, 1H), 1.3−1.6 (m, 4H), 1.66 (s, 3H), 1.67 (s, 3H), 1.94 (m, 2H), 2.06 (m, 2H), 3.02 (d, J = 6.9 Hz, 2H), 5.15 (m, 1H), 5.29 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.1 (CH_2), 16.4 (CH_3), 22.9 (CH_2), 23.4 (CH_3), 27.4 (CH_3), 27.5 (CH_3), 29.2 (CH_2), 31.5 (CH_2), 32.5 (C), 39.9 (CH_2), 48.9 (CH), 111.3 (CH), 118.5 (C), 120.3 (CH), 136.2 (C), 143.0 (C) ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{16}H_{25}NNa$ 254.1885, found 254.1876.

Compounds (±)-7a and (±)-7b. A mixture of (±)-**6a** (1.00 g, 4.33 mmol) and $NaHCO_3$ (400 mg, 4.76 mmol) in CH_2Cl_2 (21.6 mL) under argon atmosphere was cooled to −20 °C, and *m*-CPBA (820 mg, 4.76 mmol) was added. The reaction was stirred at that temperature for 90 min and then quenched with a 10% aqueous solution of $Na_2S_2O_3$. The mixture was then allowed to reach room temperature, the aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography over silica gel with a mixture of hexane/Et_2O 8:2 as eluent afforded (±)-**7a** (colorless oil) (749 mg, 70%) and (±)-**7b** (colorless oil) (56 mg, 5%).

*Data for isomer (±)-**7a**:* ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80 (s, 3H), 0.88 (s, 3H), 1.26 (m, 1H), 1.31 (s, 3H), 1.46 (m, 3H), 1.69 (s, 3H), 1.88 (m, 3H), 2.03 (m, 1H), 2.30 (m, 1H), 2.93 (br s, 1H), 3.02 (d, J = 7.0 Hz, 2H), 5.20 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.1 (CH_2), 16.4 (CH_3), 21.9 (CH_2), 25.7 (CH_2), 26.8 (CH_2), 26.9 (CH_3), 27.2 (CH_3), 27.7 (CH_3), 31.4 (C), 39.9 (CH_2), 46.8 (CH), 59.4 (C), 60.1 (CH), 111.3 (CH), 118.5 (C), 143.1 (C) ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{16}H_{25}NNaO$ 270.1834, found 270.1836.

*Data for isomer (±)-**7b**:* ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.71 (s, 3H), 0.81 (s, 3H), 1.03 (m, 1H), 1.32 (s, 3H), 1.49 (m, 3H), 1.67 (s, 3H), 1.82 (m, 3H), 2.13 (m, 1H), 2.27 (m, 1H), 2.86 (br s, 1H), 3.01 (d, J = 0.7 Hz, 2H), 5.19 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.1 (CH_2), 16.4 (CH_3), 19.8 (CH_3), 21.5 (CH_2), 22.6 (CH_3), 25.6 (CH_2), 27.7 (CH_3), 31.8 (C), 33.8 (CH_2), 41.3 (CH_2), 49.3 (CH), 60.0 (C), 60.8 (CH), 111.9 (CH), 118.4 (C), 142.2 (C) ppm.

Compound (±)-8a. A solution of Cp_2TiCl_2 (3.34 g, 13.36 mmol) and Zn (1.71 g, 26.72 mmol) in THF (27.0 mL) was strictly deoxygenated with argon until the solution turned green (ca. 15 min). At the same time, another solution of (±)-**7a** (1.00 g, 4.05 mmol) in THF (40.0 mL) was deoxygenated with argon. The epoxide solution was then added dropwise via canula over the Ti(III) solution, always maintaining the argon atmosphere. After 15 min, the reaction was quenched by addition of a saturated aqueous solution of NaH_2PO_4, and the resulting mixture, after being stirred for 30 min, was filtered through a fritted glass funnel. The aqueous layer was extracted with Et_2O, the combined organic extracts were washed with water and brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography over silica gel with a mixture hexane/EtOAc 8:2 as eluent to afford (±)-**8a** (white solid) (830 mg, 82%): mp 72−73 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.86 (s, 3H), 0.92 (s, 3H), 0.95 (s, 3H), 1.05 (m, 1H), 1.20 (s, 3H), 1.2−1.7 (m, 7H), 1.95 (m, 2H), 3.09 (m, 2H), 3.33 (dd, J_1 = 4.1 Hz, J_2 = 11.3 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.7 (CH_3), 16.9 (CH_2), 21.8 (CH_3), 23.1 (CH_3), 24.5 (CH_2), 27.8 (CH_2), 32.5 (CH_3), 33.1 (C), 39.0 (C), 40.1 (CH_2), 45.6 (CH_2), 45.9 (CH), 46.5 (CH), 61.3 (C), 83.9 (CH), 214.5 (C) ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{16}H_{26}NaO_2$ 273.1830, found 273.1860.

Compound (±)-8b. A solution of epoxide (±)-**7b** (113 mg, 0.45 mmol) in THF (4.5 mL) was made to react with a Ti(III) solution, prepared with Cp_2TiCl_2 (373 mg, 1.50 mmol) and Zn (191 mg, 3.00 mmol) in THF (3.0 mL), in exactly the same way described for the above epoxide. The residue obtained after the work up was purified by flash chromatography over silica gel with a mixture hexane/EtOAc 8:2 as eluent to afford (±)-**8b** (yellow oil) (94 mg, 82%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.90 (s, 3H), 0.94 (s, 3H), 0.94 (s, 3H), 1.23 (s, 3H), 1.2−1.7 (m, 7H), 1.95 (m, 2H), 2.75 (dd, J_1 = 6.3 Hz, J_2 = 9.7 Hz, 1H), 2.89 (dd, J_1 = 6.3 Hz, J_2 = 17.5 Hz, 1H), 2.97 (dd, J_1 = 9.7 Hz, J_2 = 17.5 Hz, 1H) 3.41 (br s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.4 (CH_2), 18.2 (CH_3), 22.0 (CH_3), 23.9 (CH_3), 25.3 (CH_2), 25.7 (CH_2), 33.0 (CH_3, C), 34.2 (CH_2), 36.5 (CH), 37.9 (C), 41.3 (CH), 43.9 (CH_2), 61.1 (C), 72.4 (CH), 214.3 (C) ppm.

Compound (±)-9. To a suspension of PCC (39 mg, 0.18 mmol) and SiO_2 (38 mg) in CH_2Cl_2 (1.0 mL) was added a solution of (±)-**8a** (30 mg, 0.12 mmol) in CH_2Cl_2 (1.0 mL). After 2 h of stirring at room temperature, the reaction was passed through a small column of SiO_2 using CH_2Cl_2 as eluent. Removal of the solvent at reduced pressure afforded (±)-**9** (yellow oil) (30 mg, 98%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.97 (s, 3H), 1.15 (s, 3H), 1.18 (s, 3H), 1.21 (s, 3H), 1.2−1.9 (m, 7H), 2.24 (dt, J_1 = 3.9 Hz, J_2 = 14.5 Hz, 1H), 2.53 (dd, J_1 = 6.6 Hz, J_2 = 9.8 Hz, 1H), 2.75 (ddd, J_1 = 5.5 Hz, J_2 = 14.5 Hz, J_3 = 14.5 Hz, 1H), 3.00 (dd, J_1 = 6.6 Hz, J_2 = 18.2 Hz, 1H), 3.17 (dd, J_1 = 9.8 Hz, J_2 = 18.2 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.1 (CH_3), 17.8 (CH_2), 21.1 (CH_3), 23.5 (CH_3), 24.3 (CH_2), 31.6 (CH_3), 32.8 (C), 34.9 (CH_2), 39.4 (CH), 40.7 (CH_2), 45.2 (CH_2), 47.8 (C), 48.5 (CH), 61.2 (C), 213.8 (C), 215.6 (C) ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{16}H_{24}O_2Na$ 271.1669, found 271.1677.

A similar procedure applied to (±)-**8b** (41 mg, 0.16 mmol) also afforded (±)-**9** (39 mg, 96%).

Compound (±)-6c. To a suspension of NaH (159 mg, 3.96 mmol) in DMF (1.4 mL) at 0 °C was added ethyl cyanoacetate (0.45 mL, 4.2 mmol) dropwise, and the mixture was stirred at room temperature for 30 min. A solution of (±)-**5** (680 mg, 2.83 mmol) in DMF (1 mL) was then added, and the reaction was stirred at 70 °C. After 7 h at this temperature, the mixture was cooled to room temperature and was quenched with water and an aqueous 2 N solution of HCl. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure furnished an oil which was diluted in DMSO (8.3 mL) and water (1.5 mL), and then NaCl (316 mg, 5.4 mmol) was added. The mixture was stirred at 180 °C for 3 h. The reaction was then allowed to reach room temperature, EtOAc was added, the mixture was washed abundantly with water and brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was

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purified by flash chromatography over silica gel with a mixture hexane/EtOAc 9:1 as eluent to afford (±)-**6c** (yellow oil) (318 mg, 46% from (±)-**5**): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.85 (s, 3H), 0.91 (s, 3H), 1.0−2.2 (m, 11H), 1.64 (s, 3H), 1.66 (s, 3H), 2.33 (m, 2H), 5.13 (br s, 1H), 5.28 (br s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 16.3 (CH_3), 17.5 (CH_2), 22.9 (CH_2), 23.3 (CH_3), 23.9 (CH_2), 27.3 (CH_3), 27.4 (CH_3), 29.5 (CH_2), 31.5 (CH_2), 32.5 (C), 40.2 (CH_2), 48.9 (CH), 117.6 (CH), 119.7 (C), 120.0 (CH), 136.4 (C), 139.8 (C); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{27}NNa$ 268.2041, found 268.2050.

Compound (±)-7c. A solution of (±)-**6c** (542 mg, 2.21 mmol) and 204 mg (2.43 mmol) of $NaHCO_3$ in CH_2Cl_2 (4.5 mL) under argon atmosphere was cooled to −20 °C, and 420 mg (4.46 mmol) of *m*-CPBA was added. The reaction was stirred at −10 °C for 90 min and then was quenched with a 10% aqueous solution of $Na_2S_2O_3$. The mixture was then allowed to reach room temperature, the aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography over silica gel with a mixture hexane/Et_2O 8:2 as eluent afforded (±)-**7c** (pale yellow oil) (208 mg, 36%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.79 (s, 3H), 0.87 (s, 3H), 1.31 (s, 3H), 1.66 (s, 3H), 0.9−2.0 (m, 11H), 2.35 (m, 2H), 2.91 (br s, 1H), 5.17 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.2 (CH_3), 17.6 (CH_2), 19.3 (CH_3), 22.0 (CH_2), 23.7 (CH_2), 25.9 (CH_2), 26.8 (CH_2), 26.9 (CH_3), 27.7 (CH_3), 33.0 (C), 39.3 (CH_2), 46.8 (CH), 59.5 (C), 60.1 (CH), 119.6 (C), 119.8 (CH), 139.9 (C); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{27}NNaO$ 284.1990, found 284.1982.

Compound (±)-8c. A solution of Cp_2TiCl_2 (657 mg, 2.63 mmol) and Zn (230 mg, 3.6 mmol) in 5.3 mL of THF was strictly deoxygenated with argon until the solution turned green (ca. 15 min). At the same time, another solution with of (±)-**7c** (208 mg, 0.80 mmol) in THF (8.0 mL) was deoxygenated with argon. The epoxide solution was then added dropwise via canula over the Ti(III) solution, always maintaining the argon atmosphere. After 15 min, the reaction was quenched by addition of a saturated aqueous solution of NaH_2PO_4, and the resulting mixture, after being stirred for 30 min, was filtered through a fritted glass funnel. The aqueous layer was extracted with Et_2O, the combined organic extracts were washed with water and brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography over silica gel with a mixture hexane/EtOAc 8:2 as eluent to afford (±)-**8c** (white solid) (67 mg, 32%), followed by (±)-**8d** (101 mg, 48%).

*Data for (±)-**8c**:* mp 108−110 °C ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.82 (s, 3H), 0.84 (s, 3H), 0.96 (s, 3H), 0.97 (s, 3H), 1.2−2.4 (m, 15H), 3.36 (dd, J_1 = 4.5 Hz, J_2 = 11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 12.1 (CH_3), 17.1 (CH_3), 18.6 (CH_2), 20.9 (CH_3), 21.7 (CH_2), 28.4 (CH_2), 32.7 (C), 32.9 (CH_3), 33.2 (CH_2), 35.6 (CH_2), 40.2 (CH_2), 43.3 (C), 48.7 (C), 55,5 (CH), 57.7 (CH), 80.1 (CH), 221.2 (C); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{28}NaO_2$ 287.1987, found 287.1980.

*Data for (±)-**8d**:* ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.70 (s, 3H), 0.90 (d, J = 6.4 Hz, 3H), 0.96 (s, 3H), 0.8−2.0 (m, 15H), 2.32 (m, 2H), 3.95 (t, J = 8.0 Hz, 1H), 4.68 (dd, J_1 = 1.0 Hz, J_2 = 6.5 Hz, 1H), 5.17 (d, J = 1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 17.4 (CH_2), 19.1 (CH_3), 19.6 (CH_3), 22.8 (CH_2), 23.0 (CH_2), 29.5 (CH_3), 32.8 (CH), 33.3 (CH_2), 35.4 (CH_2), 35.7 (CH_2), 36.2 (CH_2), 38.5 (C), 52.1 (CH), 73.8 (CH), 104.5 (CH_2), 119.7 (C), 150.9 (C); HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{29}NO$ 263.2249, found 263.2268.

Compound (±)-10. To a stirred solution of (±)-**8a** (1.35 g, 5.40 mmol) in CH_2Cl_2 (5.4 mL) and pyridine (0.6 mL, 8.10 mmol) were added Ac_2O (0.76 mL, 8.10 mmol) and a catalytic amount of DMAP. After 20 h at room temperature, the mixture was poured into water and stirred for 30 min. The aqueous layer was then extracted with Et_2O, the combined organic extracts were washed with water, an aqueous 2 N solution of HCl, an aqueous 5% solution of $NaHCO_3$, and brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was identified as (±)-**10** (colorless oil) (1.6 g, 99%): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.84 (s, 3H), 0.90 (s, 3H), 0.99 (s, 3H), 1.15 (s, 3H), 1.0−2.0 (m, 10H), 1.96 (s, 3H), 2.93 (m, 2H), 4.58 (dd, J_1 = 5.1 Hz, J_2 = 10.2 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.2 (CH_3), 16.8 (CH_2), 20.8 (CH_3), 21.6 (CH_3), 23.2 (CH_3), 23.9 (CH_2), 24.3 (CH_2), 32.2 (CH_3), 32.8 (C), 38.0 (C), 39.6 (CH_2), 44.6 (CH_2), 44.9 (CH), 46.6 (CH), 60.8 (C), 84.4 (CH), 169.9 (C), 212.5 (C) ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{18}H_{28}NaO_3$ 315.1936, found 315.1940.

Compound (±)-11. To a solution of (±)-**10** (1.54 g, 5.27 mmol) in Et_2O (16.0 mL) were added $BF_3{\cdot}OEt_2$ (1.0 mL, 7.90 mmol) and ethyl diazoacetate (0.8 mL, 7.90 mmol). The reaction was stirred in the dark at room temperature, under argon atmosphere for 24 h, and then quenched with an aqueous 2 N solution of HCl. The aqueous layer was extracted with Et_2O, the combined organic extracts were washed with water and brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography over silica gel with a mixture hexane/EtOAc 9:1 as eluent afforded (±)-**11** (pale yellow solid) (1.69 g, 85%): mp 107−109 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80 (s, 3H), 0.82 (s, 3H), 0.87 (s, 3H), 1.03 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.2−1.7 (m, 11H), 2.08 (s, 3H), 2.50 (m, 1H), 3.23 (t, J = 9.8 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.63 (dd, J_1 = 5.4 Hz, J_2 = 10.7 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.9 (CH_3), 13.9 (CH_3), 18.5 (CH_2), 21.4 (CH_3), 21.9 (CH_3), 24.5 ($2CH_2$), 26.7 (CH_3), 32.6 (CH_2), 32.7 (C), 33.1 (CH_3), 39.1 (CH_2), 40.9 (C), 50.1 (C), 52.1 (2CH), 54.3 (CH), 61.2 (CH_2), 84.2 (CH), 169.3 (C), 170.1 (C), 212.5 (C) ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{22}H_{34}NaO_5$ 401.2304, found 401.2302.

Compound (±)-12. A solution of (±)-**11** (1.69 g, 4.47 mmol) in DMSO (4.5 mL) and water (0.2 mL, 8.94 mmol) was stirred at 180 °C for 3 h. The reaction was then allowed to cool to room temperature and diluted with EtOAc, the mixture was washed with an aqueous 1 N solution of HCl and brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography over silica gel with a mixture of hexane/EtOAc 8:2 as eluent to afford (±)-**12** (white solid) (1.23 g, 90%): mp 101−105 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.78 (s, 3H), 0.82 (s, 3H), 0.86 (s, 3H), 0.97 (s, 3H), 1.0−2.5 (m, 14H), 2.06 (s, 3H), 4.63 (dd, J_1 = 4.4 Hz, J_2 = 11.2 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 10.3 (CH_3), 18.5 (CH_2), 19.3 (CH_2), 21.4 (CH_3), 21.9 (CH_3), 24.6 (CH_2), 27.9 (CH_3), 31.7 (CH_2), 32.7 (C), 33.0 (CH_3), 33.9 (CH_2), 39.2 (CH_2), 41.0 (C), 49.1 (C), 52.3 (CH), 55.9 (CH), 84.2 (CH), 170.1 (C), 220.8 (C) ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{19}H_{30}NaO_3$ 329.2093, found 329.2085.

Compound (±)-13. Triethylamine (0.5 mL, 3.4 mmol) and hydrazine monohydrate (1.2 mL, 24.2 mmol) were added to a solution of (±)-**12** (200 mg, 0.065 mmol) in EtOH (6.5 mL), and the mixture was refluxed for 30 h. After this time, the reaction was allowed to cool to room temperature and the solvent removed under reduced pressure. The residue was then dissolved in CH_2Cl_2, washed with water until neutral pH was reached and then with brine, and dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The residue was identified as the hydrazone (±)-**13** (pale yellow oil) (189 mg, 97%), and the product used in the next reaction without further purification: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.70 (s, 3H), 0.76 (s, 3H), 0.83 (s, 3H), 0.97 (s, 3H), 1.1−2.7 (m, 14H), 3.29 (dd, J_1 = 4.0 Hz, J_2 = 11.0 Hz, 1H) ppm.

Compound (±)-14. To a solution of the hydrazone (±)-**13** (189 mg, 0.61 mmol) in THF (4.2 mL) at room temperature were added Et_3N (0.9 mL, 6.38 mmol) and iodine (242 mg, 0.96 mmol) portionwise, and the reaction was stirred until gas evolution ceased. The reaction was then dissolved in Et_2O and quenched with water. The aqueous layer was extracted with Et_2O, the combined extracts washed with an aqueous 2 N solution of HCl, an aqueous 10% solution of $Na_2S_2O_3$, an aqueous saturated solution of $NaHCO_3$, and brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography over silica gel with a mixture hexane/Et_2O 98:2 as eluent afforded (±)-**14** (white solid) (257 mg, 100%): mp 103−104 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (s, 3H), 0.91 (s, 3H), 0.93 (s,

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3H), 1.01 (s, 3H), 1.1−1.7 (m, 9H), 1.86 (m, 1H), 2.02 (s, 3H), 2.35 (m, 1H), 2.45 (m, 1H), 4.58 (dd, J_1 = 4.4 Hz, J_2 = 11.5 Hz, 1H), 5.93 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.6 (CH_3), 17.9 (CH_2), 21.6 ($2CH_3$), 24.6 (CH_2), 29.6 (CH_3), 32.3 (CH_3), 32.5 (CH_2), 33.3 (C), 35.9 (CH_2), 39.7 (CH_2), 40.6 (C), 48.3 (CH), 51.2 (C), 54.8 (CH), 84.8 (CH), 111.0 (C), 136.7 (CH), 170.5 (C) ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{19}H_{29}O_2NaI$ 439.1103, found 439.1102.

Compound (±)-15. To a flask with vinyl iodide (±)-**14** (500 mg, 1.20 mmol), under argon atmosphere, were added anhydrous LiCl (153 mg, 3.10 mmol) and $Pd(PPh_3)_4$ (27.8 mg, 0.024 mmol), followed by a solution of 3-(tributylstannyl)furan[16] (645 mg, 1.80 mmol) in DMSO (10 mL). This mixture was heated for 24 h at 60 °C, cooled to room temperature, and diluted with Et_2O. The resulting solution was washed with an aqueous 5% solution of NH_3 and water until neutral pH was reached and with brine and dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. Purification of the residue by flash chromatography over silica gel with a mixture of hexane/EtOAc 8:2 as eluent afforded (±)-**15** (pale yellow solid) (389 mg, 91%): mp 95−97 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (s, 3H), 0.92 (s, 3H), 0.97 (s, 3H), 1.23 (s, 3H), 1.3−1.8 (m, 9H), 1.90 (m, 1H), 2.05 (s, 3H), 2.50 (m, 2H), 4.61 (dd, J_1 = 4.4 Hz, J_2 = 11.5 Hz, 1H), 5.64 (s, 1H), 6.54 (s, 1H), 7.34 (s, 1H), 7.38 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 11.7 (CH_3), 18.5 (CH_2), 21.6 (CH_3), 21.7 (CH_3), 24.7 (CH_2), 29.9 (CH_3), 31.3 (CH_2), 32.3 (CH_3), 33.2 (CH_2), 33.3 (C), 39.8 (CH_2), 40.8 (C), 48.1 (CH), 49.3 (C), 59.6 (CH), 85.0 (CH), 110.3 (CH), 120.9 (C), 125.5 (CH), 137.9 (CH), 142.3 (CH), 142.4 (C), 170.6 (C) ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{23}H_{32}O_3Na$ 379.2244, found 379.2256.

Compound (±)-17. A mixture of (±)-**15** (110 mg, 0.31 mmol) and $NaHCO_3$ (78 mg, 0.93 mmol) in CH_2Cl_2 (5.2 mL) under argon atmosphere was cooled to −40 °C, and *m*-CPBA (160 mg, 0.93 mmol) was added. After being stirred at that temperature for 6 h, the reaction was quenched with a 10% aqueous solution of $Na_2S_2O_3$. The mixture was then allowed to reach room temperature, the aqueous layer was extracted with CH_2Cl_2, the combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ and brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography over silica gel with a mixture of hexane/EtOAc 9:1 as eluent afforded the ketones (±)-**17a** (white solid) (43 mg, 37%) and (±)-**17b** (pale yellow oil) (31 mg, 27%).

*Data for isomer (±)-**17a**:* mp 171−173 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.76 (s, 3H), 0.89 (s, 3H), 0.93 (s, 3H), 1.06 (s, 3H), 1.1−2.0 (m, 10H), 2.06 (s, 3H), 2.61 (m, 2H), 3.49 (s, 1H), 4.63 (dd, J_1 = 4.8 Hz, J_2 = 10.8 Hz, 1H), 6.15 (s, 1H), 7.26 (s, 1H), 7.38 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.1 (CH_3), 17.6 (CH_2), 21.4 (CH_3), 21.9 (CH_3), 24.5 (CH_2), 28.2 (CH_3), 32.9 (CH_3, C), 35.8 (CH_2), 39.3 (CH_2), 40.1 (CH_2), 40.9 (C), 43.8 (C), 52.2 (CH), 53.3 (CH), 53.6 (CH), 85.1 (CH), 111.4 (CH), 118.1 (C), 141.4 (CH), 142.5 (CH), 170.6 (C), 218.8 (C) ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{23}H_{32}O_4Na$ 395.2193, found 395.2174.

*Data for isomer (±)-**17b**:* ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.86 (s, 3H), 0.93 (s, 3H), 0.95 (s, 3H), 1.34 (s, 3H), 1.2−1.7 (m, 9H), 2.04 (s, 3H), 2.13 (dd, J_1 = 4.7 Hz, J_2 = 11.7 Hz, 1H), 2.50 (dd, J_1 = 5.0 Hz, J_2 = 18.8 Hz, 1H), 2.61 (dd, J_1 = 11.9 Hz, J_2 = 18.8 Hz, 1H), 3.33 (s, 1H), 4.65 (dd, J_1 = 5.3 Hz, J_2 = 10.6 Hz, 1H), 6.23 (s, 1H), 7.30 (s, 1H), 7.39 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 12.2 (CH_3), 17.4 (CH_2), 21.5 (CH_3), 21.7 (CH_3), 24.6 (CH_2), 26.7 (CH_2), 30.9 (CH_3), 32.3 (CH_3), 33.2 (C), 39.3 (CH_2), 39.8 (CH_2), 41.1 (C), 42.1 (C), 45.5 (CH), 51.8 (CH), 57.7 (CH), 85.3 (CH), 111.5 (CH), 117.3 (C), 141.3 (CH), 142.4 (CH), 170.6 (C), 215.7 (C) ppm.

Epimerization of (±)-17b to (±)-17a. Triethylamine (1.2 mL, 8.70 mmol) was added to a solution of (±)-**17b** (115 mg, 0.31 mmol) in CH_3CN (24.0 mL), and the mixture was stirred at 45 °C for 90 min. It was the allowed to cool to room temperature, and the solvent removed under reduced pressure. The residue obtained was identified as (±)-**17b** (115 mg, 100%).

Compound (±)-18. Over a solution of (±)-**17a** (96 mg, 0.26 mmol) in CH_2Cl_2 (1.3 mL) under argon atmosphere was added triethylamine (0.18 mL, 1.29 mmol). The mixture was then cooled to −30 °C, and trimethylsilyl trifluoromethanesulfonate (0.18 mL, 1.29 mmol) was added. The reaction was stirred at this temperature for 14 h, quenched by addition of an aqueous 5% solution of $NaHCO_3$, and allowed to reach room temperature. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with water, an aqueous 5% solution of $NaHCO_3$, and brine and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure afforded an oil (108 mg) that was immediately diluted in CH_2Cl_2 (4.7 mL). Pyridine (79 μL, 0.98 mmol) was added, and the mixture was cooled to −78 °C. Then, a solution of PhSeCl (163 mg, 0.85 mmol) in CH_2Cl_2 (7.6 mL) was added dropwise. The mixture was stirred at the same temperature for 45 min and then quenched with a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Removal of the solvent under reduced pressure afforded 195 mg of a solid that were again diluted in of CH_2Cl_2 (8.8 mL) and cooled to −78 °C. A solution of *m*-CPBA (51 mg, 0.3 mmol) in CH_2Cl_2 (2.8 mL) was added dropwise, and the mixture was stirred at −78 °C for 3 h. It was then quenched by addition of an aqueous saturated solution of $Na_2S_2O_3$, and after being stirred for additional 30 min, the aqueous layer was extracted with Et_2O, the combined organic extracts were washed with water, a saturated aqueous solution of $NaHCO_3$, and brine and dried over anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography over silica gel with a mixture hexane/EtOAc 8:2 as eluent afforded (±)-**18** (white solid) (65 mg, 68%): mp 134−136 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.91 (s, 3H), 0.97 (s, 3H), 1.04 (s, 3H), 1.34 (s, 3H), 1.2−2.0 (m, 9H), 2.12 (s, 3H), 3.38 (s, 1H), 4.75 (dd, J_1 = 4.8 Hz, J_2 = 11.0 Hz, 1H), 6.06 (s, 1H), 6.24 (s, 1H), 7.42 (m, 2H) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz) δ 17.6 (CH_2), 20.2 (CH_3), 21.5 (CH_3), 21.9 (CH_3), 25.0 (CH_2), 27.8 (CH_3), 31.7 (CH_2), 32.9 (CH_3), 33.4 (C), 39.8 (CH_2), 43.7 (C), 44.2 (CH), 48.8 (C), 60.8 (CH), 78.7 (CH), 111.5 (CH), 118.8 (C), 127.2 (CH), 141.8 (CH), 142.9 (CH), 170.6 (C), 192.1 (C), 206.7 (C) ppm; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{23}H_{30}O_4Na$ 393.2036, found 393.2049.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all described compounds and X-ray data for (±)-**8c**, (±)-**12**, and (±)-**17a**. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data of compounds (±)-**8c**, (±)-**12**, and (±)-**17a** have been deposited with the Cambridge Crystallographic Data Centre with the following deposition numbers: CCDC 950577 for (±)-**12**, CCDC 950578 for (±)-**17a**, and CCDC 950579 for (±)-**8c**.

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Notes

The authors declare no competing financial interest.

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