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# Total Synthesis of the Polyene Macrolide Antibiotic Roxaticin. I. Synthesis of the Polyol Fragment of Roxaticin Using a Four-Carbon Chain Extension Strategy

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***Abstract:*** The C11-C26 polyol fragment of roxaticin containing eight chiral centers has been prepared in a reiterative manner using coupling reactions of chiral dithianes and epoxides followed by stereoselective reduction.

Polyene macrolide antibiotics belong to an important class of clinically valuable natural products and are used in treating systemic fungal infections.[1] Over 200 polyene macrolides are known, but the complete structure and stereochemistry have been determined only in several cases.[2] The unique structural and stereochemical features of this family have aroused the interest of synthetic chemists and a variety of synthetic methods for preparing alternating polyol chains has been developed,[3] culminating in the total syntheses of amphotericin B,[4] pimarolide,[5] mycoticin A,[6] and roxaticin.[7]

Roxaticin (**1**) is an oxo pentaene macrolide[8] isolated from an unidentified streptomycete strain similar to *Streptomyces ruber* and shows antifungal activity.[9] The structure was determined by X-ray crystal analysis of roxaticin heptaacetate, which indicated the presence of an alternating polyol chain containing both *syn*- and *anti*-1,3-diol units.[9] As a part of our program of synthetic studies on 1,3-polyols,[10] we have chosen roxaticin (**1**) as a synthetic target. We report the stereocontrolled total synthesis of roxaticin in this and the following papers.[11] The synthesis of the unnatural enantiomer of roxaticin was reported recently by Rychnovsky.[7] In the present paper we describe the stereocontrolled synthesis of the C11- C26 polyol chain of roxaticin using a four-carbon extension methodology.[11b]

**Synthetic Plan**. Our strategy for the construction of roxaticin (**1**) was presented in Scheme I. The oxo pentaene moiety is relatively unstable upon exposure to light, and we decided to introduce the polyene part at the final stages of the synthesis. Inspection of **1** revealed two rather obvious bonds for disconnection in the retrosynthetic sense, namely the lactone linkage and the C10 double bond. The macrocyclic ring could be formed by macrolactonization of the seco-acid. Although the presence of steric hindrance caused by the C28 methyl and C29 isopropyl substituents would decrease the reactivity of the C29 oxygen, we considered that lactonization was possible as exemplified by the synthesis of mycoticin.[6] Thus, roxaticin could be synthesized by coupling the polyol segment **2** and the polyene segment **3**, and the segment **2** could then be dissected at the C26 double bond, leading to the two advanced intermediates, sulfone **4** and aldehyde **5**. Preparation of the suitably protected C11 to C26 polyol chain **6** was

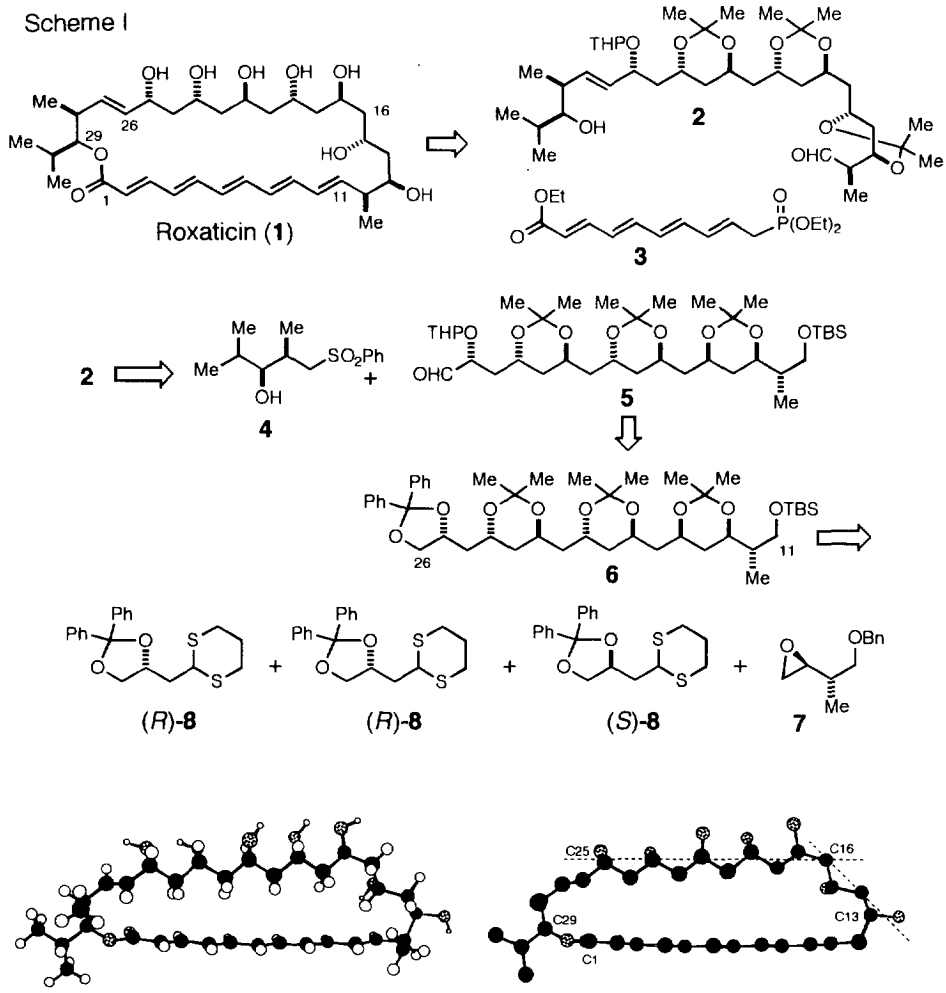
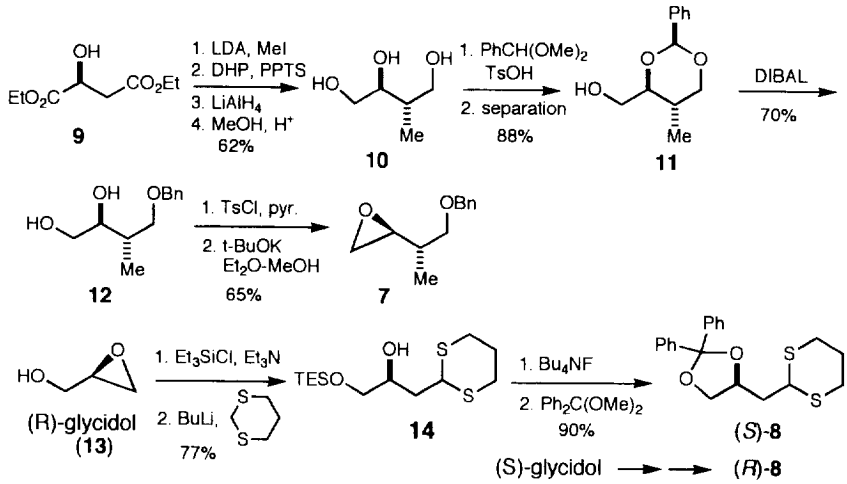


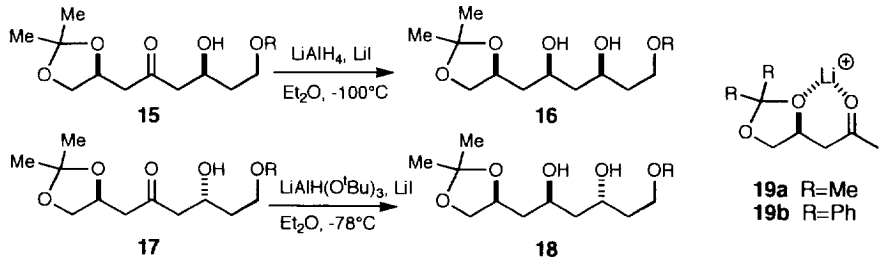

Fig. 1 Crystal structure of roxaticin heptaacetate. Acetates have been omitted for clarity.

the first synthetic goal. There are two modes of acetonide protection for the 1,3-diol units in **5** because **5** contains an odd number of hydroxyl functions. The carbon skeleton of the crystal structure of roxaticin heptaaectate is reproduced in Figure 1, which shows that C16 is a turning point of the polyol carbon-carbon skeleton and the C13 to C16 and the C16 to C26 parts assume an extended zigzag form. Cyclic protection of the C15 and C17 oxygens would reduce the flexibility of the polyol chain to disfavor macrolactonization and, therefore, triacetonide **6** was identified as a key intermediate to roxaticin. Our approach to **6** was based on the four-carbon chain extension method for 1,3-polyol synthesis.[10] Thus, sequential coupling of epoxide **7** with chiral building blocks (*S*)-**8** and then (*R*)-**8** with simple functional group manipulations would provide the requisite intermediate **6**.

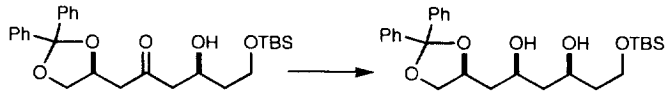
**Synthesis of Chiral Building Blocks 7 and (*R*)- and (*S*)-8.** Synthesis of the chiral epoxide **7** started from (*S*)-diethyl malate (**9**). Frater-Seebach methylation[12] of **9** gave an inseparable 10:1 mixture of *anti* and *syn* isomers which was converted into triol **10** by $LiAlH_4$ reduction.[13] Protection with benzaldehyde dimethyl acetal proceeded to the favored formation of six-membered benzylidene derivatives, and the major product **11**, isolated in 88% yield, was found to be stereochemically homogeneous by $^1H$-NMR analysis, while the minor product (4%) was a mixture of other regio- and stereoisomers. Regioselective reductive cleavage of the 1,3-dioxane ring of **11** using diisobutylaluminum hydride[14] gave benzyl ether **12** in 70% yield, which was transformed into epoxide **7** (65%) in two steps. The $C_4$ chiral building blocks employed in our previously reported method[10] were the acetonide derivatives corresponding to (*R*)- and (*S*)-**8**. However, these units are unfavorable in the present synthesis because the hydroxyl groups of the polyol segment **6** are to be protected with acetonide groups. We then chose the dithianes (*R*)- and (*S*)-**8** protected with diphenylmethylene ketal which were easily prepared from (*S*)- and (*R*)-glycidols, respectively. Triethylsilylation of (*R*)-glycidol (**13**) and the reaction with 2-lithio-1,3-dithiane gave **14** (77%), which was desilylated and subsequently protected with benzophenone dimethyl ketal leading to the chiral building block (*S*)-**8** in 90% overall yield.




**Model Studies for 1,3-Asymmetric Reduction of β-Hydroxy ketones.** In order to provide a general solution to the problem of constructing 1,3-polyols, we have developed highly diastereoselective methods for reducing β-hydroxy ketones to 1,3-diols.[10a,c] Reduction of the ketone **15** with $LiAlH_4$ in the presence of LiI in ether at -100°C proceeded with high 1,3-*syn* diastereoselectivity (95:5) to give the corresponding diol, whereas the combination of $LiAlH(O^tBu)_3$ and LiI in ether at -78°C was used to reduce the β-hydroxy ketone **17** to the *anti*-diol **18** with a high selectivity of 95:5. Lithium cation apparently was chelated by β-alkoxy ketone to form a six-membered transition state **19a**, allowing hydrides to attack the carbonyl group from the less hindered α-side with high selectivity. In the present synthesis of the polyol chain of roxaticin, the corresponding alkoxy group is to be incorporated in diphenylmethylene ketal



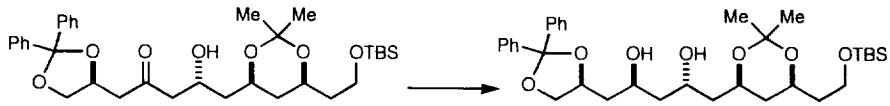

portion (**19b**), but it is not clear whether this chelated transition state is effective in the presence of the bulky phenyl groups. We needed model experiments to evaluate the lithium-chelated reduction of β-alkoxy ketones having a diphenylmethylene ketal group. The reduction was initially carried out on ketone **20** and the selectivity was determined by HPLC. Table I details the results of experiments, in which $LiAlH_4$ and $LiAlH(O^tBu)_3$ gave only moderate selectivity even in the presence of LiI, indicating that the formation of the chelated transition state was prevented by the bulky phenyl groups. The *syn*-selectivity was improved by hydroxy-directed reduction using $Et_2OMe$-$NaBH_4$[15] at -78°C in THF-methanol (4:1), yielding the *syn*-1,3-diol **21** with a 99:1 selectivity. We next examined the reduction of the ketone **22**, prepared from **20**, to the *anti*-1,3-diol **23** (Table II). $Me_4NBH(OAc)_3$[16] in acetic acid-acetonitrile reduced **22** to the *anti*-1,3-diol **23** with excellent selectivity, whereas $LiAlH(O^tBu)_3$ - LiI gave an unsatisfactory result.



**20** **21** (*syn*-isomer)

Table I Diastereoselectivity of the Hydride Reduction of **20**

| hydride | solvent | temp. (°C) | syn : anti | yield (%) |
|---|---|---|---|---|
| $LiAlH_4$ | ether | 0 | 59 : 41 | 83 |
| | ether | -78 | 60 : 40 | 94 |
| $LiAlH_4$-LiI | ether | 0 | 76 : 24 | 89 |
| | ether | -78 | 75 : 25 | 97 |
| $LiAlH(O^tBu)_3$ | ether | -78 | 42 : 58 | 85 |
| $LiAlH(O^tBu)_3$-LiI | ether | -78 | 76 : 24 | 95 |
| $NaBH_4$-$Et_2BOMe$ | THF-MeOH | -78 | 99.5 : 0.05 | 94 |



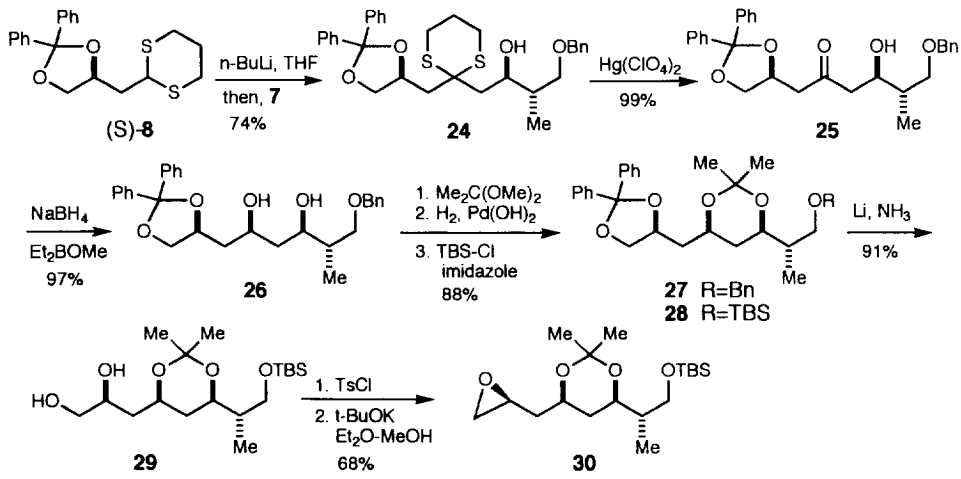
**22** **23** (*anti*-isomer)

Table II Diastereoselectivity of the Hydride Reduction of **22**

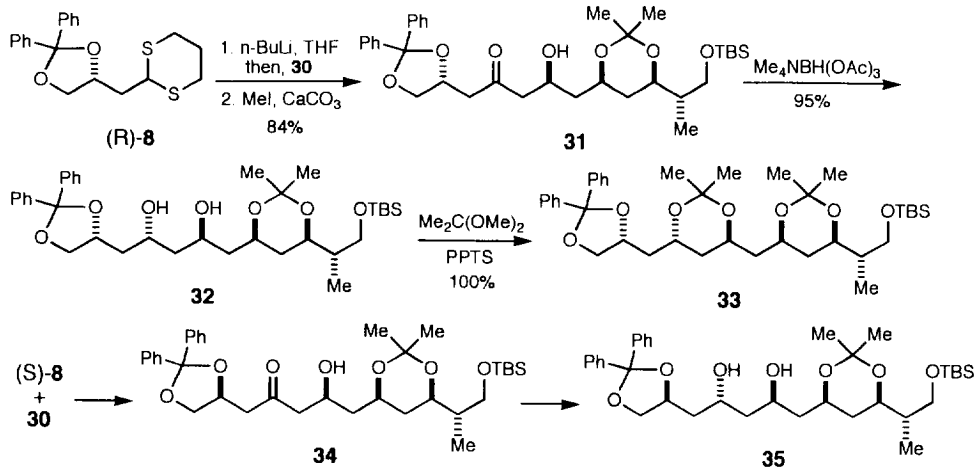
| hydride | solvent | temp. (°C) | anti : syn | yield (%) |
|---|---|---|---|---|
| $LiAlH(O^tBu)_3$-LiI | ether | 0 | 67 : 33 | 88 |
| | ether | -78 | 69 : 31 | 83 |
| $Me_4NBH(OAc)_3$ | AcOH-MeCN | -25 | 97 : 3 | 94 |

The stereochemical outcome of the above reduction products was confirmed by $^{13}C$ NMR analysis of the corresponding acetonide derivatives.[17]

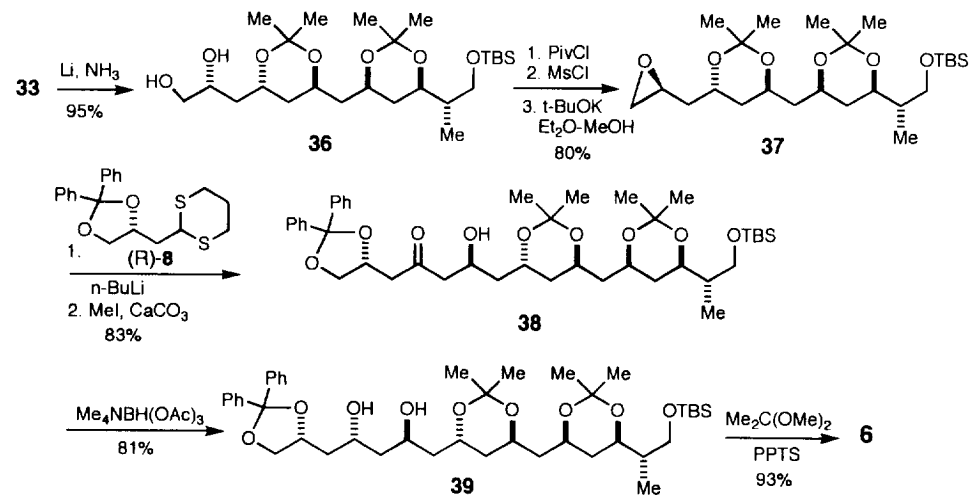
**Synthesis of the C11-C26 Segment 6.** Synthesis of **6** began with the coupling of epoxide **7** with the lithiated anion of (*S*)-**8** to give the bialkylated dithiane **24** in 74% yield. Hydrolysis of the dithioketal group with $Hg(ClO_4)_2$ in aqueous THF gave β-hydroxy ketone **25**, which could be a substrate for 1,3-diastereoselective reduction to a *syn*-diol. According to the model studies **25** was reduced with $NaBH_4$ in the presence of $Et_2BOMe$ to give the *syn*-diol **26** in 97% yield with excellent selectivity (99.7: 0.3). Protection with 2,2-dimethoxypropane and pyridinium *p*-toluenesulfonate gave acetonide **27**. The $^{13}C$ chemical shifts of acetonide methyl groups (19.69 and 30.11 ppm) confirmed the presence of a *syn*-acetonide ring.[17] In order to deprotect the diphenylmethylene ketal, the benzyl group was replaced by a *t*-butyldimethylsilyl group to afford **28** (88% from **26**), which was then subjected to metal-ammonia reduction to give diol **29** in 91% yield. The terminal 1,2-diol moiety was transformed into an epoxide *via* a tosylate leading to **30** in 68% overall yield.




In the second four-carbon elongation, both (*R*)- and (*S*)-**8** $C_4$-units were good candidates to couple with **30**, but the route using (S)-**8** was found to be less satisfactory in the stereoselective reduction step (*vide infra*). So we coupled epoxide **30** with the anion of (*R*)-**8**, giving hydroxy ketone **31** in 84% overall yield after dithiane hydrolysis . The hydroxy-directed *anti*-reduction with Evans' reagent, $Me_4NBH(OAc)_3$,[16] afforded a 97:3 mixture of *anti* and *syn* products, where the *anti*-isomer **32** was isolated in 95% yield. The relative stereochemistry of **32** was proved by the $^{13}C$ NMR analysis of the acetonide **33**, which showed one *syn*-1,3-diol (19.76 and 30.21 ppm) and one *anti*-1,3-diol (24.60 and 24.71 ppm) acetonides.[17] It is worthy noting that the *anti*-reduction of hydroxy ketone **34**, prepared by the coupling of dithiane (*S*)-**8** and epoxide **30** followed by dithiane hydrolysis, with $Me_4NBH(OAc)_3$ proceeded with only moderate selectivity (85:15) to give **35**, which is also a good substrate for further elaboration to **37**. This approach, however, was abandoned when it became clear that the selectivity of the reduction could not be improved.




Birch reduction of **33** gave **36** and the terminal 1,2-diol moiety was transformed to the β-epoxide **37** by inverting the chiral center in 76% overall yield. Final coupling of **37** with (*R*)-**8** proceeded uneventfully and hydrolysis of the dithioketal group provided hydroxy ketone **38** in 83% yield. The *anti*-1,3-diol stereochemical relationship was established by the reduction of **38** with $Me_4NBH(OAc)_3$[16] to afford a 97:3 mixture of *anti* and *syn* diastereomers, from which **39** was isolated in 81% yield by careful chromatographic separation. Protection of the diol gave the protected polyol segment **6**. Compound **6** contains the C11 to C26 subunit and eight chiral centers of roxaticin (**1**).




**Conclusion**. The polyol segment of roxaticin was efficiently constructed by employing the three-fold four-carbon chain extension approach. The dithiane-epoxide coupling/1,3-asymmetric reduction methodology proved highly successful in providing the necessary stereocenters of acyclic 1,3-polyols with excellent selectivities, thus lending itself to the construction of related

compounds. Studies directed toward the total synthesis of roxaticin are described in the following article in this issue.

## Experimental

**General.** $^1H$ and $^{13}C$ NMR spectra were measured on JEOL JNM-GX 270 and 400 spectrometers as $CDCl_3$ solutions. IR spectra were recorded on a JASCO IR-810 spectrometer. Mass spectra, including high resolution mass measurements, were determined in either EI or FAB mode with a JEOL HX-110 instrument. Optical rotations were determined on a JASCO DIP-370 digital polarimeter. Analytical thin-layer chromatography was performed on E. Merck silica gel $60F_{254}$ plates (0.25 mm) and flash chromatography was carried out with E. Merck silica gel 60 (230-400 mesh). The term "dried" refers to the drying of an organic solution over $MgSO_4$.

**(1*S*,3*S*,4*S*)-3-Hydroxymethyl-4-methyl-1-phenyl-1,3-dioxane(11).** Benzaldehyde dimethylacetal (1.39ml, 9.28mmol) and *p*-TsOH (73mg) were added to a solution of **10** (928mg, 7.73mmol) in $CH_2Cl_2$ (10ml) and the reaction mixture was stirred at room temperature for 1.5h. After addition of triethylamine (0.3ml), the mixture was concentrated under reduced pressure. The reside was purified by flash chromatography (30% EtOAc-hexane) to give **11** (1.41g, 88%) as an oil. $[\alpha]_D^{25}$ +13.1° (c=0.69, $CHCl_3$). IR ($CHCl_3$): 3600, 3420, 1460, 1390, 1120, 1070, 1020cm$^{-1}$. $^1H$ NMR (270MHz) δ: 0.83 (3H, d, *J*=6.7Hz), 2.04 (1H, m), 2.12 (1H, OH), 3.53 (1H, t, *J*=11.4Hz), 3.61 (1H, m), 3.69 (1H, m), 3.86 (1H, m), 4.15 (1H, dd, *J*=11.4, 5.0Hz), 5.54 (1H, s), 7.32-7.52 (5H). EIMS *m/z*: 208 ($M^+$).

**(2*S*,3*S*)-4-Benzyloxy-3-methylbutane-1,2-diol (12).** A 1.5M solution of diisobutylaluminum hydride in hexane (13.6ml, 20.34mmol) was added to a stirred solution of **11** (1.41g, 6.78mmol) in dry $CH_2Cl_2$ (15ml) at 0°C under an argon atmosphere and the mixture was stirred at room temperature for 17h. The reaction mixture was cooled to 0°C, and MeOH (1.5ml), saturated aqueous $NH_4Cl$ (7ml), and $CH_2Cl_2$ (20ml) were added. The reaction mixture was stirred for 5h and filtered. The precipitates were washed with EtOAc and THF. The filtrate and washings were combined and concentrated. Purification by flash chromatography (85% EtOAc/hexane) gave **12** (977mg, 70%) as a colorless oil. $[\alpha]_D^{25}$ +23.1° (c=0.42, $CHCl_3$). IR ($CHCl_3$): 3420, 1450, 1220, 1070cm$^{-1}$. $^1H$ NMR (270MHz) δ: 0.90 (3H, d, *J*=7.1Hz), 2.02 (1H, m), 2.46 (1H, br s, OH), 3.51 (1H, t, *J*=9.1Hz), 3.56 (1H, dd, *J*=9.1, 4.7Hz), 3.59 (2H, m), 3.67 (1H, m), 3.72 (1H, s, OH), 4.54 (2H, s), 7.20-7.39 (5H, m).

**(2*S*,3*S*)-4-Benzyloxy-1,2-epoxy-3-methylbutane (7).** A solution of **12** (4.88g, 23.23mmol) in pyridine (25ml) was cooled to 0°C and *p*-toluenesulfonyl chloride (5.31g, 28.87mmol) was added. The reaction mixture was stirred at 0°C for 3h and then extracted with EtOAc. The extract was washed with water and brine, dried, and evaporated. The residual pyridine was azeotropically removed with heptane two times. Purification of the residue by flash chromatography (22% EtOAc/hexane) gave a tosylate (6.09g).

The tosylate (6.09g, 16.74mmol) was dissolved in ether (70ml) and MeOH (14ml), and *t*-BuOK (2.07g, 18.42mmol) was added under stirring at 0°C. The mixture was stirred at 0°C for 1h and extracted with ether. The extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (12% EtOAc/hexane) afforded **7** (2.89g, 65% in two steps) as a colorless oil, bp 130°C (3 mmHg, Kugelrohr distillation). $[\alpha]_D^{25}$ -6.95° (c=0.49, $CHCl_3$). IR ($CHCl_3$): 1500, 1480, 1455, 1360, 1220, 1100, 935, 880cm$^{-1}$. $^1H$ NMR (270MHz) δ: 1.01 (3H, d, *J*=7.1Hz), 1.71 (1H,

m), 2.54 (1H, dd, *J*=5.0, 2.8Hz), 2.75 (1H, t, *J*=5.0Hz), 2.91 (1H, m), 3.47 (1H, dd, *J*=9.1, 5.7Hz), 3.53 (1H, dd, *J*=9.1, 5.4Hz), 4.53 (2H, s), 7.25-7.35 (5H, m). Anal. Calcd for $C_{12}H_{16}O_2$: C, 75.95; H, 8.39. Found: C, 75.81; H, 8.57.

**2-[(2*S*)-2,3-O-(Diphenylmethylidene)-2,3-dihydroxypropyl]-1,3-dithiane ((*S*)-8).** A solution of (*R*)-glycidol (**13**) (11.04g, 14.92mmol), 4-dimethylaminopyridine (150mg, 1.23 mmol), and triethylamine (31.2ml, 22.35mmol) was cooled to -30°C, and triethlychlorosilane (27.5ml, 16.4mmol) was added. The mixture was stirred at the same temperature for 30min. The reaction mixture was diluted with hexane and passed through a short column of Celite using hexane. The filtrate was concentrated and the residue was purified by flash chromatography to give an oil. Distillation gave (*R*)-triethylsilylglycidol (27.52g, 98%), bp 59°C (3mmHg). $[\alpha]_D^{25}$ -2.20° (c=0.64, $CHCl_3$). $^1H$ NMR (270MHz) δ: 0.62 (6H, q, *J*=7.7Hz), 0.97 (9H, t, *J*=7.7Hz), 2.63 (1H, dd, *J*=5.0, 2.7Hz), 2.78 (1H, t, *J*=5.0Hz), 3.10 (1H, m), 3.65 (1H, dd, *J*=11.7, 5.0Hz), 3.84 (ddd, *J*=11.7, 3.4, 3.4Hz).

A 1.6M solution of *n*-BuLi in hexane (37ml, 59.2mmol) was added to a stirred solution of 1,3-dithiane (7.08g, 59mmol) in dry THF (150ml) at -40°C under an argon atmosphere. The solution was stirred at -25°C for 2h and then (*R*)-triethylsilylglycidol (11.09g, 59mmol) was added. The reaction vessel was closed under positive pressure of argon and stored at -25°C for 19h. The reaction was quenched with saturated aqueous $NH_4Cl$ and the mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. The residue was purified by flash chromatography (18% EtOAc/hexane) to give **14** (14.35g, 79%) as a colorless oil. $^1H$ NMR (270MHz) δ: 0.63 (6H, q, *J*=7.7Hz), 0.96 (9H, t, *J*=7.7Hz), 1.80-2.18 (4H, m), 2.57 (1H, br, OH), 2.77-2.95 (4H, m), 3.45 (1H, dd, *J*=10.1, 6.7Hz), 3.64 (1H, dd, *J*=10.1, 3.7Hz), 3.98 (1H, m), 4.30 (1H, dd, *J*=9.4, 5.1Hz).

A solution of **14** (14.35g, 46.60mmol) in dry THF was treated with 1.0M $Bu_4NF$ in THF (68ml, 68mmol) and the mixture was stirred for 20h. The reaction mixture was concentrated under reduced pressure and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. The oily residue was purified by flash chromatography (80% EtOAc/hexane) to give the desilylated product (9.035g, 100%). $^1H$ NMR (270MHz) δ: 1.80-2.01 (3H, m), 2.05 (1H, s, OH), 2.13 (1H, m), 2.57 (1H, s, OH), 2.80-3.05 (4H, m), 3.49 (1H, dd, *J*=11.0, 7.1Hz), 3.68 (1H, dd, *J*=11.0, 3.5Hz), 4.06 (1H, m), 4.26 (1H, dd, *J*=8.8, 5.6Hz). EIMS *m/z*: 194 ($M^+$).

A mixture of the product (4.34g, 22.4mmol) obtained above, benzophenone dimethyl ketal (6.13g, 26.88mmol), and *p*-TsOH (200mg) in $CH_2Cl_2$ (80ml) was stirred at room temperature for 3.5h. The reaction was quenched with triethylamine (0.2ml) and the mixture was concentrated. The residue was purified by flash chromatography (8% EtOAc/hexane) to give (*S*)-**8** (7.18g, 90%) as an oil. $[\alpha]_D^{25}$ +0.52° (c=0.58, $CHCl_3$). IR ($CHCl_3$): 1445, 1420, 1200, 1085, 1065, 1025, 990, 950, 905$cm^{-1}$. $^1H$ NMR (270MHz) δ: 1.80-2.00 (2H, m), 2.04-2.24 (2H, m), 2.77-2.96 (4H, m), 3.71 (1H, dd, *J*=8.1, 7.1Hz), 4.16 (1H, dd, *J*=8.1, 6.7Hz), 4.24 (1H, dd, *J*=9.1, 5.1Hz), 4.48 (1H, m), 7.25-7.36 (6H, m), 7.53-7.45 (4H, m). Anal. Calcd for $C_{20}H_{22}O_2S_2$: C, 67.02; H, 6.19. Found: C, 67.28; H, 6.40.

**2-[(2*R*)-2,3-O-Diphenylmethylidene-2,3-dihydroxypropyl]-1,3-dithiane ((*R*)-8)** was prepared from (*S*)-glycidol in the same way as described above. $[\alpha]_D^{25}$ -0.57° (c=0.43, $CHCl_3$).

**(2*S*,6*R*,7*S*)-8-Benzyloxy-1,2-O-diphenymethylidene-7-methyloctan-4-one-1,2,6-triol. (25).** A stirred solution of (*R*)-**8** (7.04g, 19.67mmol) in dry THF (65ml) under argon at -40°C was treated with 1.6M *n*-BuLi in hexane (13.4ml, 21.45mmol). The solution was stirred at the same temperature for 2h

and then a solution of **7** (3.43g, 17.88mmol) in dry THF (5ml) was added. The reaction vessel was closed under positive pressure of argon and stored at -30°C for 40h. The reaction was quenched with saturated aqueous $NH_4Cl$, and the mixture was concentrated and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. The residue was purified by flash chromatography (18% EtOAc/hexane) to give **24** (8.95g, 91%) as an oil. $[\alpha]_D^{25}$ +22.9° (c=0.54, $CHCl_3$). IR ($CHCl_3$): 3420, 1450, 1260, 1090cm$^{-1}$. $^1$H NMR (400MHz) δ: 0.94 (3H, d, *J*=7.1Hz), 1.85 (1H, m), 1.94 (2H, m), 2.16 (1H, d, *J*=15.0Hz), 2.29 (1H, dd, *J*=15.0, 9.3Hz), 2.35 (1H, dd, *J*=15.1, 6.3Hz), 2.52 (1H, dd, *J*=15.1, 6.3Hz), 2.79 (2H, m), 2.88 (2H, m), 3.46 (1H, d, *J*=3.4Hz, OH), 3.51 (1H, t, *J*=4.9Hz), 3.52 (1H, m), 3.71 (1H, t, *J*=7.8Hz), 3.99 (1H, m), 4.20 (1H, dd, *J*=7.8, 6.6Hz), 4.44 (1H, m), 4.45 (1H, d, *J*=12.2Hz), 4.49 (1H, d, *J*=12.2Hz), 7.24-7.33 (11H, m), 7.45-7.52 (4H, m). $^{13}$C NMR (100MHz) δ: 14.36, 24.80, 26.23, 26.43, 39.36, 42.74, 43.87, 51.04, 70.82, 71.65, 73.14, 73.30, 73.72, 77.24, 109.68, 126.16, 126.21, 127.65, 127.91, 128.02, 128.15, 128.39, 138.20, 142.58, 142.68. EIMS *m/z*: 550 ($M^+$).

A mixture of **24** (5.53g, 10.06mmol), $CaCO_3$ (10.06g, 100.6mmol), and $Hg(ClO_4)_2$ (11.4g, 25.15mmol) in THF (240ml) and water (60ml) was stirred at room temperature for 30min and then filtered through a short column of Celite using EtOAc (50ml). The filtrate was concentrated to one-third of the volume and the whole was extracted with EtOAc. The extract was washed with aqueous $NaHCO_3$, water, and brine, dried, and concentrated. The residue was purified by flash chromatography (26% EtOAc/hexane) to give **25** (4.59g, 99%) as a colorless oil. $[\alpha]_D^{25}$ +35.6° (c=0.58, $CHCl_3$). IR ($CHCl_3$): 3500, 1710, 1450, 1090, 1070, 1025, 995cm$^{-1}$. $^1$H NMR (400MHz) δ: 0.88 (3H, d, *J*=7.1Hz), 1.88 (1H, m), 2.55 (1H, dd, *J*=15.8, 4.6Hz), 2.59 (1H, dd, *J*=15.8, 7.8Hz), 2.68 (1H, dd, *J*=17.1, 7.6Hz), 3.07 (1H, dd, *J*=17.1, 5.6Hz), 3.46 (1H, dd, *J*=9.3, 7.3Hz), 3.51 (1H, dd, *J*=9.3, 4.6Hz), 3.52 (1H, m), 3.70 (1H, dd, *J*=8.3, 6.6Hz), 4.01 (1H, m), 4.23 (1H, dd, *J*=8.3, 6.6Hz), 4.49 (2H, s), 4.56 (1H, quint, *J*=6.6Hz), 7.24-7.36 (11H, m), 7.42-7.54 (4H, m). $^{13}$C NMR (100MHz) δ: 13.66, 38.36, 47.83, 47.96, 70.03, 71.62, 72.42, 73.41, 73.87, 109.48, 126.09, 126.16, 127.68, 127.80, 128.07, 128.10, 128.18, 128.47, 137.85, 142.22, 142.45, 208.84. HREIMS *m/z*: calcd for $C_{29}H_{32}O_5$: 460.2248; found: 460.2272.

**(2*S*,4*S*,6*R*,7*S*)-8-Benzyloxy-1,2-O-diphenylmethylidene-7-methyloctane-1,2,4,6-tetrol (26).** A solution of **25** (9.15g, 19.94mmol) in dry THF (200ml) and dry MeOH (50ml) under an argon atmosphere was cooled to -78°C and 1.0M $Et_2BOMe$ in THF (22ml, 21.94mmol) was added. The solution was stirred for 15min and then $NaBH_4$ (905mg, 23.93mmol) was added in one portion. After being stirred at -78°C for 2h, the reaction was quenched with water and the whole was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. The residue was dissolved in MeOH (80ml) and the solvent was evaporated. This procedure was repeated several times. The residue was purified by flash chromatography (35% EtOAc/hexane) to give **26** (8.95g, 97%) as a colorless oil. $[\alpha]_D^{25}$ +13.7° (c=0.53, $CHCl_3$). IR ($CHCl_3$): 3450, 1450, 1090, 990cm$^{-1}$. $^1$H NMR (400MHz) δ: 0.89 (3H, d, *J*=7.1Hz), 1.51-2.00 (5H, m), 3.46 (1H, dd, *J*=9.4, 7.4Hz), 3.60 (1H, dd, *J*=9.4, 4.4Hz), 3.75 (1H, t, *J*=7.7Hz), 3.78 (1H, m), 4.07 (1H, m), 4.13 (1H, s, OH), 4.15 (1H, s, OH), 4.17 (1H, dd, *J*=7.7, 6.7Hz), 4.39 (1H, quint, *J*=6.7Hz), 4.51 (2H, s), 7.25-7.46 (11H, m), 7.48-7.52 (4H, m). FABMS *m/z*: 463 ($MH^+$).

**(2*S*,4*S*,6*R*,7*S*)-8-Benzyloxy-1,2-O-diphenylmethylidene-4,6-O-isopropylidene-7-methyloctane-1,2,4,6-tetrol (27).** A solution of **26** (6.56g, 14.21mmol), 2,2-dimethoxypropane (2.62ml, 21.31mmol), and pyridinium *p*-toluenesulfonate (179mg) in $CH_2Cl_2$ (70ml) was stirred at

room temperature for 3.5h. The reaction was quenched with triethylamine (1ml) and the mixture was concentrated. The residue was purified by flash chromatography (30% EtOAc/hexane) to give **27** (6.92g, 97%) as a colorless oil. $[\alpha]_D^{25}$ -2.29° (c=0.44, $CHCl_3$). IR ($CHCl_3$): 1450, 1380, 1200, 1170, 1080, 1060, 1030cm$^{-1}$. $^1$H NMR (270MHz) δ: 0.93 (3H, d, *J*=7.1Hz), 1.22 (1H, ddd, *J*=12.8, 11.8, 11.8Hz), 1.32 (3H, s), 1.33 (3H, s), 1.49 (1H, ddd, *J*=12.8, 2.4, 2.4Hz), 1.71 (1H, ddd, *J*=13.8, 5.7, 5.7Hz), 1.82 (1H, m), 2.02 (1H, ddd, *J*=13.8, 6.4, 6.4Hz), 3.40 (1H, dd, *J*=9.1, 5.7Hz), 3.47 (1H. dd, *J*=9.1, 4.7Hz), 3.76 (1H, t, *J*=7.7Hz), 3.79 (1H, m), 3.99 (1H, m), 4.12 (1H, dd, *J*=7.7, 6.4Hz), 4.33 (1H, quint, *J*=6.7Hz), 4.51 (1H, d, *J*=12.1Hz), 4.51 (1H, d, *J*=12.1Hz), 7.24-7.47 (11H, m), 7.48-7.53 (4H, m). $^{13}$C NMR (100MHz) δ: 12.74, 19.69, 30.11, 33.36, 38.69, 39.48, 66.21, 69.85, 69.88, 71.67, 73.02, 73.38, 98.37, 109.23, 126.16, 127.41, 127.50, 127.91, 127.98, 128.10, 128.27, 138.77, 142.74. HRFABMS *m/z*: calcd for $C_{32}H_{39}O_5$ ($MH^+$): 503.2795; found: 503.2828.

**(2*S*,4*S*,6*R*,7*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-1,2-O-diphenylmethylidene-4,6-O-isopropylidene-7-methyloctane-1,2,4,6-tetrol (28).** A mixture of **27** (4.03g, 8.05mmol) and $Pd(OH)_2$-C (1.01g) in EtOAc (32ml) was stirred under a hydrogen atmosphere for 3.5h. The mixture was filtered through a short column of Celite and the filtrate was concentrated. The residue was purified by flash chromatography (28% EtOAc/hexane) to give the product (3.02g, 91%). $[\alpha]_D^{25}$ +4.76° (c=0.95, $CHCl_3$). IR ($CHCl_3$): 3500, 1450, 1380, 1260, 1200, 1175, 1100, 1085, 1030, 985cm$^{-1}$. $^1$H NMR (270MHz) δ: 0.84 (3H, d, *J*=7.1Hz), 1.30 (1H, t, *J*=10.1Hz), 1.35 (3H, s), 1.39 (3H, s), 1.60 (1H, ddd, *J*=12.8, 3.4, 3.4Hz), 1.64-1.80 (2H, m), 2.02 (1H, ddd, *J*=13.8, 6.4, 6.4Hz), 2.96 (1H, br, OH), 3.59 (2H, d, *J*=6.1Hz), 3.76 (1H, m), 3.78 (1H, t, *J*=7.7Hz), 4.04 (1H, dddd, *J*=11.4, 6.1, 6.1, 2.4Hz), 4.12 (1H, dd, *J*=7.7, 6.4Hz), 4.33 (1H, quint, *J*=6.4Hz). EIMS *m/z*: 394 ($M^+$-$H_2O$).

The product (1.07g, 2.60mmol) was dissolved in dry DMF (4ml), and imidazole (728mg, 10.70mmol) and *t*-butyldimethylchlorosilane (460mg, 3.06mmol) were added. The reaction mixture was stirred at room temperature for 2h and then extracted with ether. The extract was washed with water and brine, dried, and concentrated. The reside was purified by flash chromatography (7% EtOAc/hexane) to give **28** (1.37g, 100%) as a colorless oil. $[\alpha]_D^{25}$ +0.16° (c=0.63, $CHCl_3$). IR ($CHCl_3$): 1450, 1380, 1250, 1200, 1170, 1100, 840cm$^{-1}$. $^1$H NMR (270MHz) δ: 0.03 (6H, s), 0.87 (3H, d, *J*=7.1Hz), 0.89 (9H, s), 1.22 (1H, ddd, *J*=12.8, 11.8, 11.8Hz), 1.33 (3H, s), 1.34 (3H, s), 1.53 (1H, ddd, *J*=12.8, 2.4, 2.4Hz), 1.63 (1H, m), 1.73 (1H, ddd, *J*=13.8, 5.7, 5.7Hz), 2.04 (1H, ddd, *J*=13.8, 6.4, 6.4Hz), 3.53 (1H, dd, *J*=9.4, 4.4Hz), 3.61 (1H, dd, *J*=9.4, 5.0Hz), 3.77 (1H, t, *J*=7.7Hz), 3.79 (1H, m), 4.01 (1H, m), 4.13 (1H, dd, *J*=7.7, 6.4Hz), 4.34 (1H, quint, *J*=6.7Hz), 7.26-7.37 (6H, m), 7.47-7.54 (4H, m). $^{13}$C NMR (100MHz) δ: -5.48, 12.31, 18.25, 19.66, 25.89, 30.15, 33.61, 39.58, 40.67, 63.86, 66.29, 69.41, 69.88, 73.42, 98.32, 109.24, 126.19, 127.91, 127.98, 128.10, 142.74, 142.80. EIMS *m/z*: 511 ($M^+$- $CH_3$).

**(2*S*,4*S*,6*R*,7*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-4,6-O-isopropylidene-7-methyloctane-1,2,4,6-tetrol (29).** Lithium (436mg, 62.33mmol) was added to liquid ammonia (70ml) at -78°C under an argon atmosphere and the mixture was stirred for 10min. To this solution were added EtOH (2ml) and a solution of **28** (3.64g, 6.93mmol) in dry THF (10ml) and the mixture was stirred at the same temperature for 30min. The reaction was quenched with saturated aqueous $NH_4Cl$ and the mixture was warmed gradually to room temperature. The residue was extracted with EtOAc, and the extract was washed with water and brine, dried, and concentrated. Purification of the residue by flash chromatography (55% EtOAc/hexane) gave **29** (2.27g, 91%) as a colorless oil. $[\alpha]_D^{25}$ +1.98° (c=0.58,

$CHCl_3$). IR ($CHCl_3$): 3470, 1460, 1380, 1260, 1100, 840cm$^{-1}$. $^1$H NMR (270MHz) δ: -0.02 (6H, s), 0.86 (3H, d, $J$=7.1Hz), 0.88 (9H, s), 1.24 (1H, ddd, $J$=12.8, 11.8, 11.8Hz), 1.37 (3H, s), 1.45 (3H, s), 1.49 (1H, ddd, $J$=12.8, 2.4, 2.4Hz), 1.55-1.76 (3H, m), 1.73 (1H, s, OH), 2.39 (1H, br s, OH), 3.48 (1H, m), 3.51 (1H, dd, $J$=9.4, 4.4Hz), 3.56 (1H, m), 3.61 (1H, dd, $J$=9.4, 5.0Hz), 3.84 (1H, ddd, $J$=10.1, 7.7, 2.7Hz), 3.93 (1H, m), 4.14 (1H, m). $^{13}$C NMR (100MHz) δ: -5.47, 12.30, 19.92, 21.05, 25.89, 30.17, 34.20, 39.44, 40.58, 63.78, 66.58, 69.40, 69.58, 71.56, 98.68. EIMS $m/z$: 347 ($M^+$- $CH_3$).

**(2*S*,4*S*,6*R*,7*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-1,2-epoxy-4,6-O-isopropylidene-7-methyloctane-4,6-diol (30).** A mixture of diol **29** (2.27g, 6.28mmol) and *p*-toluenesulfonyl chloride (1.44g, 7.54mmol) in pyridine (11ml) was stirred at 0°C for 4h and then extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. The residue was coevaporated with heptane four times to remove pyridine. Purification of the residue by flash chromatography (20% EtOAc/hexane) gave a tosylate (2.47g, 76%).

The tosylate (2.47g, 4.79mmol) obtained above was dissolved in ether (35ml) and MeOH (7ml) and to this stirred solution was added *t*-BuOK (644mg, 5.75mmol) at 0°C. The slurry was stirred for 45min and then extracted with ether. The extract was washed with water and brine, dried, and concentrated. The residue was purified by flash chromatography (8% EtOAc/hexane) to give **30** (1.44g, 90%) as a colorless oil. $[\alpha]_D^{25}$ -10.0° (c=0.40, $CHCl_3$). IR ($CHCl_3$): 1380, 1250, 1100, 840cm$^{-1}$. $^1$H NMR (400MHz) δ: 0.03 (6H, s), 0.87 (3H, d, $J$=7.1Hz), 0.88 (9H, s), 1.27 (1H, ddd, $J$=12.7, 11.7, 11.7Hz), 1.37 (3H, s), 1.42 (3H, s), 1.56 (1H, ddd, $J$=12.7, 2.4, 2.4Hz), 1.65 (1H, m), 1.70 (1H, ddd, $J$=14.5, 5.4, 5.4Hz), 1.78 (1H, ddd, $J$=14.5, 6.1, 6.1Hz), 2.52 (1H, dd, $J$=5.1, 2.9Hz), 2.76 (1H, dd, $J$=5.1, 4.1Hz), 3.05 (1H, m), 3.53 (1H, dd, $J$=9.8, 4.4Hz), 3.62 (1H, dd, $J$=9.8, 5.1Hz), 3.81 (1H, ddd, $J$=11.5, 7.3, 2.4Hz), 4.00 (1H, dddd, $J$=11.7, 6.1, 6.1, 2.4Hz). $^{13}$C NMR (100MHz) δ: -5.48, 12.33, 18.25, 19.79, 25.89, 30.18, 33.61, 38.99, 40.67, 46.79, 48.99, 63.88, 66.62, 69.40, 98.41. EIMS $m/z$: 329 ($M^+$- $CH_3$). HRFABMS $m/z$: calcd for $C_{18}H_{37}O_4Si$ ($MH^+$): 345.2459; found: 345.2432.

**(2*R*,6*S*,8*R*,10*R*,11*S*)-12-[(*tert*-Butyldimethylsilyl)oxy]-1,2-O-diphenylmethylidene-8,10-O-isopropylidene-11-methyldodecan-4-one-1,2,6,8,10-pentol (31).** The reaction was carried out in the same way as described for the coupling reaction of **7** and (*S*)-**8**, using (*R*)-**8** (3.47g, 9.69mmol), 1.6M *n*-BuLi in hexane (6.1ml, 9.69mmol), and **30** (2.78g, 8.08mmol). Purification by flash chromatography (14% EtOAc/hexane) gave the coupling product (5.54g, 98%) as a colorless oil. $[\alpha]_D^{25}$ -0.86° (c=0.42, $CHCl_3$). IR ($CHCl_3$): 3450, 1450, 1250, 1090, 840cm$^{-1}$. $^1$H NMR (400MHz) δ: 0.03 (6H, s), 0.87 (3H, d, $J$=7.1Hz), 0.89 (9H, s), 1.18 (1H. ddd, $J$=12.7, 11.5, 11.5Hz), 1.35 (3H, s), 1.41 (3H, s), 1.51 (1H, ddd, $J$=12.7, 2.4, 2.4Hz), 1.59 (1H, ddd, $J$=13.9, 2.4, 2.4Hz), 1.75 (1H, ddd, $J$=13.9, 8.8, 8.8Hz), 1.95 (2H, m), 2.11 (1H, dd, $J$=15.1, 2.4Hz), 2.25 (1H, dd, $J$=14.4, 12.1Hz), 2.27 (1H, dd, $J$=14.4, 2.4Hz), 2.60 (1H, dd, $J$=15.1, 6.1Hz), 2.73-2.90 (4H, m), 3.53 (1H, dd, $J$=9.8, 4.4Hz), 3.59 (1H, s, OH), 3.61 (1H, dd, $J$=9.8, 5.1Hz), 3.72 (1H, t, $J$=7.8Hz), 3.80 (1H, ddd, $J$=9.8, 7.8, 2.2Hz), 4.07 (1H, m), 4.20 (1H. m), 4.24 (1H, dd, $J$=7.8, 6.4Hz), 4.53 (1H, quint, $J$=6.4Hz), 7.26-7.53 (6H, m), 7.47-7.53 (4H, m). $^{13}$C NMR (100MHz) δ: -5.46, 12.40, 19.92, 24.73, 25.90, 26.25, 26.36, 30.19, 34.03, 40.69, 43.29, 44.54, 46.82, 50.80, 63.84, 67.22, 68.48, 69.38, 70.80, 73.97, 98.47, 109.61, 126.13, 126.17, 127.98, 128.07, 128.16, 142.40, 142.49. EIMS $m/z$: 702 ($M^+$), 687 ($M^+$- $CH_3$).

A mixture of the product (5.63g, 8.02mmol) obtained above, $CaCO_3$ (8.02g, 80.2mmol), and MeI (74.9ml, 1.20mol) in 80% aqueous acetonitrile (380ml) was stirred at room temperature for 27h. The

suspension was filtered through a short pad of Celite. The filtrate was concentrated to one-fifth of the volume and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. Purification of the residue by flash chromatography (18% EtOAc/hexane) gave **31** (4.22g, 86%) as a colorless oil. $[\alpha]_D^{25}$ -5.11° (c=0.33, $CHCl_3$). IR ($CHCl_3$): 3500, 1710, 1450, 1380, 1250, 1090, 840cm$^{-1}$. $^1$H NMR (400MHz) δ: 0.03 (6H, s), 0.86 (3H, d, *J*=7.1Hz), 0.89 (9H, s), 1.20 (1H, q, *J*=12.0Hz), 1.36 (3H, s), 1.43 (3H, s), 1.49 (1H, br d, *J*=12.0Hz), 1.54-1.68 (3H, m), 2.49 (1H, dd, *J*=16.1, 4.4Hz), 2.64 (1H, dd, *J*=16.1, 7.8Hz), 2.69 (1H, dd, *J*=17.3, 7.3Hz), 3.08 (1H, dd, *J*=17.3, 5.9Hz), 3.51 (1H, dd, *J*=9.3, 4.2Hz), 3.61 (1H, dd, *J*=9;3, 4.9Hz), 3.64 (1H, s, OH), 3.70 (1H, dd, *J*=7.6, 7.1Hz), 3.82 (1H, m), 4.11 (1H, m), 4.24 (1H, dd, *J*=7.6, 6.8Hz), 4.28 (1H, m), 4.56 (1H, quint, *J*=6.6Hz), 7.26-7.34 (6H, m), 7.46-7.51 (4H, m). $^{13}$C NMR (100MHz) δ: -5.49, 12.30, 18.24, 19.89, 25.87, 30.14, 34.02, 40.59, 42.60, 48.00, 50.35, 63.45, 67.50, 69.31, 69.73, 70.04, 72.37, 98.59, 109.45, 126.07, 126.16, 128.05, 128.11, 128.14, 142.15, 142.36, 207.91. FABMS *m/z*: 613 ($MH^+$).

**(2*R*,4*R*,6*S*,8*R*,10*R*,11*S*)-12-[(*tert*-Butyldimethylsilyl)oxy]-1,2-O-diphenylmethylidene-8,10-O-isopropylidene-11-methyldodecane-1,2,4,6,8,10-hexol (32).** A solution of $Me_4NBH(OAc)_3$ (10.37g, 39.41mmol) in dry acetonitrile (15ml) and dry acetic acid (15ml) was cooled to -25°C under an argon atmosphere and to this stirred solution was added a solution of **31** (3.45g, 5.63 mmol) in dry acetonitrile (5ml). The mixture was stirred at -25°C for 3h and then allowed to stand at the same temperature for 24h. The reaction mixture was made alkaline with 25% aqueous ammonia solution and extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. The residue was purified by flash chromatography (25% EtOAc/hexane) to give **32** (3.29g, 95%) as a colorless oil. $[\alpha]_D^{25}$ -0.36° (c=0.44, $CHCl_3$). IR ($CHCl_3$): 3500, 1450, 1380, 1250, 1100, 1030, 840cm$^{-1}$. $^1$H NMR (400MHz, $C_6D_6$) δ: 0.07 (6H, s), 0.91 (3H, d, *J*=6.8Hz), 1.01 (9H, s), 1.08-1.24 (3H, m), 1.27 (3H, s), 1.35 (3H, s), 1.46-1.56 (2H, m), 1.58-1.76 (3H, m), 1.93 (1H, ddd, *J*=13.9, 8.1, 8.1Hz), 3.48 (1H, br s, OH), 3.57 (1H, dd, *J*=9.5, 3.7Hz), 3.58 (1H, t, *J*=6.8Hz), 3.70 (1H, m), 3.72 (1H, dd, *J*=9.5, 4.9Hz), 3.76 (1H, m), 3.77 (1H, br s, OH), 3.91 (1H, t, *J*=6.8Hz), 4.19 (2H, m), 4.31 (1H, quint, *J*=6.9Hz), 7.03-7.20 (6H, m), 7.68-7.73 (4H, m). $^{13}$C NMR (100MHz, $C_6D_6$) δ: -5.33, 12.71, 18.49, 19.88, 26.10, 30.27, 34.68, 41.09, 41.25, 43.54, 44.00, 64.10, 67.42, 69.39, 69.62, 70.20, 70.55, 75.87, 98.62, 110.15, 126.66, 127.77, 128.12, 128.41, 128.54, 143.57, 143.62. EIMS *m/z*: 599 ($M^+$- $CH_3$), 537 ($M^+$- $C_6H_5$). FABMS *m/z*: 615 ($MH^+$).

**(2*R*,4*R*,6*S*,8*R*,10*R*,11*S*)-12-[(*tert*-Butyldimethylsilyl)oxy]-1,2-O-diphenylmethylidene-4,6:8,10-bis-O-isopropylidene-11-methyldodecane-1,2,4,6,8,10-hexol (33).** A solution of **32** (3.29g, 5.36mmol), 2,2-dimethoxypropane (1.05ml, 8.58mmol), and pyridinium *p*-toluenesulfonate (67mg, 0.27mmol) in $CH_2Cl_2$ (27ml) was stirred at room temperature for 3h. After addition of triethylamine (1.0ml), the reaction mixture was concentrated to dryness. The residue was purified by flash chromatography (10% EtOAc/hexane) to give **33** (3.50g, 100%) as a colorless oil. $[\alpha]_D^{25}$ +8.38° (c=0.43, $CHCl_3$). IR ($CHCl_3$): 1450, 1380, 1260, 1180, 1100, 1030, 1000, 840cm$^{-1}$. $^1$H NMR (400MHz) δ: 0.01 (6H, s), 0.84 (3H, d, *J*=7.1Hz), 0.86 (9H, s), 1.16 (1H, q, *J*=12.2Hz), 1.25 (3H, s), 1.28 (3H, s), 1.32 (3H, s), 1.35 (3H, s), 1.46 (2H, m), 1.62 (2H, m), 1.64 (1H, t, *J*=7.8Hz), 1.70 (1H, ddd, *J*=13.9, 5.6, 5.6Hz), 1.80 (1H, ddd, *J*=13.9, 7.1, 7.1Hz), 2.03 (1H, ddd, *J*=13.9, 6.6, 6.6Hz), 3.50 (1H, dd, *J*=9.5, 4.6Hz), 3.57 (1H, dd, *J*=9.5, 5.1Hz), 3.73 (1H, t, *J*=7.3Hz), 3.75 (1H, m), 3.93 (3H, m), 4.09 (1H, t, *J*=7.3Hz), 4.28 (1H, quint, *J*=6.6Hz), 7.25-7.32 (6H, m), 7.44-7.49 (4H, m). $^{13}$C NMR (100MHz) δ: -5.48, 12.29, 18.25, 19.76,

24.60, 24.71, 25.89, 30.21, 33.51, 38.13, 39.01, 40.69, 42.25, 62.89, 63.63, 63.92, 65.70, 69.45, 69.76, 73.54, 98.25, 100.27, 109.27, 126.11, 127.89, 128.00, 128.10, 142.75. EIMS *m/z*: 639 ($M^+$- $CH_3$), 577 ($M^+$-$C_6H_5$). HRFABMS *m/z*: calcd for $C_{38}H_{59}O_7Si$ ($MH^+$): 655.4027; found: 655.4061

**(2*R*,4*R*,6*S*,8*R*,10*R*,11*S*)-12-[(*tert*-Butyldimethylsilyl)oxy]-4,6:8,10-bis-O-isopropylidene-11-methyldodecane-1,2,4,6,8,10-hexol (36).** The reaction was carried out in the same way as described for **29**, but employing **33** (3.50g, 5.35mmol), to give **36** (2.49g, 95%) as a colorless oil after purification by flash chromatography (70% EtOAc/hexane). $[\alpha]_D^{25}$ +15.2° (c=0.41, $CHCl_3$). IR ($CHCl_3$): 3500, 1390, 1260, 1100, 840cm$^{-1}$. $^1$H NMR (270MHz) δ: 0.02 (6H, s), 0.86 (3H, d, *J*=7.1Hz), 0.88 (9H, s), 1.17 (1H, q, *J*=12.4Hz), 1.35 (6H, s), 1.39 (6H, s), 1.40-1.57 (3H, m), 1.58-1.89 (5H, m), 2.32 (1H, br, OH), 3.45 (1H, br, OH), 3.52 (1H, dd, *J*=9.8, 4.7Hz), 3.57 (2H, m), 3.60 (1H, dd, *J*=9.8, 5.0Hz), 3.78 (1H, m), 3.91 (2H, m), 4.00 (1H, m), 4.09 (1H, m). $^{13}$C NMR (67.5MHz) δ: -5.48, 12.27, 18.25, 19.74, 24.76, 24.93, 25.88, 30.20, 33.54, 38.52, 38.63, 40.68, 42.17, 62.95, 63.92, 65.68, 66.51, 67.17, 69.46, 71.85, 98.28, 100.63. FABMS *m/z*: 491 ($MH^+$).

**(2*S*,4*R*,6*S*,8*R*,10*R*,11*S*)-12-[(*tert*-Butyldimethylsilyl)oxy]-1,2-epoxy-4,6:8,10-bis-O-isopropylidene-11-methyldodecane-4,6,8,10-tetrol (37).** A mixture of **36** (2.49g, 5.08mmol) and pivaloyl chloride (0.75ml, 6.10mmol) in pyridine (12ml) was stirred at 0°C for 30min and then MeOH (0.5ml) was added. After being stirred for 15min, the mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (18% EtOAc/hexane) gave a pivalate (2.61g, 90%). $[\alpha]_D^{25}$ +14.7° (c=0.43, $CHCl_3$). $^1$H NMR (400MHz) δ: 0.01 (6H, s), 0.85 (3H, d, *J*=7.1Hz), 0.86 (9H, s), 1.17 (1H, q, *J*=12.1Hz), 1.19 (9H, s), 1.32 (3H, s), 1.33 (3H, s), 1.37 (6H, s), 1.30-1.85 (9H, m), 3.45 (1H, br, OH), 3.50 (1H, dd, *J*=9.8, 4.4Hz), 3.59 (1H, dd, *J*=9.8, 5.0Hz), 3.77 (1H, m), 3.90-4.14 (6H, m). EIMS *m/z*: 559 ($M^+$-$CH_3$).

A solution of the pivalate (2.61g, 4.55mmol) and triethylamine (3.0ml, 22.75mmol) in $CH_2Cl_2$ (25ml) was cooled to 0°C and methanesulfonyl chloride (0.53ml, 6.82mmol) was added. After being stirred for 1h, MeOH (0.5ml) was added to the reaction mixture and the mixture was extracted with ether. The extract was washed with water and brine, dried, and concentrated to give a mesylate (2.97g, 100%). $^1$H NMR (400MHz) δ: 0.02 (6H, s), 0.86 (3H, d, *J*=7.1Hz), 0.88 (9H, s), 1.17 (1H, ddd, *J*=12.4, 11.7, 11.7Hz), 1.22 (9H, s), 1.32 (3H, s), 1.35 (6H, s), 1.39 (3H, s), 1.48 (2H, m), 1.58-1.73 (4H, m), 1.83 (1H, ddd, *J*=14.2, 7.1, 7.1Hz), 1.96 (2H, m), 3.05 (3H, s), 3.53 (1H, dd, *J*=9.7, 4.6Hz), 3.60 (1H, dd, *J*=9.7, 5.1Hz), 3.78 (1H, m), 3.91-4.03 (3H, m), 4.18 (1H, dd, *J*=12.7, 6.6Hz), 4.18 (1H, dd, *J*=12.7, 2.7Hz), 5.01 (1H, m).

The mesylate (2.97g, 4.55mmol) was dissolved in ether (25ml) and MeOH (5ml) and the solution was cooled to 0°C. To this stirred solution was added *t*-BuOK (666mg, 5.94mmol) and the slurry was stirred for 10min at 0°C and for 1h at room temperature. The mixture was extracted with ether, and the extract was washed with water and brine, dried, and concentrated. Purification by flash chromatography (16% EtOAc/ hexane) gave **37** (1.91g, 89%) as a colorless oil. $[\alpha]_D^{25}$ +1.24° (c=0.45, $CHCl_3$). IR ($CHCl_3$): 1470, 1380, 1260, 1180, 1100, 1030, 1000, 840cm$^{-1}$. $^1$H NMR (400MHz) δ: 0.01 (6H, s), 0.85 (3H, d, *J*=7.1Hz), 0.87 (9H, s), 1.16 (1H, q, *J*=12.2Hz), 1.33 (6H, s), 1.36 (3H, s), 1.38 (3H, s), 1.39-1.53 (3H, m), 1.64 (3H, m), 1.81 (2H, m), 2.48 (1H, dd, *J*=5.1, 2.9Hz), 2.77 (1H, t, *J*=5.1Hz), 3.03 (1H, m), 3.52 (1H, dd, *J*=9.8, 4.4Hz), 3.58 (1H, dd, *J*=9.8, 5.4Hz), 3.77 (1H, m), 3.95 (1H, m), 4.00 (1H, m), 4.04 (1H, m). $^{13}$C NMR (100MHz) δ: -5.49, 12.27, 18.23, 19.74, 24.72, 24.75, 25.86, 30.19, 33.52, 38.38, 39.10,

40.67, 42.23, 47.14, 49.44, 62.89, 63.91, 64.49, 65.69, 69.44, 98.24, 100.37. EIMS *m/z*: 457 ($M^+$- $CH_3$). HRFABMS *m/z*: calcd for $C_{25}H_{49}O_6Si$ ($MH^+$): 473.3296; found: 473.3362

**2*R*,6*S*,8*R*,10*R*,12R,14*R*,15*S*)-16-[(*tert*-Butyldimethylsilyl)oxy]-1,2-O-diphenylmethylidene-8,10:12,14-bis-O-isopropylidene-15-methylhexadecan-4-one-1,2,6,8,10,12,14-heptol (38).** The coupling reaction was carried out in the same manner as described for **31**, but employing (*R*)-**8** (1.73g, 4.84mmol), 1.6M *n*-BuLi in hexane (3.8ml, 6.04mmol), and **37** (1.91g, 4.03mmol), to give the product (3.26g, 97%) as a colorless oil. $[\alpha]_D^{25}$ +7.21° (c=0.46, $CHCl_3$). IR ($CHCl_3$): 3500, 1450, 1380, 1260, 1100cm$^{-1}$. $^1$H NMR (400MHz) δ: 0.03 (6H, s), 0.87 (3H, d, *J*=7.1Hz), 0.89 (9H, s), 1.18 (1H, q, *J*=12.0Hz), 1.32 (3H, s), 1.34 (3H, s), 1.36 (3H, s), 1.40 (3H, s), 1.36-1.68 (7H, m), 1.84 (1H, ddd, *J*=13.7, 7.1, 7.1Hz), 1.95 (2H, m), 2.10 (1H, br d, *J*=15.1Hz), 2.24 (1H, dd, *J*=15.4, 4.6Hz), 2.29 (1H, dd, *J*=15.1, 8.8Hz), 2.65 (1H, dd, *J*=15.4, 6.3Hz), 2.74-2.96 (4H, m), 3.33 (1H, d, *J*=4.2Hz, OH), 3.54 (1H, dd, *J*=9.5, 4.4Hz), 3.60 (1H, dd, *J*=9.5, 5.1Hz), 3.73 (1H, t, *J*=7.8Hz), 3.79 (1H, m), 3.98 (2H, m), 4.10 (1H, m), 4.20 (1H, m), 4.24 (1H, t, *J*=7.6Hz), 4.53 (1H, quint, *J*=6.3Hz), 7.27-7.36 (6H, m), 7.41-7.52 (4H, m). $^{13}$C NMR (100MHz) δ: -5.46, 12.29, 18.25, 19.77, 24.66, 24.75, 24.79, 25.89, 26.21, 26.33, 30.22, 33.52, 38.45, 40.72, 42.31, 43.30, 43.88, 46.76, 50.79, 63.00, 63.70, 63.94, 65.51, 65.75, 69.47, 70.81, 73.94, 98.25, 100.38, 109.68, 126.10, 126.14, 128.01, 128.08, 128.13, 128.19, 142.27, 142.36. FABMS *m/z*: 831 ($MH^+$).

Dedithioketalization was carried out in the same manner as described for **31**, but employing the product (959mg, 1.16mmol) obtained above, to give **38** (735mg, 86%) as a colorless oil after purification by flash chromatography (28% EtOAc/hexane). $[\alpha]_D^{25}$ +5.71° (c=0.28, $CHCl_3$). IR ($CHCl_3$): 3500, 1710, 1380, 1250, 1180, 1100, 1030, 840cm$^{-1}$. $^1$H NMR (270MHz) δ: 0.03 (6H, s), 0.86 (3H, d, *J*=7.1Hz), 0.89 (9H, s), 1.18 (1H, q, *J*=12.1Hz), 1.32 (3H, s), 1.35 (3H, s), 1.36 (3H, s), 1.40 (3H, s), 1.42-1.72 (11H, m), 1.83 (1H, ddd, *J*=13.4, 7.4, 7.4Hz), 2.60 (2H, d, *J*=6.1Hz), 2.64 (1H, dd, *J*=17.1, 7.1Hz), 3.04 (1H, dd, *J*=17.1, 6.4Hz), 3.17 (1H, d, *J*=4.0Hz, OH), 3.53 (1H, dd, *J*=9.3, 4.7Hz), 3.61 (1H, dd, *J*=9.8, 5.4Hz), 3.71 (1H, dd, *J*=8.1, 6.4Hz), 3.78 (1H, m), 3.97 (2H, m), 4.10 (1H, m), 4.23 (1H, dd, *J*=8.1, 6.7Hz), 4.28 (1H, m), 4.56 (1H, quint, *J*=6.4Hz), 7.28-7.36 (6H, m), 7.45-7.51 (4H, m). $^{13}$C NMR (100MHz) δ: -5.47, 12.29, 18.25, 19.77, 24.77, 25.88, 30.21, 33.54, 38.03, 40.70, 41.54, 42.26, 47.73, 50.16, 63.06, 63.74, 63.93, 64.69, 65.71, 69.46, 69.94, 72.35, 98.27, 100.42, 109.57, 126.04, 126.12, 128.08, 128.17, 142.09, 142.31, 208.71. HRFABMS *m/z*: calcd for $C_{48}H_{65}O_9Si$ ($MH^+$): 741.4344; found: 741.4359.

**(2*R*,4*R*,6*S*,8*R*,10*R*,12R,14*R*,15*S*)-16-[(*tert*-Butyldimethylsilyl)oxy]-1,2-O-diphenylmethylidene-8,10:12,14-bis-O-isopropylidene-15-methylhexadecane-1,2,4,6,8,10,12,14-octol (39).** The procedure for the preparation of **31** was employed with **38** (735mg, 0.99mmol) and $Me_4NBH(OAc)_3$ (2.61g, 9.93mmol), and purification by flash chromatography (35% EtOAc/hexane) gave **39** (597mg, 81%) as an oil. $[\alpha]_D^{25}$ +4.98° (c=0.95, $CHCl_3$). IR ($CHCl_3$): 3500, 1450, 1390, 1260, 1100, 1030, 840cm$^{-1}$. $^1$H NMR (270MHz) δ: 0.01 (6H, s), 0.86 (3H, d, *J*=7.1Hz), 0.89 (9H, s), 1.17 (1H, q, *J*=12.4Hz), 1.29 (1H, m), 1.33 (3H, s), 1.36 (6H, s), 1.40 (3H, s), 1.42-1.56 (2H, m), 1.58-1.97 (9H, m), 3.36 (1H, br, OH), 3.45 (1H, br, OH), 3.53 (1H, dd, *J*=9.8, 4.4Hz), 3.61 (1H, dd, *J*=9.8, 5.4Hz), 3.74 (1H, t, *J*=7.7Hz), 3.79 (1H, m), 3.98 (2H, m), 4.16 (1H, dd, *J*=7.7, 6.7Hz), 4.20 (3H, m), 4.39 (1H, m), 7.28-7.37 (6H, m), 7.44-7.52 (4H, m). $^{13}$C NMR (67.5MHz) δ: -5.44, 12.33, 18.31, 19.81, 24.85, 25.92, 30.27, 33.59, 37.82, 40.57, 40.75, 41.89, 42.34, 43.29, 63.18, 63.97, 64.47, 65.78, 65.98, 68.33, 69.50, 70.14, 76.17, 98.31, 104.48, 110.09, 126.12, 126.19, 128.15, 128.24, 142.19. FABMS *m/z*: 765 ($MNa^+$), 743 ($MH^+$).

**(2*R*,4*R*,6*S*,8*R*,10*R*,12R,14*R*,15*S*)-16-[(*tert*-Butyldimethylsilyl)oxy]-1,2-O-diphenylmethylidene-4,6:8,10:12,14-tris-O-isopropylidene-15-methylhexadecane-1,2,4,6,8,10,12,14-octol (6).** The procedure for the preparation of **33** was employed with **39** (456mg, 0.615mmol) and 2,2-dimethoxypropane (0.1ml, 0.81mmol), and purification by flash chromatography (15% EtOAc/hexane) gave **6** (447mg, 93%) as a colorless oil. $[\alpha]_D^{25}$ +16.0° (c=0.94, $CHCl_3$). IR ($CHCl_3$):1450, 1380, 1220, 1190, 1090, 1030, 840cm$^{-1}$. $^1$H NMR (400MHz) δ: 0.03 (6H, s), 0.87 (3H, d, *J*=7.3Hz), 0.89 (9H, s), 1.27 (3H, s), 1.30 (3H, s), 1.33 (6H, s), 1.35 (3H, s), 1.39 (3H, s), 1.45-1.67 (9H, m), 1.72(1H, ddd, *J*=14.4, 9.0, 9.0Hz), 1.83 (1H, ddd, *J*=13.7, 7.1, 7.1Hz), 2.05 (1H, ddd, *J*=13.7, 6.6, 6.6Hz), 3.53 (1H, dd, *J*=9.5, 4.4Hz), 3.60 (1H, dd, *J*=9.5, 5.1Hz), 3.76 (1H, t, *J*=7.6Hz), 3.78 (1H, m), 3.97 (5H, m), 4.12 (1H, t, *J*=7.3Hz), 4.30 (1H, quint, *J*=6.6Hz), 7.27-7.35 (6H, m), 7.47-7.52 94H, m). $^{13}$C NMR (100MHz) δ: -5.48, 12.29, 18.25, 19.74, 24.55, 24.73, 24.73, 24.82,25.89, 30.21, 33.51, 38.57, 38.69, 39.05, 40.70, 41.96, 42.34, 62.64, 62.67, 62.96, 63.72, 63.94, 65.75, 69.45, 69.78, 73.56, 98.24, 100.28, 100.35, 109.24, 126.08, 126.11, 127.88, 127.98, 128.10, 142.72. HRFABMS *m/z*: calcd for $C_{45}H_{71}O_9Si$ ($MH^+$): 783.4863; found, 783.4839.

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