Studies on Macrocyclic Diterpenoids. Part 10. First Total Synthesis of (±)-Isosarcophytol-A

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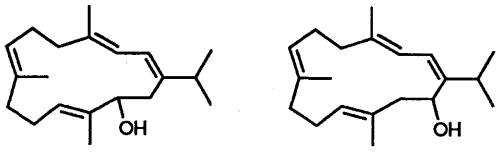
The first total synthesis of (±)-isosarcophytol-A, a marine natural cembrenoid, has been achieved in a seven-step synthesis starting from *E,E*-farnesyl acetate. A titanium-induced dicarbonyl macrocyclization is the key step.

Recently, a number of diterpenoid natural products containing a 14-membered ring have been isolated from terrestrial and especially from marine sources. An ever-increasing interest in the chemistry of such natural products is a result of their remarkably wide range of biological activities and challenging structural features. Over the past decade, though synthetic studies in the area have made a great progress, the lack of a general and efficient method for the construction of 14-membered rings have made the cembranes an attractive target for total synthesis.[1] Among the macrocyclizations described in the literature, the titanium-induced intramolecular cyclization of a dicarbonyl precursor developed by McMurry and his coworkers[2] is useful for preparing carbocyclic rings of all sizes. Total syntheses of natural potent antitumour cembrenoids, *e.g.* sarcophytol-B,[3] (±)-crassin and (±)-isolobophytolide[4] have been so accomplished. Earlier employing this method, we synthesized cembrene-C,[5] (±)-cembrene-A[6] and sarcophytol-A benzyl ether.[7] Here we describe the synthesis of (±)-isosarcophytol-A **1** by the same method from *E,E*-farnesyl acetate in seven steps.[8]

Isosarcophytol-A **1**,[9] a cembrane alcohol, was first isolated from Australian soft coral (*Nephthea brassica*) in 1982, by Bowden *et al.* and its structure was established as (1,3,7,11-all *E*,13*S*)-cembra-1,3,7,11-tetraen-13-ol, an isomer of another diterpenoid sarcophytol-A **2**[10] which has been reported to both inhibit[11] the activity of the powerful tumour promoter teleocidin and exhibit potent antitumour activity.[12] So far as we know, bioactivity tests for and the synthesis of **1** have not previously been reported.



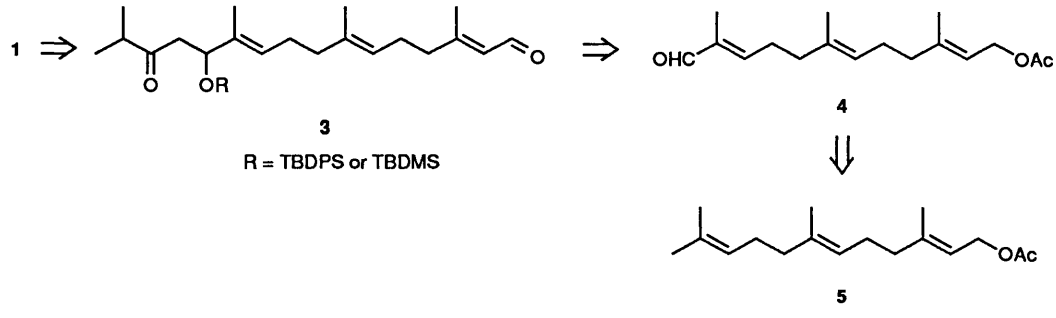
1 **2**

Our synthetic strategy starting from farnesyl acetate **5** is outlined in Scheme 1 and involves the formation of the 14-membered ring by the titanium-induced cyclization of the dicarbonylsilyl ether precursor **3**, prepared from the enal **4** by Aldol condensation with the lithium enolate of methyl isopropyl ketone utilizing Heathcock's procedure[13] as the key step.

Thus, our synthetic route is described in Scheme 2.

E,E-Farnesyl acetate **5** was exposed[14] to 75% *tert*-butyl hydroperoxide in the presence of catalytic amounts of selenium dioxide (0.1 equiv.) in methylene dichloride at 15 °C and followed by reduction with sodium borohydride in methanol at 0 °C to give the terminal all-*trans* allylic alcohol **6** (60%), along with the secondary alcohol **7** (21%; based on the consumed starting material after two cycles). The alcohol **6** was then oxidized with active manganese dioxide in the presence of anhydrous sodium carbonate (1.0 equiv.)[15] in methylene dichloride at room temperature to yield the corresponding enal **4** (95%), which was condensed[13] at −78 °C with the lithium enolate of methyl isopropyl ketone [formed by lithium diisopropylamide (LDA) treatment at −78 °C] and quenched at −50 °C with saturated aqueous ammonium chloride to afford the ketol **8** (86%). Protection[16] of the hydroxy group of **8** with 1 equiv. of *tert*-butyldiphenylsilyl chloride (TBDPSCl) or *tert*-butyldimethylsilyl chloride (TBDMSCl) catalysed by triethylamine and 4-dimethylaminopyridine (DMAP) in dimethylformide (DMF) at 60 °C gave the silyl ethers **9a** or **9b** (90%). These protected alcohols were then subjected to mild hydrolysis with anhydrous potassium carbonate in methanol at 0 °C to remove the acetoxy group, followed by oxidation of the resulting alcohols with active manganese dioxide–sodium carbonate[15] in methylene dichloride to afford the desired keto enal dicarbonyl precursors **3a** and **3b** (80%). It is noteworthy that the tetrahydropyranoxy ether of the alcohol **8** yielded the eliminated hydrolytic product keto alcohol **11** by treatment with anhydrous potassium carbonate in methanol even at −20 °C. The structure of compound **11** was confirmed by its IR, ^{1}H NMR and MS spectral data.

The macrocyclization of the precursors **3a** and **3b**, the key

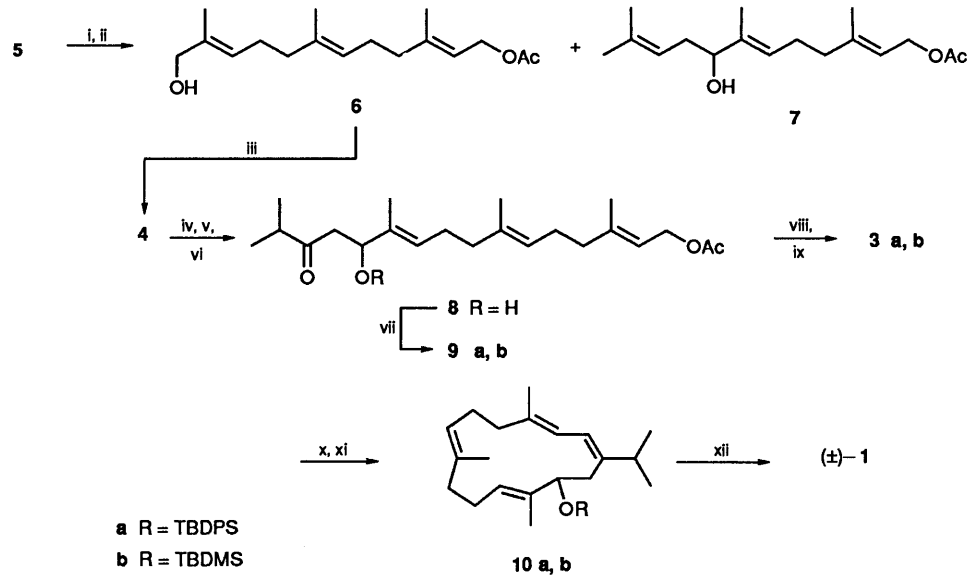


3
R = TBDPS or TBDMS

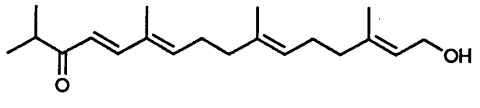
4

5

Scheme 1



Scheme 2 *Reagents and conditions:* i, SeO_2, Bu^tO_2H, CH_2Cl_2, 15 °C; ii, $NaBH_4$, MeOH, 0 °C (60%); iii, MnO_2, Na_2CO_2, CH_2Cl_2, room temp. (95%); iv, Pr^iCOMe, LDA, THF, −78 °C, 40 min; v, **4**, 15 min; vi, sat. aq. NH_4Cl, −50 °C (86%); vii, TBDPSCl or TBDMSCl, Et_3N, DMAP, DMF, 60 °C (90%); viii, K_2CO_3, MeOH, 0 °C; ix, MnO_2, Na_2CO_3, CH_2Cl_2, room temp. (80%); x, $TiCl_4$–Zn, py, THF, reflux, 2.5 h; xi, addn. of **3** in THF over 30 h (78%); xii, TBAF, THF, 0 °C (100%).



11

step of the synthesis, was carried out[17] by their slow addition *via* a syringe as dilute solutions in dry tetrahydrofuran (THF), to a low-valent titanium slurry at reflux, prepared *in situ* by reduction of the $TiCl_4$·THF complex of powdered zinc in tetrahydrofuran in the presence of pyridine. The expected coupled products **10a** and **10b** (78%), obtained after careful flash column chromatography, were deprotected by treatment with tetrabutylammonium fluoride (TBAF) in THF at 0 °C to give quantitatively the title compound (±)-**1** as a colourless oil. The spectral data of (±)-**1** were consistent with those of literature.* Bioactivity tests and further enantioselective conversion of (±)-**1** into enantiomerically pure isosarcophytol-A are in progress.

Experimental

IR Spectra were recorded on a FT-170SX spectrometer. ^1H NMR spectra were obtained on Bruker FT-80A or AM-400 instruments in $CDCl_3$ solution with tetramethyl silane (TMS) as the internal standard. *J*-Values are given in Hz. Mass spectra (MS) were measured on a ZAB-HS or a MAT-44S spectrometer and signals given in *m/z* with relative intensity (%) in parentheses. All solvents were purified and dried by standard techniques just before use. All reactions were routinely carried out under an inert atmosphere of argon and monitored by thin layer chromatography (TLC) using silica gel (GF_{254}). Products were purified by flash column chromatography (FCC) on silica gel (200 ~ 300 mesh) made in Qing Dao Marine Chemical Factory. In the work-up, all extracted organic phases were washed with brine, then dried over anhydrous magnesium sulfate and filtered prior to concentration under reduced pressure.

* Standard sample of natural isosarcophytol-A for direct comparison was not available.

(2E,6E,10E)-12-*Hydroxy*-3,7,11-*trimethyldodeca*-2,6,10-*trienyl Acetate* **6** *and* (2E,6E,10E)-8-*Hydroxy*-3,7,11-*trimethyldodeca*-2,6,10-*trienyl Acetate* **7**.—To a stirred mixture of selenium dioxide (150 mg, 1.35 mmol) and 75% *tert*-butyl hydroperoxide (4.8 cm^3, ~40 mmol) in methylene dichloride (25 cm^3) was added dropwise a solution of *E,E*-farnesyl acetate (prepared in 100% yield from commercially available farnesol by standard acetylation with Ac_2O–Py; 3.5 g, 13.3 mmol) in methylene dichloride (10 cm^3) at 15 °C. After being stirred for a period of 3 h at that temperature, the reaction mixture was diluted with diethyl ether (50 cm^3) and then washed with 10% aqueous potassium hydroxide (3 × 20 cm^3), water (20 cm^3) and brine (20 cm^3), and dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure afforded the crude product as an oil contaminated with a small amount of *tert*-butyl hydroperoxide. The residue was then taken up in methanol (15 cm^3) and sodium borohydride (115 mg, 3 mmol) was added portionwise to the resulting mixture at 0 °C with stirring. After concentration under reduced pressure, the residue was dissolved in diethyl ether (40 cm^3) and the solution washed with water and brine and dried. Removal of the solvent by rotary evaporation under reduced pressure gave the crude product which was then purified by flash column chromatography (light petroleum–acetone 12:1) to yield the primary alcohol **6** (1.80 g, 60%) as the major product and the secondary alcohol **7** (650 mg, 21%), both colourless oils, along with recovered starting material **5** (600 mg). Compound **6** ν_{max}/cm^{-1} 3446 (s, OH) and 1740 (s, C=O); δ_H 1.61 (3 H, s, CH_3), 1.67 (3 H, s, CH_3O), 1.71 (3 H, s, CH_3), 2.04 (3 H, s, CH_3CO), 2.00–2.45 (8 H, m), 3.98 (2 H, s, CH_2O), 4.59 (2 H, d, *J* 7.1, CH_2OAc) and 4.95–5.35 (3 H, br m, CH=) (Found: C, 72.7; H, 9.7. Calc. for $C_{17}H_{28}O_3$: C, 72.92; H, 10.08%); **7**: ν_{max}/cm^{-1} 3475 (s, OH) and 1741 (s, C=O); δ_H 1.63 (3 H, s, CH_3), 1.70 (6 H, br s, CH_3), 2.05 (3 H, s, CH_3CO), 2.10–2.35 (6 H, m), 3.98 (1 H, t, *J* 7.1, CHO), 4.58 (2 H, d, *J* 7.2, CH_2OAc) and 4.90–5.35 (3 H, br m, CH=) (Found: C, 72.7; H, 9.9%).

(2E,6E,10E)-11-*Formyl*-3,7-*dimethyldodeca*-2,6,10-*triethyl Acetate* **4**.—To a suspension of active manganese dioxide (5.2 g, 60 mmol) and powdered sodium carbonate in anhydrous methylene dichloride (25 cm^3) was added dropwise a solution

of the alcohol **6** (1.1 g, 3.9 mmol) in methylene dichloride (5 cm^3) at room temp. with vigorous stirring. After the reaction mixture had been stirred for a further 2 h, diethyl ether (20 cm^3) was added to the mixture which was then filtered through a short column of silica gel. The filtrate was evaporated under reduced pressure to give an oil which was purified by flash column chromatography (light petroleum–ethyl acetate, 8:1) to afford the formyl ester **4** (0.94 g, 95%); ν_{max}/cm^{-1} 2712w, 1739s (C=O) and 1688s (C=O); δ_H 1.63 (3 H, s, CH_3), 1.70 (3 H, s, CH_3), 1.74 (3 H, s, CH_3), 2.05 (3 H, s, CH_3CO), 2.0–2.4 (8 H, m), 4.59 (2 H, d, *J* 7.2, CH_2OAc), 4.95–5.35 (2 H, br m, CH=), 6.46 (1 H, t, *J* 7.1, CH=) and 9.98 (1 H, s, CHO) (Found: C, 73.2; H, 9.4. Calc. for $C_{17}H_{26}O_3$: C, 73.45; H, 9.43).

(2E,6E,10E)-12-*Hydroxy*-3,7,11,15-*tetramethyl*-14-*oxohexadeca*-2,6,10-*trienyl Acetate* **8**.—To a stirred solution of diisopropylamine (200 mg, 2 mmol) in dry THF (1.6 cm^3) was added dropwise a hexane solution of butyllithium (0.82 mol dm^{-3}; 2.6 cm^3, 2.1 mmol) at −40 °C over 5 min. After being stirred for an additional 0.5 h at −40 °C, the resulting mixture was cooled to −78 °C (solid CO_2–acetone bath) and syringed dropwise into a solution of methyl isopropyl ketone (180 mg, 2.1 mmol) in THF (1 cm^3). The reaction mixture was stirred for a further 40 min after which a solution of the formyl ester **8** in THF (1 cm^3) (450 mg, 1.62 mmol) was added dropwise to it at −78 °C. The resulting mixture was stirred for 15 min at −78 °C and allowed to warm gradually to −50 °C, when it was quenched with saturated aqueous ammonium chloride (2 cm^3). The cooling bath was removed and the reaction mixture was warmed slowly to room temperature. The resulting mixture was diluted with water (5 cm^3) and diethyl ether (10 cm^3) and organic phase was separated; the aqueous layer was then extracted with diethyl ether (2 × 10 cm^3). The combined organic phases were washed with water and brine, dried, and evaporated under reduced pressure. Purification of the residue by flash column chromatography (light petroleum–ethyl acetate, 6:1) gave the ester **8** (510 mg, 86%) as a colourless oil, ν_{max}/cm^{-1} 3487 (s, OH), 1739 (s, C=O) and 1712 (s, C=O); δ_H 1.09 (6 H, br s, 2 × CH_3), 1.71 (3 H, s, CH_3), 2.04 (3 H, s, CH_3CO), 2.05–2.20 (8 H, m), 2.61–2.89 (3 H, m), 4.42 (1 H, t, *J* 7.1, CHO), 4.58 (2 H, d, *J* 7.2, CH_2OAc) and 5.10–5.50 (3 H, br m, CH=); *m/z* (EI) 364 ($M^{\bullet+}$, 1%), 346 (M − 18, 5) and 304 (M − 60, 14) (Found: C, 72.5; H, 9.85. Calc. for $C_{22}H_{36}O_4$: C, 72.60; H, 9.97%).

(2E,6E,10E)-12-tert-*Butyldiphenylsiloxy*-3,7,11,15-*tetramethyl*-14-*oxohexadeca*-2,6,10-*trienyl Acetate* **9a** *and* (2E,6E,10E)-2-tert-*Butyldimethylsiloxy*-3,7,11,15-*tetramethyl*-14-*oxohexadeca*-2,6,10-*trienyl Acetate* **9b**.—To a stirred mixture of DMAP (40 mg, 0.33 mmol), dry triethylamine (120 mg, 1.2 mmol) and the alcohol **8** (350 mg, 0.96 mmol) in anhydrous dimethylformamide (DMF) (2 cm^3) was added dropwise TBDPSCl (310 mg, 1.1 mmol) or an equivalent of TBDMSCl at room temperature. Then the resulting mixture was heated to 60 °C for 4 h with stirring then allowed to cool. After addition of water (8 cm^3) the reaction mixture was extracted with diethyl ether (3 × 10 cm^3). The combined organic phases were washed with water (3 × 5 cm^3) and brine (5 cm^3), dried, and evaporated under reduced pressure. The residue was purified by flash column chromatography (light petroleum–ethyl acetate 10:1) to give the silyl ether **9a** (or **9b**) (520 mg, 90%) compound **9a**: ν_{max}/cm^{-1} 1740 (s, C=O) and 1715 (s, C=O); δ_H 1.04 (9 H, s, *tert*-butyl), 1.16 (6 H, d, *J* 7.1, isopropyl-CH_3), 1.58 (6 H, br s, 2 × CH_3), 1.71 (3 H, s, CH_3), 1.83–2.15 (8 H, m), 2.05 (3 H, s, CH_3CO), 2.25–2.45 (1 H, m), 2.65 (2 H, t, *J* 7.2), 4.49 (1 H, t, *J* 7.0), 4.59 (2 H, d, *J* 7.2, CH_2OAc), 4.95–5.40 (3 H, br m, CH=) and 7.40–7.70 (10 H, m, ArH); *m/z* (EI) 602 ($M^{\bullet+}$, 1%), 545 (M − 57, 3) and 199 (100) (Found: C, 75.6; H, 9.0. Calc. for $C_{38}H_{54}O_4Si$: C, 75.81; H, 9.04%). Compound **9b** ν_{max}/cm^{-1} 1742 (s, C=O), 1713 (s, C=O), 1644 and 1029; δ_H 0.05 (6 H, s, CH_3), 1.05 (9 H, s, *tert*-butyl), 1.11 (6 H, d, *J* 7.1, isopropyl-CH_3), 1.59 (6 H, br s, 2 × CH_3), 1.68 (3 H, s, CH_3), 1.80–2.20 (8 H, m), 2.06 (3 H, s, CH_3CO), 2.35 (1 H, m), 4.50 (1 H, t, *J* 7.2), 4.62 (2 H, d, *J* 7.1, CH_2OAc) and 4.90–5.35 (3 H, br m, CH=); *m/z* (EI) 478 ($M^{\bullet+}$, 1%), 463 (M − 15, 5), 421 (M − 57, 6), 363 (14), 303 (22) and 57 (100) (Found: C, 70.15; H, 10.4. Calc. for $C_{28}H_{50}SiO_4$: C, 70.36; H, 10.54%).

(2E,6E,10E)-12-tert-*Butyldiphenylsiloxyl*-3,7,11,15-*tetramethyl*-15-*oxohexadeca*-2,6,10-*trienal* **3a** *and* (2E,6E,10E)-12-tert-*Butyldimethylsiloxyl*-14-*oxohexadeca*-2,6,10-*trienal* **3b**.—A mixture of the protected alcohol **9a** (100 mg, 0.17 mmol) or equivalent **9b** and powdered potassium carbonate (35 mg, 0.25 mmol) in methanol (1.5 cm^3) was stirred vigorously for 1 h at 0 °C. After the addition of water (4 cm^3) the reaction mixture was extracted with methylene chloride (3 × 6 cm^3), the combined organic layers washed with water and brine and dried. Evaporation of the solvent under reduced pressure gave the crude product, which without further purification was taken up in anhydrous methylene chloride (5 cm^3) and magnesium dioxide (900 mg, 10.4 mmol) was added to the resulting solution. The suspension was stirred for 2 h at room temperature and then diluted with diethyl ether (6 cm^3). The mixture was filtered through a short column of silica gel and the resulting filtrate was concentrated under reduced pressure to give a crude oil which was purified by flash column chromatography (light petroleum–ethyl acetate, 10:1) to afford the siloxyl enal **3a** (or **3b**) (75 mg, 80%) as colourless oils. Compound **3a** ν_{max}/cm^{-1} 2725(w), 1715 (s, C=O) and 1673 (s, C=O); δ_H 0.96 (6 H, d, *J* 7.2, isopropyl-CH_3), 1.04 (9 H, s, *tert*-butyl), 1.53 (6 H, br s, 2 × CH_3), 1.75–1.90 (4 H, m), 2.10–2.25 (7 H, m), 2.40–2.47 (1 H, m), 2.53–2.73 (2 H, m), 4.95 (1 H, t, *J* 7.5), 5.00 (2 H, br t, *J* 7.2, CH=), 5.87 (1 H, d, *J* 8.5, CH=), 7.35–7.64 (10 H, m, ArH) and 9.99 (1 H, d, *J* 8.5, CHO); *m/z* (EI) 558 ($M^{\bullet+}$, 1%), 517 (M − 41, 3), 501 (M − 57, 11) and 199 (100) (Found: C, 77.3; H, 9.0. Calc. for $C_{36}H_{50}O_3Si$: C, 77.49; H, 9.03%). Compound **3b** ν_{max}/cm^{-1} 1713 (s, C=O) and 1676 (s, C=O); δ_H 0.06 (6 H, s, CH_3), 0.95 (6 H, d, *J* 7.1, isopropyl-CH_3), 1.04 (9 H, s, *tert*-butyl), 1.53 (3 H, s, CH_3), 1.67 (6 H, br s, 2 × CH_3), 1.85–2.20 (8 H, m), 2.40–2.75 (3 H, m), 4.55 (1 H, t, *J* 8.5, CH=) and 10.00 (1 H, d, *J* 8.5, CHO); *m/z* (EI) 419 ($M^{\bullet+}$ − 15, 1%), 377 (M − 57, 20), 171 (18), 143 (31) and 75 (100) (Found: C, 71.8; H, 10.6. Calc. for $C_{26}H_{46}O_3Si$: C, 71.95; H, 10.68%).

(2E,6E,10E,12E)-3,7,11,15-*Tetramethyl*-14-*oxohexadeca*-2,6,10,12-*tetraenol* **11**.—A mixture of the tetrahydropyranyl ether, prepared from the alcohol **8** by treatment with dihydropyran in the presence of *p*-TsOH in methylene dichloride (95% yield; 290 mg, 0.65 mmol), and powdered potassium carbonate (100 mg, 0.72 mmol) in methanol (4 cm^3) was stirred for 0.5 h at −20 °C. The reaction mixture was allowed to warm to room temperature and concentrated under reduced pressure. The residue was taken up in diethyl ether (10 cm^3) and washed with water and brine, dried, and evaporated under reduced pressure to give a crude oil which was purified by flash column chromatography (light petroleum–ethyl acetate, 5:1) to afford the ketol **12** (183 mg, 93%), ν_{max}/cm^{-1} 3278 (s, OH), 3049, 1668 (s, C=O) and 1643 (w, C=), 1592; δ_H 1.12 (6 H, d, *J* 6.9, isopropyl-CH_3), 1.61, 1.66 and 1.78 (9 H, 3 × s, 3 × CH_3), 1.82–2.50 (8 H, m), 2.87 (sept, 1 H, *J* 6.9), 4.15 (2 H, d, *J* 6.3, CH_2O), 5.80–6.05 (1 H, m, CH=), 6.14 (1 H, d, *J* 15.7, CH=) and 7.24 (1 H, d, *J* 15.7, CH=); *m/z* (EI) 304 ($M^{\bullet+}$, 2%), 289 (M − 15, 3), 261 (M − 43, 5), 109 (43), 81 (82) and 43 (100) (Found: C, 78.9; H, 10.55. Calc. for $C_{20}H_{32}O_2$: C, 79.02; H, 10.61%).

(1E,3E,7E,11E)-13-tert-*Butyldiphenylsiloxyl*-1-*isopropyl*-

4,8,12-*trimethylcyclotetradeca*-1,3,7,11-tetraene **10a** *and* (1E,-3E,7E,11E)-13-tert-*Butyldimethylsiloxyl*-1-*isopropyl*-4,8,12-*trimethylcyclotetradeca*-1,3,7,11-*tetraene* **10b**.—Titanium tetrachloride (0.8 cm^3, 1.4 g, 7.3 mmol was added carefully to anhydrous THF (30 cm^3) *via* a dry syringe at −78 °C with efficient stirring over 5 min. After removal of the cooling bath, to the resulting tetrahydrofuran suspension of $TiCl_4$-THF complex was added zinc powder (950 mg, 14.6 mmol) and pyridine (0.15 cm^3). The suspension was then heated to reflux for 2.5 h, and the enal **3a** (73 mg, 0.13 mmol) or **3b** was added slowly as a dilute solution in dry tetrahydrofuran (35 cm^3) over 26 h. After the addition was complete, the reaction mixture was refluxed for an additional 4 h and then cooled to room temperature and diluted with pentane (30 cm^3) with vigorous stirring. The resulting mixture was filtered rapidly through a short column of silica gel to give a clear filtrate which was concentrated under reduced pressure to yield a crude oil. Purification of this by flash column chromatography (eluting with pentane) afforded the cyclized silyl ether **10a** (53 mg) or corresponding **10b** as colourless oils (78%). Compound **10a** ν_{max}/cm^{-1} 3049, 1653 (m, C=C), 1359, 1109, 1051 and 703; δ_H 1.04 (6 H, d, *J* 7.1, isopropyl-CH_3), 1.08 (9 H, s, *tert*-butyl), 1.49, 1.60, 1.67 (each 3 H, 3 s, 3 × CH_3), 1.90–2.24 (8 H, m), 2.25–2.73 (1 H, m), 2.70 (1 H, dd, *J* 7.8, 13.2), 2.79 (sept, 1 H, *J* 6.8), 4.00 (1 H, dd, *J* 3.7, 7.7), 4.90 (1 H, br m), 5.03 (1 H, t, *J* 6.5, 5.73 (1 H, d, *J* 11.4), 5.91 (1 H, d, *J* 11.4) and 7.27–7.75 (10 H, m); *m/z* (EI) 526 ($M^{\bullet+}$, 29%), 469 (M − 57, 14), 389 (13), 265 (51), 199 (100), 135 (65) and 57 (33) (Found: C, 82.1; H, 9.5. Calc. for $C_{36}H_{50}OSi$: C, 82.20; H, 9.58%). Compound **10b** ν_{max}/cm^{-1} 2957, 2855, 1664, 1608, 1463, 1382, 1058, 837 and 775; δ_H 0.05 (6 H, s, CH_3), 0.91 (9 H, s, *tert*-butyl), 1.11 (6 H, d, *J* 6.8, isopropyl-CH_3), 1.58, 1.63, 1.78 (each 3 H, 3 × s, 3 × CH_3), 2.00–2.40 (9 H, m), 2.53 (1 H, sept, *J* 6.8), 2.67 (1 H, dd, *J* 7.7, 13.3), 3.98 (1 H, t, *J* 5.0), 4.95–5.10 (1 H, br m, CH=), 5.10–5.30 (1 H, m, CH=), 5.78 (1 H, d, *J* 11.3, CH=) and 6.07 (1 H, d, *J* 11.3, CH=); *m/z* (EI) 402 ($M^{\bullet+}$, 21%), 387 (M − 15, 5), 359 (M − 43, 3), 265 (50), 209 (43), 198 (71), 141 (93) and 73 (100) (Found: C, 77.5; H, 11.5. Calc. for $C_{26}H_{46}OSi$: C, 77.68; H, 11.53%).

Synthesis of (±)-*Isosarcophytol-A* **1**.—To a stirred solution of the silyl ether **10a** (46 mg, 0.087 mmol) or equivalent **10b** in THF (1.5 cm^3) was added a solution of TBAF in THF (1 mol dm^{-3}, 0.2 cm^3) at 0 °C. The resulting mixture was then stirred for 10 min and concentrated under reduced pressure to give a residue which was taken in diethyl ether (5 cm^3) and the solution washed with water and brine (each 1 cm^3) and dried. Removal of the solvent by rotary evaporation gave a crude oil which then was subjected to purification by flash column chromatography (eluting with pentane–diethyl ether, 15:1) to afford the title compound (±)-**1** (25 mg, 100%) as colourless oil, ν_{max}/cm^{-1} 3378 (s, OH), 2959, 2856, 1667, 1644, 1449, 1381, 1008 and 874; δ_H 1.12 (6 H, d, *J* 6.9, isopropyl-CH_3), 1.52, 1.63, 1.74 (each 3 H, 3 × s, 3 × CH_3), 1.90–2.45 (9 H, m), 2.55 (1 H, sept, *J* 6.8), 2.75 (1 H, dd, *J* 7.1), 4.11 (1 H, t, *J* 7.1), 4.95–5.38 (2 H, m, CH=), 5.77 (1 H, d, *J* 11.5) and 6.07 (1 H, d, *J* 11.5); *m/z* (EI) 288 ($M^{\bullet+}$, 23%), 271 (M − 17, 2), 245 (M − 43, 3), 136 (15), 137 (100), 121 (21), 95 (42), 93 (27), 81 (34), 57 (31), 55 (30) and 18 (33) (Found: C, 83.35; H, 11.1. Calc. for $C_{20}H_{32}O$: C, 83.41; H, 11.20%).

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References

1 M. A. Tius, *Chem. Rev.*, 1988, **88**, 719.
2 J. E. McMurry, *Chem. Rev.*, 1989, **89**, 1513.
3 J. E. McMurry, J. G. Rico and You-nan Shih, *Tetrahedron Lett.*, 1989, **30**, 1173.
4 J. E. McMurry and R. G. Dushin, *J. Am. Chem. Soc.*, 1990, **112**, 6942.
5 J. Mao, Y. Li, Z. Hou, Y. Li and X. Liang, *Science in China* (*series B*), 1992, **35**, 257.
6 W. Li, Y. Li and Y. Li, *Chinese J. Chem.*, 1992, **10**, 92.
7 W. Li, Y. Li and Y. Li, *Journal of Lanzhou University*, 1991, **27**, 135.
8 For preliminary communication, see: Y. Li, W. Li and Y. Li, *Tetrahedron Lett.*, 1992, **33**, 1225.
9 A. J. Blackman, B. F. Bowden, J. C. Coll, B. Frich, M. Mahendran and S. J. Mitchell, *Aust. J. Chem.*, 1982, **35**, 1873.
10 M. Kobayashi, T. Nakagawa and H. Mitsuhashi, *Chem. Pharm. Bull.*, 1979, **27**, 2382.
11 H. Fujiki and T. Sugimura, *Cancer Surveys*, 1983, **2**, 539.
12 Japanese patent **81** 61318 to Mitsubishi Kasei Corporation.
13 C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn and J. Lampe, *J. Org. Chem.*, 1980, **45**, 1066.
14 J. A. Marshall, T. M. Jenson and B. S. DeHoff, *J. Org. Chem.*, 1987, **52**, 3860.
15 X. Xiao and G. D. Prestwich, *Synth. Commun.*, 1990, **20**, 3125.
16 S. J. Chaudhary and O. Hernandez, *Tetrahedron Lett.*, 1979, 99.
17 D. Tanner and O. Wennerstrom, *Acta Chem. Scand.*, 1983, **37b**, 693.

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