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Efficient synthesis of the key intermediate triptophenolide methyl ether for the synthesis of (−)-triptolide

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ABSTRACT

An efficient synthesis of triptophenolide methyl ether **4** from the readily available abietic acid **3** in nine steps is described and successfully applied to the synthesis of (−)-triptolide **1**. The route is of characteristic of low cost, high yield and easy operation. In addition, every reaction in this route has been successfully scaled-up to a 100 g substrate level without loss of yield.

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] (−)-Triptolide **1** and (−)-triptonide **2** (Fig. 1), the major 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] Right after its isolation, (−)-triptolide **1** and (−)-triptonide **2** were shown to possess potent antitumour, antiinflammatory, immunosuppressive and antifertile activities.[5–12] Because (−)-triptolide and (−)-triptonide remain scarcely accessible from the natural source, a great deal of effort[13–19] were made on the total synthesis of triptolide, its related compounds and the key intermediate triptophenolide methyl ether **4**,[20] which is also a natural product isolated from TWHF, among which Van Tamelen and co-workers[14] accomplished the total synthesis of triptophenolide methyl ether **4** and (−)-triptolide **1** from the resin acid L-dehydroabietic acid in 0.98% and 0.014% yield, respectively. We recently completed the total synthesis of triptophenolide methyl ether **4** and (−)-triptolide **1** by a route utilizing the readily available abietic acid **3** as the practical starting material. In addition, the pathway described herein requires only nine steps

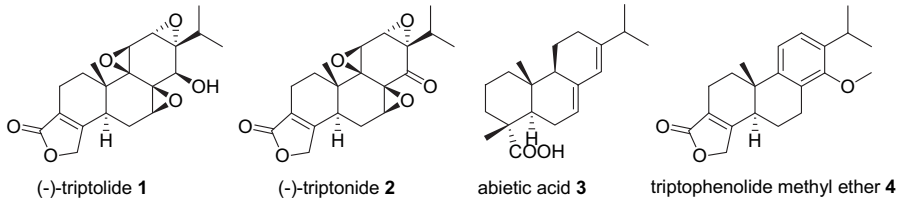

Figure 1. (−)-Triptolide, (−)-triptonide, abietic acid and triptophenolide methyl ether.

to provide the key intermediate triptophenolide methyl ether **4** in 43.9% yield and the total yield of (−)-triptonide **2** by this approach was about 21% from abietic acid. The results are reported in this paper.

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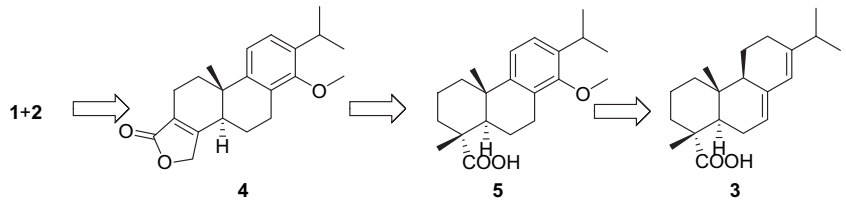
2. Results and discussion

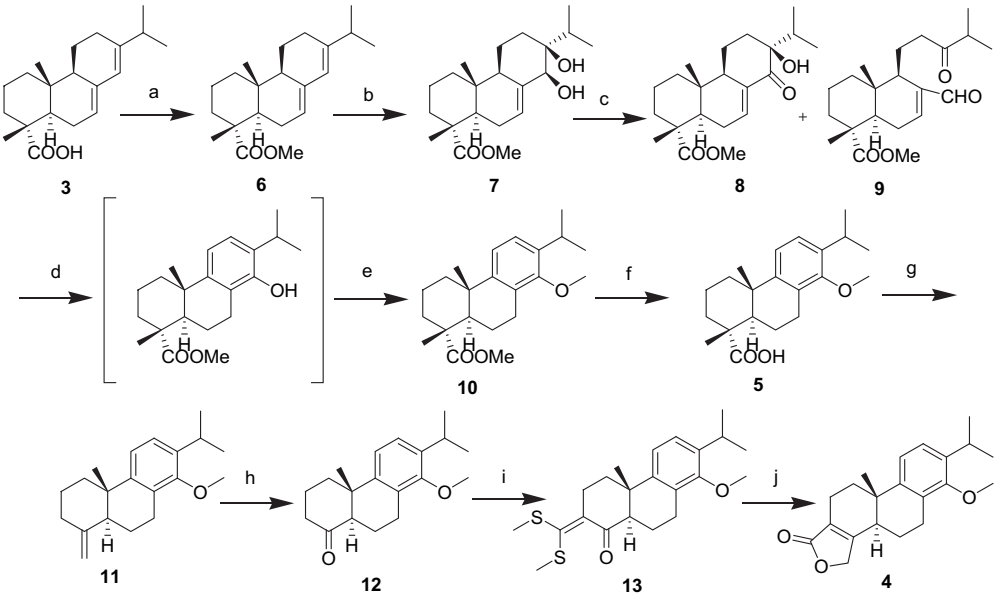
Our own interest in **1** grew out of a desire to find an efficient route for its total synthesis, so we chose the very accessible abietic acid **3** as the starting material after analyzing the structure of **1** and **3**. Our retrosynthetic route for compound **1** is depicted in Scheme 1. The crucial steps include triepoxide construction from the triptophenolide methyl ether **4**, lactone formation from 14-methoxydehydroabietic acid **5** and construction of 14-methoxydehydroabietic acid from abietic acid.



Scheme 1. Retrosynthetic analysis of (−)-triptolide **1** and (−)-triptonide **2** from abietic acid **3**.

Our synthetic efforts began with the esterification of carboxylic acid **3** to provide the corresponding methyl ester **6** in quantitative yield (Scheme 2). A survey of various protocols, including Matteson's procedure, revealed that a modification of Sharpless' original procedure[21] using potassium osmate, pyridine and NMO (*N*-methylmorpholine-*N*-oxide) in aqueous acetone afforded 13,14-diol **7** in 85% yield by regioselective dihydroxylation of methyl ester **6**. As little as 0.002 equiv of potassium osmate could be used without loss of efficiency and inexpensive aqueous NMO (60%) was found to be as effective as the anhydrous solid NMO typically used in this reaction.

Reactions of the acid **5** with oxalyl chloride gave acid chloride, which was converted into the corresponding pyridyl sulfide by treatment with the sodium salt of *N*-hydroxypyridine-2-thione in refluxing toluene. Subsequent oxidation of the pyridyl sulfide with *m*-chloroperbenzoic acid in dichloromethane at −78 °C or oxone in methanol and water at −40 °C gave sulfoxide, which underwent elimination at 80 °C to afford the corresponding C4-(18)-alkenes **11** in 84% yield for the three steps and the conversion from **5** to **11** was performed without purification of intermediates. Removal of the methylene in **11** by ozonolysis afforded the ketone **12** in 96% yield. The compound **12** was subjected to reaction with carbon disulfide in the presence of 2.3 equiv of lithium 4-methyl-2,6-di-*tert*-butylphenoxide followed by addition of methyl iodide, affording the ketene dithioacetal **13** in 97.5% yield. Treatment of **13** with the dimethylsulfonium methylide converted the ketone function to an



Scheme 2. Synthesis of triptophenolide methyl ether **4** from abietic acid **3** via 14-methoxydehydroabietic acid **5**. Reagents and conditions: (a) Me_2SO_4, K_2CO_3, acetone, rt, 3 h, 100%; (b) $K_2OsO_4\cdot(H_2O)_2$, NMO, pyridine, acetone/water=5:1, reflux, 7 days, 85%; (c) DMSO, $SO_3\cdot$Py, Et_3N, CH_2Cl_2, rt, 5 h, 96%, (**8**:**9**=99:1); (d) TsOH, toluene, reflux, 8 h; (e) Me_2SO_4, K_2CO_3, acetone, reflux, overnight, 91% over two steps; (f) KOH, ethylene glycol, 130 °C, 10 h, 100%; (g) (1) $(COCl)_2$, DMF, THF; (2) sodium salt of *N*-hydroxypyridine-2-thione, DMAP, toluene, reflux, 3 h; (3) *m*-CPBA, CH_2Cl_2, −78 °C, 2 h; then benzene, reflux, 1–2 h, 84% for three steps; (h) O_3, CH_3OH/CH_2Cl_2=1:1, rt, 5 h, 96%; (i) CS_2, lithium 4-methyl-2,6-di-*tert*-butylphenoxide, THF, rt, 15 h; then CH_3I, rt, 2 h, 97.5%; (j) $(CH_3)_3SI$, *n*-BuLi, THF, −60 °C, 30 min; then hydrochloric acid/methanol, rt, 24 h, 76%.

With a reliable procedure for the synthesis of 13,14-diol **7**, we turned our attention to the synthesis of hydroxyl ketone **8**, resulting from the oxidation of 13,14-diol **7**. Among the oxidizing agents we screened,[22] DMSO activated by pyridine−SO_3 complex[23] was found to be the best for this transformation and the desired compound **8** was obtained in 95% yield while the main product keto aldehyde **9** was obtained in good yield under other oxidizing conditions. Treatment of ketone **8** with TsOH in refluxing toluene resulted in phenol, which without purification, upon protection of hydroxyl with dimethyl sulfate afforded methoxy ester **10** in 91% yield for the two steps. Subsequent hydrolysis of methyl ester furnished the desired 14-methoxydehydroabietic acid **5** in quantitative yield.

epoxide, which without isolation, was treated with hydrochloric acid/methanol to provide the crucial intermediate triptophenolide methyl ether **4**.[15,24] The results of Corey–Chaykovsky epoxidation reaction of ketene dithioacetal **13** with trimethylsulfonium iodide in the presence of different alkali followed by acid hydrolysis in different acid condition are summarized in Table 1. We found that

Table 1
The Corey–Chaykovsky epoxidation reaction of **13** followed by acid hydrolysis in different acid condition

Substrate	Alkali	Temperature	Concentration[a] (M/L)	Yield[b] (%)
13	KOH	60 °C	1	35
13	KOH	60 °C	5	21
13	KOH	60 °C	0.5	24
13	NaH	0 °C to rt	1	64
13	NaH	0 °C to rt	5	47
13	NaH	0 °C to rt	0.5	49
13	^{t}BuOK	rt to 50 °C	1	34
13	^{t}BuOK	rt to 50 °C	5	28
13	^{t}BuOK	rt to 50 °C	0.5	33
13	*n*-BuLi	−60 °C	1	76
13	*n*-BuLi	−60 °C	5	47
13	*n*-BuLi	−60 °C	0.5	65

[a] Concentration of HCl.
[b] Isolated yield.

reaction of compound **13** with trimethylsulfonium iodide in the presence of *n*-BuLi in THF at −60 °C followed by direct acid hydrolysis in 1 M/L hydrochloric acid/methanol afforded triptophenolide methyl ether **4** in a higher yield (76%). All the intermediate compounds including triptophenolide methyl ether were fully characterized by ^{1}H NMR, ^{13}C NMR and mass spectral data. Comparison of our physical and spectroscopic data with the published data[17] confirmed our successful synthesis of triptophenolide methyl ether ($[\alpha]_D^{25}$ +42.1 (*c* 0.30, CH_2Cl_2); lit.[17] $[\alpha]_D^{25}$ +40.3 (*c* 0.37, CH_2Cl_2)).

With the important compound **4** in hand, the compound **4** was converted into (−)-triptolide **1** by a sequence similar to that developed previously for construction of the C-ring functionality (Scheme 3).[13–17] Considering that ketone **15** was obtained by CrO_3/AcOH oxidation of triptophenolide methyl ether **4** in poor yield (20–40%),[13–17] treatment of **4** with ammonium ceric nitrate[25] in H_2O/CH_3CN provided the C-7α alcohol **14**, which upon oxidation of hydroxyl with Collins reagent afforded ketone **15** in 76% yield for the two steps. With the compound **15** in hand, we accomplished the remaining steps towards (−)-triptolide and (−)-triptonide by following Yang's procedure for the synthesis of (−)-triptolide.[17] The synthesized (−)-triptonide **2** and (−)-triptolide **1** showed the identical NMR spectra and optical rotation to the data reported in the literature.[4]

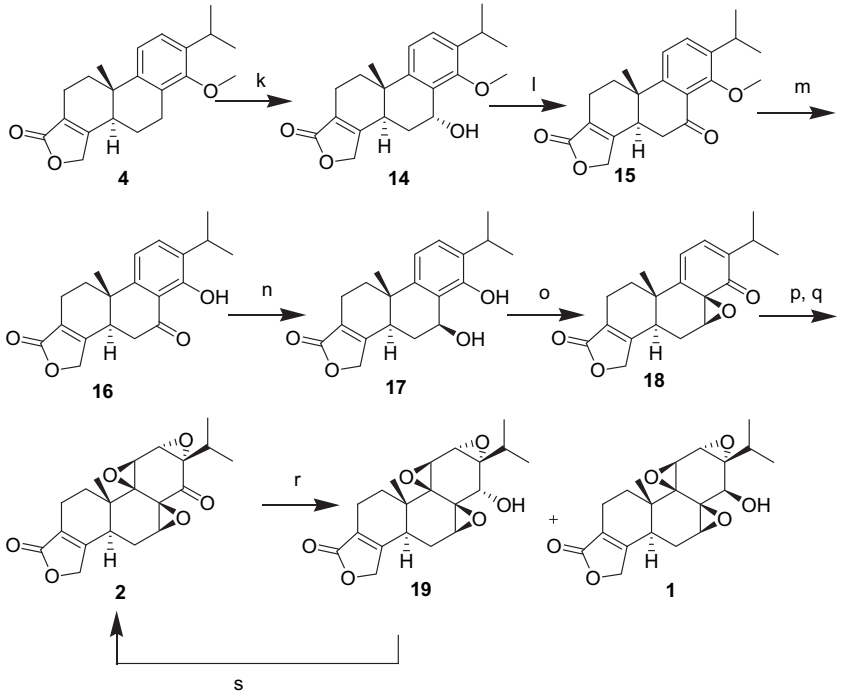
3. Conclusion

In summary, we have established an efficient route for the synthesis of (−)-triptolide **1** with high yield, low cost and easy operation. In nine steps, this synthesis afforded the key compound **4** in 43.9% overall yield from the readily accessible known starting material **3** and no any expensive reagent was used. In addition, all reactions of this route have been successfully scaled-up to a 100 g substrate level without loss of yield and this synthesis of **4** necessitates the purification of only four intermediates. More importantly, it will allow rapid access to various triptolide analogues designed to probe the cellular processes that triptolide 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. Optical rotations were recorded on a Jasco-Dip-181 polarimeter. ^{1}H 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.



Scheme 3. Synthesis of (−)-triptolide **1** and (−)-triptonide **2** from triptophenolide methyl ether **4**. Reagents and conditions: (k) $(NH_4)_2Ce(NO_3)_6$, CH_3CN/H_2O=1:1, rt, 2 h; (l) Collins reagent, CH_2Cl_2, rt, 3 h, 76% over two steps; (m) BBr_3, CH_2Cl_2, −78 °C to rt, 99%; (n) $NaBH_4$, CH_3OH, 0 °C, 1 h, 98%; (o) $NaIO_4$, CH_3OH/H_2O=3:1, 0–25 °C, 1 h, 96%; (p) CF_3COCH_3, oxone, $NaHCO_3$, CH_3CN/aq Na_2(EDTA)=1:1, 25 °C, 4 h; (q) H_2O_2, NaOH, MeOH, 25 °C, 2 h, 68% over two steps; (r) $Eu(FOD)_3$, $NaBH_4$, CH_3OH, 0.5 h, 49% of **1** and 49% of **19**; (s) $K_2Cr_2O_7$, H_2SO_4, acetone, 60 °C, 3 h, 98%.

*4.1.1. Methyl abietadien-18-oate (**6**).* To a stirred solution of abietic acid **3** (100 g, 0.331 mol), acetone (500 mL) and K_2CO_3 (50.2 g, 0.364 mol) was added Me_2SO_4 (31.36 mL, 0.331 mol) and the resulting solution was stirred overnight at room temperature. After removing the solvent the mixture was diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered and concentrated to give **6** (104.6 g, 100%) as a colourless oil. $[\alpha]_D^{23}$ −65.3 (*c* 0.49, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.77 (s, 1H), 5.41 (m, 1H), 3.63 (s, 3H), 2.22 (m, 1H), 1.25 (s, 3H), 1.01 (d, *J*=6.9 Hz, 3H), 1.00 (d, *J*=6.9 Hz, 3H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.0, 145.3, 135.5, 122.4, 120.6, 51.8, 50.9, 46.6, 45.1, 38.3, 37.1, 34.9, 34.5, 27.5, 25.7, 22.5, 21.4, 20.8, 18.1, 17.0, 14.0; EIMS (70 eV, *m*/*z*): 316 (M^+, 100%).

*4.1.2. Methyl 13β,14β-dihydroxyabieta-7-en-18-oate (**7**).* To a solution of methyl abietadien-19-oate **6** (100 g, 0.316 mol) in acetone (1000 mL) and deionized water (200 mL) were added *N*-methylmorpholine-*N*-oxide (60 wt % in water, 74.2 g, 0.380 mol), pyridine (30.7 g, 0.316 mol) and potassium osmate dihydrate (0.23 g, 0.0006 mol). The mixture was stirred at reflux for 7 days. $NaHSO_3$ (40 g) was added and the solvent was evaporated, then AcOEt (600 mL) was added and the mixture was washed with 5% HCl (100 mL), water (100 mL) and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (H–E, 7:1) to give pure **7** (94.1 g, 85%) as a colourless solid, mp 105–107 °C; $[\alpha]_D^{25}$ −0.57 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.87 (m, 1H), 3.94 (s, 1H), 3.62 (s, 3H), 2.14 (sept, *J*=6.9 Hz, 1H), 1.99 (m, 1H), 1.88 (dd, *J*=12, 3.6 Hz, 1H), 1.86 (d, *J*=11.7 Hz, 1H), 1.76 (m, 1H), 1.73 (m, 1H), 1.70 (m, 2H), 1.65 (m, 1H), 1.53 (m, 2H), 1.40 (d, *J*=3.48 Hz, 1H), 1.37 (d, *J*=3.16 Hz, 1H), 1.31 (dd, *J*=13.2, 2.8 Hz, 1H), 1.25 (s, 3H), 1.11 (m, 1H), 0.93 (d, *J*=6.7 Hz, 3H), 0.90 (d, *J*=7 Hz, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.2, 137.9, 120.0, 76.3, 73.3, 52.0, 51.3, 46.5, 44.7, 39.1, 36.9, 35.3, 33.1, 26.4, 25.0, 19.3, 18.0, 17.9, 17.5, 16.4, 15.6; HRMS-EI: *m*/*z* calcd for $C_{21}H_{34}O_4$ $[M]^+$: 350.24516; found: 350.24535.

*4.1.3. Methyl 13β-hydroxy-14-oxoabieta-7-en-18-oate (**8**).* To a solution of **7** (100 g, 0.286 mol) in DMSO (142 mL, 2 mol) and dichloromethane (200 mL) was added at 0 °C triethylamine (165 mL, 1.14 mol), followed by portionwise addition of sulfur trioxide–pyridine complex (136.4 g, 0.858 mol). The mixture was stirred in the ice bath for 5 h at which time TLC analysis showed no starting material. The reaction mixture was diluted with ethyl acetate (1 L) and washed with 0.5 N HCl, water (300 mL) and brine. The organic phase was dried over Na_2SO_4 and concentrated to yield **8** (94.6 g, 95%) as a colourless oil; $[\alpha]_D^{24}$ +55.8 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.98 (s, 1H), 3.63 (s, 3H), 2.29 (m, 1H), 2.05 (m, 1H), 2.01 (m, 2H), 1.88 (m, 1H), 1.80 (m, 1H), 1.85 (m, 1H), 1.79 (m, 1H), 1.68 (m, 1H), 1.65 (m, 2H), 1.57 (m, 2H), 1.29 (dd, *J*=11.6, 5.1 Hz, 1H), 1.23 (s, 3H), 1.13 (m, 1H), 0.88 (d, *J*=6.7 Hz, 3H), 0.77 (d, *J*=6.7 Hz, 3H), 0.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.2, 178.5, 137.9, 135.2, 77.6, 52.0, 50.9, 46.1, 44.1, 37.6, 37.0, 35.5, 34.8, 31.4, 26.4, 18.9, 17.8, 16.6, 16.5, 16.1, 13.5; HRMS (FAB) *m*/*z* calcd for $C_{21}H_{32}O_4Na$, 371.2198; found, 371.2192.

*4.1.4. Methyl 14-methoxyabieta-8,11,13-trien-18-oate (**10**).* Ketone **8** (100 g, 0.287 mol) and *p*-toluenesulfonic acid (19 g, 0.1 mol) in toluene (500 mL) were heated at reflux for 8 h. After removing the solvent the mixture was diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$ and the solvent evaporated to give a crude product phenol. K_2CO_3 (48 g, 0.35 mmol) and Me_2SO_4 (163 mL, 1.72 mol) were added to a solution of the crude phenol in acetone (1000 mL), and the reaction mixture was kept stirring at reflux overnight. Ammonium hydroxide (100 mL) was added and the solvent was evaporated, then AcOEt (600 mL) was added and the mixture was washed with water (100 mL) and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (H–E, 50:1) to give pure **10** (85.2 g, 91%) as a colourless solid, mp 84–86 °C; $[\alpha]_D^{20}$ +44 (*c* 0.19, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.10 (d, *J*=8.1 Hz, 1H), 7.02 (d, *J*=8.1 Hz, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 3.28 (sept, *J*=6.8 Hz, 1H), 2.96 (dd, *J*=6.4, 17.6 Hz, 1H), 2.78 (m, 1H), 2.27 (d, *J*=12.4 Hz, 1H), 2.21 (dd, *J*=10.7, 1.7 Hz, 1H), 1.82–1.62 (m, 5H), 1.56–1.43 (m, 2H), 1.28 (s, 3H), 1.22 (d, *J*=3.7 Hz, 6H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.1, 154.8, 148.5, 138.0, 128.4, 123.7, 120.2, 60.4, 51.8, 47.5, 44.6, 38.1, 37.1, 36.5, 26.0, 25.1, 24.5, 23.9, 23.8, 21.2, 18.5, 16.4; EIMS (70 eV, *m*/*z*): 344 (M^+), 269 (100%).

*4.1.5. 14-Methoxyabieta-8,11,13-trien-18-oic acid (**5**).* KOH (48.8 g, 0.87 mol) and **10** (100 g, 0.29 mol) in ethylene glycol (500 mL) and water (50 mL) were heated at 120 °C for 10 h. The mixture was poured into water, acidified and the precipitate was filtrated to give the pure acid **5** (95.7 g, 100%), mp 162–164 °C; $[\alpha]_D^{24}$ +57.6 (*c* 0.59, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.10 (d, *J*=8.1 Hz, 1H), 7.02 (d, *J*=8.1 Hz, 1H), 3.74 (s, 3H), 3.30 (sept, *J*=5.7 Hz, 1H), 3.00 (dd, *J*=6.0, 5.4 Hz, 1H), 2.82 (m, 1H), 2.35–2.20 (m, 2H), 1.80–1.60 (m, 5H), 1.56–1.43 (m, 2H), 1.31 (s, 3H), 1.24 (d, *J*=5.7 Hz, 6H), 1.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 185.3, 154.7, 148.4, 138.1, 128.5, 123.7, 120.3, 60.4, 47.4, 44.3, 38.0, 37.0, 36.7, 26.0, 25.1, 24.5, 24.0, 23.9, 21.3, 18.6, 16.2; EIMS (70 eV, *m*/*z*): 330 (M^+), 315 (100%), 269 (92%), 227 (72%).

*4.1.6. 14-Methoxy-19-norabieta-4(18),8,11,13-tetraene (**11**).* Oxalyl chloride (28 mL, 0.319 mol) was added slowly to a stirred solution of the acid **5** (100 g, 0.29 mol) and dimethylformamide (0.5 mL) in dry THF (500 mL) and the mixture was stirred at room temperature overnight. Solvent was removed under reduced pressure. The crude acid chloride was dissolved in toluene (300 mL) and added to a stirred suspension of the sodium salt of *N*-hydroxypyridine-2-thione (51.4 g, 0.348 mol) and 4-dimethylaminopyridine (3.54 g, 0.029 mol) in toluene (500 mL) at reflux under nitrogen. The mixture was heated under reflux for 3 h, the cooled suspension was filtered through Celite and the solvent was removed under reduced pressure. The crude pyridyl sulfides was dissolved in dichloromethane (800 mL) and a solution of *m*-chloroperbenzoic acid (49.8 g, 0.29 mol) in dichloromethane (600 mL) was added dropwise at −78 °C. The solution was stirred for 2 h, warmed to room temperature and then added to benzene (800 ml) under reflux. The solution was heated under reflux for 1–2 h, cooled to room temperature, and the solvent removed under reduced pressure. The residue was then chromatographed on silica, with ethyl acetate/hexanes mixtures as eluent, to give the C4-(18)-alkenes **11** (69.2 g, 84%) as a white solid, mp 72–74 °C; $[\alpha]_D^{24}$ +218 (*c* 0.28, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.07 (s, 2H), 4.86 (d, *J*=1.5 Hz, 1H), 4.62 (d, *J*=1.5 Hz, 1H), 3.74 (s, 3H), 3.32 (sept, *J*=3.0 Hz, 1H), 3.10 (dd, *J*=7.2, 7.8 Hz, 1H), 2.73 (m, 1H), 2.40 (d, *J*=10.5 Hz, 1H), 2.24 (m, 2H), 2.06 (m, 1H), 1.88 (m, 1H), 1.80–1.65 (m, 3H), 1.58 (m, 1H), 1.25 (d, *J*=2.7 Hz, 3H), 1.23 (d, *J*=3.0 Hz, 3H), 1.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.8, 150.5, 146.3, 138.1, 128.6, 123.6, 121.4, 106.4, 60.4, 47.5, 39.3, 38.4, 36.2, 26.1, 24.1, 23.9, 23.9, 23.7, 22.7, 20.8; EIMS (70 eV, *m*/*z*): 284 (M^+), 269 (56%), 227 (100%).

*4.1.7. 14-Methoxy-18,19-bisnorabieta-8,11,13-trien-4-one (**12**).* A flask containing a solution of alkene **11** (100 g, 0.352 mol) in methanol (700 mL) and dichloromethane (700 mL) was placed in a dry ice-acetone bath at −78 °C for 20 min before starting ozonolysis. Ozone was generated by passing an oxygen stream through an electrical discharge-type ozone generator. The ozonolysis of **11** at −78 °C for 6 h was followed by the addition of dimethyl sulfide (62 mL, 0.7 mol) at −78 °C and the resulting solution was stirred overnight at room temperature. After removing the solvent the mixture was diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$ and the solvent evaporated to a crude product, which was dissolved in cyclohexane

and crystallized to afford pure **12** (96.1 g, 96%) as a white solid, mp 96–98 °C; $[\alpha]_D^{24}$ +153.9 (*c* 0.725, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10 (d, *J*=8.4 Hz, 1H), 7.05 (d, *J*=8.4 Hz, 1H), 3.71 (s, 3H), 3.30 (sept, *J*=3.0 Hz, 1H), 3.07 (dd, *J*=9,9 Hz, 1H), 2.69–2.55 (m, 2H), 2.42–2.37 (m, 3H), 2.14–2.00 (m, 3H), 1.92–1.70 (m, 2H), 1.22 (d, *J*=3.0 Hz, 3H), 1.20 (d, *J*=3.0 Hz, 3H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 212.3, 155.0, 144.5, 138.8, 128.4, 123.9, 120.9, 60.4, 55.0, 42.3, 40.8, 37.1, 26.1, 23.8, 23.8, 23.6, 23.0, 22.5, 16.9; EIMS (70 eV, *m*/*z*): 286 (M^+), 271 (100%).

*4.1.8. 3-(Bis-methylsulfanyl-methylene)-14-methoxy-18,19-bisnor-abieta-8,11,13-trien-4-one (**13**).* To 2,6-di-*tert*-butyl-4-methyphenol (177 g, 0.8 mol) in dry THF (1 L), under nitrogen at −20 °C, was added with stirring, *n*-BuLi (500 mL, 1.6 M solution in hexane). To the resultant cloudy yellow solution, warmed to room temperature, was added redistilled carbon disulphide (105 mL) followed by **12** (100 g, 0.348 mol). After 15 h methyl iodide (76 mL, 1.21 mol) was added and stirring was continued for a further 4 h. The solvent was evaporated, then AcOEt (1000 mL) was added and the mixture was washed with water (500 mL) and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (H–E, 100:1) to give pure **13** (132.3 g, 97.5%) as a yellow solid, mp 124–126 °C; $[\alpha]_D^{24}$ +77.7 (*c* 0.39, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10 (d, *J*=8.4 Hz, 1H), 7.06 (d, *J*=8.4 Hz, 1H), 3.72 (s, 3H), 3.41 (m, 1H), 3.29 (sept, *J*=2.4 Hz, 1H), 3.09 (dd, *J*=4.8, 4.8 Hz, 1H), 2.82–2.62 (m, 2H), 2.59 (dd, *J*=2.7, 2.7 Hz, 1H), 2.47 (m, 1H), 2.38 (s, 3H), 2.36 (s, 3H), 2.30 (m, 1H), 1.94 (m, 1H), 1.71 (m, 1H), 1.22 (d, *J*=2.4 Hz, 3H), 1.19 (d, *J*=2.1 Hz, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.9, 154.9, 144.3, 143.9, 139.2, 138.8, 128.6, 123.9, 121.1, 60.5, 55.8, 39.9, 37.0, 29.6, 26.0, 23.8, 23.8, 23.6, 23.3, 18.0, 17.7, 17.3; EIMS (70 eV, *m*/*z*): 390 (M^+), 375 (100%).

*4.1.9. Triptophenolide methyl ether (**4**).* To trimethylsulfonium iodide (62.7 g, 0.307 mol) in dry THF (800 mL), under nitrogen at −20 °C, was added with stirring, *n*-BuLi (192 mL, 1.6 M solution in hexane) and the mixture was stirred at −20 °C for 1.5 h. To the resultant cloudy solution, cooled to −60 °C, was added **13** (100 g, 0.256 mol) in THF (400 mL). The solution was stirred for 1.5 h, warmed to room temperature and water (20 mL) was added dropwise. The solvent was evaporated, then diethyl ether (1000 mL) was added and the mixture was washed with water (500 mL) and brine. The organic phase was concentrated to give a crude product, which was dissolved in the 1 M/L hydrochloric acid/methanol (800 mL) and stirring was continued for a further 24 h. The solvent was evaporated, then AcOEt (1000 mL) was added and the mixture was washed with water (500 mL) and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (H–E, 10:1) to give pure **4** (63.4 g, 76%) as a white solid, mp 175–176 °C; $[\alpha]_D^{25}$ +42.1 (*c* 0.37, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.12 (s, 2H), 4.79 (m, 2H), 3.73 (s, 3H), 3.30 (sept, *J*=6.9 Hz, 1H), 3.15–2.85 (m, 2H), 2.80–1.60 (m, 7H), 1.23 (d, *J*=6.9 Hz, 3H), 1.22 (d, *J*=6.9 Hz, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.1, 163.0, 155.4, 144.1, 139.2, 128.0, 124.9, 124.1, 120.2, 70.4, 60.5, 41.1, 36.4, 32.7, 26.1, 23.9, 23.8, 22.7, 22.2, 19.7, 18.2; EIMS (70 eV, *m*/*z*): 326 ($[M]^+$, 97%), 311 (100%).

*4.1.10. Preparation of compound **15**.* To a solution of **4** (100 g, 0.306 mol) in acetonitrile (1.5 L) and water (1.5 L), was added ammonium ceric nitrate (336 g, 0.613 mol) and the mixture was stirred at room temperature for 5 h. The solvent was evaporated, then CH_2Cl_2(1000 mL) was added and the mixture was washed with water (500 mL) and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product **14**, which was dissolved in CH_2Cl_2 (400 mL) and was added a solution of CrO_3(107 g) and pyridine(164 mL) in CH_2Cl_2 (1500 mL) at 0 °C. The stirring was continued at room temperature for a further 6 h and the organic phase was washed with 5% HCl (500 mL), brine, dried over Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (H–E, 6:1) to give pure **15** (79.2 g, 76%) as a white solid, mp 174–175.5 °C; $[\alpha]_D^{20}$ +33.6 (*c* 0.50, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.47 (d, *J*=8.2 Hz, 1H), 7.19 (d, *J*=8.2 Hz, 1H), 4.77 (m, 2H), 3.83 (s, 3H), 3.41 (sept, *J*=6.9 Hz, 1H), 3.30–2.30 (m, 6H), 1.85 (m, 1H), 1.25 (d, *J*=6.9 Hz, 3H), 1.20 (d, *J*=6.9 Hz, 3H), 1.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 173.3, 160.0, 158.4, 150.6, 142.2, 132.0, 125.8, 124.9, 118.8, 70.0, 62.7, 39.7, 37.8, 36.6, 32.0, 25.9, 23.7, 23.2, 21.5, 17.7; IR (CH_2Cl_2) 1755, 1678 cm−1; HRMS (EI) calcd for $C_{21}H_{24}O_4$ (M^+): 340.1675, found 340.1668.

*4.1.11. Preparation of compound **16**.* To a solution of **15** (100 g, 0.294 mol) in dichloromethane (1.5 L), under nitrogen at −78 °C, was added BBr_3 (33 mL, 0.352 mol) and the mixture was stirred at −78 °C for 2 h and warmed to room temperature. $NaHCO_3$ (300 mL) was added and the extracts were washed with water (500 mL) and brine. The organic phase was dried over Na_2SO_4 and concentrated to give a crude product, which was chromatographed on silica gel (H–E, 7:1) to give pure **16** (95 g, 99%) as a white solid; $[\alpha]_D^{20}$ −43.5 (*c* 0.17, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 13.05 (s, 1H), 7.42 (d, *J*=7.9 Hz, 1H), 6.88 (d, *J*=7.9 Hz, 1H), 4.77 (m, 2H), 3.35 (sept, *J*=6.9 Hz, 1H), 3.19 (m, 1H), 2.84–1.70 (m, 6H), 1.25 (d, *J*=6.9 Hz, 3H), 1.23 (d, *J*=6.9 Hz, 3H),1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.2, 173.2, 161.7, 159.6, 149.1, 136.0, 133.7, 126.1, 114.7, 113.6, 69.9, 40.3, 36.4, 31.6, 26.2, 25.3, 22.2, 22.1, 21.7, 17.8; HRMS (EI) calcd for $C_{20}H_{22}O_4$ (M^+): 326.1518, found 326.1518.

*4.1.12. Preparation of compound **17**.* To a solution of **16** (100 g, 0.307 mol) in methanol (600 mL) at 0 °C was added sodium borohydride (22.8 g, 0.6 mmol) in three portions. The mixture was warmed to room temperature in a period of 2 h. Ice-water (500 mL) was added, followed by a saturated ammonium chloride solution (300 mL). The mixture was extracted with dichloromethane. The extracts were dried with $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (H–E, 4:1) to give **17** (98.6 g, 99%) as a white solid, mp 125–127 °C; $[\alpha]_D^{20}$ +53.5 (*c* 0.20, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.14 (d, *J*=8.1 Hz, 1H), 6.85 (d, *J*=8.1 Hz, 1H), 5.21 (m, 1H), 4.76 (m, 2H), 3.78 (br d, *J*=7.0 Hz, 1H), 3.30 (sept, *J*=6.9 Hz, 1H), 2.78 (d, *J*=13.3 Hz, 1H), 2.60–1.50 (m, 6H), 1.22 (d, *J*=6.9 Hz, 6H), 1.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.0, 162.3, 154.3, 143.2, 133.9, 126.0, 125.5, 121.1, 115.5, 70.6, 69.0, 40.4, 36.5, 32.6, 30.3, 26.5, 23.1, 22.6, 22.5, 17.9; HRMS (EI) calcd for $C_{20}H_{24}O_4$ (M^+): 328.1675, found 328.1659.

*4.1.13. Preparation of compound **18**.* To a solution of **17** (100 g, 0.305 mol) in methanol (1500 mL) at 0 °C was added a solution of $NaIO_4$ (71.8 g, 0.336 mol) in water (double distilled, 500 mL). The reaction flask was covered with aluminium foil. A yellow solution with white precipitate was formed. After stirred at room temperature for 2.5 h, the precipitate was filtered off and rinsed with dichloromethane. The filtrates were concentrated, and the residue was purified by flash column chromatography (H–E, 6:1) to afford **18** (95.4 g, 96% yield) as a yellow solid, mp 82–83 °C; $[\alpha]_D^{20}$ −327.5 (*c* 0.25, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (d, *J*=6.7 Hz, 1H), 6.41 (d, *J*=6.7 Hz, 1H), 4.69 (m, 2H), 4.07 (d, *J*=5.0 Hz, 1H), 2.92 (sept, *J*=6.9 Hz, 1H), 2.60–1.50 (m, 7H), 1.15 (s, 3H), 1.12 (d, *J*=6.9 Hz, 3H), 1.10 (d, *J*=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 173.3, 160.1, 150.3, 142.3, 135.1, 125.4, 121.0, 70.0, 66.7, 57.1, 43.6, 38.2, 32.8, 26.2, 24.2, 21.7, 21.4, 17.5, 16.9; HRMS (EI) calcd for $C_{20}H_{22}O_4$ (M^+) 326.1518, found 326.1520.

*4.1.14. Preparation of (−)-triptonide (**2**).* Followed the literature method.[17] 68% yield over two steps, white solid, mp 224–226 °C; $[\alpha]_D^{20}$ −170 (*c* 0.075, CH_2Cl_2) [lit.[4] −175 (*c* 0.148, CH_2Cl_2)]; ^1H NMR (300 MHz, $CDCl_3$) δ 4.71 (m, 2H), 4.05 (d, *J*=3.0 Hz, 1H), 3.83 (d,

J=3.0 Hz, 1H), 3.42 (d, J=5.3 Hz, 1H), 2.90–1.20 (m, 8H), 1.08 (s, 3H), 0.98 (d, J=6.9 Hz, 3H), 0.89 (d, J=6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.9, 173.0, 159.4, 125.7, 69.9, 66.5, 65.1, 60.9, 60.4, 58.9, 56.0, 40.6, 35.3, 30.5, 25.8, 23.3, 18.0, 17.1, 16.3, 13.8; HRMS (EI) calcd for $C_{20}H_{22}O_6$ (M^+) 358.1416, found 358.1413.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.05.035.

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