ARTICLE

OBC
www.rsc.org/obc

Triterpenoid total synthesis. Synthesis and absolute configuration of mispyric acid†

Yusuke Imamura,[a] Hirosato Takikawa,*[a] Mitsuru Sasaki[a] and Kenji Mori*[b]

[a] *Department of Biosystems Science, Graduate School of Science and Technology, Kobe University, Rokkodai 1-1, Nada-ku, Kobe 657-8501, Japan. E-mail: takikawa@kobe-u.ac.jp; Fax: +81 78 803 5958; Tel: +81 78 803 5958*

[b] *Insect Pheromone and Traps Division, Fuji Flavor Co. Ltd., Midorigaoka 3-5-8, Hamura, Tokyo 205-8503, Japan*

Received 6th May 2004, Accepted 9th June 2004
First published as an Advance Article on the web 14th July 2004

The first synthesis of mispyric acid (**1**), an inhibitor of DNA polymerase β with a novel triterpene skeleton, was achieved by starting from isoprene (**2**), geraniol (**6**) and 1,5-dimethoxy-1,4-cyclohexadiene (**14**). The absolute configuration of the naturally occurring **1** was determined as 2*S*,4*S*.

Introduction

In 1999, Hecht and his co-workers isolated mispyric acid (**1**), a structurally unique triterpene dicarboxylic acid with a novel skeleton, from the stem bark of Australian plant *Mischocarpus pyriformis* as a DNA polymerase β inhibitor.[2] This structurally unique monocyclic triterpene is presumably derived *via* a new biogenetic pathway including direct coupling of two farnesyl units.[2] In continuation of our works on synthesis of DNA polymerase inhibitors[3] and biosynthetically unique triterpenoids,[4] we initiated the synthesis of mispyric acid (**1**). While we have already reported the first synthesis of (±)-**1** as a preliminary communication,[5] the enantioselective synthesis of **1** has never been disclosed and the absolute configuration of natural **1** has remained unknown. Herein, we report the first synthesis and determination of the absolute configuration of **1** in detail.

Our synthetic plan for **1** is shown in Scheme 1, which is based on our racemate synthesis.[5] The target compound **1** was readily obtainable from **A**, which was prepared from **B** by installation of a methyl group to the enone and subsequent methylenation of the carbonyl group. For the construction of the key intermediate **B**, two alkylations (**C** with **D**, and **E** with **F**) were chosen as the key steps. Preparation of the two alkylating agents (**D** and **F**), corresponding to the side chains, was considered to be possible by conventional methods. However, the remaining problem was how to prepare the optically active form. There was a need to carry out the asymmetric reaction or the optical resolution at an appropriate stage, because our envisioned route could not take in any optically active starting material.

Results and discussion

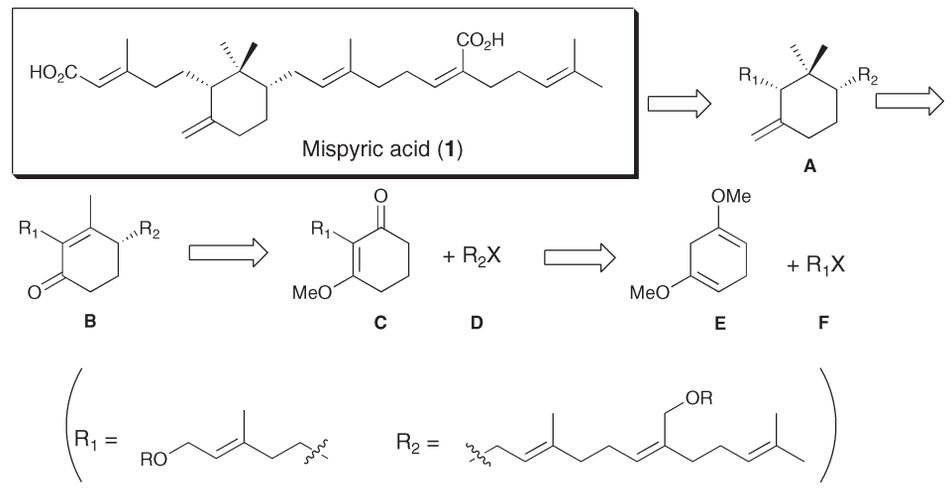
Our synthetic route to the key intermediate **B** (= **18**) is illustrated in Scheme 2. First, we synthesized the two alkylating agents as follows. According to the reported procedure, allylic chloride **3** was prepared from isoprene **2** in 3 steps.[6] The chloride **3** was converted into the corresponding bromide **4**, which was immediately exposed to the homologation reaction developed by Knochel *et al.*,[7] furnishing homoallylic iodide **5** (42% based on **3**). It should be noted that this homologation was not successful with the allylic chloride **3**. Next, an aldehyde **9** was prepared from geraniol **6** by the following four-step sequence: TBS protection (98%), regioselective epoxidation (81%), oxidative cleavage of the epoxide and re-protection (56%; 2 steps). The aldehyde **9** was then subjected to Corey–Yamamoto's modified Wittig reaction with concomitant hydroxymethylation.[8] In spite of all our efforts, the reaction of **9** with 5-methyl-4-hexenylidenetriphenylphosphorane[9] and paraformaldehyde gave the desired adduct **10** in rather low yield. The major by-product was the usual Wittig adduct lacking in a hydroxymethyl group (~30%). However, we could obtain geometrically pure **10** without contamination of the undesired (*E*)-isomer. Although other methodologies[10] might be applicable for the preparation of **10**, this route was adopted due to its brevity. After protection of the hydroxyl group of **10** as TBDPS ether (22% based on **9**), the resulting bis-silyl ether **11** was converted to the corresponding allylic bromide **13** in 2 steps (80%).

With two alkylating agents, **5** and **13**, in hand, we moved to construct the basic framework of mispyric acid. The lithiated 1,5-dimethoxy-1,4-cyclohexadiene **14**[11] was treated with **5** to give the alkylation product **15** (69%), which was then converted to **16** in conventional 3 steps (49%) as follows; treatment with acid, enol ether formation and TBS protection. For the installation of another side chain, the lithioenolate of **16** was alkylated with an allylic bromide **13** to furnish **17** (93%). This was then exposed to MeMgBr to afford the key intermediate (±)-**18** (91%).

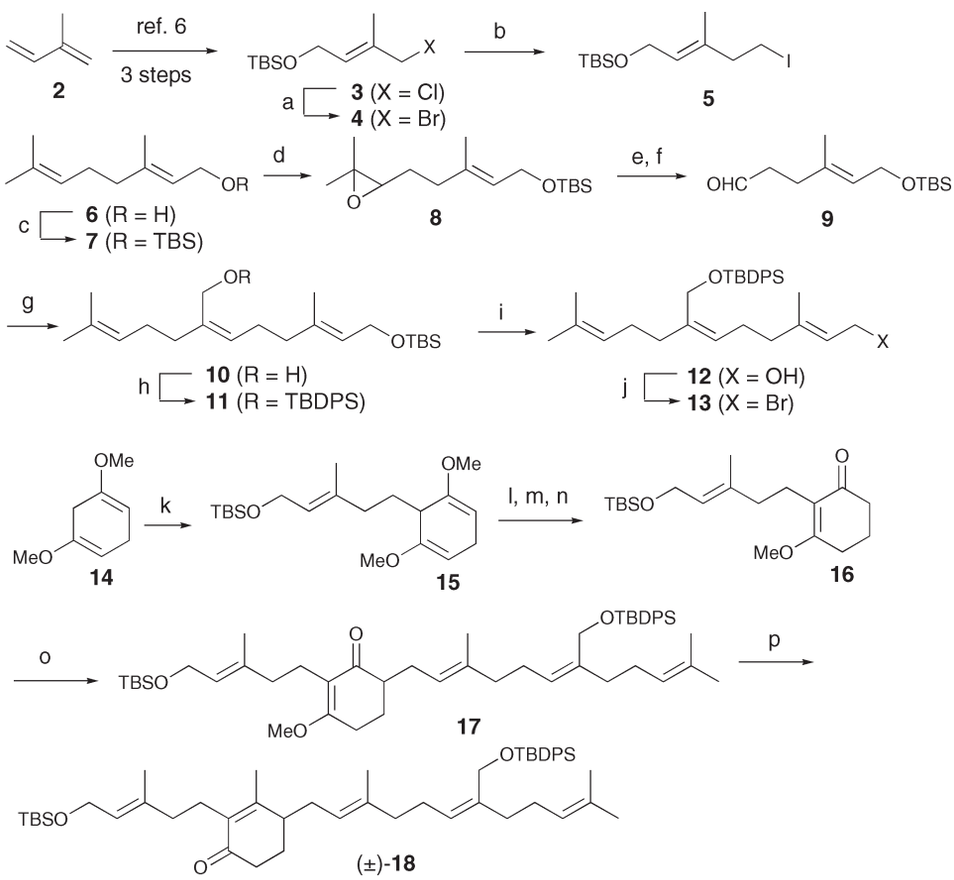
As mentioned before, there was a need to secure an optically active intermediate. For this purpose, we first envisioned utilizing asymmetric reduction. Thus, the key intermediate (±)-**18** was exposed to some chiral reducing reagents such as CBS reagent[12] and BINAL-H.[13] Unfortunately, however, these trials were unsuccessful. Therefore, we turned to optical resolution (Scheme 3). For the conventional optical resolution, (±)-**18** was reduced with L-selectride® to give the secondarily allylic alcohols (±)-**19a** and (±)-**19b** (94%; *ca.* 9 : 1). The relative configurations of both isomers were elucidated based on the similarity of ^{1}H-NMR data between **19a/b** and the structurally related compounds.[14] The minor isomer (±)-**19b** could be easily recycled to the parent ketone (±)-**18** by oxidation with *o*-iodoxybenzoic acid (IBX).[15] Our attempts to resolve (±)-**19a** by enzymatic resolution were not fruitful either, even after screening of over ten hydrolytic enzymes. The next and remaining method was the classical resolution using a chiral derivatizing reagent. After examination of some resolving reagents such as *O*-methylmandelic acid, camphanic acid and 3β-acetoxyetienic acid,[16] we eventually found that Harada's reagent **20**[17] gave the successful results as follows. Condensation of (±)-**19a** and (*S*)-**20** (>99.9% ee) was performed with DCC in the presence of DMAP to give a diastereomeric mixture of **21a** and **21b**. Although this mixture was chromatographically inseparable, removal of TBS and TBDPS protecting groups made it possible for us to separate the resulting diols **22a/b** by flash chromatography, affording the less polar isomer (40%) and more polar isomer (36%), respectively. The remaining problem was determination of the configurations of both diastereomers. Although our trial to apply a modified Mosher's method[18] was not perfectly successful due to poor resolution of the critical signals, we tentatively speculated that the less polar isomer was **22a** and the more polar was **22b** based on fragmentarily perceived $\Delta\delta$ values at 5′-and 5″-H (*vide infra*).

† Triterpenoid total synthesis. Part 8. For part 7 see ref. 1

DOI: 10.1039/b406820c



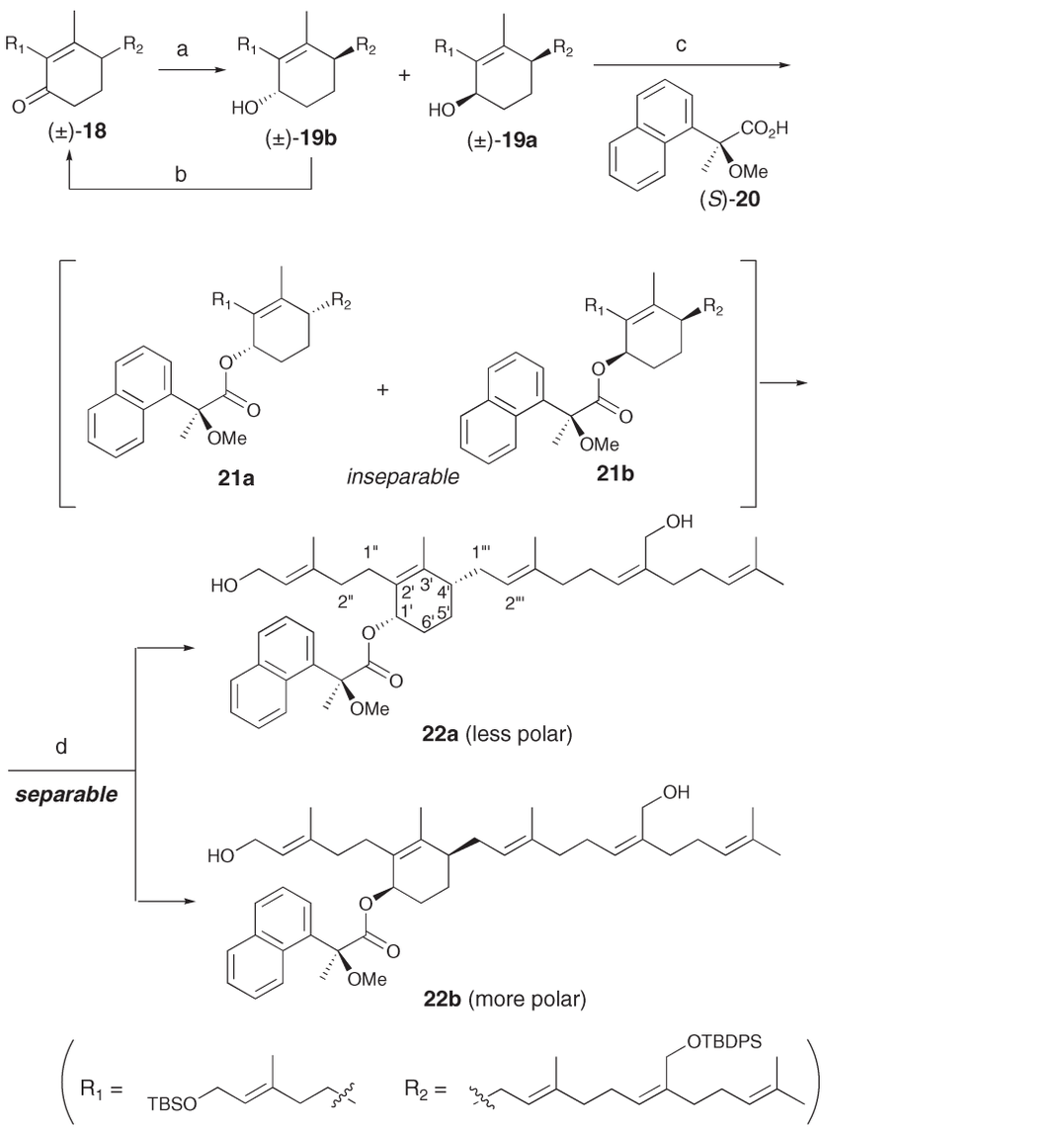
Scheme 1 Structure of mispyric acid (**1**) and its synthetic plan.



Scheme 2 Synthesis of the key intermediate (±)-**18**. *Reagents and conditions*: (a) NaBr, DMF, rt; (b) ICH_2ZnI, CuI, LiI, THF, −25 °C to rt (42% based on **3**); (c) TBSCl, imidazole, DMF (98%); (d) *m*CPBA, $CHCl_3$ (81%); (e) $HIO_4{\cdot}2H_2O$, THF–H_2O; (f) TBSCl, imidazole, DMF (56% based on **8**); (g) 5-methyl-4-hexenylidenetriphenylphosphorane, THF, −78 °C; *s*-BuLi, −25 °C; then $(CH_2O)_n$, 0 °C to rt; (h) TBDPSCl, imidazole, DMF (22% based on **9**); (i) AcOH, H_2O, THF (92%); (j) PBr_3, pyridine, Et_2O (87%); (k) *t*-BuLi, THF, −78 °C; then HMPA, **5** (69%); (l) 1 M HCl, THF; (m) CH_2N_2, Et_2O–EtOAc–MeOH, 0 °C; (n) TBSCl, imidazole, DMF (49% based on **15**); (o) LDA, THF, −78 °C; then **13**, −90 °C to rt (93%); (p) MeMgBr, THF, 5 °C to rt; then NH_4Cl aq. (91%).

Diastereomerically pure diol **22a** was converted into the corresponding bis-TBS ether **23a** (91%), which was subjected to reductive cleavage of the resolving auxiliary to furnish allylic alcohol (−)-**24** (87%). This was then exposed to cyclopropanation[19] to give (−)-**25** (95%). The bicyclic alcohol (−)-**25** was then oxidized with PDC to afford (+)-**26** (91%). Reductive cleavage of the cyclopropane ring[20] was carried out under the classical Birch conditions, Li, NH_3, THF and *t*-BuOH, to yield the desired (−)-**27** (66%). Under these conditions, unexpectedly and delightfully, the resulting **27** was proven to be free from the undesired *trans*-isomer. The desired *cis*-isomer **27** must be not only kinetically but also thermodynamically more preferable than the *trans*-isomer. Similarly, **22b** was also converted into (+)-**27**. At this stage, we applied circular dichroism (CD) spectroscopy for the confirmation of the absolute configurations of (−)- and (+)-**27**. In their CD spectra, we observed a negative Cotton effect in the case of (−)-**27**, while (+)-**27** was with a positive Cotton effect. Applications of the octant rule[21] proved the absolute configurations of (−)- and (+)-**27** to be (2*R*,4*S*) and (2*S*,4*R*), respectively, as shown in Scheme 4. These results are in agreement with our speculation based on a modified Mosher's method applied for **22a/b**.

The ketone (−)-**27** was exposed to Wittig methylenation to give (2*S*,4*S*)-**28** (80%). After removal of the two TBS groups (97%), the resulting diol (2*S*,4*S*)-**29** was oxidized stepwise with Dess–Martin periodinane (DMP)[22,23] followed by $NaClO_2$ to give the target compound (2*S*,4*S*)-**1** (68%, 2 steps), $[\alpha]_D^{27}$ +9.2 (*c* 0.22 in MeOH), {lit.,[2] $[\alpha]_D^{20}$ +12.5 (*c* 0.05 in MeOH)}. The various spectral data of synthetic (2*S*,4*S*)-**1** are in good accord with those of the natural



Scheme 3 Optical resolution of the intermediate (±)-**19a**. *Reagents and conditions*: (a) L-selectride, THF (84.6% for **19a**, 9.4% for **19b**, respectively); (b) IBX, DMSO–THF (93%); (c) (*S*)-**20**, DCC, DMAP, CH_2Cl_2; (d) TBAF, THF (40% for **22a**, 36% for **22b**, based on **19a**, respectively).

product.[2] Similarly, (2*S*,4*R*)-**27** was also converted into (2*R*,4*R*)-**1**, $[\alpha]_D^{26}$ −10.7 (*c* 0.232 in MeOH). It was noted that absolute values of specific rotation of the synthesized enantiomers fluctuated considerably, especially at low concentration. Although the reason for fluctuation of specific rotation was unclear, fortunately, the reversal of the sign has never been observed. Thus, the absolute configuration of the natural mispyric acid was determined as 2*S*,4*S*, because synthetic (2*S*,4*S*)-**1** and natural **1** were both dextrorotatory.

Conclusion

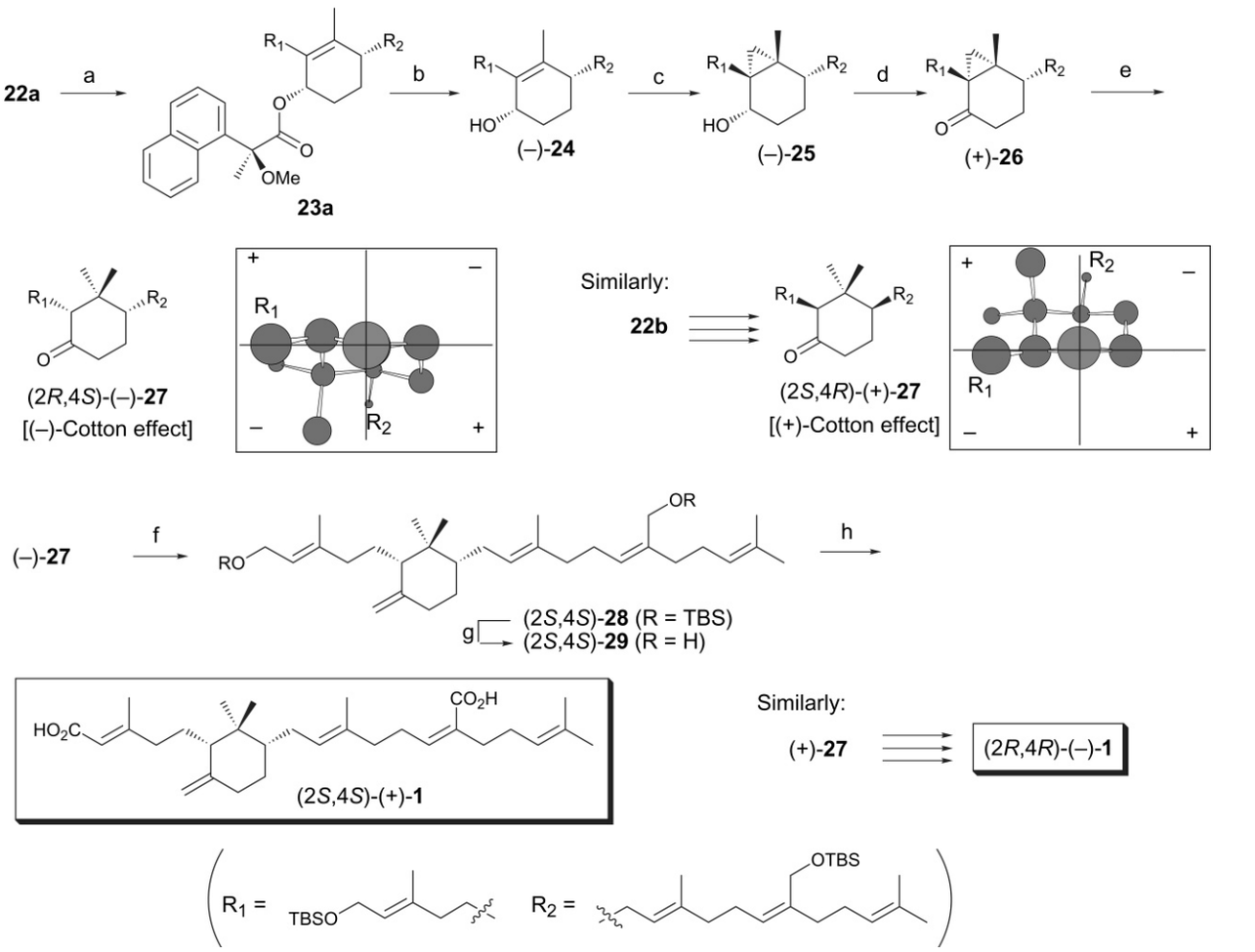
In conclusion, the first synthesis of mispyric acid (**1**), a triterpene inhibitor of DNA polymerase β, was accomplished by starting from isoprene (**2**), geraniol (**6**) and 1,5-dimethoxy-1,4-cyclohexadiene (**14**). The absolute configuration of naturally occurring mispyric acid **1** was established as 2*S*,4*S*. Detailed studies on DNA polymerase inhibitory activities of **1** employing our synthetic samples are now in progress.

Experimental

General

Mps were uncorrected. IR spectra were measured on a JASCO FT/IR-460 spectrometer. ^{1}H-NMR spectra were recorded at 300 MHz on a JEOL JNM-AL300 spectrometer, at 400 MHz on a JEOL JNM-LA400 spectrometer and at 500 MHz on a JEOL JNM-LA500 spectrometer. The peak for $CHCl_3$ in $CDCl_3$ (at δ 7.26) was used for the internal standard. Chemical shifts are reported in ppm on the δ scale and *J*-values are given in Hz. ^{13}C-NMR spectra were recorded at 75 MHz on a JEOL JNM-AL300 spectrometer, at 100 MHz on a JEOL JNM-LA400 spectrometer and at 126 MHz on a JEOL JNM-LA500 spectrometer. The peak for $CDCl_3$ (at δ 77.0) was used for the internal standard. Optical rotations were taken with a JASCO P-1010 polarimeter or a HORIBA SEPA-300 polarimeter. Mass spectra were measured with a JEOL JMS-SX102A spectrometer. CD spectra were measured with a JASCO J-720 spectrometer. Column chromatography was carried out on Merck Kieselgel 60 Art 1.07734 or Kanto Chemical Co., Inc. Silica Gel 60 N (spherical, neutral, 63–210 μm). Flash chromatography was carried out on Kanto Chemical Co., Inc. Silica Gel 60 N (spherical, neutral, 40–50 μm). TLC analyses were performed on Merck silica gel plates 60F–254.

(*E*)-1-Bromo-4-*tert*-butyldimethylsilyloxy-2-methylbut-2-ene 4. To a stirred solution of **3** (13.0 g, 55.4 mmol) in DMF (200 cm^3) was added NaBr (28.3 g, 275 mmol) at 0 °C, and the reaction mixture was stirred for 23 h at room temperature. After cooling to 0 °C, Et_2O and water were added to the resulting mixture. This mixture was extracted with Et_2O, and the extract was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting allylic bromide **4** (14.4 g) was used for the next reaction without purification. **4**: δ_H(500 MHz; $CDCl_3$) 0.07 (6 H, s, $SiMe_2$), 0.90 (9 H, s, $SiBu^t$), 1.77 (3 H, s, 2-Me), 3.95 (2 H, s, 1-H_2), 4.21 (2 H, d, *J* 6.7, 4-H_2), 5.71 (1 H, t, *J* 6.7, 3-H).



Scheme 4 Synthesis of mispyric acid (**1**). *Reagents and conditions*: (a) TBSCl, imidazole, DMF (91%); (b) $LiAlH_4$, Et_2O (87%); (c) CH_2I_2, Et_2Zn, Et_2O (95%); (d) PDC, MS 4A, CH_2Cl_2 (91%); (e) Li, NH_3, THF, *t*-BuOH, −78 °C (66%); (f) Ph_3PCH_3Br, NaHMDS, THF, 0 °C to rt (80%); (g) TBAF, THF (97%); (h) DMP, CH_2Cl_2; $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O (68% based on **29**).

(*E*)-1-*tert*-Butyldimethylsilyloxy-5-iodo-3-methylpent-2-ene 5. To a stirred solution of crude **4** (14.4 g, *ca.* 52 mmol), CuI (13.3 g, 69.8 mmol) and LiI (20.1 g, 150 mmol) in THF (250 cm^3) was added a solution of ICH_2ZnI[7b] (*ca.* 270 mmol) in THF (135 cm^3) at −25 °C under Ar. After having been stirred at room temperature overnight, the reaction mixture was cooled to 0 °C, quenched with water, and extracted with Et_2O. The extract was washed with saturated aqueous $Na_2S_2O_3$, water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give **5** (8.0 g, 42%, 2 steps) as a slightly pink oil. This homoallylic iodide **5** was immediately used in the next reaction. **5**: δ_H(500 MHz; $CDCl_3$) 0.07 (6 H, s, $SiMe_2$), 0.90 (9 H, s, SiBu^t), 1.64 (3 H, s, 3-Me), 2.56 (2 H, t, *J* 7.6, 4-H_2), 3.23 (2 H, t, *J* 7.6, 5-H_2), 4.19 (2 H, d, *J* 6.1, 1-H_2), 5.37 (1 H, t, *J* 6.1, 2-H).

(*E*)-1-*tert*-Butyldimethylsilyloxy-6,7-epoxy-3,7-dimethyloct-2-ene 8. A solution of *m*-chloroperbenzoic acid (70%; 15.2 g, 62 mmol) in $CHCl_3$ (150 cm^3) was added to a solution of **7** (14.7 g, 54.7 mmol) in $CHCl_3$ (230 cm^3) at 0 °C and the reaction mixture was stirred for 1 h at this temperature. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with water, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give **8** (12.6 g, 81%) as a colourless oil, n_D^{25} 1.4534 (Found: C, 67.43; H, 11.60. $C_{16}H_{32}O_2Si$ requires C, 67.54; H, 11.34%); ν_{max}(film)/cm^{-1} 1670w (C=C), 1255m (Si–Me), 1120s (Si–O); δ_H(400 MHz; $CDCl_3$) 0.07 (6 H, s, $SiMe_2$), 0.90 (9 H, s, SiBu^t), 1.26 (3 H, s, Me), 1.30 (3 H, s, Me), 1.58–1.74 (2 H, m, 5-H_2), 1.64 (3 H, s, MeC=C), 2.07–2.22 (2 H, m, 4-H_2), 2.71 (1 H, t, *J* 6.1, 6-H), 4.19 (2 H, d, *J* 6.3, 1-H_2), 5.34 (1 H, t, *J* 6.3, 2-H); δ_C(100 MHz; $CDCl_3$) −5.3, 16.2, 18.2, 18.6, 24.7, 25.8, 27.0, 35.9, 58.1, 60.0, 63.8, 124.8, 135.7.

(*E*)-6-*tert*-Butyldimethylsilyloxy-4-methylhex-4-enal 9. A solution of periodic acid dihydrate (31.9 g, 140 mmol) in water (130 cm^3) was added to a solution of epoxide **8** (35.7 g, 125 mmol) in THF (230 cm^3) at 0 °C. After stirring for 30 min, $NaHCO_3$ was added, and stirring was continued for 1 h. The resulting mixture was filtered through a pad of Celite, and the filtrate was extracted with Et_2O. The extract was washed with saturated aqueous $NaHCO_3$ and brine. The combined aqueous layers were further extracted with $CHCl_3$. The extract was washed with saturated aqueous $NaHCO_3$ and brine. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in DMF (250 cm^3) and cooled to 0 °C. Imidazole (21.6 g, 316 mmol) and TBSCl (24.7 g, 164 mmol) were added to this solution. The reaction mixture was stirred for 30 min at room temperature, then quenched with water at 0 °C and extracted with Et_2O. The extract was washed with water, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. After removal of a silanol under reduced pressure (*ca.* 30 °C, 2 mmHg), the residue was chromatographed on SiO_2 to give **9** (17.1 g, 56%) as a colourless oil, n_D^{25} 1.4549 (Found: C, 64.24; H, 11.01. $C_{13}H_{26}O_2Si$ requires C, 64.41; H, 10.81%); ν_{max}(film)/cm^{-1} 2715w (H–CO), 1730s (C=O), 1670w (C=C), 1255m (Si–Me), 1115s (Si–O); δ_H(400 MHz; $CDCl_3$) 0.06 (6 H, s, $SiMe_2$), 0.90 (9 H, s, SiBu^t), 1.64 (3 H, s, 4-Me), 2.33 (2 H, t, *J* 7.6, 3-H_2), 2.56 (2 H, td, *J* 7.6 and 1.7, 2-H_2), 4.19 (2 H, d, *J* 6.3, 6-H_2), 5.32 (1 H, td, *J* 6.3 and 1.2, 5-H), 9.77 (1 H, t, *J* 1.7, 1-H); δ_C(100 MHz; $CDCl_3$) −5.3, 16.3, 18.2, 25.8, 31.3, 41.7, 60.0, 125.2, 134.6, 201.9.

(2*Z*,6*E*)-8-*tert*-Butyldimethylsilyloxy-6-methyl-2-(4-methyl-3-pentenyl)-2,6-octadien-1-ol 10. To a suspension of 5-methyl-4-hexenyltriphenylphosphonium iodide (15.0 g, 30.8 mmol) in THF (200 cm^3) was added *n*-BuLi (1.59 mol dm^{-3} in *n*-hexane; 19.4 cm^3,

30.8 mmol) at 0 °C under Ar. After stirring for 30 min at this temperature, the mixture was cooled to −78 °C and a solution of aldehyde **9** (7.5 g, 31 mmol) in THF (50 cm^3) was added. After stirring for 5 min at this temperature, the reaction mixture was allowed to warm to −25 °C and treated with *sec*-BuLi (0.99 mol dm^{-3} in cyclohexane–*n*-hexane; 62.4 cm^3, 61.8 mmol). The resulting solution was allowed to warm to 0 °C and treated with paraformaldehyde (92.0%; 5.00 g, 153 mmol). After having been stirred at room temperature for 1 h, the reaction mixture was quenched with water and extracted with Et_2O. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give **10** (2.65 g). This was used in the next reaction without further purification. An analytical sample was obtained by careful re-chromatography to give pure **10** as a colourless oil, n_D^{25} 1.4876 (Found: C, 71.28; H, 11.67. $C_{21}H_{40}O_2Si$ requires C, 71.53; H, 11.43%); ν_{max}(film)/cm^{-1} 3550s (O–H), 1670w (C=C), 1255m (Si–CH_3), 1110s (Si–O); δ_H(400 MHz; $CDCl_3$) 0.06 (6 H, s, $SiMe_2$), 0.90 (9 H, s, SiBu^t), 1.60 (3 H, s, MeC=C), 1.64 (3 H, s, MeC=C), 1.68 (3 H, s, MeC=C), 2.03 (2 H, t, *J* 7.3, CH_2C=C), 2.12 (4 H, br s, 2 × CH_2C=C), 2.20 (2 H, q, *J* 7.3, CH_2C=C), 4.09 (2 H, d, *J* 5.4, CH_2OH), 4.17 (2 H, d, *J* 6.3, CH_2OH), 5.11 (1 H, m, C*H*=C), 5.24–5.31 (2 H, m, 2 × C*H*=C); δ_C(100 MHz; $CDCl_3$) −5.2, 16.4, 17.7, 18.4, 25.66, 25.70, 26.0, 26.9, 34.9, 39.4, 60.0, 60.1, 124.1, 124.8, 127.6, 131.6, 136.5, 138.8.

(6*Z*,10*E*)-12-*tert*-Butyldimethylsilyloxy-6-*tert*-butyldiphenylsilyloxymethyl-2,10-dimethyl-2,6,10-dodecatriene 11. To a stirred solution of **10** (inseparable mixture; 2.65 g, *ca.* 7.5 mmol) in DMF (27 cm^3) were added imidazole (1.28 g, 18.8 mmol) and TBDPSCl (98%; 2.21 cm^3, 8.27 mmol) at 0 °C. After having been stirred at room temperature for 40 min, the reaction mixture was quenched with water at 0 °C and extracted with Et_2O. The extract was washed with water, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give **11** (4.11 g, 22% from **9**) as a colourless oil, n_D^{25} 1.5170 (Found: C, 75.29; H, 10.14. $C_{37}H_{58}O_2Si_2$ requires C, 75.19; H, 9.89%); ν_{max}(film)/cm^{-1} 1670w (C=C), 1255m (Si–CH_3), 1110s (Si–O); δ_H(400 MHz; $CDCl_3$) 0.05 (6 H, s, $SiMe_2$), 0.89 (9 H, s, SiBu^t), 1.04 (9 H, s, SiBu^t), 1.51 (3 H, s, MeC=C), 1.59 (3 H, s, MeC=C), 1.68 (3 H, s, MeC=C), 1.91 (4 H, br s, 2 × CH_2C=C), 2.11 (2 H, q-like, *J* 7.6, CH_2C=C), 2.20 (2 H, t-like, *J* 7.6, CH_2C=C), 4.14 (2 H, d, *J* 6.4, 1-H_2), 4.17 (2 H, s, CH_2OTBDPS), 5.12 (1 H, t, *J* 7.6, C*H*=C), 5.15–5.25 (2 H, m, 2 × C*H*=C), 7.33–7.45 (6 H, m, *m*-, *p*-Ar), 7.68 (4 H, dd, *J* 8.0 and 1.7, *o*-Ar); δ_C(100 MHz; $CDCl_3$) −5.1, 16.2, 17.7, 18.4, 19.2, 25.6, 25.7, 26.0, 26.8, 27.0, 34.7, 39.7, 60.2, 61.1, 124.50, 124.55, 126.1, 127.6, 129.5, 131.2, 133.8, 135.6, 136.4, 138.3.

(2*E*,6*Z*)-7-*tert*-Butyldiphenylsilyloxymethyl-3,11-dimethyl-2,6,10-dodecatrien-1-ol 12. To a stirred mixture of **11** (1.52 g, 2.57 mmol) in THF (3 cm^3) and water (3 cm^3) was added AcOH (9 cm^3) at 0 °C. After having been stirred at room temperature for 19 h, the resulting solution was extracted with Et_2O. The extract was washed with water, saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give **12** (1.13 g, 92%) as a colourless oil, n_D^{25} 1.5169 (Found: C, 78.12; H, 9.39. $C_{31}H_{44}O_2Si$ requires C, 78.10; H, 9.30%); ν_{max}(film)/cm^{-1} 3330w (O–H), 1670w (C=C), 1110s (Si–O); δ_H(500 MHz; $CDCl_3$) 1.04 (9 H, s, SiBu^t), 1.57 (3 H, s, MeC=C), 1.59 (3 H, s, MeC=C), 1.67 (3 H, s, MeC=C), 1.91–1.94 (4 H, m, 2 × CH_2C=C), 2.11 (2 H, q-like, *J* 7.3, CH_2C=C), 2.21 (2 H, t-like, *J* 7.3, CH_2C=C), 4.10 (2 H, t, *J* 6.4, 1-H_2), 4.18 (2 H, s, CH_2OTBDPS), 5.12 (1 H, t, *J* 7.3, C*H*=C), 5.18 (1 H, br s, C*H*=C), 5.31 (1 H, t, *J* 6.4, 2-H), 7.35–7.45 (6 H, m, *m*-, *p*-Ar), 7.68 (4 H, dd, *J* 6.8 and 1.5, *o*-Ar); δ_C(100 MHz; $CDCl_3$) 16.1, 17.7, 19.2, 25.6, 25.7, 26.8, 26.9, 34.7, 39.6, 59.2, 61.1, 123.5, 124.5, 125.9, 127.6, 129.5, 131.2, 133.7, 135.6, 138.4, 139.2.

(6*Z*,10*E*)-12-Bromo-6-*tert*-butyldiphenylsilyloxymethyl-2,10-dimethyl-2,6,10-dodecatriene 13. To a stirred solution of **12** (551 mg, 1.16 mmol) in Et_2O (5.5 cm^3) was added a few drops of pyridine and PBr_3 (90%; 49 mm^3, 0.46 mmol) at −40 °C under Ar. After having been stirred at this temperature for 20 min and −20 °C for 40 min, the reaction mixture was quenched with MeOH, poured into saturated aqueous $NaHCO_3$ and pentane, and extracted with pentane. The extract was washed with saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$, filtered through neutral SiO_2 and Celite, and concentrated under reduced pressure to give crude **13** (543 mg, 87%) as a light brown oil. This was immediately used in the next reaction.

2-[(*E*)-5′-*tert*-Butyldimethylsilyloxy-3′-methyl-3′-pentenyl]-1,5-dimethoxycyclohexa-1,4-diene 15. To a stirred solution of *t*-BuLi (1.64 mol dm^{-3} in pentane; 18.7 cm^3, 30.7 mmol) in THF (200 cm^3) was added a solution of 1,5-dimethoxy-1,4-cyclohexadiene **14** (4.3 g, 31 mmol) in THF (5 cm^3) at −78 °C and the resulting solution was stirred at this temperature for 1 h. To this solution HMPA (5.4 cm^3, 31 mmol) was added, and stirring was continued for additional 10 min. Then a solution of **5** (8.0 g, 24 mmol) in THF (4 cm^3) was added, and the reaction mixture was allowed to warm to room temperature. The resulting solution was quenched with brine and extracted with Et_2O. The extract was washed with saturated aqueous $Na_2S_2O_3$, water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give **15** (5.70 g, 69%) as a colourless oil. This compound contained inseparable impurities and was not so stable, thus we immediately used it for the next reaction.

2-[(*E*)-5′-*tert*-Butyldimethylsilyloxy-3′-methyl-3′-pentenyl]-3-methoxy-2-cyclohexen-1-one 16. To a stirred solution of **15** (5.70 g, *ca.* 16 mmol) in THF (57 cm^3) was added aqueous HCl (1.0 mol dm^{-3}; 37 cm^3, 37 mmol) at 0 °C. After having been stirred at room temperature for 1 h, EtOAc and NaCl were added to the resulting solution. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure to give the crude hydroxy ketone.

This was dissolved in MeOH (15 cm^3) and EtOAc (45 cm^3), and cooled to 0 °C. Then a solution of CH_2N_2 (0.1 mol) in Et_2O (100 cm^3) was added to this solution. After having been stirred for 30 min, excess CH_2N_2 was destroyed by adding a few drops of AcOH, and the resulting solution was diluted with EtOAc, washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure.

The residue was dissolved in DMF (100 cm^3) and cooled to 0 °C. Imidazole (3.4 g, 50 mmol) and TBSCl (3.8 g, 25 mmol) were added to this solution. After having been stirred at room temperature for 1 h, the resulting mixture was quenched with water and extracted with Et_2O. The extract was washed with saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give **16** (2.66 g, 49% from **15**) as a colourless oil, n_D^{25} 1.4978 (Found: C, 67.13; H, 10.28. $C_{19}H_{34}O_3Si$ requires C, 67.40; H, 10.12%); ν_{max}(film)/cm^{-1} 1650s (C=O), 1615s (C=C), 1255m (Si–CH_3), 1110s (Si–O); δ_H(500 MHz; $CDCl_3$) 0.06 (6 H, s, $SiMe_2$), 0.90 (9 H, s, SiBu^t), 1.65 (3 H, s, MeC=C), 1.94–1.99 (4 H, m, 5- and 2′-H_2), 2.32 (2 H, t, *J* 6.4, 4-H_2), 2.38 (2 H, t, *J* 7.4, 6-H_2), 2.54 (2 H, t, *J* 6.4, 1′-H_2), 3.78 (3 H, s, MeO), 4.17 (2 H, d, *J* 6.4, 5′-H_2), 5.23 (1 H, t, *J* 6.4, 4′-H); δ_C(100 MHz; $CDCl_3$) −5.3, 16.0, 18.2, 20.1, 20.7, 24.6, 25.8, 36.2, 38.1, 54.8, 60.1, 118.8, 123.9, 137.1, 171.9, 197.9.

2-[(*E*)-5′-*tert*-Butyldimethylsilyloxy-3′-methyl-3′-pentenyl]-6-[(2″*E*,6″*Z*)-7″-*tert*-butyldiphenylsilyloxymethyl-3″,11″-dimethyl-2″,6″,10″-dodecatrienyl]-3-methoxy-2-cyclohexen-1-one 17. To a stirred solution of diisopropylamine (0.185 cm^3, 1.31 mmol) in THF (3 cm^3) was added *n*-BuLi (1.59 mol dm^{-3} in *n*-hexane; 0.79 cm^3, 1.26 mmol) at 0 °C. After having been stirred at this temperature for 30 min, the resulting LDA solution was cooled to −78 °C. Then a solution of **16** (329 mg, 0.972 mmol) in THF (1 cm^3) was added. After having been stirred at this temperature for 30 min, the mixture was cooled to −90 °C, and the solution of

13 (543 mg, 1.01 mmol) in THF (1 cm^3) was quickly added. The mixture was allowed to warm to room temperature and stirred for 1 h. The resulting solution was quenched with water and extracted with Et_2O. The extract was washed with saturated aqueous $Na_2S_2O_3$, water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give **17** (628 mg, 93% based on the consumed **16**) and recovered **16** (41 mg, 12%). **17**: colourless oil, n_D^{25} 1.5172 (Found: C, 75.27; H, 9.73. $C_{50}H_{76}O_4Si_2$ requires C, 75.32; H, 9.61%); ν_{max}(film)/cm^{-1} 1650s (C=O), 1620s (C=C), 1250m (Si–Me), 1110s (Si–O); δ_H(400 MHz; $CDCl_3$) 0.06 (6 H, s, $SiMe_2$), 0.90 (9 H, s, $SiBu^t$), 1.04 (9 H, s, $SiBu^t$), 1.50 (3 H, s, MeC=C), 1.59 (3 H, s, MeC=C), 1.65 (3 H, s, MeC=C), 1.68 (3 H, s, MeC=C) 1.89–2.16 (12 H, m, 4 × CH_2C=C, 5- and 2′-H_2), 2.20 (2 H, t, *J* 6.8, CH_2C=C), 2.36 (2 H, br t, *J* 6.9, 4-H_2), 2.41–2.46 (1 H, m, 6-H), 2.47–2.59 (2 H, m, 1′-H_2), 3.75 (3 H, s, MeO), 4.17 (2 H, d, *J* 6.4, 5′-H_2), 4.17 (2 H, s, CH_2OTBDPS), 5.02 (1 H, t, *J* 6.9, C*H*=C), 5.12 (1 H, t, *J* 6.8, C*H*=C), 5.17 (1 H, m, C*H*=C), 5.24 (1 H, t, *J* 6.4, 4′-H), 7.35–7.44 (6 H, m, *m*-, *p*-Ar), 7.68 (4 H, dd, *J* 8.0 and 1.7, *o*-Ar); δ_C(100 MHz; $CDCl_3$) −5.1, 16.0, 16.1, 17.7, 18.4, 19.2, 20.7, 23.7, 25.2, 25.7, 25.9, 26.0, 26.7, 27.0, 28.0, 34.7, 38.3, 39.9, 44.8, 54.7, 60.3, 61.2, 118.5, 122.3, 124.0, 124.5, 126.2, 127.6, 129.5, 131.1, 133.7, 135.5, 136.3, 137.5, 138.1, 170.8, 199.5.

2-[(*E*)-5′-*tert*-Butyldimethylsilyloxy-3′-methyl-3′-pentenyl]-4-[(2″*E*,6″*Z*)-7″-*tert*-butyldiphenylsilyloxymethyl-3″,11″-dimethyl-2″,6″,10″-dodecatrienyl]-3-methyl-2-cyclohexen-1-one 18. To a stirred solution of **17** (2.97 g, 3.73 mmol) in THF (50 cm^3) was added MeMgBr (0.93 mol dm^{-3} in THF; 12.0 cm^3, 11.2 mmol) at 5 °C under Ar. After having been stirred at room temperature for 3 h, the resulting solution was quenched with ice and saturated aqueous NH_4Cl, and extracted with Et_2O. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give **18** (2.64 g, 91%) as a colourless oil, n_D^{25} 1.5171 (Found: C, 76.58; H, 9.99. $C_{50}H_{76}O_3Si_2$ requires C, 76.86; H, 9.80%); ν_{max}(film)/cm^{-1} 1670s (C=O), 1625w (C=C), 1255m (Si–Me), 1110s (Si–O); δ_H(500 MHz; $CDCl_3$) 0.06 (6 H, s, $SiMe_2$), 0.90 (9 H, s, $SiBu^t$), 1.04 (9 H, s, $SiBu^t$), 1.51 (3 H, s, MeC=C), 1.59 (3 H, s, MeC=C), 1.66 (3 H, s, MeC=C), 1.69 (3 H, s, MeC=C), 1.73–1.80 (1 H, m), 1.93 (11 H, m), 2.11 (2 H, q-like, *J* 6.7, CH_2C=C), 2.16–2.23 (4 H, m), 2.26 (1 H, dt, *J* 17.1 and 4.9, 6-H), 2.31–2.47 (3 H, m), 4.17 (4 H, m, 2 × CH_2O), 5.02 (1 H, t, *J* 7.1, C*H*=C), 5.12 (1 H, t, *J* 6.7, C*H*=C), 5.18 (1 H, m, C*H*=C), 5.28 (1 H, t, *J* 6.1, 4′-H), 7.34–7.44 (6 H, m, *m*-, *p*-Ar), 7.68 (4 H, dd, *J* 7.9 and 1.2, *o*-Ar); δ_C(100 MHz; $CDCl_3$) −5.1, 16.1, 16.4, 17.7, 18.4, 19.2, 19.8, 24.0, 25.4, 25.7, 25.9, 26.0, 26.8, 27.0, 29.5, 33.6, 34.7, 38.5, 39.9, 41.5, 60.3, 61.2, 122.5, 124.50, 124.51, 126.0, 127.6, 129.5, 131.2, 133.8, 135.1, 135.6, 136.8, 136.9, 138.3, 158.6, 198.1.

(1*R,4*R**)-2-[(*E*)-5′-*tert*-Butyldimethylsilyloxy-3′-methyl-3′-pentenyl]-4-[(2″*E*,6″*Z*)-7″-*tert*-butyldiphenylsilyloxymethyl-3″,11″-dimethyl-2″,6″,10″-dodecatrienyl]-3-methyl-2-cyclohexen-1-ol 19a and its (1*S**,4*R**)-isomer 19b.** To a stirred solution of **18** (122 mg, 156 μmol) in THF (2 cm^3) was added L-Selectride® (1.0 mol dm^{-3} in THF; 234 mm^3, 234 μmol) dropwise at −78 °C under Ar. After having been stirred at −60 °C for 4 h, the reaction mixture was allowed to warm up to 5 °C, quenched with MeOH, and diluted with Et_2O. This mixture was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **19a** (103.2 mg, 84.6%) as a colourless oil (less polar) and **19b** (11.5 mg, 9.4%) also as a colourless oil (more polar). **19a**: n_D^{25} 1.5165 (Found: C, 76.42; H, 10.14. $C_{50}H_{78}O_3Si_2$ requires C, 76.67; H, 10.04%); ν_{max}(film)/cm^{-1} 3430w (O–H), 1670w (C=C), 1255m (Si–Me), 1110s (Si–O); δ_H(500 MHz; $CDCl_3$) 0.07 (6 H, s, $SiMe_2$), 0.91 (9 H, s, $SiBu^t$), 1.04 (9 H, s, $SiBu^t$), 1.28–1.38 (1 H, m), 1.39–1.47 (1 H, m), 1.51 (3 H, s, MeC=C), 1.53–1.74 (3 H, m), 1.59 (3 H, s, MeC=C), 1.66 (3 H, s, MeC=C), 1.69 (3 H, s, MeC=C), 1.92 (6 H, m), 2.07 (2 H, t, *J* 8.0, CH_2C=C), 2.12 (2 H, t, *J* 7.7, CH_2C=C), 2.16–2.32 (5 H, m), 4.02 (1 H, br s, 1-H), 4.18 (2 H, s, CH_2OTBDPS), 4.19 (2 H, d, *J* 6.4, 5′-H_2), 5.01 (1 H, m, C*H*=C), 5.13 (1 H, t, *J* 6.4, C*H*=C), 5.19 (1 H, br s, C*H*=C), 5.33 (1 H, t, *J* 6.4, 4′-H), 7.35–7.45 (6 H, m, *m*-, *p*-Ar), 7.69 (4 H, d, *J* 6.8, *o*-Ar); δ_C(126 MHz; $CDCl_3$) −5.1, 16.1, 16.4, 17.0, 17.7, 18.4, 19.2, 23.5, 25.7, 26.0, 26.8, 27.0, 28.9, 30.1, 31.2, 34.7, 38.5, 39.9, 40.8, 60.2, 61.2, 68.4, 123.2, 124.3, 124.6, 126.3, 127.6, 129.5, 131.1, 133.7, 133.8, 134.7, 135.6, 135.7, 137.4, 138.1.

19b: n_D^{26} 1.5166 (Found: C, 76.41; H, 9.79. $C_{50}H_{78}O_3Si_2$ requires C, 76.67; H, 10.04%); ν_{max}(film)/cm^{-1} 3330w (O–H), 1665w (C=C), 1255m (Si–Me), 1110s (Si–O); δ_H(400 MHz; $CDCl_3$) 0.07 (6 H, s, $SiMe_2$), 0.91 (9 H, s, $SiBu^t$), 1.04 (9 H, s, $SiBu^t$), 1.28–1.39 (1 H, m), 1.40–1.46 (1 H, m), 1.49 (3 H, s, MeC=C), 1.56 (1 H, m), 1.59 (3 H, s, MeC=C), 1.61–1.75 (2 H, m), 1.66 (3 H, s, MeC=C), 1.68 (6 H, s, 2 × MeC=C), 1.81–1.87 (2 H, m, CH_2C=C), 1.92 (4 H, m), 2.01–2.16 (5 H, m), 2.16–2.32 (4 H, m), 3.93 (1 H, br s, 1-H), 4.18 (2 H, s, CH_2OTBDPS), 4.19 (2 H, d, *J* 6.3, 5′-H_2), 5.01 (1 H, m, C*H*=C), 5.13 (1 H, t, *J* 6.6, C*H*=C), 5.19 (1 H, br s, C*H*=C), 5.31 (1 H, t, *J* 6.3, 4′-H), 7.34–7.42 (6 H, m, *m*-, *p*-Ar), 7.69 (4 H, dd, *J* 7.8 and 1.5, *o*-Ar); δ_C(126 MHz; $CDCl_3$) −5.1, 16.0, 16.5, 17.7, 17.8, 18.4, 19.2, 20.7, 25.7, 25.95, 26.01, 26.8, 27.0, 27.8, 29.2, 29.7, 34.8, 38.7, 39.9, 40.7, 60.3, 61.3, 67.1, 123.9, 124.4, 124.6, 126.3, 127.6, 129.5, 131.1, 132.5, 133.9, 135.2, 135.6, 137.1, 138.2.

Oxidation of 19b. To a solution of **19b** (33.6 mg, 43 μmol) in DMSO (1 cm^3) and THF (0.2 cm^3) was added IBX (24 mg, 86 μmol) at room temperature, and the mixture was stirred at this temperature for 2 h. The reaction mixture was diluted with water, and the resulting mixture was stirred at 0 °C for 20 min. The mixture was filtered through a pad of Celite and the precipitate was washed with Et_2O. The filtrate was extracted with Et_2O. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give **18** (31.3 mg, 93%). This was identical with **18**, which was prepared from **17**.

(2*S*,1′*S*,4′*S*)-2-[(*E*)-5″-Hydroxy-3″-methyl-3″-pentenyl]-4-[(2‴*E*,6‴*Z*)-7‴-hydroxymethyl-3‴,11‴-dimethyl-2‴,6‴,10‴-dodecatrienyl]-3-methyl-2-cyclohexen-1-yl 2-methoxy-2-(1-naphthyl)propionate 22a and its (2*S*,1′*R*,4′*R*)-diastereoisomer 22b. To a mixture of **19a** (2.504 g, 3.197 mmol), (*S*)-2-methoxy-2-(1-naphthyl)propionic acid (**20**) (3.72 g, 16.2 mmol) and DMAP (391 mg, 3.20 mmol) in CH_2Cl_2 (100 cm^3) was added DCC (5.65 g, 27.4 mmol) at 0 °C under Ar, and the mixture was stirred at room temperature for 26 h. Further addition of DMAP (185 mg, 1.51 mmol) and stirring for 20 h completed the reaction. The resulting mixture was diluted with Et_2O and filtered through a pad of Celite. The filtrate was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give the inseparable mixture of **21a** and **21b** (2.648 g, 83%) as a colourless oil.

To a mixture of **21a** and **21b** (2.648 g, 2.660 mmol) in THF (40 cm^3) was added TBAF (1.0 mol dm^{-3} in THF; 10.7 cm^3, 10.7 mmol), and the solution was stirred at room temperature for 3 h. The resulting mixture was diluted with EtOAc, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography to afford **22a** (825 mg, 40% from **19a**) as a colourless oil (less polar) and **22b** (749 mg, 36% from **19a**) also as a colourless oil (more polar).

22a: n_D^{24} 1.5172; $[\alpha]_D^{24}$ −92 (*c* 0.10 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3420m (O–H), 1725s (C=O); δ_H(500 MHz; $CDCl_3$) 1.23–1.76 (11 H, m), 1.33 (3 H, s, MeC=C), 1.49 (3 H, s, MeC=C), 1.57 (3 H, s, MeC=C), 1.60 (3 H, s, MeC=C), 1.68 (3 H, s, MeC=C), 1.84–1.95 (2 H, m), 1.98 (3 H, s, 3-H_3), 1.96–2.06 (1 H, m), 2.06–2.23 (7 H, m), 3.06 (3 H, s, MeO), 4.02 (2 H, d, *J* 6.8, 5″-H_2), 4.11 (2 H, br s, 7‴-CH_2OH), 4.97 (2 H, m, 1′- and 4″-H), 5.11 (1 H, br s, C*H*=C), 5.18 (1 H, br s, C*H*=C), 5.30 (1 H, t, *J* 7.1, C*H*=C), 7.37–7.50 (3 H, m, Ar), 7.58 (1 H, d, *J* 7.4, Ar), 7.75–7.85 (2 H, m, Ar), 8.48 (1 H, d, *J* 7.7, Ar); δ_C(126 MHz; $CDCl_3$) 16.1, 16.2, 17.0, 17.7, 21.8, 23.5, 25.6, 26.1, 26.2, 27.0, 28.2, 30.7, 35.2, 37.3, 40.0, 40.3, 50.8, 59.2, 60.2, 72.7, 81.5, 122.7, 123.1, 124.1, 124.6, 125.4, 125.6, 125.7,

126.4, 128.3, 128.5, 129.32, 129.35, 131.3, 131.7, 134.0, 135.0, 135.6, 137.2, 138.4, 139.5, 173.9; *m/z* (FAB) 665.4177 ([M + Na]$^+$. $C_{42}H_{58}O_5Na$ requires 665.4182), 665 (3%), 435 (78), 395 (3), 309 (3), 275 (15), 221 (35), 185 (100), 105 (68), 69 (87).

22b; n_D^{24} 1.5170; $[\alpha]_D^{25}$ +5.9 (*c* 0.16 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3450s (O–H), 1740s (C=O); δ_H(500 MHz; $CDCl_3$) 0.40–0.53 (1 H, m, 5′-H), 1.00–1.09 (1 H, m, 5′-H), 1.12–1.22 (1 H, m, 6′-H), 1.27–1.36 (1 H, m, 6′-H), 1.42 (3 H, s, MeC=C), 1.51 (3 H, s, MeC=C), 1.58 (3 H, s, MeC=C), 1.62 (3 H, s, MeC=C), 1.67 (3 H, s, MeC=C), 1.41–1.80 (5 H, m), 1.90–2.06 (6 H, m), 1.98 (3 H, s, 3-H$_3$), 2.06–2.23 (6 H, m, 3 × CH_2C=C), 3.09 (3 H, s, MeO), 4.15–4.20 (4 H, m, 2 × CH_2OH), 4.75 (1 H, t, *J* 6.7, C*H*=C), 5.11 (1 H, m, C*H*=C), 5.21 (1 H, br s, 1′-H), 5.26 (1 H, t, *J* 7.2, C*H*=C), 5.33 (1 H, t, *J* 6.6, 4″-H), 7.38–7.45 (3 H, m, Ar), 7.56 (1 H, d, *J* 7.4, Ar), 7.75–7.86 (2 H, m, Ar), 8.39–8.46 (1 H, m, Ar); δ_C(126 MHz; $CDCl_3$) 16.1, 16.3, 16.9, 17.7, 21.4, 22.8, 25.6, 26.1, 26.2, 27.0, 29.1, 30.8, 35.1, 38.0, 39.9, 40.1, 50.8, 59.2, 60.2, 72.4, 81.5, 122.9, 123.3, 124.1, 124.5, 125.2, 125.56, 125.61, 126.3, 128.3, 128.5, 129.0, 129.2, 131.4, 131.7, 133.9, 135.1, 135.3, 137.6, 138.3, 139.4, 174.2; *m/z* (FAB) 665.4178 ([M + Na]$^+$. $C_{42}H_{58}O_5Na$ requires 665.4182), 665 (1%), 435 (38), 395 (3), 309 (4), 275 (5), 199 (25), 185 (100), 153 (45), 105 (76), 69 (94).

Determination of the diastereomeric purities of 22a and 22b. (*S*)-2-Methoxy-2-(1-naphthyl)propionic acid (**20**) was prepared according to the reported procedure[17] and its enantiomeric purity was estimated by HPLC analysis of the corresponding methyl ester **20′**. HPLC analysis [column, Chiralcel® OD (4.6 mm × 25 cm); solvent, hexane : propan-2-ol = 9 : 1; flow rate, 0.5 cm^3 min^{-1}; detection at 254 nm]: **20′** t_R/min 10.9 [0%, (*R*)-**20′**], 12.1 [99.9%, (*S*)-**20′**]. The enantiomeric purity of (*S*)-**20** was estimated to be >99.9% ee.

The diastereomeric purities of **22a** and **22b** were estimated by HPLC analysis. HPLC analysis [column, Senshu Pak Pegasil Silica 60–5 (4.6 mm × 25 cm); solvent, hexane :propan-2-ol = 9 : 1; flow rate, 0.5 cm^3 min^{-1}; detection at 254 nm]: **22a** t_R/min 16.7 [99.9%, **22a**], 21.3 [0%, **22b**]. The diastereomeric purity of **22a** was estimated to be >99.9% de. **22b** t_R/min 16.7 [0.25%, **22a**], 21.3 [99.75%, **22b**]. The diastereomeric purity of **22b** was estimated to be 99.5% de.

(1*S*,4*S*)-2-[(*E*)-5′-*tert*-Butyldimethylsilyloxy-3′-methyl-3′-pentenyl]-4-[(2″*E*,6″*Z*)-7″-*tert*-butyldimethylsilyloxymethyl-3″,11″-dimethyl-2″,6″,10″-dodecatrienyl]-3-methyl-2-cyclohexen-1-ol (−)-24 and its enantiomer (+)-24. To a solution of **22a** (801 mg, 1.25 mmol) in DMF (10 cm^3) were added imidazole (470 mg, 6.9 mmol) and TBSCl (770 mg, 5.1 mmol) at 0 °C, and the mixture was stirred at room temperature for 30 min. The reaction mixture was cooled to 0 °C, diluted with Et_2O, quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O. The extract was washed with saturated aqueous $NaHCO_3$, water and brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give **23a** (990 mg, 91%) as a colourless oil.

To a suspension of $LiAlH_4$ (92 mg, 2.4 mmol) in Et_2O (15 cm^3) at −78 °C was added a solution of **23a** (990 mg, 1.14 mmol) in Et_2O (10 cm^3) dropwise under Ar. The mixture was allowed to warm to 0 °C over 2.5 h, stirred at 0 °C for 30 min and quenched with MeOH at −20 °C. To the resulting mixture was added saturated aqueous potassium sodium tartrate (5 cm^3). The mixture was stirred for 10 min at room temperature, and extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give (−)-**24** (664 mg, 87%) as a colourless oil, n_D^{24} 1.4933 (Found: C, 73.10; H, 11.49. $C_{40}H_{74}O_3Si_2$ requires C, 72.88; H, 11.32%); $[\alpha]_D^{24}$ −38 (*c* 0.13 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3340w (O–H), 1670w (C=C), 1255m (Si–Me), 1070s (Si–O); δ_H(500 MHz; $CDCl_3$) 0.06 (6 H, s, $SiMe_2$), 0.07 (6 H, s, $SiMe_2$), 0.901 (9 H, s, SiBu^t), 0.905 (9 H, s, SiBu^t), 1.44–1.51 (1 H, m), 1.52–1.74 (3 H, m), 1.60 (3 H, s, MeC=C), 1.61 (3 H, s, MeC=C), 1.67 (6 H, s, 2 × MeC=C), 1.68 (3 H, s, MeC=C), 1.92–2.17 (13 H, m), 2.20–2.32 (3 H, m), 4.02 (1 H, m, 1-H), 4.15 (2 H, s, 7″-CH_2OTBS), 4.18 (2 H, d, *J* 6.4, 5′-H$_2$), 5.06–5.13 (2 H, m, 2 × C*H*=C), 5.19 (1 H, t, *J* 7.1, C*H*=C), 5.32 (1 H, t, *J* 6.4, 4′-H); δ_C(126 MHz; $CDCl_3$) −5.3, −5.1, 16.2, 16.5, 17.0, 17.7, 18.3, 18.4, 23.5, 25.7, 25.95, 26.02, 26.2, 27.0, 29.0, 30.2, 31.2, 34.7, 38.5, 40.1, 40.8, 60.2, 60.5, 68.4, 123.2, 124.3, 124.5, 126.1, 133.70, 133.72, 134.7, 135.9, 137.4, 138.5.

The enantiomeric allylic alcohol (+)-**24** (568 mg, 81%, 2 steps) was prepared from diastereomeric ester **22b** (688 mg, 1.07 mmol). This was identical with its enantiomer in all respects except the sign of optical rotation. (+)-**24**: n_D^{24} 1.4940 (Found: C, 73.03; H, 11.51. $C_{40}H_{74}O_3Si_2$ requires C, 72.88; H, 11.32%); $[\alpha]_D^{25}$ +37 (*c* 0.12 in $CHCl_3$).

(1*R*,2*S*,5*S*,6*R*)-1-[(*E*)-5′-*tert*-Butyldimethylsilyloxy-3′-methyl-3′-pentenyl]-5-[(2″*E*,6″*Z*)-7″-*tert*-butyldimethylsilyloxymethyl-3″,11″-dimethyl-2″,6″,10″-dodecatrienyl]-6-methylbicyclo[4.1.0]heptan-2-ol (−)-25 and its enantiomer (+)-25. To a solution of (−)-**24** (465 mg, 705 μmol) were added CH_2I_2 (114 mm^3, 1.43 mmol) and Et_2Zn (0.99 mol cm^{-3} in *n*-hexane; 1.45 cm^3, 1.44 mmol) at room temperature under Ar. The mixture was stirred at room temperature for 3.5 h. It was then quenched with saturated aqueous NH_4Cl at 0 °C and extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give (−)-**25** (450 mg, 95%) as a colourless oil, n_D^{24} 1.4902; $[\alpha]_D^{24}$ −11 (*c* 0.10 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3360w (O–H), 3055w (cyclopropyl C–H), 1670w (C=C), 1255m (Si–Me), 1070s (Si–O); δ_H(500 MHz; $CDCl_3$) −0.08 (1 H, d, *J* 4.6, 7-H), 0.06 (12 H, s, 2 × $SiMe_2$), 0.69 (1 H, d, *J* 4.6, 7-H), 0.90 (18 H, s, 2 × SiBu^t), 0.95–1.05 (1 H, m), 1.17 (3 H, s, 6-Me), 1.23–1.40 (4 H, m), 1.46–1.53 (1 H, m), 1.59 (6 H, s, 2 × MeC=C), 1.63 (3 H, s, MeC=C), 1.67 (3 H, s, MeC=C), 1.64–1.72 (1 H, m), 1.79 (1 H, dt, *J* 14.1 and 9.2), 1.86 (1 H, dq, *J* 13.8 and 5.5), 1.97–2.18 (10 H, m), 2.18–2.26 (1 H, m), 4.03 (1 H, br s, 2-H), 4.14 (2 H, s, 7″-CH_2OTBS), 4.18 (2 H, d, *J* 6.4, 5′-H$_2$), 5.10 (1 H, br s, C*H*=C), 5.13–5.24 (2 H, m, 2 × C*H*=C), 5.31 (1 H, t, *J* 6.4, 4′-H); δ_C(126 MHz; $CDCl_3$) −5.3, −5.1, 16.1, 16.3, 16.5, 17.7, 18.3, 18.4, 21.0, 22.3, 25.7, 25.9, 26.0, 26.1, 27.0, 27.7, 29.6, 31.3, 32.1, 33.2, 34.7, 37.0, 39.9, 40.1, 60.3, 60.5, 69.0, 123.8, 124.2, 124.5, 126.2, 131.1, 135.3, 137.2, 138.5; *m/z* (EI) 672.5318 (M$^+$. $C_{41}H_{76}O_3Si_2$ requires 672.5333).

The enantiomeric cyclopropyl alcohol (+)-**25** (556 mg, 96%) was prepared from (+)-**24** (567 mg, 860 μmol). This was identical with its enantiomer in all respects except the sign of optical rotation. (+)-**25**: n_D^{24} 1.4906; $[\alpha]_D^{23}$ +12 (*c* 0.11 in $CHCl_3$); *m/z* (EI) 672.5344 (M$^+$. $C_{41}H_{76}O_3Si_2$ requires 672.5333).

(1*R*,5*S*,6*R*)-1-[(*E*)-5′-*tert*-Butyldimethylsilyloxy-3′-methyl-3′-pentenyl]-5-[(2″*E*,6″*Z*)-7″-*tert*-butyldimethylsilyloxymethyl-3″,11″-dimethyl-2″,6″,10″-dodecatrienyl]-6-methylbicyclo[4.1.0]heptan-2-one (+)-26 and its enantiomer (−)-26. To a suspension of PDC (132 mg, 351 μmol) and powdered MS 4A (126 mg) in CH_2Cl_2 (2 cm^3) was added a solution of (−)-**25** (150 mg, 233 μmol) in CH_2Cl_2 (2 cm^3). The reaction mixture was stirred at room temperature for 3 h, and then filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give (+)-**26** (136 mg, 91%) as a colourless oil, n_D^{27} 1.4883; $[\alpha]_D^{23}$ +5.7 (*c* 0.11 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3060w (cyclopropyl C–H), 1690s (C=O), 1255m (Si–Me), 1070s (Si–O); δ_H(500 MHz; $CDCl_3$) 0.06 (12 H, s, 2 × $SiMe_2$), 0.54 (1 H, d, *J* 5.2, 7-H), 0.89 (18 H, s, 2 × SiBu^t), 1.13–1.27 (2 H, m), 1.30 (3 H, s, 6-Me), 1.32 (1 H, d, *J* 5.2, 7-H), 1.59 (3 H, s, MeC=C), 1.61 (3 H, s, MeC=C), 1.62 (3 H, s, MeC=C), 1.67 (3 H, s, MeC=C), 1.58–1.75 (2 H, m), 1.82–1.89 (1 H, m), 1.90–2.12 (9 H, m), 2.14 (2 H, q-like, *J* 7.4, CH_2C=C), 2.31 (1 H, dt, *J* 17.7 and 4.6, 3-H), 2.35–2.43 (1 H, m), 2.50 (1 H, dq, *J* 13.7 and 5.5), 4.14 (2 H, s, 7″-CH_2OTBS), 4.16 (2 H, d, *J* 6.1, 5′-H$_2$), 5.10 (1 H, br s, C*H*=C), 5.14–5.22 (2 H, m, 2 × C*H*=C), 5.26 (1 H, t, *J* 6.1, 4′-H); δ_C(126 MHz; $CDCl_3$) −5.3, −5.1, 16.1, 16.3, 17.7, 18.3, 18.4, 19.0, 21.7, 23.8, 25.7, 25.9, 25.99, 26.03, 27.0, 29.1, 30.4, 31.3, 34.7, 37.3, 37.4, 38.6, 38.9, 40.1, 60.3, 60.5, 122.3, 124.3, 124.4, 126.0, 131.2, 136.1, 137.1, 138.6, 209.3; *m/z* (EI) 670.5173

(M^+. $C_{41}H_{74}O_3Si_2$ requires 670.5176), 670 (2%), 613 (10), 538 (10), 481 (6), 469 (2), 406 (5), 389 (5), 377 (2), 335 (6), 281 (5), 253 (12), 203 (18), 175 (16), 135 (32), 81 (38), 75 (100).

The enantiomeric cyclopropyl ketone (−)-**26** (120 mg, 90%) was prepared from (+)-**25** (134 mg, 199 μmol). This was identical with its enantiomer in all respects except the sign of optical rotation. (−)-**26**: n_D^{27} 1.4876; $[\alpha]_D^{25}$ −5.6 (*c* 0.10 in $CHCl_3$); *m*/*z* (EI) 670.5176 (M^+. $C_{41}H_{74}O_3Si_2$ requires 670.5176).

(2*R*,4*S*)-2-[(*E*)-5′-*tert*-Butyldimethylsilyloxy-3′-methyl-3′-pentenyl]-4-[(2″*E*,6″*Z*)-7″-*tert*-butyldimethylsilyloxymethyl-3″,11″-dimethyl-2″,6″,10″-dodecatrienyl]-3,3-dimethylcyclohexan-1-one (−)-27 and its enantiomer (+)-27. To a solution of *t*-BuOH (81 mg, 1.1 mmol) in THF (1 cm^3) were added NH_3 (*ca.* 5 cm^3) and Li (15 mg, 2.2 mmol) at −78 °C under Ar, and the mixture was stirred at this temperature for 40 min. To the mixture was added a solution of (+)-**26** (106 mg, 158 μmol) and *t*-BuOH (70 mg, 0.9 mmol) in THF (1 cm^3) dropwise. After having been stirred at −78 °C for 1.5 h, the reaction mixture was quenched with MeOH at this temperature, and allowed to warm to room temperature. After having been stirred for 1 h, water and Et_2O were added, and the mixture was extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography to afford (−)-**27** (70 mg, 66%) as a colourless oil, n_D^{25} 1.4868; $[\alpha]_D^{25}$ −12 (*c* 0.11 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1715s (C=O), 1670w (C=C), 1255m (Si–Me), 1070s (Si–O); δ_H(500 MHz; $CDCl_3$) 0.06 (12 H, s, 2 × $SiMe_2$), 0.60 (3 H, s, 3-Me), 0.90 (18 H, s, 2 × SiBu^t), 1.09 (3 H, s, 3-Me), 1.32–1.45 (2 H, m), 1.56–1.63 (1 H, m, 4-H), 1.59 (3 H, s, MeC=C), 1.60 (3 H, s, MeC=C), 1.61 (3 H, s, MeC=C), 1.66–1.73 (1 H, m, C*H*HC=C), 1.68 (3 H, s, MeC=C), 1.74–1.82 (1 H, m), 1.88–1.97 (1 H, m), 1.99–2.17 (10 H, m), 2.11–2.17 (1 H, m, 2-H), 2.20–2.26 (1 H, m, C*H*HC=C), 2.27–2.33 (2 H, m, 6-H and C*H*HC=C), 4.15 (2 H, s, 7″-CH_2OTBS), 4.17 (2 H, d, *J* 6.5, 5′-H_2), 5.08–5.16 (2 H, m, 2 × C*H*=C), 5.19 (1 H, t, *J* 6.7, C*H*=C), 5.25 (1 H, t, *J* 6.5, 4′-H); δ_C(126 MHz; $CDCl_3$) −5.3, −5.1, 15.5, 16.10, 16.15, 17.7, 18.3, 18.4, 20.8, 25.7, 25.95, 26.02, 26.05, 26.8, 27.0, 28.5, 29.2, 34.7, 38.9, 40.0, 42.5, 43.4, 48.1, 60.1, 60.2, 60.5, 124.0, 124.5, 124.8, 126.1, 131.2, 135.8, 137.0, 138.6, 212.5; *m*/*z* (EI) 672.5335 (M^+. $C_{41}H_{76}O_3Si_2$ requires 672.5333), 672 (1%), 657 (1), 615 (4), 603 (2), 540 (4), 523 (2), 483 (6), 415 (4), 391 (9), 339 (2), 293 (2), 253 (16), 185 (12), 135 (35), 81 (48), 75 (100); Δε −1.3 (296 nm, *c* 0.0015 mol dm^{-3} in $CHCl_3$).

The enantiomeric ketone (+)-**27** (60 mg, 60%) was prepared from (−)-**26** (100 mg, 149 μmol). This was identical with its enantiomer in all respects except the sign of optical rotation and CD spectrum. (+)-**27**: n_D^{24} 1.4860; $[\alpha]_D^{25}$ +12 (*c* 0.12 in $CHCl_3$); *m*/*z* (EI) 672.5340 (M^+. $C_{41}H_{76}O_3Si_2$ requires 672.5333); Δε +1.3 (293 nm, *c* 0.0018 mol dm^{-3} in $CHCl_3$).

(2*S*,4*S*)-2-[(*E*)-5′-*tert*-Butyldimethylsilyloxy-3′-methyl-3′-pentenyl]-4-[(2″*E*,6″*Z*)-7″-*tert*-butyldimethylsilyloxymethyl-3″,11″-dimethyl-2″,6″,10″-dodecatrienyl]-3,3-dimethyl-1-methylenecyclohexane (−)-28 and its enantiomer (+)-28. To a suspension of Ph_3PCH_3Br (223 mg, 624 μmol) in THF (2 cm^3) was added NaHMDS (1.0 mol dm^{-3} in THF; 530 mm^3, 530 μmol) at 0 °C under Ar. After having been stirred for 15 min, a solution of (−)-**27** (71 mg, 105 μmol) in THF (1.5 cm^3) was added dropwise to the mixture at 0 °C. After having been stirred at room temperature for 5 h, the resulting mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The extract was washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on SiO_2 to give (−)-**28** (57 mg, 80%) as a colourless oil, n_D^{22} 1.4922; $[\alpha]_D^{21}$ −0.8 (*c* 0.11 in $CHCl_3$); ν_{max}(film)/cm^{-1} 1670s (C=C), 1645w (C=C), 1255m (Si–Me), 1070s (Si–O); δ_H(500 MHz; $CDCl_3$) 0.07 (6 H, s, $SiMe_2$), 0.08 (6 H, s, $SiMe_2$), 0.58 (3 H, s, 3-Me), 0.91 (18 H, s, 2 × SiBu^t), 1.03 (3 H, s, 3-Me), 1.11 (1 H, td, *J* 12.5 and 4.3, 5-H), 1.20 (1 H, t, *J* 10.7, 4-H), 1.48–1.55 (1 H, m), 1.57 (3 H, s, MeC=C), 1.60 (3 H, s, MeC=C), 1.63 (3 H, s, MeC=C), 1.62–1.69 (2 H, m), 1.68 (3 H, s, MeC=C), 1.71–1.78 (1 H, m), 1.78–1.86 (1 H, m), 1.90 (1 H, td, *J* 12.5 and 4.3, 6-H), 2.01 (2 H, t, *J* 7.7, CH_2C=C), 2.06–2.11 (4 H, m, 2 × CH_2C=C), 2.11–2.20 (5 H, m, 2 × CH_2C=C and C*H*HC=C), 2.28 (1 H, dt, *J* 12.5 and 4.3, 6-H), 4.15 (2 H, s, 7″-CH_2OTBS), 4.20 (2 H, d, *J* 6.4, 5′-H_2), 4.54 (1 H, s, C*H*H=C), 4.84 (1 H, s, C*H*H=C), 5.08–5.14 (2 H, m, 2 × C*H*=C), 5.20 (1 H, t, *J* 7.3, C*H*=C), 5.29 (1 H, t, *J* 6.4, 4′-H); δ_C(126 MHz; $CDCl_3$) −5.3, −5.0, 15.1, 16.1, 16.4, 17.7, 18.36, 18.43, 23.3, 25.7, 25.97, 26.03, 26.1, 26.6, 27.0, 29.2, 30.2, 34.7, 37.6, 38.6, 39.6, 40.1, 48.8, 53.4, 60.3, 60.5, 106.3, 124.2, 124.6, 125.0, 126.2, 131.1, 134.9, 137.6, 138.5, 149.0; *m*/*z* (EI) 670.5544 (M^+. $C_{42}H_{78}O_2Si_2$ requires 670.5540), 670 (5%), 613 (23), 601 (5), 538 (8), 523 (2), 481 (13), 469 (2), 406 (6), 391 (2), 337 (4), 277 (5), 266 (44), 203 (17), 201 (12), 135 (21), 81 (24), 75 (100).

The enantiomeric pentaene (+)-**28** (59 mg, 82%) was prepared from (+)-**27** (72 mg, 107 μmol). This was identical with its enantiomer in all respects except the sign of optical rotation. (+)-**28**: n_D^{22} 1.4926; $[\alpha]_D^{21}$ +1.0 (*c* 0.11 in $CHCl_3$); *m*/*z* (EI) 670.5538 (M^+. $C_{42}H_{78}O_2Si_2$ requires 670.5540).

(2*S*,4*S*)-2-[(*E*)-5′-Hydroxy-3′-methyl-3′-pentenyl]-4-[(2″*E*,6″*Z*)-7″-hydroxymethyl-3″,11″-dimethyl-2″,6″,10″-dodecatrienyl]-3,3-dimethyl-1-methylenecyclohexane (−)-29 and its enantiomer (+)-29. To a solution of (−)-**28** (57 mg, 85 μmol) in THF (2 cm^3) was added TBAF (1.0 mol dm^{-3} in THF; 0.34 cm^3, 0.34 mmol), and the mixture was stirred at room temperature for 2 h. The resulting mixture was diluted with EtOAc, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography to afford (−)-**29** (36.5 mg, 97%) as a colourless oil, n_D^{23} 1.5186; $[\alpha]_D^{24}$ −4 (*c* 0.07 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3330s (O–H), 1670w (C=C), 1645m (C=C); δ_H(500 MHz; $CDCl_3$) 0.57 (3 H, s, 3-Me), 1.02 (3 H, s, 3-Me), 1.11 (1 H, td, *J* 12.5 and 4.3, 5-H), 1.14–1.23 (3 H, m), 1.50–1.57 (1 H, m), 1.58 (3 H, s, MeC=C), 1.61 (3 H, s, MeC=C), 1.58–1.66 (1 H, m), 1.69 (6 H, s, 2 × MeC=C), 1.71–1.78 (1 H, m), 1.80–1.87 (1 H, m), 1.90 (1 H, td, *J* 12.5 and 4.3, 6-H), 2.02 (2 H, t, *J* 7.3, CH_2C=C), 2.08–2.22 (10 H, m, 5 × CH_2C=C), 2.28 (1 H, dt, *J* 12.5 and 4.3, 6-H), 4.11 (2 H, s, 7″-CH_2OH), 4.15 (2 H, d, *J* 7.0, 5′-H_2), 4.53 (1 H, s, C*H*H=C), 4.84 (1 H, s, C*H*H=C), 5.08–5.14 (2 H, m, 2 × C*H*=C), 5.30 (1 H, t, *J* 7.4, C*H*=C), 5.40 (1 H, t, *J* 7.0, 4′-H); δ_C(126 MHz; $CDCl_3$) 15.0, 16.1, 16.3, 17.7, 23.3, 25.7, 26.2, 26.6, 27.1, 29.2, 30.3, 35.2, 37.6, 38.5, 39.6, 40.0, 48.8, 53.4, 59.4, 60.4, 106.3, 123.1, 124.1, 125.3, 128.6, 131.7, 134.7, 138.3, 140.5, 148.8; *m*/*z* (EI) 442.3806 (M^+. $C_{30}H_{50}O_2$ requires 442.3811), 442 (1%), 424 (5), 409 (3), 391 (3), 355 (3), 337 (2), 271 (5), 257 (4), 217 (6), 201 (15), 161 (13), 135 (30), 95 (32), 69 (100).

The enantiomeric diol (+)-**29** (37 mg, 95%) was prepared from (+)-**28** (59 mg, 88 μmol). This was identical with its enantiomer in all respects except optical rotation. (+)-**29**: n_D^{20} 1.5174; $[\alpha]_D^{21}$ +1.6 (*c* 0.11 in $CHCl_3$); *m*/*z* (EI) 442.3816 (M^+. $C_{30}H_{50}O_2$ requires 442.3811).

(2*S*,4*S*)-(+)-2-[(*E*)-4′-Carboxy-3′-methyl-3′-butenyl]-4-[(2″*E*,6″*Z*)-7″-carboxy-3″,11″-dimethyl-2″,6″,10″-dodecatrienyl]-3,3-dimethyl-1-methylenecyclohexane (mispyric acid) 1 and its enantiomer (−)-1. To a solution of (−)-**29** (14.9 mg, 34 μmol) in CH_2Cl_2 (2 cm^3) was added Dess–Martin periodinane (97%; 50.7 mg, 116 μmol) at 0 °C, and the mixture was stirred at room temperature for 10 min. The reaction mixture was diluted with Et_2O, saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$, and extracted with Et_2O. The extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was used in the next reaction without purification.

To a solution of the crude aldehyde in *t*-BuOH (1.5 cm^3) and 2-methyl-2-butene (0.4 cm^3) was added a freshly prepared aqueous $NaClO_2$ ($NaClO_2$, 79%, 40 mg, 0.35 mmol; NaH_2PO_4, 91 mg, 0.76 mmol; H_2O, 0.3 cm^3), and the reaction mixture was stirred at room temperature for 1 h. The mixture was diluted with EtOAc, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography

to afford (+)-**1** (10.8 mg, 68% from (−)-**29**) as a colourless oil, $[\alpha]_D^{27}$ +9.2 (*c* 0.22 in MeOH); ν_{max}(film)/cm^{-1} 3500–2500s (carboxyl O–H), 1690s (C=O), 1645s (C=C); δ_H(300 MHz, $CDCl_3$) 0.59 (3 H, s, 3-Me), 1.03 (3 H, s, 3-Me), 1.06–1.25 (2 H, m, 4- and 5-H), 1.59 (6 H, s, 3″- and 11″-Me), 1.59–1.67 (3 H, m, 2-, 1′- and 1″-H), 1.68 (3 H, s, 11″-Me), 1.69–1.80 (2 H, m, 1′- and 5-H), 1.90 (1 H, td, *J* 12.0 and 4.2, 6-H), 1.97–2.08 (1 H, m, 4″-H), 2.08–2.16 (4 H, m, 2′-H_2, 1″- and 4″-H), 2.18 (3 H, s, 3′-Me), 2.23–2.40 (5 H, m, 6-H, 8″- and 9″-H_2), 2.62 (2 H, q, *J* 7.2, 5″-H_2), 4.51 (1 H, s, C*H*H=C), 4.86 (1 H, s, C*H*H=C), 5.04–5.16 (2 H, m, 2″- and 10″-H), 5.69 (1 H, s, 4′-H), 6.00 (1 H, t, *J* 7.2, 6″-H); δ_C(75 MHz, $CDCl_3$) 15.0, 16.0, 17.7, 19.2, 23.0, 25.7, 26.6, 27.9, 28.1, 29.1, 30.2, 34.5, 37.5, 39.2, 39.7, 40.2, 48.6, 53.2, 106.5, 114.8, 123.4, 125.3, 130.6, 132.2, 134.5, 145.6, 148.5, 164.1, 172.0, 173.3; *m*/*z* (EI) 470.3414 (M^+. $C_{30}H_{46}O_4$ requires 470.3396), 470 (2%), 452 (12), 434 (5), 383 (8), 365 (6), 355 (3), 303 (7), 285 (6), 235 (8), 217 (12), 189 (20), 135 (36), 93 (33), 69 (100).

The enantiomeric mispyric acid (−)-**1** (11.6 mg, 69%) was prepared from (+)-**29** (15.7 mg, 35 μmol). This was identical with its enantiomer in all respects except optical rotation. (−)-**1**: $[\alpha]_D^{26}$ −10.7 (*c* 0.232 in MeOH); *m*/*z* (EI) 470.3412 (M^+. $C_{30}H_{46}O_4$ requires 470.3396).

Acknowledgements

We thank Dr. T. Tashiro (RIKEN) for his supports of this work.

References

1 Part 7. M. Ichihashi, H. Takikawa and K. Mori, *Biosci. Biotechnol. Biochem.*, 2001, **65**, 2569–2572.
2 D.-A. Sun, J.-Z. Deng, S. R. Starck and S. M. Hecht, *J. Am. Chem. Soc.*, 1999, **121**, 6120–6124.
3 H. Takikawa, D. Nozawa, A. Kayo, S.-E. Muto and K. Mori, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2467–2478.
4 (*a*) K. Mori, H. Takikawa and M. Kido, *J. Chem. Soc., Perkin Trans. 1*, 1993, 169–179; (*b*) M. Yoshida, H. Takikawa and K. Mori, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1007–1017.
5 Y. Imamura, H. Takikawa and K. Mori, *Tetrahedron Lett.*, 2002, **43**, 5743–5746.
6 (*a*) M. Ohsugi, S. Takahashi, I. Ichimoto and H. Ueda, *Nippon Nôgeikagaku Kaishi*, 1973, **47**, 807–811; (*b*) S. Kurosawa and K. Mori, *Eur. J. Org. Chem.*, 2000, 955–962.
7 (*a*) P. Knochel, T.-S. Chou, H. G. Chen, M. C. P. Yeh and M. J. Rozema, *J. Org. Chem.*, 1989, **54**, 5202–5204; (*b*) for the preparation of ICH_2ZnI, see: D. Seyferth and S. B. Andrews, *J. Organomet. Chem.*, 1971, **30**, 151–166.
8 E. J. Corey and H. Yamamoto, *J. Am. Chem. Soc.*, 1970, **92**, 6637–6638.
9 For the preparation of 5-methyl-4-hexenyltriphenylphosphonium iodide, see: D. E. Cane and M. Tandon, *Tetrahedron Lett.*, 1994, **35**, 5355–5358.
10 For example: (*a*) K. Tago, M. Arai and H. Kogen, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2073–2078; (*b*) H. Takikawa, J. Koizumi, Y. Kato and K. Mori, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2271–2276.
11 E. Piers and J. R. Grierson, *J. Org. Chem.*, 1977, **42**, 3755–3757.
12 (*a*) E. J. Corey, R. K. Bakshi and S. Shibata, *J. Am. Chem. Soc.*, 1987, **109**, 5551–5553; (*b*) for a review, see: E. J. Corey and C. J. Helal, *Angew. Chem., Int. Ed.*, 1998, **37**, 1986–2012.
13 (*a*) R. Noyori, I. Tomino and Y. Tanimoto, *J. Am. Chem. Soc.*, 1979, **101**, 3129–3131; (*b*) R. Noyori, I. Tomino, Y. Tanimoto and M. Nishizawa, *J. Am. Chem. Soc.*, 1984, **106**, 6709–6716.
14 F.-J. Gottschalk, H. Marschall-Weyerstahl and P. Weyerstahl, *Liebigs Ann. Chem.*, 1985, 462–467.
15 (*a*) M. Frigerio and M. Santagostino, *Tetrahedron Lett.*, 1994, **35**, 8019–8022; (*b*) for the preparation of IBX, see: M. Frigerio, M. Santagostino and S. Sputore, *J. Org. Chem.*, 1999, **64**, 4537–4538.
16 (*a*) J. Staunton and E. J. Eisenbraun, *Org. Synth. Coll. Vol. 5*, 1973, 8–11; (*b*) K. Mori, *Tetrahedron*, 1974, **30**, 1065–1072.
17 (*a*) A. Ichikawa, S. Hiradate, A. Sugio, S. Kuwahara, M. Watanabe and N. Harada, *Tetrahedron: Asymmetry*, 1999, **10**, 4075–4078; (*b*) N. Harada, M. Watanabe, S. Kuwahara, A. Sugio, Y. Kasai and A. Ichikawa, *Tetrahedron: Asymmetry*, 2000, **11**, 1249–1253.
18 I. Ohtani, T. Kusumi, Y. Kashman and H. Kakisawa, *J. Am. Chem. Soc.*, 1991, **113**, 4092–4096.
19 (*a*) J. Nishimura, N. Kawabata and J. Furukawa, *Tetrahedron*, 1969, **25**, 2647–2659; (*b*) R. Hara, T. Furukawa, H. Kashima, H. Kusama, Y. Horiguchi and I. Kuwajima, *J. Am. Chem. Soc.*, 1999, **121**, 3072–3082.
20 W. G. Dauben and E. J. Deviny, *J. Org. Chem.*, 1966, **31**, 3794–3798.
21 (*a*) P. Crabbé, *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry*, Holden-Day, San Francisco, 1965, ch. 6; (*b*) D. A. Lightner, in *Circular Dichroism, Principle and Application*, 2nd edn., N. Berova, K. Nakanishi and R. W. Woody, Eds., Wiley-VCH: ,New York, 2000, ch. 10.
22 (*a*) D. B. Dess and J. C. Martin, *J. Org. Chem.*, 1983, **48**, 4155–4156; (*b*) D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.*, 1991, **113**, 7277–7287.
23 When PDC was used instead of DMP, a considerable amount of isomerization of 6″-geometry took place (5%–30%).