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SYNTHESIS AND STRUCTURE REVISION OF BIFURCARENONE, A UNIQUE MONOCYCLIC DITERPENE IN COMBINATION WITH A HYDROQUINONE C_7 UNIT AS AN INHIBITOR OF MITOTIC CELL DIVISION†

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Abstract -- Bifurcarenone, a C_{27} hydroquinone isolated from the brown seaweed Bifurcaria galapagensis, was synthesized as its racemate, and shown to be **2**. The structure **1**, originally proposed for bifurcarenone, was also synthesized, and found to be different from the natural product.

(-)-Bifurcarenone is an inhibitor of mitotic cell division isolated from the brown seaweed (Bifurcaria galapagensis) harvested in Galapagos Islands.[1] It possesses a structurally unprecedented monocyclic diterpenoid moiety in combination with a hydroquinone C_7 unit. Fenical et al. proposed **1** as its structure on the basis of chemical and spectral studies, although nothing is known about its absolute configuration.[1] We became interested in synthesizing (±)-**1** because of the unique structure coupled with its bioactivity. Owing to the ambiguity in assigning the (Z)-geometry to the non-conjugated double bond of bifurcarenone only on the basis of its ^{13}C NMR spectrum, we felt it necessary to develop a synthetic route which would enable us to prepare both (±)-**1** and its (E)-isomer (±)-**2** with no ambiguity concerning the geometry of the non-conjugated double bond. Our synthesis as described herein enabled us to assign not **1** but **2** (unknown absolute configuration) as the structure of bifurcarenone on the basis of the direct spectral comparison with the natural product.

Our synthetic plan for bifurcarenone was quite straightforward. The target molecule was dissected into three building blocks : the cyclopentane part (±)-**3**, the aromatic part **4** (for the synthesis of **1**) or **5** (for **2**), and the commercially available C_5 unit **6** (Fig.1). The first phase of the synthesis was therefore the

†Diterpenoid Total Synthesis — 27. Part 26, K. Mori and M. Komatsu, Tetrahedron **1987**, 43, 3409-3412. Dedicated to the memory of the late Professor Edgar Lederer (5 June, 1908-19 October, 1988), whose monograph on chromatography was an indispensable reference source throughout K. M.'s young days.

††Research Fellow on leave from Otsuka Pharmaceutical Co., Ltd. (1987-1989).

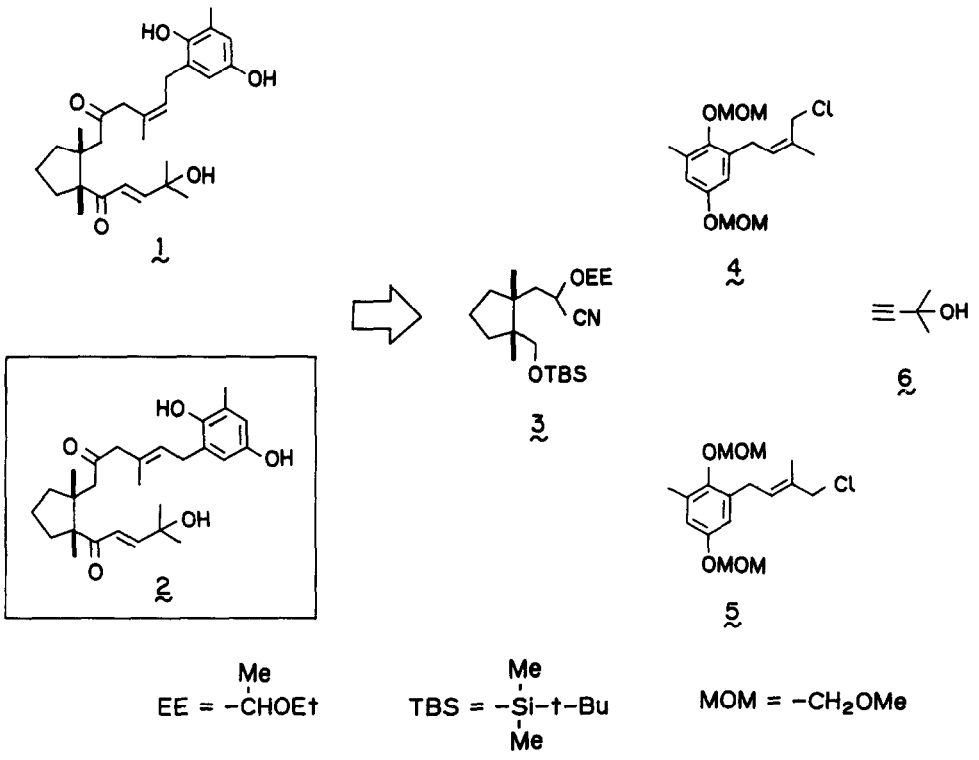


Fig. 1. Retrosynthetic analysis of bifurcarenone.

preparation of **3**, **4** and **5**. The second task was the combination of the three building blocks to furnish (±)-**1** or (±)-**2**.

Preparation of the cyclopentane building block (3). As shown in Fig. 2, the building block (±)-**3** was synthesized from the known bicyclic ketone **7**.[2,3] The Baeyer-Villiger oxidation of **7** yielded the lactone (±)-**8**, which was reduced with DIBAL to (±)-**9**.[4] Treatment of the lactol (±)-**9** with 1,3-propanedithiol in the presence of Et_2AlCl yielded the dithiane alcohol (±)-**10**.[4] After protecting the OH group of (±)-**10** as t-butyldimethylsilyl (TBS) ether, the resulting (±)-**11** was treated with $HgCl_2$ and $CaCO_3$ to give the aldehyde (±)-**12**.[4] The trimethylsilyl (TMS)-protected cyanohydrin (±)-**13** was prepared from (±)-**12** by treatment with TMSCN and a catalytic amount of ZnI_2.[5] Removal of the TMS protective group of (±)-**13** by treatment with methanolic citric acid[6] to give (±)-**14** was followed by re-protection of its OH group to give the ethoxyethyl (EE)-protected cyanohydrin (±)-**3**, the desired building block, in 32% overall yield from **7** in eight steps.

Preparation of the aromatic building blocks (4 and 5). The synthesis of the aromatic building blocks **4** and **5** started from o-cresol **15** as shown in Fig. 3.

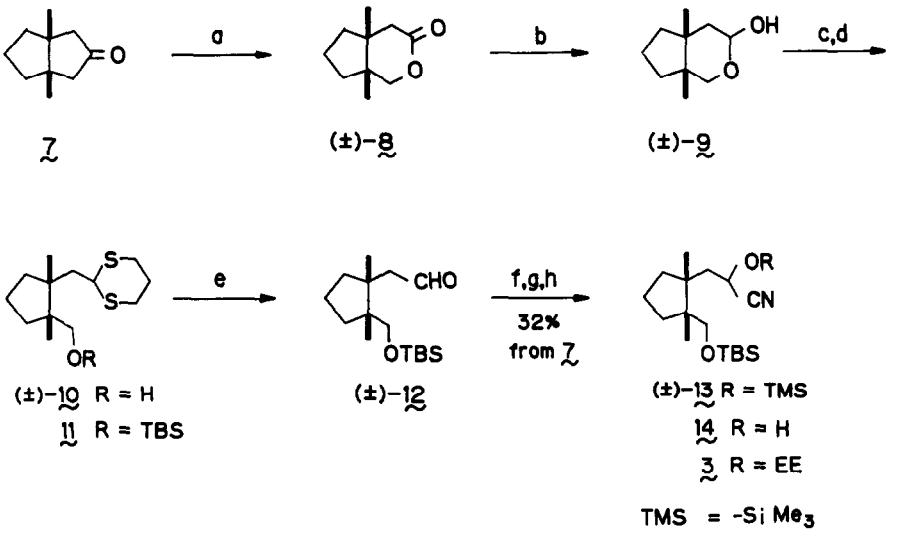


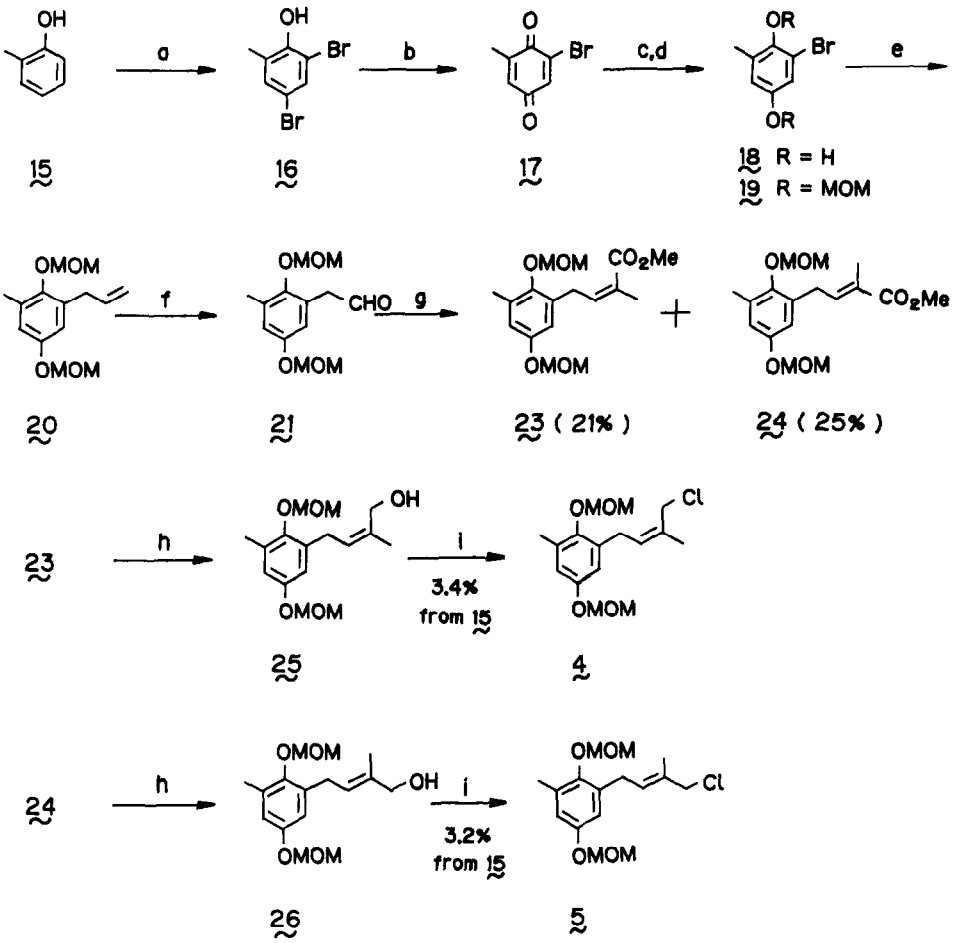
Fig. 2. Synthesis of the cyclopentane building block **3**.

Bromination of **15** to **16** was followed by its chromic acid oxidation to give the quinone **17**. After reduction of **17** with $Na_2S_2O_4$ to the hydroquinone **18**, the OH groups of **18** were protected as methoxymethyl (MOM) ethers to give **19**.[7] Addition of n-BuLi to **19** effected transmetallation to give the carbanion, which was treated with CuI to give the arylcopper. Addition of allyl bromide to the arylcopper yielded **20**. Lemieux-Johnson oxidation of **20** afforded the aldehyde **21**.

The Horner-Emmons reaction between **21** and trimethyl α-phosphonopropionate (**22**) gave a mixture of the α,β-unsaturated esters **23** and **24**. These two were separable by SiO_2 chromatography. The less polar ester showed the signal due to $C=CCH_3$ at δ=1.93. When these three protons were irradiated, a distinct increase in the signal area at δ=6.07 (C=CH) was observed, indicating the presence of NOE between CH_3 and CH. Accordingly, the less polar ester was **23**. The more polar ester exhibited NOE between $C=CCH_3$ (δ=1.95) and $C=CCH_2$ (δ=3.54), supporting the (E)-geometry of its double bond as depicted in **24**.

The two esters **23** and **24** were separately reduced to the alcohols **25** and **26**. Treatment of the alcohols **25** and **26** with Ph_3P and CCl_4 gave the desired building blocks **4** and **5**, respectively.

Synthesis of the proposed structure (1) of bifurcarenone. Because Fenical et al. proposed **1** with a (Z)-double bond as the structure of bifurcarenone, we first synthesized (±)-**1** as shown in Fig.4. Alkylation of the carbanion derived from (±)-

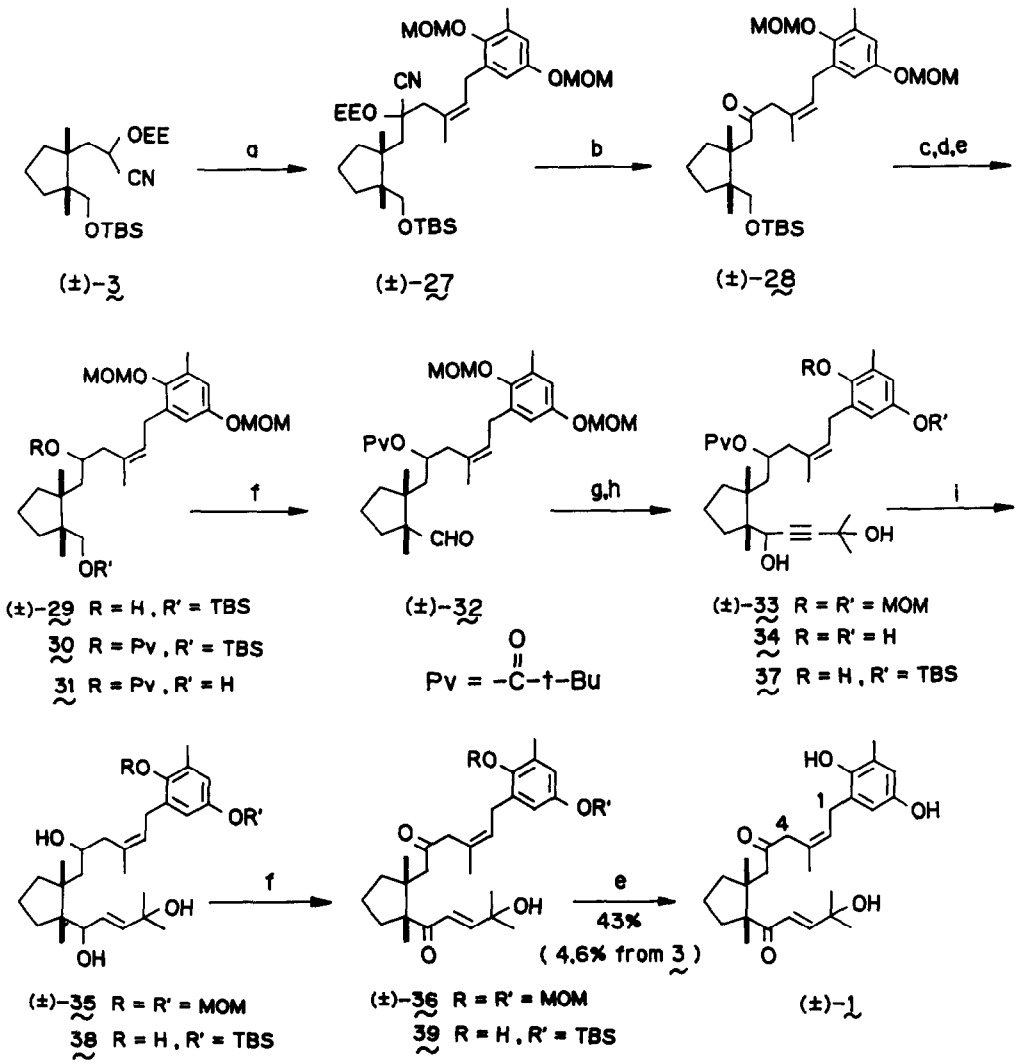


Reagents: (a) Br_2(99%); (b) CrO_3/AcOH; (c) $Na_2S_2O_4$(38% from 16); (d) MOMCl, $MeO(CH_2)_2ONa$(57%); (e) n-BuLi,CuI,CH_2=$CHCH_2Br$(88%); (f) OsO_4,$NaIO_4$/Et_2O-H_2O; (g) $(MeO)_2P(O)CHMeCO_2Me$(22),NaH/THF; (h) LAH/Et_2O(99% for 25; 94% for 26); (i) Ph_3P/CCl_4(86% for 4; 72% for 5).

Fig. 3. Synthesis of the aromatic building blocks 4 and 5.

3 with (Z)-allyl chloride 4 yielded (±)-27. Selective removal of the EE protective group of (±)-27 was achieved with HCl-$CHCl_3$. The resulting cyanohydrin was treated with 2% NaOH soln in the presence of ether to give (±)-28. To avoid the migration of the non-conjugated double bond in the remaining course of the synthesis to give a conjugated ketone, the CO group of (±)-28 was tentatively reduced to furnish (±)-29. The OH group of (±)-29 was then protected as the pivaloyl (Pv) ester (±)-30.

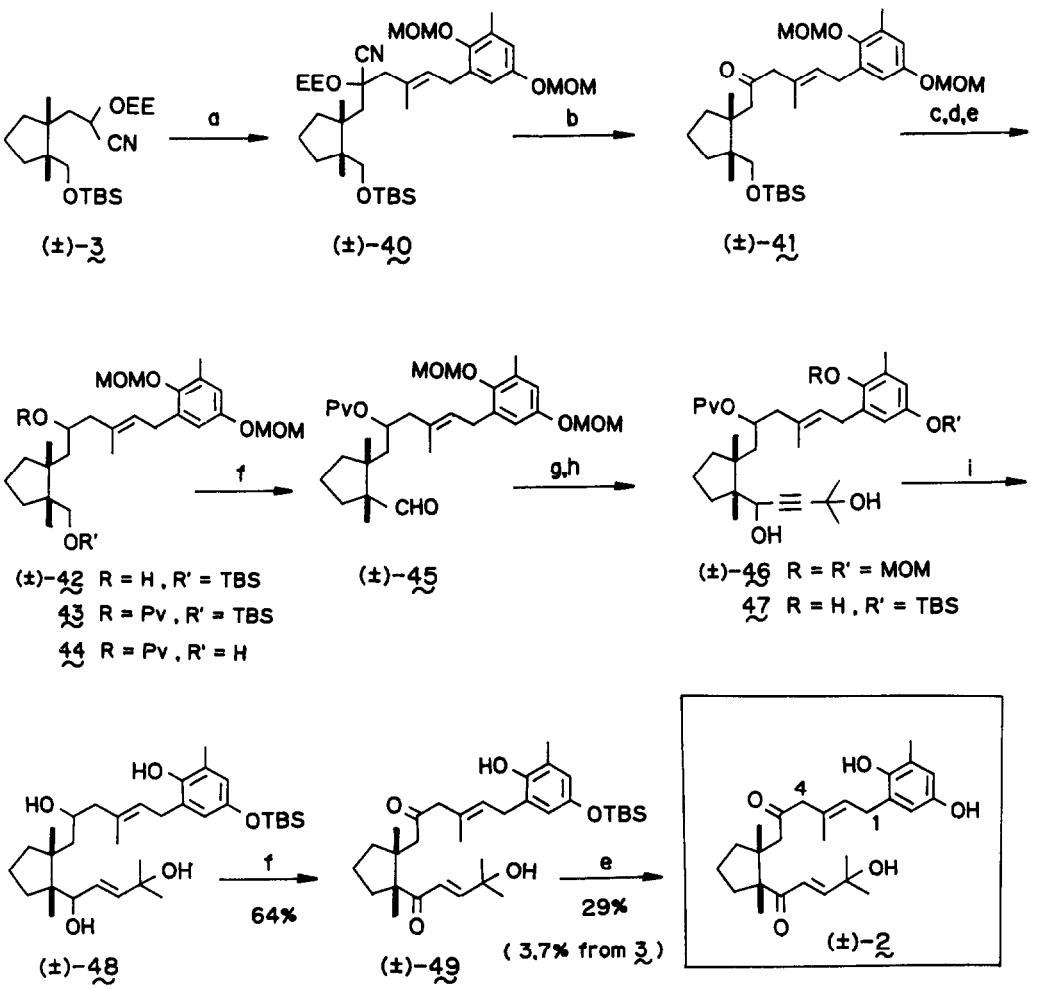
To attach the remaining C_5 unit 6, (±)-30 was converted to the aldehyde (±)-32 by first removing the silyl protective group of (±)-30 by short treatment with HF



Reagents: (a) LDA,4(70%); (b) HCl/$CHCl_3$; 2% NaOH/Et_2O(87%); (c) $NaBH_4$(87%); (d) t-BuCOCl(98%); (e) 10% HF/MeCN(77%); (f) $(COCl)_2$,DMSO,Et_3N(94%); (g) 6, n-BuLi/THF-HMPA(99%); (h) 6N HCl/THF; TBSCl,imidazole/DMF(52%); (i) LAH(35% for 33 → 35; 78% for 37 → 38).

Fig. 4. Synthesis of the (Z)-isomer (1) of (±)-bifurcarenone

to give (±)-31 followed by its Swern oxidation[8] to (±)-32. Addition of the dianion of 6 to (±)-32 yielded (±)-33. LAH reduction of (±)-33 gave (±)-35 with an (E)-double bond. Swern oxidation of (±)-35 furnished (±)-36 in low yield. Deprotection of the MOM groups of (±)-36 to give (±)-1, however, was unsuccessful under several



Reagents: (a) LDA,5(63%); (b) $HCl/CHCl_3$; 2% $NaOH/Et_2O$(89%); (c) $NaBH_4$(78%); (d) t-BuCOCl(94%); (e) 10% HF/MeCN(88%); (f) $(COCl)_2$,DMSO,Et_3N(88%); (g) 6, n-BuLi/THF-HMPA(97%); (h) 6N HCl/THF; TBSCl,imidazole/DMF(94%); (i) LAH(69%).

Fig. 5. Synthesis of (±)-bifurcarenone (2).

conditions (BBr_3/CH_2Cl_2; HCl/MeOH; $HCl/CHCl_3$; HF/MeCN), only yielding unidentified product(s).

We therefore decided to remove the MOM protective groups at the stage of (±)-33. Treatment of (±)-33 with 6N HCl/THF (1:1)[9] gave (±)-34. To avoid the oxidation of the hydroquinone moiety to quinone in the later stage of oxidation, it was necessary to protect the phenolic OH groups of (±)-34. When (±)-34 was treated

with TBSCl, only one of the two phenolic OH groups of (±)-34 was protected to give a product (±)-37. The structure (±)-37 was tentatively assigned to it, considering the less crowded nature of the OH group at C-4' located meta to both the substituents. Reduction of (±)-37 with LAH gave (±)-38, of which Swern oxidation furnished (±)-39. Deprotection of the silyl protective group of (±)-39 with HF yielded the target molecule (±)-1.

When its ^{1}H NMR spectrum was measured, there were two apparent differences between the spectrum of (±)-1 and the literature data for bifurcarenone.[1] The natural bifurcarenone was reported to show the signals due to protons at C-1 and C-4 at δ=3.34 (2H) and 3.04 (2H), respectively.[1] Instead, our (±)-1 showed the signals at δ=3.22 (2H), 3.17 (1H) and 3.18 (1H). Moreover the ^{13}C NMR spectrum of (±)-1 was not completely identical with that reported for bifurcarenone.[1] We therefore reasoned that the natural product must be 2 or its antipode.

Synthesis of (±)-bifurcarenone (2). With our experience in synthesizing (±)-1, the synthesis of (±)-2 from (±)-3, 5 and 6 was straightforward as shown in Fig. 5. The overall yield of (±)-2 was 1.2% in twenty steps from 7. In the case of (±)-2, the ^{1}H NMR signals due to protons at C-1 and C-4 appeared at δ=3.34 (lit.[1] 3.34) and 3.05 (lit.[1] 3.04). The IR, ^{1}H NMR and ^{13}C NMR spectra of (±)-2 were completely identical to those of (-)-bifurcarenone obtained by purification of the crude sample kindly sent to us by Prof. Fenical.

In conclusion, the first total synthesis of (±)-bifurcarenone (2) was accomplished, resulting in the revision of the geometry of the non-conjugated double bond in the proposed structure 1. A chiral synthesis of 2 is now in progress, and will be reported in due course.

EXPERIMENTAL

All m.ps were uncorrected. IR spectra were measured as films on a Jasco IRA-102 spectrometer unless otherwise stated. ^{1}H NMR spectra were recorded with TMS as an internal standard at 100 MHz on a JEOL JNM FX-100 spectrometer unless otherwise stated. 500 MHz ^{1}H NMR and 126 MHz ^{13}C NMR spectra were recorded on a JEOL JNM GSX-500 spectrometer. Mass spectra were recorded on a JEOL DX-303 spectrometer at 70 eV. Merck Kieselgel 60 Art. 7734 was used for SiO_2 column chromatography.

(1R*,6R*)-1,6-Dimethyl-3-oxabicyclo[4.3.0]nonan-4-one 8. To a soln of 7 (30.0 g, 0.197 mol) in CH_2Cl_2 (700 ml) was added m-chloroperbenzoic acid (80%, 51.0 g, 0.236 mol) and the mixture was heated under reflux for 20 h. After cooling, a soln of 10% $Na_2S_2O_3$ aq (300 ml) was slowly added to the mixture. The CH_2Cl_2 soln was washed with 10% NaOH aq and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (500 g). Elution with hexane-AcOEt (10:1) gave 32.5 g (98%) of 8 as white, granular crystals, m.p. 148-150°C; νmax 2960 (s), 1740 (s), 1470 (m), 1450 (m), 1390 (m), 1370 (m), 1290 (s), 1260 (s), 1210 (s), 1050 (s), 760 (s) cm^{-1}; δ (60 MHz, CCl_4) 0.98 (3H, s), 1.00 (3H, s), 1.5-2.0 (6H, m), 2.20 (1H, d, J=13 Hz), 2.30 (1H, d, J=13 Hz), 3.80 (2H, s). (Found: C, 71.30; H, 9.52. Calc for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59%).

(1R*,6R*)-1,6-Dimethyl-3-oxabicyclo[4,3,0]nonan-4-ol **9**. To a soln of **8** (21.0 g, 0.125 mol) in dry toluene (700 ml) was added dropwise DIBAL (1.0 M in toluene, 140 ml, 0.140 mol) at 0°C under Ar. After stirring overnight at room temp, the reaction mixture was quenched by adding ice-water. The organic layer was dried ($MgSO_4$) and concentrated. The residue was chromatographed over SiO_2 (400 g). Elution with hexane-AcOEt (10:1-4:1) gave 21 g (99%) of **9**, n_D^{16} 1.5116; νmax 3400 (s), 2950 (s), 2870 (s), 1450 (s), 1370 (s), 1350 (s), 1110 (s), 1070 (s), 1020 (s), 980 (s), 860 (s) cm^{-1}; δ ($CDCl_3$) 0.86, 0.94 and 0.98 (total 6H, each s), 1.1-2.3 (8H, m), 3.2-3.7 (2H, m), 3.80 (1H, OH), 4.90 and 4.98 (total 1H, each dd, J=3, 8 Hz). (Found: C, 70.56; H, 10.54. Calc for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66%)

(1'R*,2'R*)-2-(1',2'-Dimethyl-2'-hydroxymethylcyclopentylmethyl)-1,3-dithiane **10**. To a soln of **9** (55.0 g, 0.323 mol), 1,3-propanedithiol (50.0 ml, 53.9 g, 0.498 mol) in dry CH_2Cl_2 (1 l) was added dropwise Et_2AlCl (1 M in hexane, 500 ml, 0.500 mol) at 0°C under Ar. After stirring overnight at room temp, the reaction mixture was quenched with 15% NaOH aq (80 ml). The organic soln was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (700 g). Elution with hexane-AcOEt (50:1-4:1) gave 54 g (64%) of **10**, n_D^{16} 1.5612; νmax 3420 (s), 2960 (s), 2890 (s), 1470 (m), 1450 (m), 1420 (m), 1380 (m), 1270 (m), 1240 (m), 1020 (s), cm^{-1}; δ (60 MHz, CCl_4) 0.89 (3H, s), 0.96 (3H, s), 1.2-2.0 (10H, m), 2.58 (1H, OH), 2.5-2.9 (4H, m), 3.35 (2H, s), 3.88 (1H, t, J=7 Hz). (Found: C, 59.91; H, 8.90. Calc for $C_{13}H_{24}OS_2$: C, 59.95; H, 9.29%).

(1'R*,2'R*)-2-(2'-t-Butyldimethylsiloxymethyl-1',2'-dimethylcyclopentylmethyl)-1,3-dithiane **11**. A mixture of **10** (46.0 g, 0.177 mol), imidazole (31.0 g, 0.455 mol) and t-$BuMe_2SiCl$ (34.0 g, 0.226 mol) in DMF (500 ml) was stirred overnight at room temp. The reaction mixture was poured into water and extracted with ether. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (2 kg). Elution with hexane-AcOEt (1:0-20:1) gave 63.8 g (98%) of **11** as white, granular crystals, m.p. 39.0-39.5°C; νmax 2960 (s), 2900 (m), 2870 (m), 1460 (s), 1250 (s), 1080 (s), 840 (s) cm^{-1}; δ (60 MHz, CCl_4) 0.02 (6H, s), 0.88 (12H, s), 0.95 (3H, s), 1.0-2.1 (10H, m), 2.68 (4H, m), 3.30 (2H, s), 3.87 (1H, t, J=6 Hz). (Found: C, 60.40; H, 9.85. Calc for $C_{19}H_{38}OS_2Si$: C, 60.90; H, 9.85%).

(1'R*,2'R*)-2-(2'-t-Butyldimethylsiloxymethyl-1',2'-dimethylcyclopentyl)acetaldehyde **12**. A mixture of **11** (30.0 g, 80.1 mmol), $HgCl_2$ (90.0 g, 331 mmol) and $CaCO_3$ (36.0 g, 360 mmol) in MeCN (500 ml) and water (200 ml) was heated under reflux for 4 h. After cooling, the precipitate was filtered through a celite pad and washed thoroughly with MeCN. The filtrate was concentrated, and the residue was extracted with ether. The extract was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over SiO_2 (150 g). Elution with hexane-AcOEt (20:1) gave 18 g (79%) of unstable **12**, νmax 2960 (s), 2940 (s), 2860 (s), 2740 (m), 1720 (s), 1460 (s), 1380 (m), 1250 (s), 1080 (s), 1010 (m), 840 (s), 770 (s) cm^{-1}; δ (60 MHz, CCl_4) 0.00 (6H, s), 0.88 (12H, s), 1.10 (3H, s), 1.40-1.90 (6H, m), 2.28 (2H, d, J=3 Hz), 3.28 (1H, d, J=9 Hz), 3.42 (1H, d, J=9 Hz), 9.80 (1H, t, J=3 Hz). This was immediately used for the next step.

(1'R*,2'R*)-3-(2'-t-Butyldimethylsiloxymethyl-1',2'-dimethylcyclopentyl)-2-hydroxypropionitrile **14**. To a soln of **12** (18.0 g, 63.3 mmol) and trimethylsilyl cyanide (95%, 10 ml, 71 mmol) was added ZnI_2 (cat. amount) with ice-cooling. After stirring overnight at room temp, the reaction mixture was poured into water and extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated in vacuo to give 20 g of crude **13**. A mixture of 20 g of crude **13** and citric acid (0.50 g, 2.6 mmol) in MeOH (100 ml) was stirred overnight at room temp. The reaction mixture was concentrated. The residue was dissolved in ether, washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (100 g). Elution with hexane-AcOEt (10:1) gave 16 g (81% from **12**) of **14**, as a diastereomeric mixture, n_D^{22} 1.4651; νmax 3480 (s), 2960 (s), 2880 (s), 2860 (s), 2250 (vw), 1480 (s), 1390 (m), 1260 (s), 1080 (s), 840 (s), 780 (s) cm^{-1}; δ ($CDCl_3$) 0.06, 0.12 and 0.13 (total 6H, each s), 0.91 and 0.95 (total 9H, each s), 0.98 (3H, s), 1.02 (3H, s), 1.4-1.8 (7H, m), 1.9-2.4 (2H, m), 3.26, 3.32, 3.42 and 3.65 (total 2H, each d, J=10 Hz), 4.4-4.7 (1 H, m). (Found: C, 65.33; H, 10.58; N, 4.27. Calc for $C_{17}H_{33}O_2NSi$: C, 65.53; H, 10.68; N, 4.50%).

(1'R*,2R*)-3-(2'-t-Butyldimethylsiloxymethyl-1',2'-dimethylcyclopentyl)-2-(ethoxyethoxy)propionitrile **3**. A mixture of **14** (12.3 g, 39.5 mmol), ethyl vinyl ether (3.40 g, 40.4 mmol) and PPTS (0.5 g) in CH_2Cl_2 (100 ml) was stirred for 3 h. The reaction mixture was diluted with CH_2Cl_2, washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (150 g). Elution with hexane-AcOEt (40:1) gave 13.4 g (88%) of **3** as a diastereomeric mixture, n_D^{22} 1.4524; νmax 2960 (s), 2880 (s), 2200 (vw), 1470 (s), 1390 (s), 1250 (s), 1080 (s), 940 (m), 840 (s), 780 (s) cm^{-1}; δ ($CDCl_3$) 0.06 (6H, s), 0.89 (3H, s), 0.92 (9H, s), 0.95 and 0.97 (total 3H, each s), 1.1-1.45 (6H, m), 1.5-1.8 (6H, m), 1.8-2.0 (2H, m), 3.35 (1H, d, J=11 Hz), 3.39 (1H, d, J=11 Hz), 3.5-3.8 (2H, m), 4.30 and 4.55 (total 1H, each m), 4.85 (1H, m). (Found: C, 65.76; H, 10.67; N, 3.62. Calc for $C_{21}H_{41}O_3NSi$: C, 65.74; H, 10.77; N, 3.65%).

2-Bromo-6-methylhydroquinone **18.** To a soln of **16** (398 g, 1.50 mol) in 80% AcOH (1 l) was added dropwise a soln of CrO_3 (165 g, 1.65 mol) in water (500 ml) with ice-cooling over 3 h. After stirring for further 2 h at 0°C, the reaction mixture was poured into water and extracted with $CHCl_3$. The extract was washed with sat $NaHCO_3$ soln and brine, dried ($MgSO_4$) and concentrated in vacuo to give 245 g of crude **17**, δ (60 MHz, CCl_4) 2.21 (3H, d, J=1 Hz), 6.44 (1H, dd, J=1, 2 Hz), 7.02 (1H, d, J=2 Hz). To a soln of crude **17** (245 g) in 95% EtOH (2 l) and water (500 ml) was added portionwise $Na_2S_2O_4$ (200 g, 1.15 mol) at 60°C over 1 h and the reaction mixture was stirred at 60°C for further 1 h. After cooling, the reaction mixture was concentrated. The residue was dissolved in CH_2Cl_2, washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (3 kg). Elution with hexane-AcOEt (50:1-10:1) gave 116 g (38%) of **18**. This was recrystallized from CH_2Cl_2 to give colorless plates m.p. 117-118°C; νmax 3650 (s), 3550 (s), 3350 (s), 1590 (m), 1480 (s), 1420 (s), 1320 (s), 1180 (s), 1100 (m), 1000 (m) cm^{-1}; δ ($CDCl_3$) 2.27 (3H, s), 3.80 (1H, OH), 5.16 (1H, OH), 6.60 (1H, d, J=3 Hz), 6.81 (1H, d, J=3 Hz). (Found: C, 41.39; H, 3.50. Calc for $C_7H_7O_2Br$: C, 41.41; H, 3.48%).

3-Bromo-2,5-bis(methoxymethoxy)toluene **19.** To a soln of $MeOCH_2CH_2ONa$ [prepared from 23.5 g (1.03 mol) of Na] in $MeOCH_2CH_2OH$ (800 ml) was added dropwise a soln of **18** (50.0 g, 0.246 mol) in $MeOCH_2CH_2OH$ (200 ml) at -10~0°C. To this was added dropwise $MeOCH_2Cl$ (59.6 g, 0.740 mol) at -10~0°C and the reaction mixture was stirred overnight at room temp. The reaction mixture was concentrated. The residue was diluted with ice-water and extracted with ether. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (500 g). Elution with hexane-AcOEt (20:1) gave 41.2 g (57%) of oily **19**, n_D^{22} 1.5268; νmax 2960 (s), 1600 (s), 1570 (s), 1480 (s), 1400 (s), 1310 (m), 1220 (s), 1200 (s), 1160 (s), 1080 (S), 1040 (s), 970 (s), 860 (S), 830 (s), 760 (s) cm^{-1}; δ ($CDCl_3$) 2.34 (3H, s), 3.48 (3H, s), 3.65 (3H, s), 5.02 (2H, s), 5.10 (2H, s), 6.82 (1H, d, J=3 Hz), 7.09 (1H, d, J=3 Hz). (Found: C, 45.32; H, 5.12. Calc for $C_{11}H_{15}O_4Br$: C, 45.38; H, 5.19%).

3-Allyl-2,5-bis(methoxymethoxy)toluene **20.** A soln of n-BuLi in n-hexane (1.59 M, 120 ml, 0.191 mol) was added dropwise to a stirred and cooled soln of **19** (41.2 g, 0.141 mol) in dry Et_2O (700 ml) at -50~-40°C under Ar. The mixture was stirred for 30 min at -50~-40°C. To the stirred mixture was added CuI (13.0 g, 68.3 mmol) at -50~-40°C. The mixture was stirred for 2 h at -50~-40°C. To the stirred mixture was added dropwise allyl bromide (14.7 ml, 20.6 g, 0.170 mol). The mixture was stirred overnight at room temp. The mixture was poured into ice-water and extracted with ether. The extract was washed with water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (300 g). Elution with hexane-AcOEt (20:1) gave 31.5 g (88%) of **20**, n_D^{15} 1.5095; νmax 2960 (s), 2850 (m), 1640 (m), 1600 (s), 1500 (m), 1480 (s), 1440 (m), 1400 (s), 1320 (s), 1220 (s), 1180 (s), 1160 (s), 1080 (s), 1040 (s), 980 (s), 920 (s), 860 (s) cm^{-1}; δ ($CDCl_3$) 2.28 (3H, s), 3.40 (2H, ddd, J=7, 2, 2 Hz), 3.47 (3H, s), 3.60 (3H, s), 4.90 (2H, s), 4.9-5.1 (2H, m), 5.11 (2H, s), 5.96 (1H, ddt, J=8, 10, 7 Hz), 6.70 (2H, m). (Found: C, 66.67; H, 7.85. Calc for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99%).

[2,5-Bis(methoxymethoxy)-3-methylphenyl]acetaldehyde **21.** A mixture of **20** (20.0 g, 79.3 mmol), OsO_4 (1.00 g, 3.93 mmol) and $NaIO_4$ (34.4 g, 161 mmol) in ether (400 ml) and water (400 ml) was stirred for 6 h at room temp. The mixture was diluted with water. To the ether soln was added 10% Na_2S aq soln. The precipitate was filtered through a celite pad and washed thoroughly with ether. The ether soln was washed with water and brine, dried (Na_2SO_4) and concentrated in vacuo to give 20 g of unstable **21**, δ (60 MHz, CCl_4) 2.24 (3H, s), 3.40 (3H, s), 3.48 (3H, s), 3.52 (2H, d, J=2 Hz), 4.79 (2H, s), 5.03 (2H, s), 6.6-6.9 (2H, m), 9.68 (1H, t, J=2 Hz). This was employed for the next step without further purification.

Methyl (Z)-4-[2,5-bis(methoxymethoxy)-3-methylphenyl]-2-methyl-2-butenoate **23** and methyl (E)-4-[2,5-bis(methoxymethoxy)-3-methylphenyl]-2-methyl-2-butenoate **24.** 60% NaH in mineral oil (3.80 g, 95.0 mmol) was washed with n-pentane, and NaH was suspended in dry THF (400 ml). To this suspension was added dropwise at room temp a soln of trimethyl phosphonopropionate (15.4 g, 78.9 mmol) in THF (50 ml) under Ar. The stirring was continued for 30 min at room temp. To the stirred and cooled mixture at -70°C was added dropwise a soln of **21** (20 g) in THF (20 ml) over 5 min. After stirring for 30 min at -70°C, the mixture was quenched by adding sat NH_4Cl soln and extracted with ether. The extract was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (400 g). Elution with hexane-AcOEt (10:1) first yielded the (Z)-isomer **23** (5.5 g, 21%), n_D^{25} 1.5086; νmax 2980 (s), 2850 (s), 1720 (s), 1640 (m), 1600 (s), 1480 (s), 1440 (s), 1400 (m), 1360 (m), 1320 (m), 1220 (s), 1160 (s), 1130 (m), 1080 (s), 1040 (s), 980 (s), 860 (m) cm^{-1}; δ (400 MHz, $CDCl_3$, JEOL JNM GX-400) 1.93 (3H, dq, J=2, 1 Hz), 2.28 (3H, s), 3.47 (3H, s), 3.57 (3H, s), 3.77 (3H, s), 3.84 (2H, dq, J=1, 7 Hz), 4.90 (2H, s), 5.10 (2H, s), 6.07 (1H, tq, J=7, 2 Hz), 6.70 (1H, d, J=3 Hz), 6.75 (1H, d, J=3 Hz). Nuclear Overhauser enhancement difference spectroscopy (NOEDS) on **23** gave the following results : presaturation of the methyl protons at 1.93 ppm resulted in an NOE of the vinyl proton at 6.07 ppm ; TLC (Merck Kieselgel 60 F-254 Art. 5715, developed with hexane-AcOEt=4:1) Rf=0.51. (Found: C, 62.61; H, 7.38. Calc for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46%). The next fraction afforded the mixture of **23** and **24** (2.7 g, 11%). Further elution afforded the (E)-isomer **24** (6.3 g, 25%), n_D^{20} 1.5134; νmax 2960 (s), 2850 (m), 1720 (s), 1640 (m), 1600 (s), 1480 (s), 1440 (s), 1400 (m), 1360 (m),

1260 (s), 1200 (s), 1160 (s), 1080 (s), 1040 (s), 980 (s), 860 (s) cm^{-1}; δ (400 MHz, $CDCl_3$) 1.95 (3H, dq, J=2, 1 Hz), 2.28 (3H, s), 3.47 (3H, s), 3.54 (2H, d, J=8 Hz), 3.58 (3H, s), 3.73 (3H, s), 4.91 (2H, s), 5.10 (2H, s), 6.64 (1H, d, J=3 Hz), 6.76 (1H, d, J=3 Hz), 6.88 (1H, tq, J=8, 1 Hz). NOEDS on **24** : presaturation of the methyl protons at 1.95 ppm resulted in an NOE of the methylene protons at 3.54 ppm, TLC (Merck Kieselgel 60 F-254 Art. 5715, hexane-AcOEt=4:1) Rf=0.45, (Found: C, 62.89; H, 7.34. Calc for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46%).

4-[2,5-Bis(methoxymethoxy)-3-methylphenyl]-2-methyl-2-buten-1-ol

(a) (Z)-isomer **25**. To a stirred suspension of LAH (2.00 g, 52.7 mmol) in ether (100 ml) was added a soln of **23** (17.2 g, 53.0 mmol) in ether (100 ml) at 0°C. After stirring for 1 h at room temp, the reaction mixture was quenched by adding water (2.0 ml), 15% NaOH aq (2.0 ml) and water (6.0 ml). The ether soln was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (300 g). Elution with hexane-AcOEt (10:1) gave 15.6 g (99%) of **25**, n_D^{22} 1.5170; νmax 3450 (s), 2960 (s), 1600 (s), 1480 (s), 1440 (m), 1400 (m), 1320 (m), 1220 (m), 1160 (s), 1080 (s), 1040 (s), 980 (s), 860 (m) cm^{-1}; δ ($CDCl_3$) 1.84 (3H, d, J=2 Hz), 2.28 (3H, s), 3.41 (2H, d, J=8 Hz), 3.49 (3H, s), 3.60 (3H, s), 4.21 (2H, s), 4.91 (2H, s), 5.11 (2H, s), 5.41 (1H, dt, J=2, 8 Hz), 6.70 (1H, d, J=3 Hz), 6.73 (1H, d, J=3 Hz). (Found: C, 64.99; H, 8.41. Calc for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16%).

(b) (E)-isomer **26**. In the same manner as described above, 6.2 g of **24** gave 5.3 g (94%) of **26**, n_D^{20} 1.5167; νmax 3450 (s), 2950 (s), 1600 (s), 1480 (s), 1400 (m), 1320 (m), 1220 (m), 1190 (m), 1160 (s), 1080 (s), 1040 (s), 980 (s), 860 (s) cm^{-1}; δ ($CDCl_3$) 1.70 (1H, OH), 1.79 (3H, s), 2.28 (3H, s), 3.41 (2H, d, J=8 Hz), 3.48 (3H, s), 3.60 (3H, s), 4.05 (2H, s), 4.91 (2H, s), 5.11 (2H, s), 5.58 (1H, dt, J=2, 8 Hz), 6.68 (1H, d, J=3 Hz), 6.73 (1H, d, J=3 Hz). (Found: C, 64.79; H, 7.76. Calc for $C_{16}H_{24}O_5$: C, 64.84; H, 8.16%).

3-[4-Chloro-3-methyl-2-butenyl]-2,5-bis(methoxymethoxy)toluene

(a) (Z)-isomer **4**. A mixture of **25** (3.62 g, 12.2 mmol) and PPh_3 (3.20 g, 12.2 mmol) in CCl_4 (100 ml) was heated under reflux for 20 h. The mixture was concentrated. The residue was filtered through SiO_2 (50 g) using $CHCl_3$ to remove the Ph_3PO. The filtrate was concentrated in vacuo. The residue was chromatographed over SiO_2 (100 g). Elution with hexane-AcOEt (50:1-20:1) gave 3.3 g (86%) of **4**, n_D^{22} 1.5180; νmax 2970 (s), 1600 (s), 1480 (s), 1400 (m), 1320 (s), 1260 (m), 1220 (m), 1190 (m), 1160 (s), 1080 (s), 1040 (s), 980 (s), 860 (s) cm^{-1}; δ ($CDCl_3$) 1.84 (3H, d, J=2 Hz), 2.28 (3H, s), 3.42 (2H, d, J=8 Hz), 3.48 (3H, s), 3.60 (3H, s), 4.04 (2H, s), 4.90 (2H, s), 5.10 (2H, s), 5.70 (1H, dt, J=2, 8 Hz), 6.65 (1H, d, J=3 Hz), 6.74 (1H, d, J=3 Hz). (Found: C, 60.61; H, 7.21. Calc for $C_{16}H_{23}O_4Cl$: C, 61.04; H, 7.36%).

(b) (E)-isomer **5**. In the same manner as described above, 3.0 g of **26** gave 2.3 g (72%) of **5**, n_D^{22} 1.5170; νmax 2960 (s), 1600 (s), 1480 (s), 1440 (m), 1400 (m), 1320 (m), 1260 (m), 1160 (s), 1080 (s), 1040 (s), 980 (s), 860 (s) cm^{-1}; δ ($CDCl_3$) 1.86 (3H, d, J=2 Hz), 2.28 (3H, s), 3.42 (2H, d, J=8 Hz), 3.47 (3H, s), 3.60 (3H, s), 4.07 (2H, s), 4.90 (2H, s), 5.10 (2H, s), 5.70 (1H, dt, J=2, 8 Hz), 6.60 (1H, d, J=3 Hz), 6.74 (1H, d, J=3 Hz). (Found: C, 61.11; H, 7.16. Calc for $C_{16}H_{23}O_4Cl$: C, 61.04; H, 7.36%).

(1'R*,2'R*)-2-(2'-t-Butyldimethylsiloxymethyl-1',2'-dimethylcyclopentylmethyl)-2-ethoxyethoxy-6-[2,5-bis(methoxymethoxy)-3-methylphenyl]-4-methyl-4-hexenonitrile

(a) (Z)-isomer **27**. To a soln of **3** (3.80 g, 9.90 mmol) in THF (40 ml) and HMPA (1 ml) was added dropwise at -50~-40°C an LDA soln which was prepared from diisopropylamine (1.70 ml, 12.1 mmol) and n-BuLi (1.59 M 7.50 ml, 11.9 mmol) in THF (10.8 ml). After stirring for 1 h at -50~-40°C, a soln of **4** (2.60 g, 8.26 mmol) in THF (10 ml) was added, and the mixture was stirred for further 40 min at 0°C. The mixture was poured into sat NH_4Cl soln and extracted with ether. The extract was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over SiO_2 (100 g). Elution with hexane-AcOEt (20:1) gave 3.86 g (70 %) of **27** as a diastereomeric mixture, n_D^{22} 1.4925; νmax 2980 (s), 1710 (m), 1600 (s), 1480 (s), 1390 (s), 1320 (s), 1260 (s), 1160 (s), 1080 (s), 1040 (s), 980 (s), 840 (s), 780 (s) cm^{-1}; δ ($CDCl_3$) 0.00 and 0.04 (total 6H, each s), 0.84 (3H, s), 0.88 (9H, s), 0.90 (3H, s), 1.0-1.45 (6H, m), 1.5-2.0 (11H, m), 2.28 (3H, s), 2.1-2.5 (2H, m), 3.2-3.7 (6H, m), 3.47 (3H, s), 3.58 (3H, s), 4.90 (2H, s), 5.10 (2H, s), 5.20 (1H, m), 5.55 (1H, t, J=8 Hz), 6.66 (1H, d, J=3 Hz), 6.73 (1H, d, J=3 Hz). (Found: C, 66.66; H, 9.43; N, 1.99. Calc for $C_{37}H_{63}O_7NSi$: C, 67.13; H, 9.59; N, 2.12%).

(b) (E)-isomer **40**. In the same manner as described above, 5.6 g of **3** and 4.6 g of **5** gave 6.1 g (63%) of **40** as a diastereomeric mixture, n_D^{22} 1.4908; νmax 2980 (s), 1600 (s), 1480 (s), 1390 (s), 1320 (m), 1260 (s), 1160 (s), 1080 (s), 1040 (s), 980 (s), 860 (s), 840 (s), 780 (s) cm^{-1}; δ ($CDCl_3$) 0.00 (3H, s), 0.02 and 0.04 (total 3H, each s), 0.81 (3H, s), 0.88 (9H, s), 0.90 (3H, s), 0.95-1.5 (6H, m), 1.5-2.0 (8H, m), 1.89 (3H, s), 2.28 (3H, s), 2.3-3.0 (2H, m), 3.2-3.9 (6H, m), 3.48 (3H, s), 3.60 (3H, s), 4.91 (2H, s), 5.10 (2H, s), 5.15 (1H, m), 5.55 (1H, t, J=7 Hz), 6.68 (1H, d, J=3 Hz), 6.73 (1H, d, J=3 Hz). (Found: C, 66.83; H, 9.51; N, 2.29. Calc for $C_{37}H_{63}O_7NSi$: C, 67.13; H, 9.59; N, 2.12%).

(1'R*,2'R*)-1-(2'-t-Butyldimethylsiloxymethyl-1',2'-dimethylcyclopentyl)-6-[2,5-bis(methoxymethoxy)-3-methylphenyl]-4-methyl-4-hexen-2-one

(a) (Z)-isomer **28**. A mixture of conc. HCl (0.5 ml) and $MgSO_4$ (5 g) in $CHCl_3$ (100 ml) was stirred for 1 h at room temp. The mixture was filtered and the filtrate was added to **27** (3.86 g, 5.83 mmol). The mixture was stirred for 1 h at room temp and concentrated in vacuo. To the residue was added a soln of 2% NaOH aq (50 ml) and ether (100 ml). The mixture was stirred for 1 h at room temp. The ether soln was washed with water and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over SiO_2 (150 g). Elution with hexane-AcOEt (40:1) gave 2.85 g (87%) of **28**, n_D^{22} 1.4976; νmax 2950 (s), 1740 (s), 1720 (s), 1600 (s), 1480 (s), 1320 (m), 1250 (m), 1150 (s), 1080 (s), 1040 (s), 980 (s), 840 (s), 780 (s) cm^{-1}; δ ($CDCl_3$) 0.04 (6H, s), 0.88 (3H, s), 0.91 (9H, s), 0.98 (3H, s), 1.4-1.8 (6H, m), 1.56 (3H, s), 2.1-2.5 (2H, m), 2.28 (3H, s), 3.25-3.5 (6H, m), 3.48 (3H, s), 3.61 (3H, s), 4.92 (2H, s), 5.11 (2H, s), 5.41 (1H, t, J=8 Hz), 6.72 (2H, m). (Found: C, 68.31; H, 9.52. Calc for $C_{32}H_{54}O_6Si$: C, 68.28; H, 9.67%).

(b) (E)-isomer **41**. In the same manner as described above, 6.1 g of **40** gave 4.6 g (89%) of **41**, n_D^{22} 1.4966; νmax 2950 (s), 1710 (s), 1600 (s), 1480 (s), 1400 (m), 1320 (m), 1250 (m), 1190 (m), 1160 (s), 1080 (s), 1040 (s), 980 (s), 860 (s), 840 (s), 780 (s) cm^{-1}; δ ($CDCl_3$) 0.03 (6H, s), 0.88 (3H, s), 0.90 (9H, s), 0.97 (3H, s), 1.4-1.8 (6H, m), 1.73 (3H, d, J=2 Hz), 2.28 (3H, s), 2.38 (1H, d, J=15 Hz), 2.50 (1H, d, J=15 Hz), 3.12 (2H, s), 3.31 (1H, d, J=10 Hz), 3.37 (1H, d, J=10 Hz), 3.41 (2H, d, J=8 Hz), 3.47 (3H, s), 3.60 (3H, s), 4.91 (2H, s), 5.12 (2H, s), 5.39 (1H, dt, J=2, 8 Hz), 6.70 (1H, d, J=3 Hz), 6.73 (1H, d, J=3 Hz). (Found: C, 67.84; H, 9.50. Calc for $C_{32}H_{54}O_6Si$: C, 68.28; H, 9.67%).

(1'R*,2'R*)-1-(2'-t-Butyldimethylsiloxymethyl-1',2'-dimethylcyclopentyl)-6-[2,5-bis(methoxymethoxy)-3-methylphenyl]-4-methyl-4-hexen-2-ol

(a) (Z)-isomer **29**. To a soln of **28** (2.80 g, 4.97 mmol) in MeOH (50 ml) was added $NaBH_4$ (280 mg, 7.40 mmol) at room temp. After stirring overnight at room temp, the reaction mixture was concentrated. The residue was diluted with water and extracted with ether. The extract was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over SiO_2 (150 g). Elution with hexane-AcOEt (30:1) gave 2.45 g (87%) of **29**, n_D^{22} 1.4990; νmax 3400 (s), 2950 (s), 1600 (s), 1480 (s), 1400 (m), 1320 (m), 1250 (s), 1160 (s), 1080 (s), 1040 (s), 980 (s), 860 (s), 840 (s), 780 (s) cm^{-1}; δ ($CDCl_3$) 0.03 and 0.05 (total 6H, each s), 0.88 (3H, s), 0.90 (9H, s), 0.93 (3H, s), 1.4-1.8 (9H, m), 1.78 (3H, s), 2.1-2.6 (2H, m), 2.28 (3H, s), 3.2-3.45 (4H, m), 3.48 (3H, s), 3.60 (3H, s), 3.90 (1H, m), 4.91 (2H, s), 5.10 (2H, s), 5.48 (1H, t, J=8 Hz), 6.71 (2H, m). (Found: C, 68.21; H, 9.85. Calc for $C_{32}H_{56}O_6Si$: C, 68.04; H, 9.99%).

(b) (E)-isomer **42**. In the same manner as described above, 4.6 g of **41** gave 3.6 g (78 %) of **42** as a diastereomeric mixture, n_D^{25} 1.4871; νmax 3420 (s), 2960 (s), 1730 (m), 1590 (s), 1470 (s), 1390 (m), 1250 (s), 1150 (s), 1080 (s), 1030 (s), 980 (s), 850 (s), 830 (s), 770 (s) cm^{-1}; δ ($CDCl_3$) 0.02 and 0.04 (total 6H, each s), 0.87 (3H, s), 0.90 (9H, s), 0.92 (3H, s), 1.2-1.9 (8H, m), 1.75 (3H, s), 2.0-2.2 (2H, m), 2.27 (3H, s), 3.2-3.5 (4H, m), 3.48 (3H, s), 3.60 (3H, s), 3.84 (1H, m), 4.91 (2H, s), 5.10 (2H, s), 5.40 (1H, t, J=7 Hz), 6.70 (2H, m). (Found: C, 68.04; H, 9.69. Calc for $C_{32}H_{56}O_6$: C, 68.04; H, 9.99%).

(1'R*,2'R*)-1-(2'-t-Butyldimethylsiloxymethyl-1',2'-dimethylcyclopentyl)-6-[2,5-bis(methoxymethoxy)-3-methylphenyl]-4-methyl-4-hexen-2-yl pivalate

(a) (Z)-isomer **30**. To a soln of **29** (1.70 g, 3.01 mmol) and DMAP (cat. amount) in pyridine (25 ml) was added t-BuCOCl (1.00 ml, 0.98 g, 8.12 mmol) at 0°C. After stirring overnight at room temp, the mixture was poured into water and extracted with ether. The ether soln was washed with N-HCl, sat $CuSO_4$ soln, water and brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (100 g). Elution with hexane-AcOEt (20:1) gave 1.92 g (98%) of **30** as a diastereomeric mixture, n_D^{20} 1.4892; νmax 2980 (s), 1720 (s), 1600 (m), 1480 (s), 1400 (m), 1280 (m), 1250 (m), 1160 (s), 1080 (s), 1040 (s), 980 (s), 860 (s), 840 (s) cm^{-1}; δ ($CDCl_3$) 0.01 (6H, s), 0.81 (3H, s), 0.86 (3H, s), 0.88 (9H, s), 1.17 (9H, s), 1.3-1.7 (8H, m), 1.78 (3H, s), 2.1-2.4 (2H, m), 2.28 (3H, s), 3.30 (2H, s), 3.37 (2H, d, J=8 Hz), 3.45 (3H, s), 3.58 (3H, s), 4.88 (2H, s), 5.08 (2H, s), 5.20 (1H, m), 5.38 (1H, t, J=8 Hz), 6.63 (1H, d, J=3 Hz), 6.71 (1H, d, J=3 Hz). (Found: C, 68.35; H, 9.67. Calc for $C_{37}H_{64}O_7Si$: C, 68.47; H, 9.94%).

(b) (E)-isomer **43**. In the same manner as described above, 3.6 g of **42** gave 3.9 g (94 %) of **43** as a diastereomeric mixture, n_D^{23} 1.4776; νmax 2980 (s), 1720 (s), 1600 (m), 1480 (s), 1400 (m), 1280 (m), 1260 (m), 1160 (s), 1080 (s), 1040 (s), 980 (s), 860 (s), 840 (s), 780 (s) cm^{-1}; δ ($CDCl_3$) 0.03 (6H, s), 0.82 (3H, s), 0.86 (3H, s), 0.91 (9H, s), 1.16 (9H, s), 1.7-1.9 (8H, m), 1.77 (3H, s), 2.20 (2H, m), 2.28 (3H, s), 3.32 (2H, s), 3.35 (2H, d, J=8 Hz), 3.47 (3H, s), 3.59 (3H, s), 4.90 (2H, s), 5.09 (2H, s), 5.11 (1H, m), 5.32 (1H, t, J=8 Hz), 6.64 (1H, d, J=3 Hz), 6.72 (1H, d, J=3 Hz). (Found: C, 68.41; H, 9.67. Calc for $C_{37}H_{64}O_7Si$: C, 68.47; H, 9.94%).

(1'R*,2'R*)-1-(1',2'-Dimethyl-2'-hydroxymethylcyclopentyl)-6-[2,5-bis(methoxymethoxy)-3-methylphenyl]-4-methyl-4-hexen-2-yl pivalate

(a) (Z)-isomer **31**. A mixture of **30** (1.90 g, 2.93 mmol) in 10% aq HF (5 ml) and MeCN (25 ml) was stirred for 2.7 h. The reaction mixture was neutralized by adding sat $NaHCO_3$ soln and extracted with ether. The extract was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over SiO_2 (100 g). Elution with hexane-AcOEt (20:1-10:1) gave 1.2 g (77%) of **31** as a diastereomeric mixture, n_D^{20} 1.5065; νmax 3500 (s), 2980 (s), 2900 (m), 1720 (s), 1600 (m), 1480 (s), 1400 (m), 1280 (s), 1160 (s), 1080 (s), 1040 (s), 980 (s) cm^{-1}; δ ($CDCl_3$) 0.85-0.90 (6H, m), 1.20 (9H, s), 1.4-1.7 (9H, m), 1.81 (3H, s), 2.30 (3H, s), 2.2-2.5 (2H, m), 3.34 (2H, s), 3.40 (2H, d, J=8 Hz), 3.48 (3H, s), 3.61 (3H, s), 4.92 (2H, s), 5.11 (2H, s), 5.25 (1H, m), 5.43 (1H, t, J=8 Hz), 6.67 (1H, d, J=3 Hz), 6.72 (1H, d, J=3 Hz). (Found: C, 69.49; H, 9.05. Calc for $C_{31}H_{50}O_7$: C, 69.63; H, 9.43%).

(b) (E)-isomer **44**. In the same manner as described above, 1.8 g of **43** gave 1.3 g (88%) of **44** as a diastereomeric mixture, n_D^{22} 1.4880; νmax 3550 (s), 2960 (s), 1720 (s), 1600 (s), 1480 (s), 1280 (s), 1160 (s), 1080 (s), 1040 (s), 980 (s) cm^{-1}; δ ($CDCl_3$) 0.80 and 0.86 (total 3H, each s), 0.88 and 0.90 (total 3H, each s), 1.17 (9H, s), 1.2-2.2 (9H, m), 1.76 (3H, s), 2.0-2.3 (2H, m), 2.28 (3H, s), 3.2-3.4 (4H, m), 3.48 (3H, s), 3.60 (3H, s), 4.90 (2H, s), 5.08 (1H, m), 5.10 (2H, s), 5.31 (1H, t, J=8 Hz), 6.66 (1H, d, J=3 Hz), 6.72 (1H, d, J=3 Hz). (Found: C, 69.36; H, 9.23. Calc for $C_{31}H_{50}O_7$: C, 69.63; H, 9.43%).

(1'R*,2'R*)-1-(2'-Formyl-1',2'-dimethylcyclopentyl)-6-[2,5-bis(methoxymethoxy)-3-methylphenyl]-4-methyl-4-hexen-2-yl pivalate

(a) (Z)-isomer **32**. To a soln of oxalyl chloride (0.33 ml, 0.48 g, 3.8 mmol) in CH_2Cl_2 (30 ml) was added dropwise DMSO (0.54 ml, 0.59 g, 7.6 mmol) at -70°C. After stirring for 5 min at -70°C, to this was added a soln of **31** (1.2 g, 2.2 mmol) in CH_2Cl_2 (5 ml) and the mixture was stirred for 15 min. Then Et_3N (2.1 ml, 1.5 g, 15 mmol) was added dropwise at -70°C and the temp was gradually raised to room temp. The reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over SiO_2 (50 g). Elution with hexane-AcOEt (10:1) gave 1.12 g (94%) of **32** as a diastereomeric mixture, n_D^{20} 1.5024; νmax 2980 (s), 2950 (s), 2900 (s), 1720 (s), 1600 (s), 1480 (s), 1280 (s), 1160 (s), 1080 (s), 1040 (s), 980 (s) cm^{-1}; δ ($CDCl_3$) 0.95 (3H, s), 1.00 (3H, s), 1.20 (9H, s), 1.3-1.8 (8H, m), 1.78 (3H, s), 2.1-2.5 (2H, m), 2.28 (3H, s), 3.37 (2H, d, J=8 Hz), 3.48 (3H, s), 3.60 (3H, s), 4.93 (2H, s), 5.13 (2H, s), 5.20 (1H, m), 5.43 (1H, t, J=8 Hz), 6.62 (1H, d, J=3 Hz), 6.74 (1H, d, J=3 Hz), 9.62 (1H, s). (Found: C, 69.97; H, 9.01. Calc for $C_{31}H_{48}O_7$: C, 69.89; H, 9.08%).

(b) (E)-isomer **45**. In the same manner as described above, 320 mg of **44** gave 280 mg (88 %) of **45** as a diastereomeric mixture, n_D^{23} 1.4946; νmax 2950 (s), 2700 (m), 1720 (s), 1600 (s), 1480 (s), 1280 (s), 1160 (s), 1080 (s), 1040 (s), 980 (s) cm^{-1}; δ ($CDCl_3$) 0.90 and 0.92 (total 3H, each s), 1.00 and 1.02 (total 3H, each s), 1.15 (9H, s), 1.3-1.9 (8H, m), 1.73 (3H, s), 2.0-2.3 (2H, m), 2.27 (3H, s), 3.32 (2H, d, J=8 Hz), 3.48 (3H, s), 3.60 (3H, s), 4.90 (2H, s), 5.08(2H, s), 5.30 (1H, t, J=8 Hz), 6.62 (1H, d, J=3 Hz), 6.71 (1H, d, J=3 Hz), 9.58 and 9.63 (total 1H, each s). (Found: C, 69.56; H, 8.93. Calc for $C_{31}H_{48}O_7$: C, 69.89; H, 9.08%).

(1'R*,2'R*)-1-[2'-(1,4-Dihydroxy-4-methyl-2-pentynyl)-1',2'-dimethylcyclopentyl]-6-[2,5-bis(methoxymethoxy)-3-methylphenyl]-4-methyl-4-hexen-2-yl pivalate

(a) (Z)-isomer **33**. A soln of n-BuLi in n-hexane (1.59 M, 4.60 ml, 7.31 mmol) was added dropwise to a stirred and cooled soln of 3-methyl-1-butyn-3-ol **6** (260 mg, 3.09 mmol) in dry THF (25 ml) and HMPA (0.5 ml) at -50°C under Ar. The mixture was stirred for 2 h at -5~0°C. To the stirred mixture was added dropwise a soln of **32** (1.12 g, 2.11 mmol) in dry THF (5 ml) at -60°C and the temp was gradually raised to room temp. The mixture was poured into sat NH_4Cl soln and extracted with ether. The extract was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over SiO_2 (50 g). Elution with hexane-AcOEt (10:1-4:1) gave 1.29 g (99%) of **33** as a diastereomeric mixture ; νmax 3480 (s), 2980 (s), 1740 (sh), 1720 (s), 1600 (s), 1480 (s), 1380 (s), 1280 (m), 1240 (s), 1160 (s), 1040 (s), 980 (s) cm^{-1}; δ ($CDCl_3$) 0.90-1.05 (6H, m), 1.21 (9H, s), 1.4-2.0 (9H, m), 1.51 (6H, s), 1.82 (3H, s), 2.1-2.5 (2H, m), 2.30 (3H, s), 3.3-3.5 (2H, m), 3.49 (3H, s), 3.62 (3H, s), 4.10 (1H, OH), 4.92 and 4.93 (total 2H, each s), 5.14 and 5.15 (total 2H, each s), 5.1-5.6 (2H, m), 6.6-6.8 (2H, m). (Found: C, 70.30; H, 8.92. Calc for $C_{36}H_{56}O_8$: C, 70.10; H, 9.15%).

(b) (E)-isomer **46**. In the same manner as described above, 980 mg of **45** gave 1.10 g (97 %) of **46** as a diastereomeric mixture, νmax 3450 (s), 2960 (s), 1720 (s), 1600 (s), 1480 (s), 1370 (m), 1280 (m), 1160 (s), 1080 (m), 1040 (s), 980 (s), 860 (m) cm^{-1}; δ ($CDCl_3$) 0.85-1.10 (6H, m), 1.18 (9H, s), 1.6-1.8 (9H, m), 1.53 (6H, s), 1.77 (3H, s), 2.0-2.3 (2H, m), 2.29 (3H, s), 3.35 (2H, d, J=8 Hz), 3.49 and 3.51 (total 3H, each s), 3.61 (3H, s), 4.21 and 4.22 (total 1H, each s), 4.92 (2H, s), 5.12 and 5.17 (total 2H, each s), 5.1-5.5 (2H, m), 6.6-6.8 (2H, m). (Found: C, 70.04; H, 9.16. Calc for $C_{36}H_{56}O_8$: C, 70.10; H, 9.15%).

(1'R*,2'R*,4z)-1-[2'-(1,4-Dihydroxy-4-methyl-2-pentynyl)-1',2'-dimethylcyclopentyl]-6-(2,5-dihydroxy-3-methylphenyl)-4-methyl-4-hexen-2-yl pivalate **34**. A soln of **33** (1.27 g, 2.06 mmol) in 6 N-HCl (15 ml) and THF (15 ml) was stirred for 3 h. The mixture was extracted with $CHCl_3$. The extract was washed with brine, dried ($MgSO_4$) and concentrated to give 1.40 g of crude **34**, vmax 3400 (s), 2980 (s), 2880 (s), 1720 (s), 1460 (s), 1280 (s), 1160 (s), 1020 (s), 960 (s), 860 (s), 760 (s) cm^{-1}. This was employed for the next step without further purification.

(1'R*,2'R*)-6-(5-t-Butyldimethylsiloxy-2-hydroxy-3-methylphenyl)-1-[2'-(1,4-dihydroxy-4-methyl-2-pentynyl)-1',2'-dimethylcyclopentyl]-4-methyl-4-hexen-2-yl pivalate

(a) (Z)-isomer **37**. A mixture of crude **34** (1.4 g, ca. 2.0 mmol), imidazole (0.41 g, 6.0 mmol) and t-$BuMe_2SiCl$ (0.45 g, 3.0 mmol) in DMF (50 ml) was stirred overnight at room temp. The reaction mixture was poured into water and extracted with ether. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over SiO_2 (50 g). Elution with hexane-AcOEt (6:1-4:1) gave 690 mg (52% from **34**) of **37** as a diastereomeric mixture, when **34** (110 mg, 0.208 mmol) was treated with excess t-$BuMe_2SiCl$ (75 mg, 0.498 mmol), only **37** (92 mg, 69%) was obtained, vmax 3450 (s), 2980 (s), 2950 (s), 2900 (s), 1720 (s), 1710 (sh), 1600 (s), 1480 (s), 1380 (s), 1330 (s), 1290 (s), 1260 (s), 1160 (s), 1040 (s), 960 (s), 860 (s), 780 (s) cm^{-1}; δ ($CDCl_3$) 0.17 (6H, s), 0.8-0.9 (3H, m), 1.00 (9H, s), 1.05 (3H, s), 1.20 (9H, s), 1.51 (6H, s), 1.4-2.1 (10H, m), 1.81 (3H, s), 2.20 (3H, s) 2.2-2.5 (2H, m), 3.2-3.5 (3H, m), 4.40 (1H, m), 5.0-5.5 (2H, m), 6.40-6.55 (2H, m). MS: m/z 642 (M^+, 12%), 641 (15%), 640 (32%), 606 (5%), 522 (6%), 289 (100%, base peak).

(b) (E)-isomer **47**. In the same manner as described above, 400 mg of **46** gave 390 mg (94 %) of **47** as a diastereomeric mixture, vmax 3450 (s), 2980 (s), 2960 (s), 2900 (s), 2880 (m), 1720 (s), 1600 (m), 1480 (s), 1380 (s), 1330 (s), 1280 (s), 1260 (s), 1160 (s), 1040 (s), 1000 (m), 960 (m), 880 (s), 860 (s), 840 (s), 780 (s) cm^{-1}; δ ($CDCl_3$) 0.16 (6H, s), 0.92 and 0.94 (total 3H, each s), 1.00 (9H, s), 1.03 and 1.07 (total 3H, each s), 1.15 and 1.18 (total 9H, each s), 1.4-2.0 (10H, m), 1.50 (6H, s), 1.82 (3H, s), 2.20 (3H, s), 2.1-2.5 (2H, m), 3.1-3.4 (2H, m), 4.40 and 4.44 (total 1H, each s), 5.0-5.4 (3H,m), 6.45 (1H, d, J=3 Hz), 6.48 (1H, d, J=3 Hz). (Found: C, 71.01; H, 9.45. Calc for $C_{38}H_{62}O_6Si$: C, 70.98; H, 9.72%).

(1'R*,2'R*,2"E)-6-(5-t-Butyldimethylsiloxy-2-hydroxy-3-methylphenyl)-1-[2'-(1",4"-dihydroxy-4"-methyl-2"-pentenyl)-1',2'-dimethylcyclopentyl]-4-methyl-4-hexen-2-ol

(a) (Z)-isomer **38**. To a stirred suspension of LAH (320 mg, 8.43 mmol) in dry ether (20 ml) was added a soln of **37** (690 mg, 1.07 mmol) in dry ether (10 ml) with ice-cooling. After stirring for 2 h at room temp, the reaction mixture was quenched by adding water, acidified with N-HCl, and extracted with $CHCl_3$. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over SiO_2 (30 g). Elution with hexane-AcOEt (10:1-2:1) gave 470 mg (78%) of **38** as a diastereomeric mixture, vmax 3400 (s), 2960 (s), 1660 (s), 1600 (s), 1480 (s), 1380 (s), 1330 (s), 1260 (s), 1200 (s), 1160 (s), 1030 (s), 860 (s), 780 (s) cm^{-1}; δ ($CDCl_3$) 0.17 (6H, s), 0.93 (3H, s), 0.98 (9H, s), 1.08 (3H, s), 1.33 (6H, s), 1.5-1.8 (11H, m), 1.9-2.1 (2H, m), 2.17 (3H, s), 2.5-2.8 (2H, m), 3.4-3.7 (2H, m), 3.9-4.3 (2H, m), 5.2-5.3 (2H, m), 5.35 (1H, m), 6.47 (2H, m).MS: m/z 560 (M^+, 4%), 558 (6%), 542 (10%), 524 (100%, base peak), 305 (18%), 289 (56%).

(b) (E)-isomer **48** In the same manner as described above, 150 mg of **47** gave 90 mg (69 %) of **48** as a diastereomeric mixture, vmax 3620 (m), 3450 (m), 2960 (s), 1600 (s), 1480 (s), 1380 (m), 1320 (m), 1200 (s), 1020 (m), 850 (s) cm^{-1}; δ ($CDCl_3$) 0.15 (6H, s), 0.90 (3H, s), 0.98 (9H, s), 1.05 (3H, s), 1.32 (6H, s), 1.4-1.7 (11H, m), 1.79 (3H, s), 2.16 (3H, s), 2.0-2.4 (2H, m), 3.30 (2H, d, J=8 Hz), 3.7-4.2 (3H, m), 5.38 (1H, t, J=8 Hz), 5.6-6.0 (2H, m), 6.4-6.5 (2H, m). (Found: C, 70.47; H, 10.00. Calc for $C_{33}H_{56}O_5Si$: C, 70.66; H, 10.06%).

(1'R*,2'R*,2"E)-6-(5-t-Butyldimethylsiloxy-2-hydroxy-3-methylphenyl)-1-[1',2'-dimethyl-2'-(4"-hydroxy-4"-methyl-2"-pentenoyl)cyclopentyl]-4-methyl-4-hexen-2-one

(a) (Z)-isomer **39**. To a soln of oxalyl chloride (0.24 ml, 0.35 g, 2.8 mmol) in CH_2Cl_2 (16 ml) was added dropwise DMSO (0.40 ml, 0.44 g, 5.6 mmol) at -70°C. After stirring for 5 min at -70°C, to this was added a soln of **38** (200 mg, 0.357 mmol) in CH_2Cl_2 (5 ml) and the mixture was stirred for 15 min. Then Et_3N (1.60 ml, 1.16 g, 11.5 mmol) was added dropwise at -70°C and the temp was gradually raised to room temp. The reaction mixture was poured into water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over SiO_2 (10 g). Elution with hexane-AcOEt (10:1-4:1) gave 140 mg (71%) of **39**, vmax 3500 (s), 2980 (s), 1710 (s), 1680 (s), 1640 (s), 1620 (s), 1590 (s), 1460 (s), 1450 (s), 1380 (s), 1260 (s), 1190 (s), 1040 (s), 840 (s), 780 (s) cm^{-1}; δ ($CDCl_3$) 0.20 (6H, s), 0.97 (9H, s), 1.18 (3H, s), 1.19 (3H, s), 1.38 (3H, s), 1.40 (3H, s), 1.5-1.9 (9H, m), 2.03 (3H, s), 2.1-2.4 (2H, m), 2.7-3.0 (2H, m), 3.0-3.1 (2H, m), 5.10 (1H, m), 5.28 (1H, m), 6.60 (2H, m), 6.68 (1H, d, J=15 Hz), 6.91 (1H, d, J=15 Hz). (Found: C, 71.54; H, 9.30. Calc for $C_{33}H_{52}O_5Si$: C, 71.18; H, 9.41%).

(b) (E)-isomer **49**. In the same manner as described above, 190 mg of **48** gave 120 mg (64%) of **49**, vmax 3480 (s), 2980 (s), 2950 (s), 2900 (m), 2880 (m), 1720 (s), 1680 (s), 1640 (s), 1600 (s), 1460 (s), 1380 (s), 1320 (m), 1260 (s), 1200 (m), 840 (s), 780 (s) cm^{-1}; δ ($CDCl_3$) 0.20 (6H, s), 0.98 (9H, s), 1.1-1.2 (6H, m), 1.40 (6H, s), 1.4-1.9 (6H, m), 1.60 (3H, s), 2.05 (3H, s), 2.1-3.0 (4H, m), 3.03 (2H, s), 3.30 (1H, br.s), 4.90 (1H, br.s), 5.28 (1H, m), 6.60 (2H, m), 6.65 (1H, d, J=16 Hz), 6.90 (1H, d, J=16 Hz). (Found: C, 71.03; H, 9.45. Calc for $C_{33}H_{52}O_5Si$:

C, 71.18; H, 9.41%).

(1'R*,2'R*,2"E)-6-(2,5-Dihydroxy-3-methylphenyl)-1-[1',2'-dimethyl-2'-(4"-hydroxy-4"-methyl-2"-pentenoyl)-cyclopentyl]-4-methyl-4-hexen-2-one

(a) (Z)-isomer **1**. A mixture of **39** (100 mg, 0.180 mmol) in 10% HF aq (2 ml) and MeCN (10 ml) was stirred for 5 h. The mixture was neutralized by adding sat $NaHCO_3$ soln and extracted with $CHCl_3$. The extract was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed over SiO_2 (5 g). Elution with hexane-AcOEt (5:1-2:1) gave 34 mg (43%) of **1**, νmax ($CHCl_3$) 3450 (s), 1710 (s), 1680 (s), 1620 (s), 1460 (s), 1320 (s), 1180 (s), 1140 (s) cm^{-1}; δ (500 MHz, $CDCl_3$) 1.19 (3H, s), 1.21 (3H, s), 1.32 (3H, s), 1.35 (3H, s), 1.55 (1H, m), 1.66 (3H, d, J=1 Hz), 1.70-1.80 (3H, m), 1.88 (1H, OH), 1.93 (1H, m), 2.23 (3H, s), 2.33 (1H, d, J=17.5 Hz), 2.35 (1H, m), 2.52 (1H, d, J=17.5 Hz), 3.17 (1H, d, J=15 Hz), 3.18 (1H, d, J=15 Hz), 3.22 (2H, d, J=7 Hz), 5.38 (1H, OH), 5.42 (1H, t, J= 7Hz), 5.70 (1H, OH), 6.43 (1H, d, J=3 Hz), 6.53 (1H, d, J=3 Hz), 6.68 (1H, d, J=15 Hz), 6.87 (1H, d, J=15 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 16.4, 20.1, 20.4, 21.4, 24.2, 29.4, 30.2, 30.9, 34.5, 37.4, 47.0, 48.3, 48.5, 60.0, 71.1, 114.1, 115.8, 122.8, 126.0, 126.8, 126.9, 129.9, 146.1, 149.0, 153.0, 205.4, 208.8. (Found: C, 73.28; H, 8.53. Calc for $C_{27}H_{38}O_5$: C, 73.27; H, 8.65%).

(b) (E)-isomer **2**. In the same manner as described above, 100 mg of **49** gave 23 mg (29%) of **2**, νmax ($CHCl_3$) 3450 (s), 1710 (s), 1680 (s), 1620 (s), 1460 (s), 1380 (m), 1320 (s), 1180 (s) cm^{-1}; δ (500 MHz, $CDCl_3$) 1.19 (3H, s), 1.21 (3H, s), 1.30 (3H, s), 1.32 (3H, s), 1.55 (1H, m), 1.62 (3H, s), 1.65 (1H, OH), 1.70-1.80 (3H, m), 1.99 (1H, m), 2.23 (3H, s), 2.36 (1H, m), 2.37 (1H, d, J=16 Hz), 2.46 (1H, d, J=16 Hz), 3.05 (2H, s), 3.34 (2H, d, J=7.5 Hz), 4.55 (1H, OH), 5.45 (1H, t, J=7.5 Hz), 6.45 (1H, d, J=3 Hz), 6.56 (1H, d, J=3 Hz), 6.67 (1H, d, J=16 Hz), 6.88 (1H, d, J=16 Hz), 7.00 (1H, OH); ^{13}C-NMR (126 MHz, $CDCl_3$) δ 16.2, 20.1, 20.2, 21.1, 28.3, 29.4 (3C), 34.1, 36.4, 46.0, 46.9, 56.9, 60.4, 71.2, 112.9, 115.4, 122.5, 125.1, 127.5 (2C), 131.6, 145.3, 150.0, 153.8, 206.3, 209.2; The spectral data of (±)-**2** were identical with those of the natural **2**. (Found: C, 73.44; H, 8.97. Calc for $C_{27}H_{38}O_5$: C, 73.27; H, 8.65%).

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