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First total synthesis of tripdiolide

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ABSTRACT

The first total synthesis of tripdiolide **1** from the readily available abietic acid **3** in 22 steps is described and this synthesis furnishes a 5.8% overall yield of **1** with an average yield of 87%.

1. Introduction

Tripterygium wilfordii Hook. f. (TWHF), commonly known as Lei Gong Teng (Thunder God Vine), has been used in Traditional Chinese Medicine to treat autoimmune and inflammatory diseases, such as rheumatoid arthritis for centuries.[1–3] Tripdiolide **1** and Triptolide **2** (Fig. 1), the two major diterpene bioactive components responsible for the clinical properties of TWHF, were first isolated from TWHF extracts and characterized as a diterpenoid triepoxide lactone containing an 18 (4→3) abeo-abietane skeleton in 1972.[4] Tripdiolide **1** has also been reported to be effective in the treatment of leukaemia[4–6] and to have anti-cancer, anti-inflammatory, immunosuppressive and anti-fertility activities.[7–11] In addition, tripdiolide **1** had a wider therapeutic index[12] than most of the other diterpenoids in TWHF, e.g., triptolide **2**, whose 14-succinyl sodium salt (PG490-88),[13] a water-soluble prodrug converted to triptolide in serum, entered into phase I clinical trials in Europe for the treatment of solid tumors in 2003. All these properties mentioned above suggest that tripdiolide **1** should be a promising drug, however, tripdiolide unfortunately remains scarcely accessible from the natural source and the scarcity of this substance (0.0008% of dry root weight)[14] hampered further biological studies. Although synthesis of Triptolide has been reported,[15] there is no publication on the synthesis of Tripdiolide. Herein we described the first total synthesis of tripdiolide **1** by a route utilizing the readily available abietic acid **3** as the practical starting material. The results are reported in this paper.

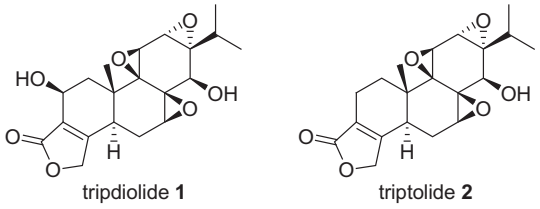

Fig. 1. Tripdiolide and triptolide.

2. Results and discussion

Structurally, tripdiolide **1** has α,β-unsaturated lactone ring, three epoxide adducts and C2-β-hydroxyl group and our own interest in **1** grew out of a desire to find an efficient route for its total synthesis, so we chose the very accessible abietic acid **3** as the starting material after analyzing the structure of **1** and **3**. Our retrosynthetic route for compound **1** is depicted in Scheme 1. The crucial steps include the introduction of C2-β-hydroxyl and α,β-unsaturated lactone ring and triepoxide construction from the 2β-hydroxyl triptophenolide methyl ether **4**.

Synthesis of 2β-hydroxyl triptophenolide methyl ether **4** started with known abietic acid **3**, which was converted to C4-(18)-alkenes **5** by the known procedure reported by us (Scheme 2).[16] Allylic oxidation of **5** with SeO_2/TBHP provided C-3 α alcohol **6**, which was oxidized readily under Swern conditions[17] to the enone **7** in 83% yield for the two steps. When compound **7** was treated with

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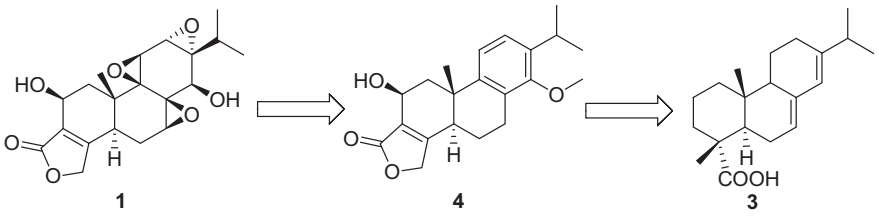
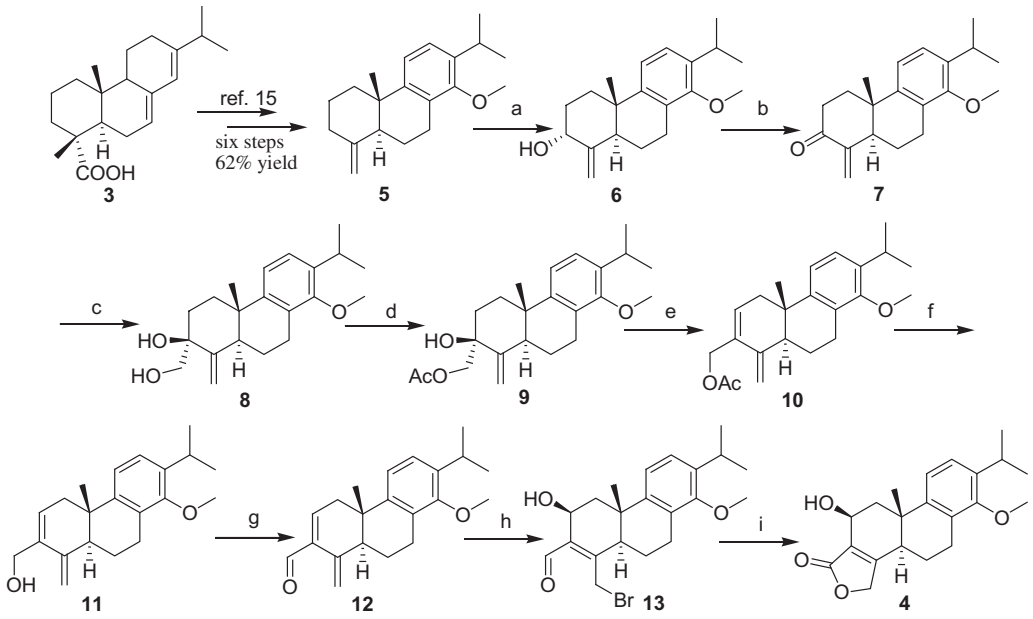


Scheme 1. Retrosynthetic analysis of Tripdiolide **1** from abietic acid **3**.



Scheme 2. Synthesis of 2β-hydroxyl triptophenolide methyl ether **4** from abietic acid **3**. Reagents and conditions: (a) SeO_2, *t*-BuO_2H, CH_2Cl_2, rt, overnight, 88%; (b) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C, 2 h, 94%; (c) (isopropoxy-dimethylsilyl) methyl chloride, Mg, THF, −30 °C, 55 min; then KF, $KHCO_3$, 30% H_2O_2, THF, MeOH, rt, overnight, 80% over 2 steps; (d) Ac_2O, Py, rt, 3 h, 98%; (e) $SOCl_2$, Py, rt, 8 h, 81%; (f) K_2CO_3, MeOH, H_2O, rt, 2 h, 98%; (g) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, rt, 3 h, 97%; (h) NBS, acetone, H_2O, rt, 4h, 73%; (i) $NaClO_2$, 2-Methyl-2-butene, NaH_2PO_4, *t*-BuOH, THF, H_2O, rt, 3 h, 85%.

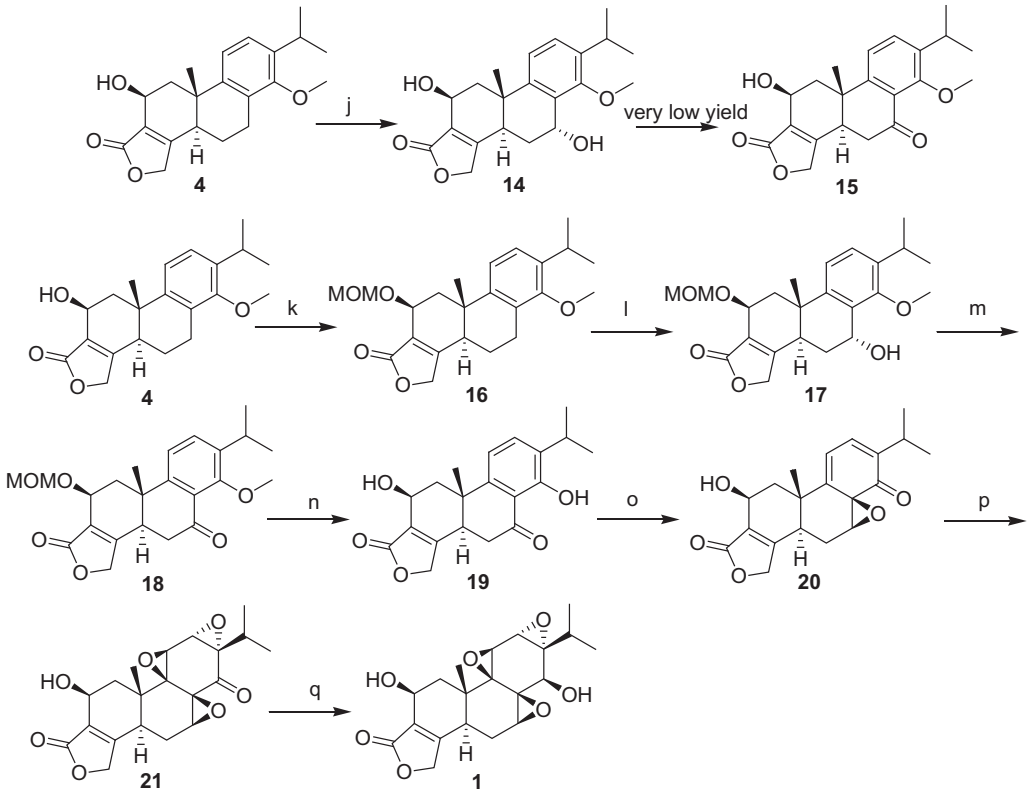
isopropoxy-dimethylsilylmethylmagnesium chloride[18] in THF at −30 °C, nucleophilic addition proceeded smoothly providing β-hydroxysilane intermediate, which without purification, was subjected to oxidative cleavage of the corresponding Si–C bond by potassium fluoride and 30% hydrogen peroxide to give 1,2-diol **8** as a single stereoisomer in 80% yield. Protection of primary hydroxyl group with acetic anhydride provided compound **9**, which was treated with $SOCl_2$ in pyridine, affording **10** in 79% yield for the two steps. The acetyl group can be removed simply from **10** by stirring with K_2CO_3 in MeOH and H_2O, providing compound **11** in 98% yield. Subsequent oxidation of **11** proceeded smoothly with Dess–Martin periodinane to afford diene aldehyde **12**, which without purification, upon oxidation of diene with NBS[19] in acetone and H_2O gave 1,4-product **13** in 71% yield for the two steps, along with a small trace of 2α-hydroxyl isomer (2β/2α=15:1). The results of reaction of diene aldehyde **12** with NBS in different solvents at different temperature are summarized in Table 1. We found that treatment of **12** with NBS in acetone and water (5:1) at room temperature afforded **13** in a higher yield (73%). When aldehyde **13** was oxidized with sodium chlorite,[20] lactonization of the resulting bromo acid occurred spontaneously to give the desired 2β-hydroxyl triptophenolide methyl ether **4** in 85% yield.

With the key intermediate **4** in hand, we switched to the construction of triepoxide. Treatment of **4** with ammonium ceric nitrate[21] in H_2O/CH_3CN provided the C-7α alcohol **14** in 81% yield (Scheme 3). However, we were disappointed to find that exposure of compound **14** to a variety of oxidizing agents[22] only afforded a small trace of desired ketone **15** and direct oxidation of **4** with some oxidizing agents, such as CrO_3/HOAc or sodium dichromate, also failed to give ketone **15**, which proved unstable to a variety of conditions, including silica gel chromatography. Considering that the instability of **15** may be related to the presence of 2β-hydroxyl group, exposure of the key intermediate **4** to MOMCl gave compound **16** in 92% yield. Treatment of **16** with ammonium ceric nitrate in H_2O/CH_3CN provided the alcohol **17** in 89% yield, which upon oxidation of hydroxyl with pyridinium dichromate delivered ketone **18** in 97% yield. As predicted, **18** was a stable intermediate and readily purified by silica gel chromatography. In addition, the MOM and methyl protecting group can be removed simultaneously under the BBr_3 deprotection condition, affording phenol **19** in 97% yield. With the important intermediate **19** in hand, the compound **19** was converted into tripdiolide **1** by a sequence similar to that developed previously for construction of the *C*-ring functionality.[15f]

Table 1
The reaction of diene aldehyde **12** with NBS in different solvents at different temperature

Substrate	Solvent	Temperature	Yield[a]
12	DMSO/H_2O=1:1	rt	37%
12	DMSO/H_2O=5:1	rt	42%
12	Acetone/H_2O=1:1	rt	59%
12	Acetone/H_2O=5:1	rt	73%
12	THF/H_2O=1:1	rt	47%
12	THF/H_2O=5:1	rt	56%
12	Acetone/H_2O=5:1	0 °C	57%
12	Acetone/H_2O=5:1	40 °C	50%

[a] Isolated yield of compound **13**.



Scheme 3. Synthesis of tripdiolide **1** from 2β-hydroxyl triptophenolide methyl ether **4**. Reagents and conditions: (j) $(NH_4)_2Ce(NO_3)_6$, CH_3CN/H_2O=1/1, rt, 3 h, 81%; (k) MOMCl, *N*,*N*-diisopropylethylamine, CH_2Cl_2, rt, overnight, 92%; (l) $(NH_4)_2Ce(NO_3)_6$, CH_3CN/H_2O=1/1, rt, 2 h, 89%; (m) PDC, CH_2Cl_2, rt, overnight, 97%; (n) BBr_3, CH_2Cl_2, −78 °C to rt, 97%; (o) $NaBH_4$, CH_3OH, 0 °C, 1 h; then $NaIO_4$, CH_3OH/H_2O=3/1, 0 °C, 1 h, 94%; (p) CF_3COCH_3, Oxone, $NaHCO_3$, CH_3CN/aqueous $Na_2(EDTA)$=1:1, 25 °C, 4 h; then H_2O_2, NaOH, MeOH, 25 °C, 2 h, 69%; (q) $Eu(fod)_3$, $NaBH_4$, CH_3OH, −78 °C, 1 h, 47%.

Treatment of **19** with $NaBH_4$ in MeOH gave C-7β alcohol, which without purification, upon oxidation with sodium periodate[23] provided C7,8-β-epoxy dienone **20** in 94% yield for the two steps. When methyl(trifluoromethyl)dioxirane generated in situ was used,[24] the second C9,11-β-epoxide was introduced as a single diastereomer. Further epoxidation with basic H_2O_2 provided 2β-hydroxyl triptonide **21** having triepoxides as the sole epoxidation product in 69% yield for the two steps. Finally, reduction of triptonide **21** with $NaBH_4$ in MeOH in the presence of $Eu(fod)_3$[15f] furnished tripdiolide **1** (47%) together with its C14-α-hydroxyl epimer (45%). The synthesized tripdiolide **1** and compound **21** showed the identical NMR spectra and optical rotation to the data reported in the literature.[25]

3. Conclusion

In summary, we have established an efficient route for the synthesis of tripdiolide **1** from readily accessible abietic acid **3**. Notably, this synthesis furnishes a 5.8% overall yield of **1** with an average yield of 87% and features an NBS-mediated oxidation of **12** followed by treatment with sodium chlorite to spontaneously install the α,β-unsaturated lactone ring and the C2 stereogenic hydroxyl group with excellent stereocontrol. More importantly, it will allow rapid access to various tripdiolide analogues designed to probe the cellular processes that tripdiolide interferes with.

4. Experimental section

4.1. General

Mass spectra and high-resolution mass spectra were measured on a Finnigan MAT-95 mass spectrometer. Melting points were determined on a Buchi 510 melting point apparatus and are uncorrected. IR spectra were recorded on a Nicollet Magna FT-IR-750 spectrometer using KBr pellets. Optical rotations were recorded on a Jasco-Dip-181 polarimeter. ^1H and ^{13}C NMR spectra were determined on Bruker AM-300, Bruker AM-400 instruments using tetramethylsilane as internal reference. Data are presented as follows: chemical shift, multiplicity (s=singlet, br s=broad singlet, d=doublet, br d=broad doublet, t=triplet, m=multiplet), *J*=coupling constant in hertz (Hz). The signals of the ^{13}C NMR were assigned utilizing DEPT experiments and on the basis of literature data. Silica gel 60H (200–300 mesh) manufactured by Qingdao Haiyang Chemical Group Co. (China) was used for general chromatography.

*4.1.1. (2R,4aS,10aR)-7-isopropyl-8-methoxy-4a-methyl-1-methylene-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-ol (**6**).* To a solution of compound **5** (13 g, 0.045 mol) in CH_2Cl_2 (500 mL) were added *t*-BuOOH (70 wt % in water, 19.1 mL, 0.135 mol) and SeO_2 (2.5 g, 0.022 mol). The mixture was stirred at room temperature overnight. $NaHSO_3$ (5 g) was added and the mixture was washed with brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (5% EtOAc in *n*-hexane) to give pure **6** (11.9 g, 88%) as a colourless solid, ^1H NMR ($CDCl_3$, 300 MHz) δ 7.07 (s, 2H), 5.08 (s, 1H), 4.76 (t, *J*=1.8 Hz, 1H), 4.36 (s, 1H), 3.73 (s, 3H), 3.30 (sept, *J*=3.0 Hz, 1H), 3.14–3.04 (m, 1H), 2.80–2.67 (m, 2H), 2.08–1.60 (m, 7H), 1.23 (d, *J*=3.0 Hz, 3H), 1.21 (d, *J*=2.4 Hz, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.8, 151.6, 145.7, 138.2, 128.4, 123.6, 121.3, 109.8, 72.7, 60.4, 41.1, 39.0, 32.4, 30.1, 26.0, 24.0, 23.9, 23.8, 21.8, 20.3; LRMS (EI, 70 eV) *m*/*z* (%) 300 (M^+, 10), 267 (100); HRMS (EI) calcd for $C_{20}H_{28}O_2$ (M^+): 300.2090, found 300.2086.

*4.1.2. (4aS,10aR)-7-isopropyl-8-methoxy-4a-methyl-1-methylene-3,4,4a,9,10,10a-hexahydrophenanthren-2(1H)-one (**7**).* To a solution

of DMSO (7.1 mL) in CH_2Cl_2 (200 mL) were added $(COCl)_2$ (4.9 mL) at −78 °C under nitrogen and the mixture was stirred at −78 °C for 30 min. To the resultant solution was added **6** (15 g, 0.05 mol) in CH_2Cl_2 (100 mL). The solution was stirred at −78 °C for 40 min and Et_3N (36 mL) was added dropwise. The solution was stirred for 30 min, warmed to room temperature, and water (20 mL) was added dropwise. The mixture was washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (2% EtOAc in *n*-hexane) to give pure **7** (14 g, 94%) as a colourless solid, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.11 (s, 2H), 5.98 (s, 1H), 5.23 (s, 1H), 3.74 (s, 3H), 3.31 (sept, J=3.9 Hz, 1H), 3.16 (dd, J=18.0, 4.2 Hz, 1H), 2.78–2.45 (m, 5H), 2.14–1.90 (m, 2H), 1.74–1.60 (m, 1H), 1.24 (d, J=3.9 Hz, 3H), 1.21 (d, J=3.9 Hz, 3H), 1.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.1, 154.8, 148.3, 144.0, 138.7, 128.4, 124.1, 121.7, 118.4, 60.5, 46.1, 37.2, 36.7, 36.1, 26.1, 24.0, 23.8, 23.8, 22.2, 20.3; LRMS (EI, 70 eV) *m*/*z* (%) 298 (M^+, 78), 241 (100); HRMS (EI) calcd for $C_{20}H_{26}O_2$ (M^+): 298.1932, found 298.1940.

*4.1.3. (2S,4aS,10aR)-2-(hydroxymethyl)-7-isopropyl-8-methoxy-4a-methyl-1-methylene-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-ol (**8**).* A solution of **7** (0.298 g, 1.0 mmol) in THF (6.0 mL) was added to the Grignard reagent [prepared from chloromethyldimethylisopropoxysilane (0.627 mL, 3.5 mmol), 1,2-dibromoethane (two drops), and Mg (0.096 g, 4.0 mmol) in THF (4.0 mL) according to the Tamao's procedure[18] under Ar atmosphere. After stirring at −30 °C for 55 min, the mixture was quenched with an aqueous NH_4Cl solution (10%) and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4, and concentrated to give a single adduct as colourless oil. To a stirred mixture of colourless crude adduct, MeOH (5.0 mL), THF (5.0 mL), $KHCO_3$ (0.150 g, 1.5 mmol), and KF (0.282 g, 3.0 mmol) was added H_2O_2 (30%, 0.5 mL, 5.0 mmol) at room temperature. The mixture was stirred at room temperature until starting material disappeared. An aqueous $Na_2S_2O_3$ solution (50%) was added slowly to the mixture and stirred until a negative starch/iodide test was observed. The mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified via column chromatography (10% EtOAc in *n*-hexane) to provide compound **8** (0.264 g, 80%) as a white solid, mp 158–160 °C; $[\alpha]_D^{25}$ +273 (*c* 0.15, CH_2Cl_2); IR (KBr) 3388, 2960, 2935, 2867, 1060, 1031 cm^{-1}, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.06 (m, 2H), 5.38 (s, 1H), 4.99 (s, 1H), 3.76–3.72 (m, 4H), 3.55 (d, J=11.1 Hz, 1H), 3.30 (sept, J=3.0 Hz, 1H), 3.15–3.06 (m, 1H), 2.78–2.64 (m, 1H), 2.46 (br s, 1H), 2.26–2.19 (m, 2H), 2.08–1.56 (m, 6H), 1.23 (d, J=2.7 Hz, 3H), 1.21 (d, J=3.0 Hz, 3H), 1.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.9, 151.1, 145.2, 138.5, 128.3, 123.9, 121.4, 108.6, 75.6, 66.8, 60.4, 44.5, 39.0, 35.6, 33.0, 26.0, 24.2, 23.8, 23.8, 22.3, 21.2; LRMS (EI, 70 eV) *m*/*z* (%) 330 (M^+, 15), 299 (100); HRMS (EI) calcd for $C_{21}H_{30}O_3$ (M^+): 330.2195, found 330.2187.

*4.1.4. ((2S,4aS,10aR)-2-hydroxy-7-isopropyl-8-methoxy-4a-methyl-1-methylene-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2-yl)methyl acetate (**9**).* To a solution of compound **8** (4.2 g, 0.013 mol) in pyridine (20 mL) was added Ac_2O (12 mL, 0.13 mol). The mixture was stirred at room temperature for 3 h and CH_2Cl_2 was added. The organic layer was washed with 5% HCl and brine, dried over Na_2SO_4, and concentrated to give a crude product, which was chromatographed on silica gel (3% EtOAc in *n*-hexane) to give pure **9** (4.7 g, 98%) as a colourless oil, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.05 (m, 2H), 5.36 (s, 1H), 4.93 (s, 1H), 4.34 (d, J=11.7 Hz, 1H), 4.15 (d, J=11.1 Hz, 1H), 3.73 (s, 3H), 3.30 (sept, J=3.6 Hz, 1H), 3.10 (dd, J=17.4, 5.7 Hz, 1H), 2.80–2.65 (m, 2H), 2.32–1.62 (m, 10H), 1.23 (d, J=3.6 Hz, 3H), 1.21 (d, J=3.6 Hz, 3H), 1.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 154.9, 150.4, 145.2, 138.5, 128.3, 123.8, 121.4, 108.5, 74.8, 68.4, 60.4, 44.5, 38.9, 35.6, 32.9, 26.0, 24.3, 23.9, 23.8, 22.2, 21.2, 20.7; LRMS (EI, 70 eV) *m*/*z* (%) 372 (M^+, 27), 299 (100); HRMS (EI) calcd for $C_{23}H_{32}O_4$ (M^+): 372.2300, found 372.2302.

*4.1.5. ((4aS,10aS)-7-isopropyl-8-methoxy-4a-methyl-1-methylene-1,4,4a,9,10,10a-hexahydrophenanthren-2-yl)methyl acetate (**10**).* To a solution of compound **9** (70 mg, 0.188 mmol) in pyridine (0.5 mL) was added $SOCl_2$ (0.034 mL, 0.47 mmol). The mixture was stirred at room temperature for 8 h and CH_2Cl_2 was added. The organic layer was washed with 5% $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated to give a crude product, which was chromatographed on silica gel (0.5% EtOAc in *n*-hexane) to give pure **10** (53.9 mg, 81%) as a colourless solid, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.11–7.02 (m, 2H), 5.95 (d, J=4.5 Hz, 1H), 5.12 (s, 1H), 5.03 (s, 1H), 4.88 (d, J=12.9 Hz, 1H), 4.69 (d, J=12.6 Hz, 1H), 3.73 (s, 3H), 3.31 (sept, J=6.0 Hz, 1H), 3.14 (dd, J=17.4, 5.1 Hz, 1H), 2.72–2.56 (m, 2H), 2.44–2.36 (m, 2H), 2.20–2.10 (m, 1H), 2.09 (s, 3H), 1.67–1.51 (m, 1H), 1.23 (d, J=6.3 Hz, 3H), 1.21 (d, J=6.0 Hz, 3H), 0.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 154.5, 144.8, 144.1, 138.3, 132.2, 129.2, 128.6, 124.0, 121.9, 107.7, 65.1, 60.5, 43.9, 41.0, 36.8, 26.1, 23.9, 23.9, 23.8, 23.1, 21.0, 20.1; LRMS (EI, 70 eV) *m*/*z* (%) 354 (M^+, 56), 279 (100); HRMS (EI) calcd for $C_{23}H_{30}O_3$ (M^+): 354.2195, found 354.2197.

*4.1.6. ((4aS,10aS)-7-isopropyl-8-methoxy-4a-methyl-1-methylene-1,4,4a,9,10,10a-hexahydrophenanthren-2-yl)methanol (**11**).* To a solution of compound **10** (354 mg, 1.0 mmol) in MeOH (20 mL) and water (5 mL) was added K_2CO_3 (552 mg, 4.0 mmol). The mixture was stirred at room temperature for 3 h and the solvent was evaporated, then AcOEt was added and the mixture was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (10% EtOAc in *n*-hexane) to give pure **11** (305 mg, 98%) as a colourless solid, mp 122–124 °C; $[\alpha]_D^{25}$ +246 (*c* 0.105, CH_2Cl_2); IR (KBr) 3421, 2962, 2935, 2869, 2836, 1648, 1608, 1033 cm^{-1}, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.10–7.03 (m, 2H), 5.90 (d, J=5.2 Hz, 1H), 5.20 (s, 1H), 5.03 (s, 1H), 4.46–4.26 (m, 2H), 3.73 (s, 3H), 3.30 (sept, J=6.8 Hz, 1H), 3.16–3.09 (m, 1H), 2.70–2.58 (m, 2H), 2.42–2.35 (m, 2H), 2.18–2.11 (m, 1H), 1.63–1.50 (m, 2H), 1.22 (d, J=6.8 Hz, 3H), 1.21 (d, J=6.8 Hz, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.5, 145.0, 144.4, 138.2, 136.5, 128.6, 126.3, 124.0, 121.9, 107.2, 63.9, 60.5, 44.1, 40.9, 36.9, 26.0, 24.0, 23.9, 23.8, 23.2, 20.1; LRMS (EI, 70 eV) *m*/*z* (%) 312 (M^+, 100); HRMS (EI) calcd for $C_{21}H_{28}O_2$(M^+): 312.2090, found 312.2093.

*4.1.7. (3S,4aS,10aR)-1-(bromomethyl)-3-hydroxy-7-isopropyl-8-methoxy-4a-methyl-3,4,4a,9,10,10a-hexahydrophenanthrene-2-carbaldehyde (**13**).* To a solution of compound **11** (330 mg, 1.06 mmol) in CH_2Cl_2 (20 mL) were added $NaHCO_3$ (266 mg, 3.18 mmol) and Dess–Martin periodinane (672 mg, 1.59 mmol). The mixture was stirred at room temperature for 3 h and water (20 mL) was added. The mixture was washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product **12**, which without purification, was dissolved in acetone (20 mL) and water (4 mL) and was added NBS (198 mg, 1.11 mmol). The mixture was stirred at room temperature for 4 h and the solvent was evaporated, then AcOEt was added and the mixture was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (10% EtOAc in *n*-hexane) to give pure **13** (305 mg, 71% over two steps) as a colourless solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.3 (s, 1H), 7.16–7.10 (m, 2H), 4.74 (d, J=6.4 Hz, 1H), 4.70 (d, J=10.8 Hz, 1H), 4.37 (d, J=10.8 Hz, 1H), 3.73 (s, 3H), 3.29 (sept, J=7.2 Hz, 1H), 3.26–3.13 (m, 2H), 2.89–2.79 (m, 1H), 2.67–2.59 (m, 2H), 2.42–2.36 (m, 1H), 1.92–1.80 (m, 2H), 1.41 (s, 3H), 1.21 (d, J=7.2 Hz, 3H), 1.19 (d, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.7, 155.3, 154.9, 144.2, 138.8, 137.1, 127.7, 124.2, 121.0, 63.1, 60.5, 45.0, 41.6, 35.1, 26.1, 24.2, 24.2, 24.2, 23.9, 23.8, 19.3; LRMS (EI, 70 eV) *m*/*z* (%)

406 (M^+, 30), 309 (100); HRMS (EI) calcd for $C_{21}H_{27}BrO_3$ (M^+): 406.1144, found 406.1153.

*4.1.8. 2β-Hydroxyl triptophenolide methyl ether (**4**).* To a solution of compound **13** (25 mg, 0.06 mmol) in THF (3 mL), *t*-BuOH (3 mL) and H_2O (1 mL) were added 2-methyl-2-butene (0.25 mL), $NaH_2PO_4.2H_2O$ (47 mg, 0.3 mmol) and $NaClO_2$ (27 mg, 0.3 mmol). The mixture was stirred at room temperature for 3 h and the solvent was evaporated, then AcOEt was added and the mixture was washed with brine. The organic layer was dried over Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (15% EtOAc in *n*-hexane) to give pure **4** (17.4 mg, 85%) as a colourless solid, mp 192–194 °C; $[\alpha]_D^{25}$ +30 (*c* 0.06, CH_2Cl_2); IR (KBr) 3477, 2962, 2931, 1749, 1675, 1033 cm^{-1}, ^1H NMR ($CDCl_3$, 300 MHz) δ 7.14 (m, 2H), 4.88 (m, 2H), 4.75 (d, *J*=7.5 Hz, 1H), 3.73 (s, 3H), 3.29 (sept, *J*=3.9 Hz, 1H), 3.14–2.85 (m, 2H), 2.75–2.60 (m, 2H), 2.04–1.90 (m, 3H), 1.24 (d, *J*=3.9 Hz, 3H), 1.21 (d, *J*=3.9 Hz, 3H), 1.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.7, 165.2, 155.3, 143.8, 139.1, 127.5, 126.6, 124.3, 120.7, 70.6, 60.5, 60.3, 41.9, 41.5, 36.0, 26.1, 24.0, 23.9, 23.7, 22.9, 19.5; LRMS (EI, 70 eV) *m*/*z* (%) 342 (M^+, 100); HRMS (EI) calcd for $C_{21}H_{26}O_4$ (M^+): 342.1831, found 342.1829.

*4.1.9. (3bR,5R,9bS,11S)-5,11-dihydroxy-7-isopropyl-6-methoxy-9b-methyl-3b,4,5,9b,10,11-hexahydrophenanthro[2,1-c]furan-1(3H)-one (**14**).* To a solution of **4** (100 mg, 0.292 mmol) in acetonitrile (4 mL) and water (4 mL), was added ammonium ceric nitrate (320 mg, 0.585 mmol) and the mixture was stirred at room temperature for 3 h. The solvent was evaporated, then CH_2Cl_2 was added and the mixture was washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (20% EtOAc in *n*-hexane) to give pure **14** (84.6 mg, 81%) as a colourless solid, ^1H NMR ($CDCl_3$, 300 MHz) δ 7.27–7.17 (m, 2H), 5.10–5.08 (m, 1H), 5.00–4.81 (m, 2H), 4.76 (d, *J*=4.5 Hz, 1H), 3.88 (s, 3H), 3.28 (sept, *J*=5.1 Hz, 1H), 3.12 (br s, 1H), 3.05 (d, *J*=8.7 Hz, 1H), 2.69 (d, *J*=11.1 Hz, 1H), 2.18–1.91 (m, 3H), 1.30 (d, *J*=5.1 Hz, 3H), 1.18 (d, *J*=5.1 Hz, 3H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.6, 165.3, 156.1, 143.6, 139.8, 129.7, 127.1, 126.9, 121.3, 70.7, 62.7, 62.2, 60.3, 41.7, 36.9, 36.2, 27.9, 26.1, 24.3, 23.6, 23.3; LRMS (EI, 70 eV) *m*/*z* (%) 358 (M^+, 100); HRMS (EI) calcd for $C_{21}H_{26}O_5$ (M^+): 358.1780, found 358.1780.

*4.1.10. (3bR,9bS,11S)-7-isopropyl-6-methoxy-11-(methoxymethoxy)-9b-methyl-3b,4,5,9b,10,11-hexahydrophenanthro[2,1-c]furan-1(3H)-one (**16**).* To a solution of compound **4** (26 mg, 0.076 mmol) in CH_2Cl_2 (3 mL) were added MOMCl (0.029 mL, 0.38 mol) and *N*,*N*-Diisopropylethylamine (0.066 mL, 0.38 mmol). The mixture was stirred at room temperature overnight and water (3 mL) was added. The mixture was washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (7% EtOAc in *n*-hexane) to give pure **16** (26.9 mg, 92%) as a colourless solid, mp 90–92 °C; $[\alpha]_D^{25}$ +35 (*c* 0.1, CH_2Cl_2); IR (KBr) 3446, 2962, 2935, 2887, 1753, 1675, 1027 cm^{-1}, ^1H NMR ($CDCl_3$, 400 MHz) δ 7.12 (s, 2H), 5.01 (d, *J*=7.2 Hz, 1H), 4.84 (m, 3H), 4.59 (m, 1H), 3.73 (s, 3H), 3.54 (s, 3H), 3.29 (sept, *J*=4.8 Hz, 1H), 3.10–2.89 (m, 2H), 2.78 (d, *J*=14.4 Hz, 1H), 2.60 (m, 1H), 2.00–1.82 (m, 3H), 1.23 (d, *J*=4.8 Hz, 3H), 1.22 (d, *J*=4.8 Hz, 3H), 1.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8, 166.0, 155.4, 144.0, 139.2, 127.5, 125.5, 124.2, 120.2, 96.4, 70.1, 65.2, 60.5, 55.8, 41.6, 40.2, 35.7, 26.1, 23.9, 23.9, 23.8, 22.7, 19.5; LRMS (EI, 70 eV) *m*/*z* (%) 386 (M^+, 56), 326 (100); HRMS (EI) calcd for $C_{23}H_{30}O_5$ (M^+): 386.2093, found 386.2107.

*4.1.11. (3bR,5R,9bS,11S)-5-hydroxy-7-isopropyl-6-methoxy-11-(methoxymethoxy)-9b-methyl-3b,4,5,9b,10,11-hexahydrophenanthro[2,1-c]furan-1(3H)-one (**17**).* To a solution of **16** (113 mg, 0.292 mmol) in acetonitrile (4 mL) and water (4 mL), was added ammonium ceric nitrate (320 mg, 0.585 mmol) and the mixture was stirred at room temperature for 5 h. The solvent was evaporated, then CH_2Cl_2 was added and the mixture was washed with water and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (20% EtOAc in *n*-hexane) to give pure **17** (104.4 mg, 89%) as a colourless solid, ^1H NMR ($CDCl_3$, 300 MHz) δ 7.26–7.15 (m, 2H), 5.09 (d, *J*=4.2 Hz, 1H), 5.01 (d, *J*=6.9 Hz, 1H), 4.84 (m, 3H), 4.60 (d, *J*=4.8 Hz, 1H), 3.88 (s, 3H), 3.53 (s, 3H), 3.28 (sept, *J*=7.2 Hz, 1H), 3.10 (br s, 1H), 3.02 (d, *J*=12.9 Hz, 1H), 2.75 (d, *J*=14.4 Hz, 1H), 2.20–2.03 (m, 2H), 1.85 (dd, *J*=14.4, 5.4 Hz, 1H), 1.30 (d, *J*=7.2 Hz, 3H), 1.18 (d, *J*=7.2 Hz, 3H), 1.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.7, 166.1, 156.2, 143.7, 139.8, 129.8, 126.9, 125.9, 120.9, 96.5, 70.2, 65.3, 62.7, 62.2, 55.9, 40.3, 37.1, 36.0, 28.0, 26.1, 24.3, 23.7, 23.3; LRMS (EI, 70 eV) *m*/*z* (%) 402 (M^+, 44), 309 (100); HRMS (EI) calcd for $C_{23}H_{30}O_6$ (M^+): 402.2042, found 402.2028.

*4.1.12. (3bR,9bS,11S)-7-isopropyl-6-methoxy-11-(methoxymethoxy)-9b-methyl-3b,4,10,11-tetrahydrophenanthro[2,1-c]furan-1,5(3H,9bH)-dione (**18**).* To a solution of compound **17** (38 mg, 0.094 mmol) in anhydrous CH_2Cl_2 (3 mL) were added pyridinium dichromate (70.6 mg, 0.188 mol) and molecular sieves 4 A (120 mg). The mixture was stirred at room temperature overnight, diluted with ethyl acetate, and filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure to give a crude product, which was chromatographed on silica gel (15% EtOAc in *n*-hexane) to give pure **18** (36.5 mg, 97%) as a colourless solid, mp 106–108 °C, ^1H NMR ($CDCl_3$, 400 MHz) δ 7.47 (d, *J*=8.4 Hz, 1H), 7.19 (d, *J*=8.4 Hz, 1H), 5.01 (d, *J*=6.8 Hz, 1H), 4.83–4.81 (m, 3H), 4.65 (d, *J*=5.6 Hz, 1H), 3.82 (s, 3H), 3.52 (s, 3H), 3.41 (sept, *J*=7.2 Hz, 1H), 3.08 (dd, *J*=14.0, 7.2 Hz, 1H), 2.80 (m, 3H), 1.97 (dd, *J*=14.4, 5.2 Hz, 1H), 1.29 (s, 3H), 1.25 (d, *J*=7.2 Hz, 3H), 1.19 (d, *J*=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.5, 172.1, 163.2, 158.4, 150.8, 142.1, 132.0, 126.2, 124.4, 118.7, 96.5, 69.7, 64.4, 62.6, 55.9, 40.1, 39.2, 37.3, 36.1, 25.8, 23.7, 23.1, 23.1; LRMS (EI, 70 eV) *m*/*z* (%) 400 (M^+, 37), 385 (100); HRMS (EI) calcd for $C_{23}H_{28}O_6$ (M^+): 400.1886, found 400.1871.

*4.1.13. (3bR,9bS,11S)-6,11-dihydroxy-7-isopropyl-9b-methyl-3b,4,10,11-tetrahydrophenanthro[2,1-c]furan-1,5(3H,9bH)-dione (**19**).* To a solution of **18** (25 mg, 0.062 mmol) in dichloromethane (2 mL), under nitrogen at −78 °C, was added BBr_3 (0.018 mL, 0.186 mol) and the mixture was stirred at −78 °C for 1 h and warmed to room temperature. An aqueous $NaHCO_3$ solution (10%) was added and the extracts were washed with brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (20% EtOAc in *n*-hexane) to give pure **19** (20.7 mg, 97%) as a white solid, ^1H NMR ($CDCl_3$, 300 MHz) δ 13.04 (s, 1H), 7.44 (d, *J*=8.1 Hz, 1H), 6.90 (d, *J*=8.1 Hz, 1H), 4.89–4.78 (m, 3H), 3.36 (sept, *J*=6.6 Hz, 1H), 3.17–3.10 (m, 1H), 2.89–2.73 (m, 3H), 2.62–2.60 (m, 1H), 2.06 (dd, *J*=14.4, 6.3 Hz, 1H), 1.31 (s, 3H), 1.25 (d, *J*=6.6 Hz, 3H), 1.23 (d, *J*=6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.8, 172.9, 162.0, 161.7, 149.1, 135.9, 133.9, 127.5, 114.2, 113.9, 70.1, 59.5, 40.7, 40.6, 36.0, 36.0, 26.1, 23.2, 22.1, 22.0; LRMS (EI, 70 eV) *m*/*z* (%) 342 (M^+, 40), 327 (100); HRMS (EI) calcd for $C_{20}H_{22}O_5$ (M^+): 342.1467, found 342.1467.

*4.1.14. 7,8-β-Epoxy-2β,19-dihydroxy-14-oxo-18 (4→3)abeo-abieta-3,9,12-trien-18-oic acid lactone (**20**).* To a solution of **19** (30 mg, 0.088 mmol) in methanol (2 mL) at 0 °C was added sodium borohydride (3.3 mg, 0.088 mmol) in three portions. After stirring at 0 °C for 30 min, the mixture was quenched with an aqueous NH_4Cl solution (10%) and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4, and concentrated to give a crude product. The crude product was dissolved in MeOH (3 mL) and a solution of $NaIO_4$ (19.8 mg, 0.092 mmol) in water (1 mL) was added at 0 °C. After stirring at 0 °C for 50 min, the mixture was

extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4, and concentrated to give a crude product, which was chromatographed on silica gel (50% EtOAc in *n*-hexane) to give pure **20** (20.7 mg, 97%) as a yellow solid, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.97 (d, J=6.6 Hz, 1H), 6.44 (d, J=6.6 Hz, 1H), 4.79 (s, 2H), 4.70 (d, J=6.0 Hz, 1H), 4.12 (d, J=5.1 Hz, 1H), 2.92 (sept, J=6.9 Hz, 1H), 2.53 (dd, J=11.7, 6.0 Hz, 1H), 2.40 (d, J=14.4 Hz, 1H), 2.29 (m, 1H), 2.22 (d, J=13.5 Hz, 1H), 1.90 (dd, J=14.4, 5.7 Hz, 1H), 1.32 (s, 3H), 1.09 (d, J=6.9 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.0, 172.9, 162.5, 149.8, 142.1, 135.0, 126.8, 121.4, 70.1, 66.2, 59.4, 56.8, 43.5, 41.4, 38.0, 26.1, 23.7, 21.6, 21.3, 18.7; LRMS (EI, 70 eV) m/z (%) 342 (M^+, 38), 327 (100); HRMS (EI) calcd for $C_{20}H_{22}O_5$ (M^+): 342.1467, found 342.1469.

*4.1.15. 2β-Hydroxyl triptonide (**21**).* To a solution of compound **20** (218 mg, 0.64 mmol) in acetonitrile (6 mL) was added an aqueous Na_2(EDTA) solution (4×10^{-4} M, 6 mL). The resulting homogeneous solution was cooled to 0 °C, followed by addition of 1,1,1-trifluoroacetone (0.3 mL) via a precooled syringe. To this homogeneous solution was added in portions a mixture of sodium bicarbonate (0.13 g, 1.55 mmol) and Oxone (0.308 g, 1.0 mmol) in a period of 1 h (pH 7–7.5). The reaction was monitored by TLC. The mixture was poured into water and extracted with dichloromethane. The extracts were dried (Na_2SO_4), filtered, and concentrated to give a crude product, which was dissolved in MeOH (10 mL) and was added H_2O_2 (30%, 0.5 mL, 5.0 mmol) at room temperature. After stirring for 1 h, the mixture was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4, and concentrated to give a crude product, which was chromatographed on silica gel (50% EtOAc in *n*-hexane) to give pure **21** (164 mg, 69%) as a white solid, mp 234–236 °C; $[\alpha]_D^{25}$ −30 (*c* 0.05, $CHCl_3$); IR (KBr) 3270, 2932, 1757, 1731, 1143 cm^{-1}, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.78 (s, 2H), 4.63 (m, 1H), 4.07 (d, J=2.7 Hz, 1H), 3.83 (d, J=2.7 Hz, 1H), 3.42 (d, J=5.1 Hz, 1H), 2.76 (dd, J=12.9, 5.1 Hz, 1H), 2.39 (sept, J=6.9 Hz, 1H), 2.26 (m, 1H), 2.12 (d, J=13.2 Hz, 1H), 1.89 (d, J=13.8 Hz, 1H), 1.54 (dd, J=13.5, 5.7 Hz, 1H), 1.26 (s, 3H), 0.97 (d, J=6.9 Hz, 3H), 0.88 (d, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.7, 172.6, 161.5, 127.0, 70.0, 66.5, 65.1, 60.9, 60.2, 59.2, 58.8, 56.6, 40.9, 38.9, 35.4, 25.8, 22.8, 18.0, 16.2, 15.4; LRMS (EI, 70 eV) m/z (%) 374 (M^+, 2), 113 (100); HRMS (EI) calcd for $C_{20}H_{22}O_7$ (M^+): 374.1366, found 374.1341.

*4.1.16. Preparation of tripdiolide (**1**).* To a solution of **21** (3.74 mg, 0.01 mmol) and Eu(FOD)$_3$ (10 mg, 0.01 mmol) in MeOH (0.4 mL) at −78 °C was added $NaBH_4$ (0.38 mg, 0.01 mmol) in MeOH (0.4 mL). After stirring for 1 h, the mixture was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4, and concentrated to give a crude product, which was chromatographed on silica gel (50% EtOAc in *n*-hexane) to give pure **1** (1.76 mg, 47%) as a white solid, mp 220–222 °C; $[\alpha]_D^{25}$ −110.2 (*c* 0.170, MeOH); IR (KBr) 3580, 3530, 2911, 1759, 1680, 1449, 1415, 1350, 1230, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.74 (s, 2H), 4.58 (d, J=5.6 Hz, 1H), 3.90 (d, J=3.2 Hz, 1H), 3.49 (d, J=3.2 Hz, 1H), 3.38 (br s, 1H), 3.34 (d, J=5.3 Hz, 1H), 2.74 (br s, 1H), 2.62 (m, 1H), 2.20 (m, 2H), 2.05 (dd, J=14.7, 13.1 Hz, 1H), 1.83 (br d, J=13.8 Hz, 1H), 1.41 (dd, J=13.8, 5.6 Hz, 1H), 1.29 (s, 3H), 0.98 (dd, J=6.9 Hz, 3H), 0.85 (dd, J=6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.7, 162.0, 126.9, 73.4, 70.1, 66.3, 65.7, 60.8, 60.0, 59.3, 57.4, 54.5, 40.8, 38.1, 35.9, 28.2, 23.3, 17.7, 16.8, 15.3; LRMS (EI, 70 eV) m/z (%) 376 (M^+, 0.5); HRMS (EI) calcd for $C_{20}H_{24}O_7$ (M^+): 376.1522, found 376.1523.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.12.014.

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