

## DETERMINATION OF THE ABSOLUTE CONFIGURATION OF BIFURCARENONE BY THE SYNTHESIS OF ITS (1'R,2'R)-ISOMER†

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**Abstract** — (1'R,2'R)-Isomer of bifurcarenone (**1**) was synthesized. By comparing its ORD spectrum with that of the natural product, the marine C<sub>27</sub> hydroquinone isolated as an inhibitor of mitotic cell division was shown to be (1'S,2'S)-**1**.

In 1980 Fenical and his co-workers isolated bifurcarenone, an inhibitor of mitotic cell division, from the brown seaweed (*Bifurcaria galapagensis*) harvested in Galapagos Islands.<sup>1</sup> Its structure was proposed as **2** on the basis of chemical and spectroscopic studies, without assignment of the absolute configuration.<sup>1</sup> Our synthesis of (±)-**2**, however, revealed its spectroscopic properties to be different from those of natural bifurcarenone.<sup>2</sup> By synthesizing (±)-**1**, we were able to show that the natural product is either (1'R,2'R)-**1** or its antipode. Herein we report a synthesis of (1'R,2'R)-**1**. This enabled us to assign (1'S,2'S)-**1** for the structure of natural bifurcarenone.

Our synthetic plan for (1'R,2'R)-bifurcarenone (**1**) is shown in Fig. 1. Optical resolution of a hemiacetal (±)-**3** seems feasible *via* an acetal **4**, which can be derived from (±)-**3** and (-)-menthol. Previous examples are recorded on the resolution of racemic hemiacetals *via* their acetals with optically pure alcohols.<sup>3,4</sup> The resolved acetal **3** can be converted to **5**, the racemate of which was an intermediate in our previous synthesis of (±)-**1**. Accordingly, optically active **1** can be synthesized from optically active **5**.

### Synthesis and Optical Resolution of the Hemiacetal (±)-**3**

The known lactone (±)-**6**<sup>2,5</sup> served as the starting material of the present synthesis, like in our previous synthesis of (±)-**1**. As shown in Fig. 2, LAH reduction of (±)-**6** gave a diol (±)-**7**, which was treated with 1 eq of trityl chloride to give (±)-**8** as the major product in 58% yield from (±)-**6**. Another monotrityl ether (±)-**9** and *bis*-trityl ether (±)-**10** were also obtained as by-products. Swern oxidation<sup>6</sup> of (±)-**8** furnished an aldehyde (±)-**11** in 98% yield, which was treated with 80% AcOH to give the desired hemiacetal (±)-**3** together with its dimer (±)-**12**.

Four diastereomers (**4a-4d**) of the acetal **4** was provided by heating (±)-**3** and (±)-**12** with (-)-menthol in the presence of *p*-TsOH in benzene at reflux. The ratio of these four diastereomers was estimated to be **4a:4b:4c:4d** = 43:32:19:7 by <sup>1</sup>H NMR analysis at 250 MHz (see Experimental). Fractional recrystallization of the crude mixture was repeated eight times to give pure **4a**, m.p. 85.5-86.5°C, in 14% yield from (±)-**11**. The structure **4a** was given to this acetal by its X-ray crystallographic analysis as shown in Fig. 3. The mother liquor was further purified by SiO<sub>2</sub> chromatography to give pure **4b**, m.p. 66.5-67.5°C, the structure of

†Diterpenoid Total Synthesis — 28. Part 27, Mori, K. and Uno, T. *Tetrahedron* **1989**, *45*, 1945-1958. The experimental part of this work was taken from a part of the forthcoming doctoral dissertation of Uno, T. The X-ray crystallographic work was done by Kido, M.

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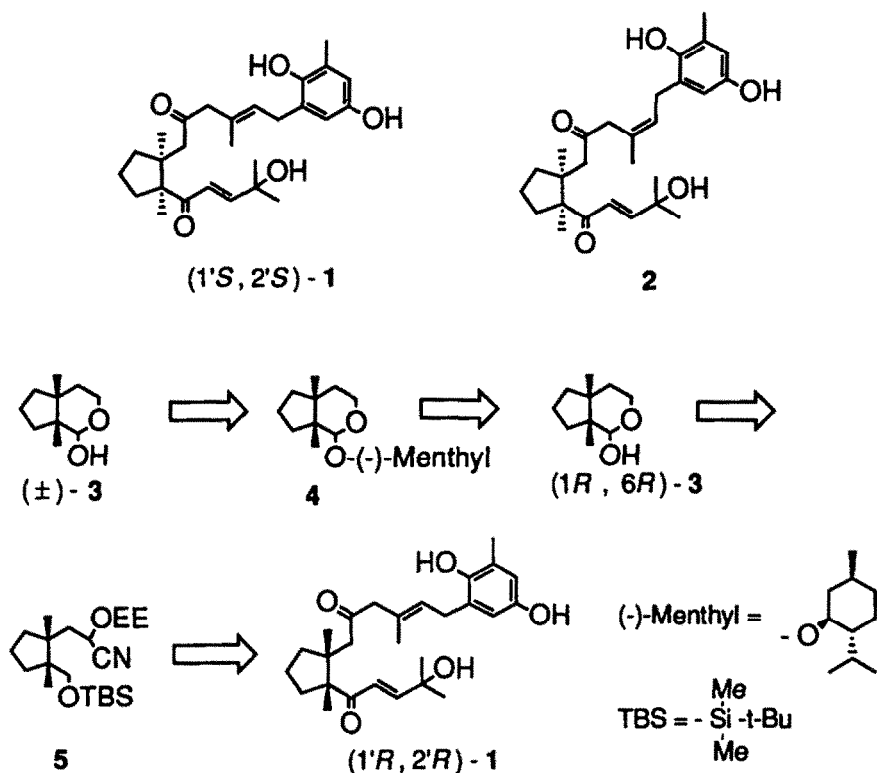


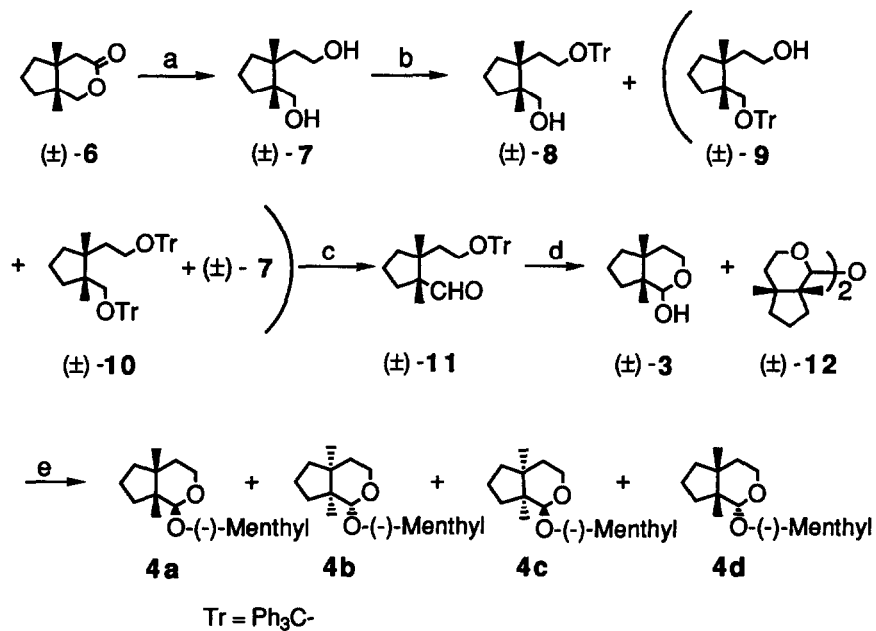
Fig.1. Synthetic plan for  $(1'R, 2'R)$ -bifurcarenone (**1**).

which was also solved by its X-ray crystallographic analysis (Fig. 3). The structures of the remaining two acetals, **4c** and **4d**, were determined by their derivation from **4b** and **4a**, respectively, by equilibration under acidic condition.

The pure acetal **4a** was then treated with 2*N* HCl to give  $(1R, 6R)$ -**3**, which was reduced with LAH to give a diol  $(1R, 2R)$ -**7** (Fig. 4). Tritylation of  $(1R, 2R)$ -**7** was carried out in the same manner as for  $(\pm)$ -**7** to give the monotrityl ether  $(1R, 2R)$ -**8** together with by-products. The free OH group of **8** was then protected as *t*-butyldimethylsilyl (TBS) ether. The resulting  $(1R, 2R)$ -**13** was treated with  $\text{Na}/\text{NH}_3$  to remove the trityl protective group, giving  $(1R, 2R)$ -**14**. Swern oxidation of **14** yielded an aldehyde  $(1R, 2R)$ -**15**. Beyond this step, we followed the procedure developed by us for the synthesis of  $(\pm)$ -**1**,<sup>2</sup> and  $(1R, 2R)$ -**5** was prepared from **15**. The overall yield of  $(1R, 2R)$ -**5** from **4a** was 34% in nine steps.

#### Synthesis of $(1'R, 2'R)$ -Bifurcarenone (**1**).

According to the previously reported method for the synthesis of  $(\pm)$ -**1**, we converted  $(1R, 2R)$ -**5** to  $(1'R, 2'R)$ -**1** as shown in Fig. 5. The anion derived from **5** and LDA was alkylated with **18**<sup>2</sup> to give **19**. Selective removal of the EE protective group of **19** with  $\text{HCl}-\text{CHCl}_3$  was followed by treatment with 2%  $\text{NaOH}-\text{Et}_2\text{O}$  to give a ketone **20**. This was reduced with  $\text{NaBH}_4$  to give **21**, the hydroxy group of which was protected by acylation with pivaloyl chloride to furnish **22**. Deprotection of the silyl ether of **22** yielded **23**, Swern oxidation of which gave an aldehyde **24**. Addition of the dianion derived from 3-methyl-1-butyne-3-ol to **24**



Reagents: (a) LAH(91%); (b) TrCl(64%); (c) (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N (98%); (d) 80% AcOH ; (e) (-)-Menthyl, *p*-TsOH

Fig.2. Synthesis and optical resolution of the hemiacetal (±) - 3

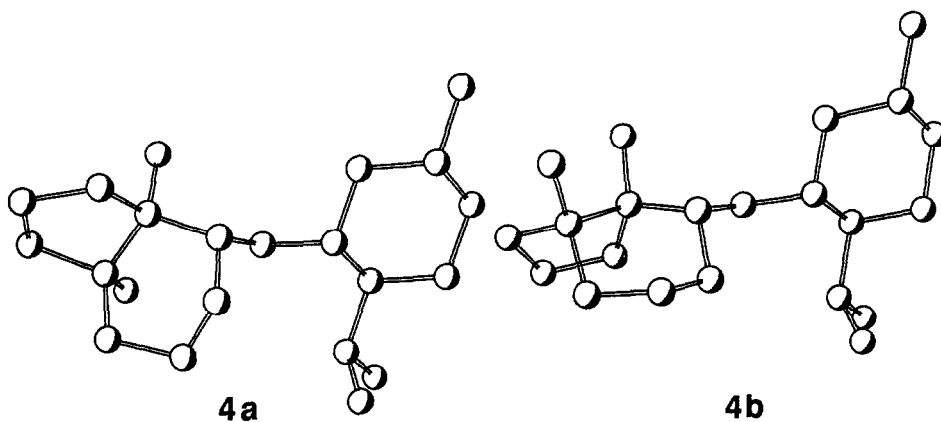
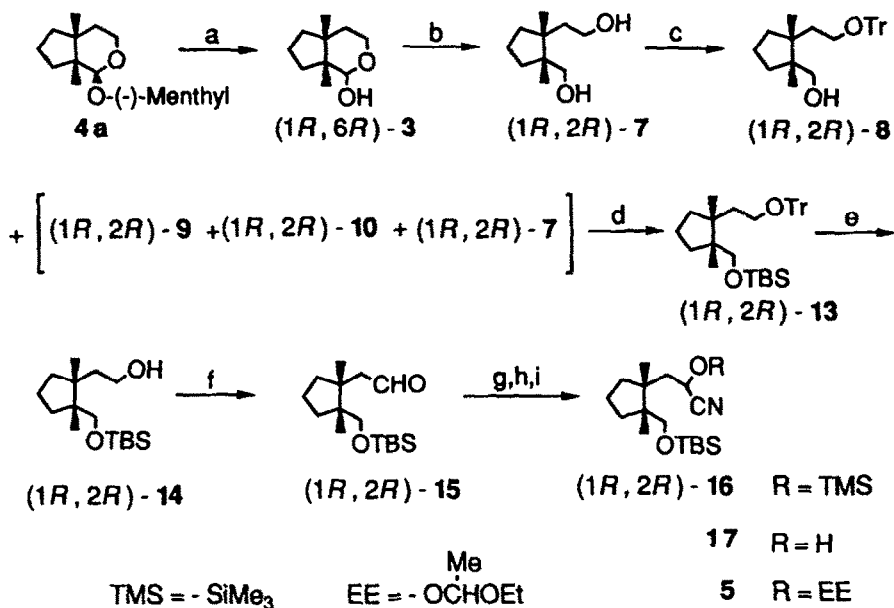


Fig.3. Structures of 4a and 4b .



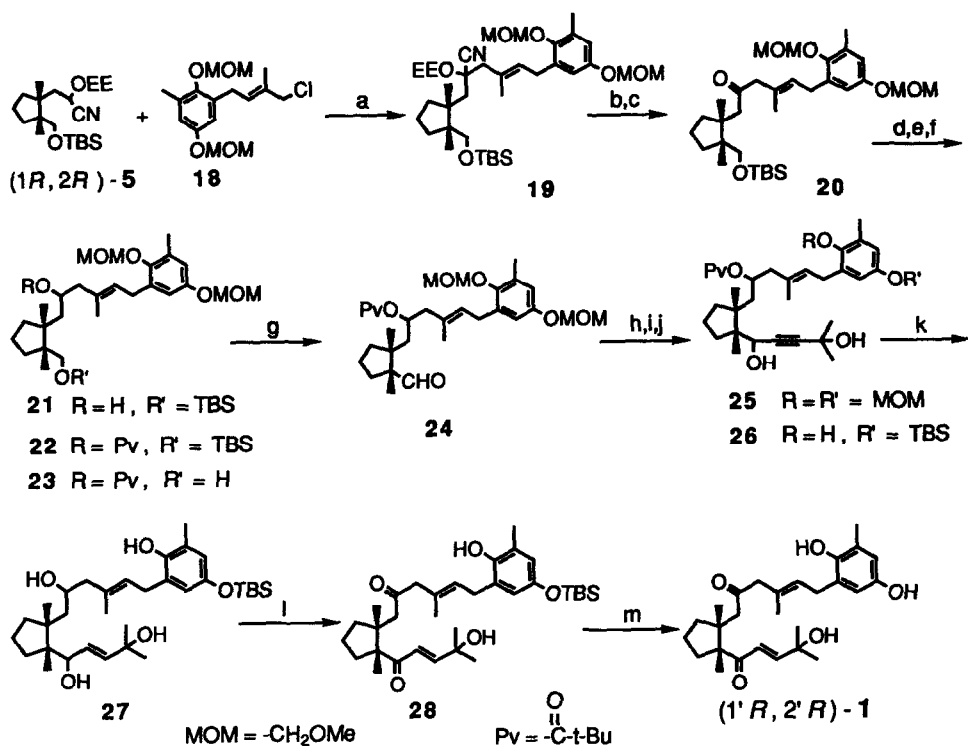
Reagents: (a) 2N HCl/acetone (98%); (b) LAH (86%); (c) TrCl(64%); (d) TBSCl, imidazole/DMF (99%); (e) Na/NH<sub>3</sub> (98%); (f) (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N (97%); (g) TMSCN, ZnI<sub>2</sub>; (h) citric acid/MeOH [80% from (1R,2R)-15]; (i) EtOCH=CH<sub>2</sub>, PPTS/CH<sub>2</sub>Cl<sub>2</sub> (84%)

Fig.4. Synthesis of the key chiral building block 5.

furnished 25. Removal of the MOM protective groups of 25 was followed by partial silylation with TBSCl to give 26. LAH reduction of 26 effected both reduction of the triple bond to an (*E*)-double bond and removal of the pivaloyl protective group to furnish 27. Swern oxidation of 27 afforded 28, which was desilylated with HP to give (1'*R*,2'*R*)-bifurcarenone (1) in 6.0% yield in eleven steps from 5 or 0.16% overall yield in twenty six steps from 6.

#### Absolute Configuration of Bifurcarenone (1)

To establish the absolute configuration of the natural product, we measured the ORD spectra of both the natural and the synthetic bifurcarenone. As shown in Fig. 6, (1'*R*,2'*R*)-1 showed an ORD spectrum antipodal to that of the natural bifurcarenone (1). The absolute configuration of bifurcarenone was therefore determined to be 1'*S*,2'*S*.



Reagents: (a) LDA, **18** (74%); (b) HCl/CHCl<sub>3</sub>; (c) 2% NaOH/Et<sub>2</sub>O (76% from **19**); (d) NaBH<sub>4</sub> (98%); (e) *t*-BuCOCl (96%); (f) (*t*-Bu)<sub>4</sub>NF (86%); (g) (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N (95%); (h) 3-methyl-1-butyn-3-ol, *n*-BuLi/THF-HMPA (90%); (i) 6N HCl/THF; (j) TBSCl, imidazole/DMF (76%); (k) LAH (83%) (l) (COCl)<sub>2</sub>, DMSO, Et<sub>3</sub>N (95%); (m) 10% HF/MeCN (88%).

Fig.5. Synthesis of (1'R, 2'R)-bifurcarenone (**1**).

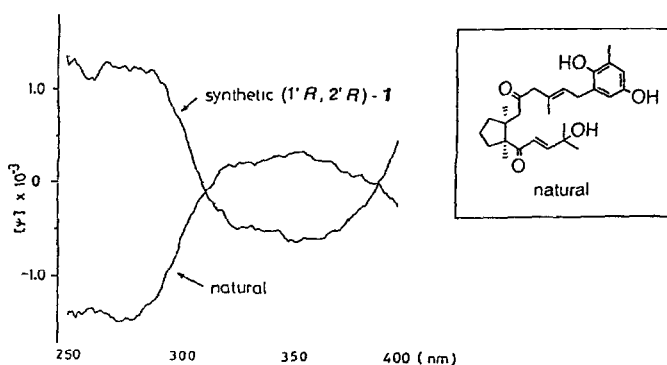


Fig.6. ORD curves of the natural and synthetic bifurcarenone (in MeOH).

## EXPERIMENTAL

All m.ps were uncorrected. IR spectra were measured as films on a Jasco IRA-102 spectrometer unless otherwise stated.  $^1\text{H}$  NMR spectra were recorded with TMS as an internal standard at 100 MHz on a JEOL JNM FX-100 spectrometer unless otherwise stated. 250 MHz  $^1\text{H}$  NMR spectra were recorded on a Bruker AC 250 spectrometer. Optical rotations were measured on a Jasco DIP 140 polarimeter. ORD spectra were measured on a Jasco J-20C spectropolarimeter. Mass spectra were recorded on a JEOL DX-303 spectrometer at 70 eV. Merck Kieselgel 60 Art. 7734 was used for  $\text{SiO}_2$  column chromatography.

(1*R*\*,2*R*\*)-2-Hydroxymethyl-1,2-dimethylcyclopentaneethanol 7. To a stirred suspension of LAH (12.5 g, 0.329 mmol) in ether (800 ml) was added a soln of **6** (50.0 g, 0.297 mol) in ether (200 ml) at 0°C. After stirring overnight at room temp, the reaction mixture was quenched by adding water (12.5 ml), 15% NaOH aq (12.5 ml) and water (37.5 ml). The ether soln was dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo*. The residue was chromatographed over  $\text{SiO}_2$  (1 kg). Elution with *n*-hexane-AcOEt (20:1-0:1) gave 46.8 g (91%) of **7**. This was recrystallized from *n*-hexane-Et<sub>2</sub>O to give colorless needles, m.p. 67.0-67.5°C;  $\nu_{\text{max}}$  (KBr) 3350 (s), 2980 (s), 2880 (s), 1480 (m), 1450 (m), 1380 (m), 1360 (m), 1050 (s), 1030 (s), 990 (m)  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 0.92 (3H, s), 0.98 (3H, s), 1.3-1.9 (8H, m), 1.91 (2H, s, OH), 3.44 (1H, d,  $J=11$  Hz), 3.52 (1H, d,  $J=11$  Hz), 3.6-3.9 (2H, m). (Found: C, 69.62; H, 11.63. Calc for  $\text{C}_{10}\text{H}_{20}\text{O}_2$ : C, 69.72; H, 11.70%).

(1*R*\*,2*R*\*)-1,2-Dimethyl-2-(2-triphenylmethoxyethyl)cyclopentanemethanol 8. A mixture of **7** (100 g, 0.580 mol), triphenylmethyl chloride (162 g, 0.581 mol), Et<sub>3</sub>N (97.6 ml, 0.700 mol), DMAP (0.1 g, 0.8 mmol) in DMF (1.5 l) 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 ( $\text{MgSO}_4$ ) and concentrated *in vacuo*. The residue was chromatographed over  $\text{SiO}_2$  (2 kg). Elution with *n*-hexane-AcOEt (20:1) first yielded **10** (38 g, 10%),  $\nu_{\text{max}}$  (KBr) 3070 (m), 3050 (m), 3000 (m), 2930 (s), 2850 (s), 1610 (m), 1500 (s), 1460 (s), 1390 (m), 1230 (m), 1210 (m), 1190 (m), 1160 (m), 1080 (s), 1060 (s), 1040 (s), 990 (s), 910 (s)  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 0.70 (3H, s), 0.99 (3H, s), 1.1-1.9 (9H, m), 2.7-3.2 (4H, m), 7.1-7.6 (30H, m). Further elution afforded **8** (153 g, 64%). This was recrystallized from *n*-hexane-Et<sub>2</sub>O to give colorless plates, m.p. 117.0-117.5°C;  $\nu_{\text{max}}$  3650 (s), 3450 (s), 3110 (m), 3080 (m), 3050 (m), 2980 (s), 2900 (s), 1600 (m), 1500 (s), 1450 (s), 1390 (m), 1320 (m), 1220 (s), 1180 (m), 1160 (m), 1070 (s), 1040 (s), 1020 (s), 900 (m), 770 (s), 760 (s), 750 (s), 700 (s)  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 0.71 (3H, s), 0.85 (3H, s), 1.1-1.9 (9H, m), 3.0-3.3 (2H, m), 3.40 (1H, d,  $J=11$  Hz), 3.44 (1H, d,  $J=11$  Hz), 7.1-7.6 (15H, m). (Found: C, 83.88; H, 8.25. Calc for  $\text{C}_{29}\text{H}_{34}\text{O}_2$ : C, 84.01; H, 8.27%). Third fraction afforded **9** (9 g, 4%);  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 3610 (m), 3020 (s), 2960 (s), 2880 (s), 1600 (w), 1500 (m), 1450 (s), 1220 (s), 1060 (s), 780 (s)  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 0.85 (3H, s), 1.05 (3H, s), 1.0-2.0 (9H, m), 2.92 (2H, s), 3.3-3.6 (2H, m), 7.1-7.6 (15H, m). Further elution afforded **7** (11 g, 10%).

(1*R*\*,2*R*\*)-1,2-Dimethyl-2-(2-triphenylmethoxyethyl)cyclopentanecarbaldehyde 11. To a soln of oxalyl chloride (31.6 ml, 46 g, 0.36 mol) in  $\text{CH}_2\text{Cl}_2$  (1.3 l) was added dropwise DMSO (51 ml, 56 g, 0.72 mol) at -70°C. After stirring for 10 min at -70°C, to this was added a soln of **8** (100 g, 0.24 mol) in  $\text{CH}_2\text{Cl}_2$  (100 ml) and the mixture was stirred for 15 min. Then Et<sub>3</sub>N (202 ml, 147 g, 1.45 mol) was added dropwise and the temp was gradually raised to room temp. The reaction mixture was poured into water and extracted with  $\text{CH}_2\text{Cl}_2$ . The extract was washed with water and brine, dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo*. The residue was chromatographed over  $\text{SiO}_2$  (2 kg). Elution with *n*-hexane-AcOEt (10:1) gave **98** g (98%) of **11**. This was recrystallized from *n*-hexane-Et<sub>2</sub>O to give colorless prisms, m.p. 144.0-145.0°C;  $\nu_{\text{max}}$  (KBr) 3150 (m), 3100 (m), 2980 (s), 2950 (s), 2900 (s), 2830 (m), 2720 (m), 1720 (s), 1600 (m), 1490 (s), 1450 (s), 1380 (m), 1220 (m), 1080 (s), 1030 (m), 900 (m), 780 (m), 760 (s), 750 (s), 710 (s)  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 0.64 (3H, s), 0.86 (3H, s), 0.9-2.1 (8H, m), 2.8-3.2 (2H, m), 7.0-7.4 (15H, m), 9.55 (1H, s). (Found: C, 84.15; H, 7.79. Calc for  $\text{C}_{29}\text{H}_{32}\text{O}_2$ : C, 84.42; H, 7.82%).

(1*R*,6*R*,1'*R*,2'*S*,5'*R*)-1,6-Dimethyl-2-[5'-methyl-2'-(1-methylethyl)cyclohexyloxy]-3-oxabicyclo[4.3.0]nonane 4a. A soln of ( $\pm$ )-**11** (56.0 g, 0.136 mol) in 80% AcOH (400 ml) was stirred for 4 h at 70°C. After cooling, the precipitate was filtered. The filtrate was concentrated *in vacuo*. The residue was mixed with *n*-hexane (1 l). The precipitate was filtered off and the filtrate was concentrated *in vacuo*. The residue was extracted with ether. The extract was washed with water and brine, dried ( $\text{MgSO}_4$ ), and concentrated *in vacuo* to give 27 g of ( $\pm$ )-**3** and ( $\pm$ )-**12** as a diastereomeric mixture. ( $\pm$ )-**3** showed the following properties:

$\nu_{\max}$  3400 (s), 2980 (s), 2890 (s), 1460 (s), 1380 (s), 1330 (m), 1270 (m), 1220 (m), 1180 (m), 1080 (s), 1000 (s), 970 (m), 950 (m), 900 (m), 840 (m), 730 (m)  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 0.92 (3H, s), 1.00 and 1.02 (total 3H, each s), 1.2-1.8 (8H, m), 2.95 (1H, OH), 3.5-4.1 (2H, m), 4.59 and 4.70 (total 1H, each s). ( $\pm$ )-**12** showed the following properties:  $\nu_{\max}$  (KBr) 2950 (s), 2870 (s), 2730 (m), 1470 (s), 1390 (s), 1370 (s), 1330 (s), 1280 (m), 1260 (m), 1120 (s), 1100 (s), 1080 (s), 1040 (s), 1020 (s), 980 (s), 950 (s)  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 0.9-1.0 (6H, m), 1.0-1.2 (6H, m), 1.3-1.45 (2H, m), 1.45-1.8 (12H, m), 2.0-2.2 (2H, m), 3.4-3.6 (2H, m), 3.8-4.0 (2H, m), 4.6-4.7 (2H, m). MS:  $m/z$  322 ( $\text{M}^+$ ), 153 (100).

The mixture of crude ( $\pm$ )-**3** and ( $\pm$ )-**12** (27 g) and (-)-menthol (30 g, 0.19 mol) and *p*-TsOH·H<sub>2</sub>O (0.1 g) in benzene (700 ml) was heated under reflux for 2 h with azeotropic removal of water by a Dean-Stark apparatus. After cooling, the reaction mixture was washed with sat NaHCO<sub>3</sub> soln and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residue was chromatographed over SiO<sub>2</sub> (1 kg). Elution with *n*-hexane-AcOEt (20:1) gave 39 g (93% from **8**) of a mixture of **4a**, **4b**, **4c** and **4d** (42:32:19:7 as determined by its 250 MHz <sup>1</sup>H NMR spectrum in which 2-H of **4a** appeared at  $\delta$  4.47, that of **4b** appeared at  $\delta$  4.32, that of **4c** appeared at  $\delta$  4.37 and that of **4d** appeared at  $\delta$  4.28). This was fractionally recrystallized from MeOH to give 5.9 g (14%) of pure **4a** as colorless needles, m.p. 85.5-86.5°C;  $[\alpha]_{\text{D}}^{20}$  -18.2° ( $c=1.02$ , acetone);  $\nu_{\max}$  (KBr) 2970 (s), 2870 (s), 2730 (m), 1450 (s), 1380 (s), 1360 (s), 1330 (s), 1280 (m), 1250 (m), 1240 (m), 1180 (m), 1120 (s), 1100 (s), 1030 (s), 1000 (s), 960 (s), 920 (m), 860 (m), 840 (m)  $\text{cm}^{-1}$ ;  $\delta$  (250 MHz,  $\text{CDCl}_3$ ) 0.78 (3H, d,  $J=7$  Hz), 0.84 (3H, s), 0.91 (6H, d,  $J=7$  Hz), 1.02 (3H, s), 1.0-1.4 (5H, m), 1.4-1.7 (9H, m), 2.0-2.15 (2H, m), 2.35 (1H, m), 3.35-3.55 (2H, m), 3.90 (1H, ddd,  $J=3, 10, 12$  Hz), 4.47 (1H, s). (Found: C, 77.80; H, 11.77. Calc for C<sub>20</sub>H<sub>36</sub>O<sub>2</sub>: C, 77.86; H, 11.76%). The mother liquor was purified by SiO<sub>2</sub> chromatography (*n*-hexane-AcOEt 1:0-2000:1). The earlier fractions were concentrated and the residue was recrystallized from MeOH to give pure **4b** as colorless needles, m.p. 66.5-67.5°C,  $[\alpha]_{\text{D}}^{20}$  -134° ( $c=1.0$ , acetone),  $\nu_{\max}$  (KBr) 2950 (s), 2870 (s), 2740 (m), 2670 (m), 1460 (s), 1380 (s), 1370 (s), 1330 (s), 1270 (m), 1220 (m), 1180 (m), 1120 (s), 1080 (s), 1040 (s), 1020 (s), 1000 (s), 980 (m), 880 (m), 840 (m)  $\text{cm}^{-1}$ ;  $\delta$  (250 MHz,  $\text{CDCl}_3$ ) 0.79 (3H, d,  $J=7$  Hz), 0.84 (3H, s), 0.88 (3H, d,  $J=7$  Hz), 0.92 (3H, d,  $J=7$  Hz), 0.95 (3H, s), 1.0-1.4 (5H, m), 1.4-1.7 (9H, m), 2.0-2.3 (3H, m), 3.39 (1H, dt,  $J=4, 11$  Hz), 3.50 (1H, dt,  $J=3, 12$  Hz), 3.81 (1H, dt,  $J=12, 4$  Hz), 4.32 (1H, s). (Found: C, 77.80; H, 11.44. Calc for C<sub>20</sub>H<sub>36</sub>O<sub>2</sub>: C, 77.86; H, 11.77%).

**Equilibration of 4a to a mixture of 4a and 4d.** A soln of **4a** (5 mg), (-)-menthol (1 mg) and *p*-TsOH (cat. amount) in benzene (2 ml) was heated under reflux for 2 h. After cooling, the reaction mixture was washed with sat NaHCO<sub>3</sub> soln and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residue was chromatographed over SiO<sub>2</sub> (2 g). Elution with *n*-hexane-AcOEt (20:1) gave 4.2 mg (84%) of a mixture of **4a** and **4d** (4:1 as determined by its 250 MHz <sup>1</sup>H NMR spectrum in which 2-H of **4a** appeared at  $\delta$  4.47 and that of **4d** appeared at  $\delta$  4.28).

**Equilibration of 4b to a mixture of 4b and 4c.** A soln of **4b** (5 mg), (-)-menthol (1 mg) and *p*-TsOH (cat. amount) in benzene (2 ml) was heated under reflux for 2 h. Subsequent work-up as described for the preparation of **4d** yielded 4.6 mg (92%) of a mixture of **4b** and **4c** (11:9 as determined by its 250 MHz <sup>1</sup>H NMR spectrum in which 2-H of **4b** appeared at  $\delta$  4.32 and that of **4d** appeared at  $\delta$  4.37).

**(1*R*,6*R*)-1,6-Dimethyl-2-oxabicyclo[4.3.0]nonan-2-ol (1*R*,6*R*)-3.** A soln of **4a** (20 g, 64.8 mmol) in 2N HCl (50 ml) and acetone (700 ml) was stirred overnight at room temp. The mixture was extracted with Et<sub>2</sub>O. The extract was washed with water and brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo*. The residue was chromatographed over SiO<sub>2</sub> (600 g). Elution with *n*-hexane-AcOEt (20:1) gave 10.7 g (98%) of (1*R*,6*R*)-**3**, m.p. 69-98°C,  $[\alpha]_{\text{D}}^{15}$  -0.28° ( $c=1.09$ , *n*-hexane); The IR and NMR spectra of (1*R*,6*R*)-**3** were identical with those of ( $\pm$ )-**3**. (Found: C, 70.36; H, 10.66. Calc for C<sub>10</sub>H<sub>18</sub>O<sub>2</sub>: C, 70.55; H, 10.66%).

**(1*R*,2*R*)-2-Hydroxymethyl-1,2-dimethylcyclopentaneethanol (1*R*,2*R*)-7.** To a stirred suspension of LAH (2.9 g, 78 mmol) in ether (500 ml) was added a soln of (1*R*,6*R*)-**3** (11.0 g, 65.0 mmol) in ether (50 ml) at 0°C. After stirring overnight at room temp, the reaction mixture was quenched by adding water (2.9 ml), 15% NaOH aq (2.9 ml) and water (8.7 ml). The ether soln was dried (MgSO<sub>4</sub>) and concentrated *in vacuo* to give 9.6 g (86%) of (1*R*,2*R*)-**7**. This was recrystallized from *n*-hexane-Et<sub>2</sub>O to give colorless needles, m.p. 80.5-81.0°C;  $[\alpha]_{\text{D}}^{15}$  -19.2° ( $c=1.05$ , MeOH); The IR and NMR spectra of (1*R*,2*R*)-**7** were identical with those of ( $\pm$ )-**7**. (Found: C, 69.57; H, 11.33. Calc for C<sub>10</sub>H<sub>20</sub>O<sub>2</sub>: C, 69.72; H, 11.70%).

(1*R*,2*R*)-1,2-Dimethyl-2-(2-triphenylmethoxyethyl)cyclopentanemethanol (1*R*,2*R*)-8. In the same manner as described for ( $\pm$ )-8 8.0 g of (1*R*,2*R*)-7 gave 12.4 g (64%) of 14. This was recrystallized from *n*-hexane-Et<sub>2</sub>O to give colorless plates, m.p. 102.0-102.5°C;  $[\alpha]_D^{25}$  -9.6° (c = 1.14, MeOH); The IR and NMR spectra of (1*R*,2*R*)-8 were identical with those of ( $\pm$ )-8. (Found: C, 83.70; H, 8.32. Calc for C<sub>29</sub>H<sub>34</sub>O<sub>2</sub>: C, 84.01; H, 8.27%).

(1*R*,2*R*)-1-*t*-Butyldimethylsilyloxymethyl-1,2-dimethyl-2-(2-triphenylmethoxyethyl)cyclopentane 13. A mixture of (1*R*,2*R*)-8 (11.2 g, 27.0 mmol), imidazole (4.10 g, 60.2 mmol), *t*-BuMe<sub>2</sub>SiCl (4.50 g, 29.9 mmol) and DMAP (cat. amount) in DMF (200 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<sub>4</sub>) and concentrated *in vacuo*. The residue was chromatographed over SiO<sub>2</sub> (300 g). Elution with *n*-hexane-AcOEt (50:1) gave 14.2 g (99%) of 13. This was recrystallized from *n*-hexane to give colorless needles, m.p. 81.0-81.5°C,  $[\alpha]_D^{24}$  -9.87° (c = 1.56, CHCl<sub>3</sub>);  $\nu_{\max}$  (KBr) 3050 (m), 2950 (s), 2930 (s), 2870 (s), 2850 (s), 1490 (s), 1470 (s), 1450 (s), 1250 (s), 1080 (s), 1060 (s), 860 (s), 840 (s), 770 (s) cm<sup>-1</sup>;  $\delta$  (CDCl<sub>3</sub>) 0.05 (6H, s), 0.69 (3H, s), 0.80 (3H, s), 0.93 (9H, s), 1.2-1.8 (8H, m), 2.9-3.4 (2H, m), 3.34 (1H, d, *J* = 10 Hz), 3.37 (1H, d, *J* = 10 Hz), 7.2-7.5 (15H, m). (Found: C, 79.59; H, 9.18. Calc for C<sub>35</sub>H<sub>48</sub>O<sub>2</sub>Si: C, 79.49; H, 9.15%).

(1*R*,2*R*)-2-*t*-Butyldimethylsilyloxymethyl-1,2-dimethylcyclopentaneethanol 14. To a soln of Na (3.00 g, 0.130 mol) in refluxing ammonia (500 ml) was added a soln of 13 (13.7 g, 25.9 mmol) in ether (70 ml) over 20 min and the mixture was stirred for 1.5 h. To this were added NH<sub>4</sub>Cl (20.6 g) and ether (100 ml) with vigorous stirring and the ammonia was evaporated. The residue was diluted with water and extracted with ether. The extract was washed with brine, dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The residue was chromatographed over SiO<sub>2</sub> (300 g). Elution with *n*-hexane-AcOEt (30:1-10:1) gave 7.3 g (98%) of 14 as an oil,  $n_D^{17}$  1.4592;  $[\alpha]_D^{16}$  -7.7° (c = 1.21, MeOH);  $\nu_{\max}$  3320 (s), 2950 (s), 2870 (s), 1460 (s), 1380 (m), 1360 (m), 1250 (s), 1080 (s), 1000 (m), 830 (s), 770 (s) cm<sup>-1</sup>;  $\delta$  (CDCl<sub>3</sub>) 0.03 (6H, s), 0.89 (3H, s), 0.92 (12H, s), 1.2-1.8 (9H, m), 3.36 (1H, d, *J* = 10 Hz), 3.41 (1H, d, *J* = 10 Hz), 3.6-3.9 (2H, m). (Found: C, 67.39; H, 11.77. Calc for C<sub>16</sub>H<sub>34</sub>O<sub>2</sub>Si: C, 67.07; H, 12.09%).

(1*R*,2*R*)-2-*t*-Butyldimethylsilyloxymethyl-1,2-dimethylcyclopentaneacetaldehyde 15 To a soln of oxalyl chloride (3.5 ml, 5.1 g, 40 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (300 ml) was added dropwise DMSO (5.6 ml, 6.2 g, 80 mmol) at -70°C. After stirring for 10 min at -70°C, to this was added a soln of 14 (100 g, 0.24 mol) in CH<sub>2</sub>Cl<sub>2</sub> (30 ml), and the mixture was stirred for 15 min. Then Et<sub>3</sub>N (202 ml, 147 g, 1.45 mol) was added dropwise and the temp was gradually raised to room temp. The reaction mixture was poured into water and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The extract was washed with water and brine, dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The residue was chromatographed over SiO<sub>2</sub> (200 g). Elution with *n*-hexane-AcOEt (10:1) gave 6.9 g (97 %) of 15.  $n_D^{16}$  1.4610;  $[\alpha]_D^{16}$  -2.9° (c = 1.15, MeOH);  $\nu_{\max}$  (KBr) 2960 (s), 2900 (s), 2750 (m), 1720 (s), 1460 (s), 1380 (m), 1260 (s), 1080 (s), 1010 (m), 840 (s), 780 (s) cm<sup>-1</sup>;  $\delta$  (CDCl<sub>3</sub>) 0.02 (6H, s), 0.88 (9H, s), 0.90 (3H, s), 1.10 (3H, s), 1.40-1.90 (6H, m), 2.31 (1H, dd, *J* = 3, 15 Hz), 2.40 (1H, dd, *J* = 3, 15 Hz), 3.28 (1H, d, *J* = 10 Hz), 3.42 (1H, d, *J* = 10 Hz), 9.85 (1H, t, *J* = 3 Hz). (Found: C, 84.15; H, 7.79. Calc for C<sub>29</sub>H<sub>32</sub>O<sub>2</sub>: C, 84.42; H, 7.82%).

(1*R*,2*R*)-3-(2-*t*-Butyldimethylsilyloxymethyl-1,2'-dimethylcyclopentyl)-2-hydroxypropanenitrile 17. To a soln of 15 (6.0 g, 21.1 mmol) and trimethylsilyl cyanide (95%, 3.4 ml, 24 mmol) was added ZnI<sub>2</sub> (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<sub>2</sub>SO<sub>4</sub>) and concentrated *in vacuo* to give 7.5 g of crude 16. A mixture of 7.5 g of crude 16 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. The ether soln was washed with water and brine, dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The residue was chromatographed over SiO<sub>2</sub> (100 g). Elution with *n*-hexane-AcOEt (30:1) gave 5.23 g (80% from 15) of 17 as a diastereomeric mixture,  $n_D^{15}$  1.4662;  $[\alpha]_D^{15}$  -11.7° (c = 1.14, MeOH);  $\nu_{\max}$  3450 (s), 2960 (s), 2880 (s), 2860 (s), 2250 (vw), 1460 (s), 1390 (m), 1250 (s), 1080 (s), 840 (s), 780 (s) cm<sup>-1</sup>;  $\delta$  (CDCl<sub>3</sub>) 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 (6H, m), 1.9-2.4 (2H, m), 2.60 (1H, OH), 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, 65.68; H, 10.43; N, 4.24. Calc for C<sub>17</sub>H<sub>33</sub>O<sub>2</sub>NSi: C, 65.33; H, 10.58; N, 4.27%).

(1*R*,2*R*)-3-(2-*t*-Butyldimethylsilyloxymethyl-1,2'-dimethylcyclopentyl)-2-(ethoxyethoxy)propanenitrile 5. A mixture of 17



(3.90 g, 12.5 mmol), ethyl vinyl ether (1.20 g, 16.3 mmol) and PPTS (cat. amount) in  $\text{CH}_2\text{Cl}_2$  (70 ml) was stirred for 3 h. The reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$ , washed with sat  $\text{NaHCO}_3$  soln and brine, dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo*. The residue was chromatographed over  $\text{SiO}_2$  (100 g). Elution with *n*-hexane-AcOEt (40:1) gave 4.02 g (84%) of **5** as a diastereomeric mixture,  $n_D^{19}$  1.4519;  $[\alpha]_D^{18}$   $-5.9^\circ$  ( $c=1.33$ , MeOH);  $\nu_{\text{max}}$  2960 (s), 2940 (s), 2890 (s), 2860 (s), 2240 (vw), 1470 (s), 1390 (s), 1250 (s), 1080 (s), 940 (m), 840 (s), 780 (s)  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 0.02, 0.03, 0.11 and 0.12 (total 6H, each s), 0.89 (3H, s), 0.90 and 0.93 (total 9H, each s), 0.98 and 1.01 (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, 65.63; H, 10.46; N, 3.54. Calc for  $\text{C}_{21}\text{H}_{41}\text{O}_3\text{NSi}$ : C, 65.74; H, 10.77; N, 3.65%).

(1*R*,2*R*,4*E*)-2-(2'-*t*-Butyldimethylsilyloxymethyl-1',2'-dimethylcyclopentylmethyl)-2-ethoxyethoxy-6-[2,5-bis(methoxymethoxy)-3-methylphenyl]-4-methyl-4-hexenenitrile **19**. To a soln of **5** (5.30 g, 13.8 mmol) in THF (100 ml) and HMPA (2 ml) was added dropwise at  $-50$ – $-40^\circ\text{C}$  an LDA soln which was prepared from diisopropylamine (2.32 ml, 16.5 mmol) and *n*-BuLi (1.50 M 11.0 ml, 16.6 mmol) in THF (10.8 ml). After stirring for 1 h at  $-50$ – $-40^\circ\text{C}$ , a soln of **18** (4.30 g, 13.8 mmol) in THF (10 ml) was added, and the mixture was stirred for further 40 min at  $0^\circ\text{C}$ . The mixture was poured into sat  $\text{NH}_4\text{Cl}$  soln and extracted with ether. The extract was washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo*. The residue was chromatographed over  $\text{SiO}_2$  (150 g). Elution with *n*-hexane-AcOEt (20:1-10:1) gave 6.80 g (74%) of **19** as a diastereomeric mixture,  $n_D^{22}$  1.4970;  $[\alpha]_D^{15}$   $+0.73^\circ$  ( $c=1.52$ , MeOH);  $\nu_{\text{max}}$  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)  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 0.00-0.03 (6H, m), 0.83 (3H, s), 0.87 (3H, s), 0.88 (9H, s), 1.0-1.4 (6H, m), 1.5-2.0 (8H, m), 1.85 (3H, s), 2.28 (3H, s), 2.1-3.0 (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), 5.53 (1H, t,  $J=7$  Hz), 6.68 (1H, d,  $J=3$  Hz), 6.73 (1H, d,  $J=3$  Hz). This was employed in the next step without further purification.

(1*R*,2*R*,4*E*)-1-(2'-*t*-Butyldimethylsilyloxymethyl-1',2'-dimethylcyclopentyl)-6-[2,5-bis(methoxymethoxy)-3-methylphenyl]-4-methyl-4-hexen-2-one **20**. A mixture of conc. HCl (2 ml) and  $\text{MgSO}_4$  (10 g) in  $\text{CHCl}_3$  (200 ml) was stirred for 1 h at room temp. The mixture was filtered and the filtrate was added to **19** (6.00 g, 9.13 mmol). After stirring for 2 h at room temp, to this was added  $\text{K}_2\text{CO}_3$  (4.0 g), and the mixture was concentrated *in vacuo*. To the residue were added a soln of 2% NaOH aq (200 ml) and ether (200 ml). The mixture was stirred for 2 h at room temp. The ether soln was washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo*. The residue was chromatographed over  $\text{SiO}_2$  (100 g). Elution with *n*-hexane-AcOEt (50:1) gave 3.90 g (76%) of **20**,  $n_D^{16}$  1.5014;  $[\alpha]_D^{16}$   $+3.4^\circ$  ( $c=1.08$ , MeOH);  $\nu_{\text{max}}$  2950 (s), 1710 (s), 1600 (s), 1480 (s), 1320 (m), 1250 (m), 1160 (s), 1080 (s), 1040 (s), 980 (s), 860 (s), 840 (s), 780 (s)  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 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), 3.11 (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, 68.07; H, 9.32. Calc for  $\text{C}_{32}\text{H}_{54}\text{O}_6\text{Si}$ : C, 68.28; H, 9.67%).

(1*R*,2*R*,4*E*)-1-(2'-*t*-Butyldimethylsilyloxymethyl-1',2'-dimethylcyclopentyl)-6-[2,5-bis(methoxymethoxy)-3-methylphenyl]-4-methyl-4-hexen-2-ol **21**. To a soln of **20** (2.95 g, 5.24 mmol) in MeOH (50 ml) was added  $\text{NaBH}_4$  (400 mg, 10.6 mmol) at room temp. After stirring 3 h at room temp, the reaction mixture was concentrated. The residue was diluted with ice-water and extracted with ether. The extract was washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo*. The residue was chromatographed over  $\text{SiO}_2$  (80 g). Elution with *n*-hexane-AcOEt (20:1) gave 2.90 g (98%) of **21** as a diastereomeric mixture,  $n_D^{17}$  1.5011;  $[\alpha]_D^{17}$   $-5.9^\circ$  ( $c=1.95$ , MeOH);  $\nu_{\text{max}}$  3520 (s), 2960 (s), 1600 (s), 1470 (s), 1400 (m), 1250 (s), 1160 (s), 1080 (s), 1040 (s), 980 (s), 860 (s), 840 (s), 770 (s)  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 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 (9H, 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, 68.20; H, 10.00. Calc for  $\text{C}_{32}\text{H}_{56}\text{O}_6$ : C, 68.04; H, 9.99%).

(1*R*,2*R*,4*E*)-1-(2'-*t*-Butyldimethylsilyloxymethyl-1',2'-dimethylcyclopentyl)-6-[2,5-bis(methoxymethoxy)-3-methylphenyl]-4-methyl-4-hexen-2-yl pivalate **22**. To a soln of **21** (2.80 g, 4.96 mmol) and DMAP (cat. amount) in pyridine (25 ml) was added *t*-BuCOCl (1.30 ml, 1.27 g, 10.6 mmol) at  $0^\circ\text{C}$ . After stirring overnight at room temp, the mixture was poured into water and extracted with ether. The ether soln was washed with 2N HCl, sat  $\text{CuSO}_4$  soln, water, sat  $\text{NaHCO}_3$  aq and brine, dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo*. The residue was chromatographed over  $\text{SiO}_2$  (70 g). Elution with *n*-hexane-AcOEt

(20:1-10:1) gave 3.10 g (96%) of **22** as a diastereomeric mixture,  $n_D^{16}$  1.4825;  $[\alpha]_D^{16}$  -3.0° (c = 1.88, MeOH);  $\nu_{\max}$  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)  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 0.03 (6H, s), 0.82 (3H, s), 0.86 (3H, s), 0.91 (9H, s), 1.16 (9H, s), 1.4-1.8 (8H, m), 1.77 (3H, s), 2.20 (2H, m), 2.28 (3H, s), 3.25-3.4 (4H, m), 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, 68.28; H, 9.74. Calc for  $\text{C}_{37}\text{H}_{64}\text{O}_7\text{Si}$ : C, 68.47; H, 9.94%).

(1*R*,2*R*,4*E*)-1-(1',2'-Dimethyl-2'-hydroxymethylcyclopentyl)-6-[2,6-bis(methoxymethoxy)-3-methylphenyl]-4-methyl-4-hexen-2-yl pivalate **23**. A mixture of **22** (2.74 g, 4.22 mmol) in a soln of (*n*-Bu)<sub>4</sub>NF in THF (1.0 M, 15 ml, 15 mmol) and THF (20 ml) was stirred for 5 h. The reaction mixture was extracted with ether. The extract was washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo*. The residue was chromatographed over  $\text{SiO}_2$  (90 g). Elution with *n*-hexane-AcOEt (20:1-10:1) gave 1.95 g (86%) of **23** as a diastereomeric mixture,  $n_D^{16}$  1.5034;  $[\alpha]_D^{20}$  -8.5° (c = 1.10, MeOH);  $\nu_{\max}$  3550 (s), 2960 (s), 1720 (s), 1600 (s), 1480 (s), 1280 (s), 1160 (s), 1080 (s), 1040 (s), 980 (s)  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 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), 2.0-2.6 (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, 69.58; H, 9.52. Calc for  $\text{C}_{31}\text{H}_{50}\text{O}_7$ : C, 69.63; H, 9.43%).

(1*R*,2*R*,4*E*)-1-(2'-Formyl-1',2'-dimethylcyclopentyl)-6-[2,6-bis(methoxymethoxy)-3-methylphenyl]-4-methyl-4-hexen-2-yl pivalate **24**. To a soln of oxalyl chloride (0.47 ml, 0.71 g, 5.5 mmol) in  $\text{CH}_2\text{Cl}_2$  (60 ml) was added dropwise DMSO (0.79 ml, 0.87 g, 11.0 mmol) at -70°C. After stirring for 5 min at -70°C, to this was added a soln of **23** (1.97 g, 3.68 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 ml), and the mixture was stirred for 15 min. Then  $\text{Et}_3\text{N}$  (3.1 ml, 2.3 g, 22 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  $\text{CH}_2\text{Cl}_2$ . The extract was washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo*. The residue was chromatographed over  $\text{SiO}_2$  (50 g). Elution with *n*-hexane-AcOEt (20:1) gave 1.87 g (95%) of **24** as a diastereomeric mixture,  $n_D^{21}$  1.5020;  $[\alpha]_D^{20}$  -6.7° (c = 2.71, MeOH);  $\nu_{\max}$  2980 (s), 2720 (m), 1720 (s), 1600 (s), 1480 (s), 1280 (s), 1160 (s), 1080 (s), 1040 (s), 980 (s)  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 0.90 and 0.92 (total 3H, each s), 1.00 and 1.02 (3H, 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), 5.15 (1H, m), 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, 69.83; H, 9.09. Calc for  $\text{C}_{31}\text{H}_{48}\text{O}_7$ : C, 69.89; H, 9.08%).

(1*R*,2*R*,4*E*)-1-[2'-(1,4-Dihydroxy-4-methyl-2-pentynyl)-1',2'-dimethylcyclopentyl]-6-[2,6-bis(methoxymethoxy)-3-methylphenyl]-4-methyl-4-hexen-2-yl pivalate **25**. A soln of *n*-BuLi in *n*-hexane (1.50 M, 8.50 ml, 12.8 mmol) was added dropwise to a stirred and cooled soln of 3-methyl-1-butyne-3-ol (490 mg, 5.82 mmol) in dry THF (40 ml) and HMPA (0.8 ml) at -50°C under Ar. The mixture was stirred for 2 h at -30-20°C. To the stirred mixture was added dropwise a soln of **24** (1.70 g, 3.20 mmol) in dry THF (5 ml) at -60°C and the temp was gradually raised to room temp. The mixture was poured into sat  $\text{NH}_4\text{Cl}$  soln and extracted with ether. The extract was washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo*. The residue was chromatographed over  $\text{SiO}_2$  (50 g). Elution with *n*-hexane-AcOEt (10:1-3:1) gave 1.78 g (90%) of **25** as a diastereomeric mixture;  $[\alpha]_D^{16}$  +0.82° (c = 1.15, MeOH);  $\nu_{\max}$  3450 (s), 2960 (s), 1720 (s), 1600 (s), 1480 (s), 1380 (m), 1280 (m), 1160 (s), 1080 (m), 1040 (s), 980 (s), 860 (m)  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 0.9-1.10 (6H, m), 1.17 and 1.18 (total 9H, each s), 1.4-1.9 (10H, m), 1.52 (6H, s), 1.78 (3H, s), 2.0-2.3 (2H, m), 2.29 (3H, s), 3.35 (2H, d,  $J=8$  Hz), 3.49 and 3.50 (total 3H, each s), 3.61 (3H, s), 4.31 and 4.42 (total 1H, each d,  $J=6$  Hz), 4.92 (2H, s), 5.12 and 5.17 (total 2H, each s), 5.1-5.5 (2H, m), 5.6-5.8 (2H, m). (Found: C, 70.07; H, 8.88. Calc for  $\text{C}_{36}\text{H}_{56}\text{O}_8$ : C, 70.10; H, 9.15%).

(1*R*,2*R*,4*E*)-6-(5-*t*-Butyldimethylalkoxy-2-hydroxy-3-methylphenyl)-1-[2'-(1,4-dihydroxy-4-methyl-2-pentynyl)-1',2'-dimethylcyclopentyl]-4-methyl-4-hexen-2-yl pivalate **26**. A soln of **25** (1.70 g, 2.76 mmol) in 6*N* HCl (15 ml) and THF (15 ml) was stirred for 3 h. The mixture was extracted with  $\text{CHCl}_3$ . The extract was washed with brine, dried ( $\text{MgSO}_4$ ) and concentrated to give 1.80 g of crude oil. A mixture of crude oil (1.8 g, ca. 2.6 mmol), imidazole (0.56 g, 8.2 mmol) and *t*-BuMg<sub>2</sub>SiCl (0.63 g, 4.2 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 ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo*. The residue was chromatographed over  $\text{SiO}_2$  (50 g). Elution with *n*-hexane-AcOEt (6:1-3:1) gave 1.35 g (76% from **25**) of **26** as a diastereomeric

mixture,  $[\alpha]_D^{18} + 3.6^\circ$  ( $c = 1.53$ , MeOH);  $\nu_{\max}$  3450 (s), 2970 (s), 2940 (s), 2880 (m), 1720 (s), 1600 (m), 1480 (s), 1330 (s), 1280 (s), 1260 (s), 1220 (s), 1160 (vs), 1040 (s), 1000 (m), 950 (m), 880 (s), 860 (s), 840 (s),  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 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), 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, 9.79. Calc for  $\text{C}_{38}\text{H}_{62}\text{O}_6\text{Si}$ : C, 70.98; H, 9.72%).

(1*R*,2*R*,2*E*,4*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 **27**. To a stirred suspension of LAH (187 mg, 4.93 mmol) in dry ether (20 ml) was added a soln of **26** (400 mg, 0.62 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  $\text{CHCl}_3$ . The extract was washed with water and brine, dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo*. The residue was chromatographed over  $\text{SiO}_2$  (30 g). Elution with *n*-hexane-AcOEt (4:1-2:1) gave 290 mg (83%) of **27** as a diastereomeric mixture,  $[\alpha]_D^{18} + 0.37^\circ$  ( $c = 1.08$ , MeOH);  $\nu_{\max}$  3620 (m), 3400 (m), 2990 (s), 2960 (s), 2900 (m), 2880 (m), 1600 (m), 1480 (s), 1380 (m), 1320 (m), 1260 (s), 1160 (s), 1040 (m), 860 (s)  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 0.15 (6H, s), 0.90 (3H, s), 0.98 (9H, s), 1.05 (3H, s), 1.32 (6H, s), 1.4-1.9 (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, 70.89; H, 10.03. Calc for  $\text{C}_{33}\text{H}_{56}\text{O}_5\text{Si}$ : C, 70.66; H, 10.06%).

(1*R*,2*R*,2*E*,4*E*)-6-(5-*t*-Butyldimethylsiloxy-2-hydroxy-3-methylphenyl)-1-[1',2'-dimethyl-2'-(4'-hydroxy-4'-methyl-2'-pentenyl)cyclopentyl]-4-methyl-4-hexen-2-one **28**. To a soln of oxalyl chloride (0.16 ml, 0.23 g, 1.9 mmol) in  $\text{CH}_2\text{Cl}_2$  (5 ml) was added dropwise DMSO (0.26 ml, 0.29 g, 3.6 mmol) at  $-70^\circ\text{C}$ . After stirring for 5 min at  $-70^\circ\text{C}$ , to this was added a soln of **27** (130 mg, 0.232 mmol) in  $\text{CH}_2\text{Cl}_2$  (1 ml) and the mixture was stirred for 15 min. Then  $\text{Et}_3\text{N}$  (1.00 ml, 0.725 g, 7.19 mmol) was added dropwise at  $-70^\circ\text{C}$  and the temp was gradually raised to room temp. The reaction mixture was poured into water and extracted with  $\text{CH}_2\text{Cl}_2$ . The extract was washed with water and brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo*. The residue was chromatographed over  $\text{SiO}_2$  (5 g). Elution with *n*-hexane-AcOEt (8:1-4:1) gave 70 mg (54%) of **28**.  $[\alpha]_D^{16} 0.0^\circ$  ( $c = 0.47$ , MeOH);  $\nu_{\max}$  3480 (s), 2960 (s), 2930 (s), 2900 (m), 2860 (m), 1710 (s), 1680 (s), 1640 (s), 1590 (s), 1460 (s), 1380 (s), 1320 (m), 1280 (m), 1250 (s), 1190 (m), 840 (s), 780 (s)  $\text{cm}^{-1}$ ;  $\delta$  ( $\text{CDCl}_3$ ) 0.20 (6H, s), 0.98 (9H, s), 1.1-1.3 (6H, m), 1.40 (6H, s), 1.4-1.9 (6H, m), 1.60 (3H, s), 2.05 (3H, s), 2.1-3.1 (6H, m), 3.50 (1H, OH), 3.70 (1H, OH), 5.28 (1H, m), 6.60 (2H, m), 6.65 (1H, d,  $J = 16$  Hz), 6.90 (1H, d,  $J = 16$  Hz). (Found: C, 71.01; H, 9.45. Calc for  $\text{C}_{33}\text{H}_{52}\text{O}_5\text{Si}$ : C, 71.18; H, 9.41%).

(1*R*,2*R*,2*E*,4*E*)-6-(2,5-Dihydroxy-3-methylphenyl)-1-[1',2'-dimethyl-2'-(4'-hydroxy-4'-methyl-2'-pentenyl)-cyclopentyl]-4-methyl-4-hexen-2-one (bifurcarenone) **1**. A mixture of **28** (70 mg, 0.126 mmol) in 10% HF aq (1 ml) and MeCN (5 ml) was stirred for 5 h. The mixture was neutralized by adding sat  $\text{NaHCO}_3$  soln and extracted with  $\text{CHCl}_3$ . The extract was washed with brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated *in vacuo*. The residue was chromatographed over  $\text{SiO}_2$  (30 g). Elution with *n*-hexane-AcOEt (3:2) gave 25 mg (45%) of **1**,  $[\alpha]_D^{17} 0.0^\circ$  ( $c = 0.42$ ,  $\text{CHCl}_3$ ); ORD ( $c = 0.054$ , MeOH, at  $24^\circ$ )  $[[\alpha], \nu(\text{nm})]$  116 (210), 505 (238), 218 (260), 268 (255), 0 (310), -125 (353), 0 (391);  $\nu_{\max}$  ( $\text{CHCl}_3$ ) 3450 (s), 2980 (s), 2950 (s), 1710 (s), 1680 (s), 1620 (s), 1460 (s), 1380 (m), 1320 (s), 1280 (m), 1240 (m), 1180 (s)  $\text{cm}^{-1}$ ;  $\delta$  (250 MHz,  $\text{CDCl}_3$ ) 1.19 (3H, s), 1.20 (3H, s), 1.30 (3H, s), 1.33 (3H, s), 1.62 (3H, s), 1.40-2.00 (6H, m), 2.23 (3H, s), 2.35 (1H, m), 2.36 (1H, d,  $J = 16$  Hz), 2.45 (1H, d,  $J = 16$  Hz), 3.05 (2H, s), 3.33 (2H, d,  $J = 7$  Hz), 4.75 (1H, OH), 5.44 (1H, t,  $J = 7$  Hz), 6.45 (1H, d,  $J = 3$  Hz), 6.56 (1H, d,  $J = 3$  Hz), 6.67 (1H, d,  $J = 15$  Hz), 6.88 (1H, d,  $J = 15$  Hz), 7.00 (1H, OH). The spectral data of **1** were identical with those of the natural **1**. (Found: C, 73.47; H, 8.51. Calc for  $\text{C}_{27}\text{H}_{38}\text{O}_5$ : C, 73.27; H, 8.65%).

#### X-ray Analysis of **4a**

X-ray diffraction measurements were performed on a Rigaku AFC-66 diffractometer with graphite monochromated MoK $\alpha$  radiation. Crystal data and data collection parameters are given in Table 1. The intensities were measured in the  $\omega/2\theta$  scan mode, and corrected for Lorentz and polarization effects, but not for absorption.

The structure was solved by direct method using MULTAN.<sup>7</sup> All H atoms were found from the difference Fourier maps. The refinement of atomic parameters was carried out by a block-diagonal least-squares method. Thermal parameters were refined anisotropically for all non-hydrogen atoms and isotropically for the hydrogen atoms. Atomic scattering factors were taken from ref.

8. A least-squares refinement on the basis of 1495 observed reflection led to a final  $R = 0.058$ . The PLUTO<sup>9</sup> computer drawing of the two symmetrically independent molecules is shown in Fig. 3.

#### X-ray Analysis of 4b

X-ray diffraction measurements were performed on a Syntex R3 diffractometer. Data collection, reduction and refinement were as described for 4a. Crystal data and data collection parameters are given in Table 1. Solution and refinement were also carried out as described for 4a. Of the 72 H atoms, 54 were located near expected positions in a difference Fourier maps. Least-squares refinement on the basis of 2040 observed reflections led to a final  $R = 0.078$ . The PLUTO computer drawing of 4b is shown in Fig. 3. Supplementary materials are available on request.<sup>10</sup>

Table 1. Crystal Data for 4a and 4b

compound	4a	4b
formula	$C_{20}H_{16}O_2$	$C_{20}H_{16}O_2$
lattice type	orthorhombic	monoclinic
space group	$P2_12_12_1$	$P2_1$
cell dimensions		
a, Å	11.296 (3)	7.634 (4)
b, Å	22.109 (4)	15.320 (9)
c, Å	7.590(3)	16.694 (7)
$\alpha$ , deg	90	90
$\beta$ , deg	90	92.40 (4)
$\gamma$ , deg	90	90
cell vol, Å <sup>3</sup>	1893.1	1950.7
z	4	4
Dc, g cm <sup>-3</sup>	1.08	1.05
$\mu$ (calcd), cm <sup>-1</sup>	0.7	0.7
2 $\theta$ range, deg	1-50	1-45
no. of unique reflens		
measd	1782	2671
obsd	1495	2040
R-factor	0.058	0.078

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