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Stereochemical assignment of the C23–C35 portion of sphinxolide/reidispongiolide class of natural products by asymmetric synthesis

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Abstract—The absolute configuration of the seven stereogenic centers contained in the C23–C35 portion of reidispongiolide A is determined by asymmetric synthesis of the corresponding fragment obtained by ozonolysis of the natural macrolide.

1. Introduction

The sphinxolides[1] and reidispongiolides[2] are 26-membered lactones isolated in our laboratories from two New Caledonian marine sponges *Neosiphonia superstes* and *Reidispongia coerulea*. They exhibit an extraordinary in vitro activity against various human tumor cell lines and a potent actin-depolimerizating activity.[3] Other related natural products exhibiting the same mechanism of action include aplyronins,[4] scytophycins,[5] mycalolides,[6] ulapualides,[7] halichondramides[8] and kabiramides.[9] All the aforementioned macrolides of marine origin display a very similar 11-carbon, stereochemically complex, acyclic side chain with an *N*-methyl-*N*-formylamido end-group that seems to play a crucial role in determining the mode of action. We have elucidated the gross structure of members of sphinxolides and reidispongiolides by means of spectral data but the stereochemistry remained unassigned.

In the framework of a project devoted to the determination of the relative and absolute configuration of this interesting class of natural products, we have recently applied the *J*-based configurational analysis method[10] and we have assigned the relative configuration of the C7–C8, C10–C15, C24–C28 and C32–C34 subunits of sphinxolide.[11] Further, we have deduced the absolute stereochemistry of three stereogenic centers contained in the C17–C22 fragment of reidispongiolide by asymmetric synthesis of four possible diastereoisomers of the corresponding degradation fragment.[12]

Herein, we report the elucidation of the relative and of the absolute configuration of seven stereogenic centers contained in the C23–C35 portion of reidispongiolide A by comparison of the spectral data of synthetic compounds **3** and **4** with those of natural C23–C35 fragment **2** obtained by ozonolysis of reidispongiolide A (Fig. 1).

The application of the *J*-based configurational analysis method to sphinxolide disclosed the 24*S**,25*S**,26*S**, 27*S**,28*S** relative configuration for the C24–C28 subunit and the 32*R**,33*R** relative configuration for the C32–C33 subunit, leaving the total relative configuration and the absolute configuration of the sphinxolide side chain still undetermined. It is interesting to note that the relative stereochemistry of C24–C28 and C32–C33 subunits of the sphinxolide family determined by Murata's approach was identical to that established for the corresponding stereogenic centers in the aplyronine and scytophycin side chains. However, an unambigous determination of the relative stereochemistry of the sphinxolide side chain is necessary because recent studies[13] indicated that, despite the structural similarity,

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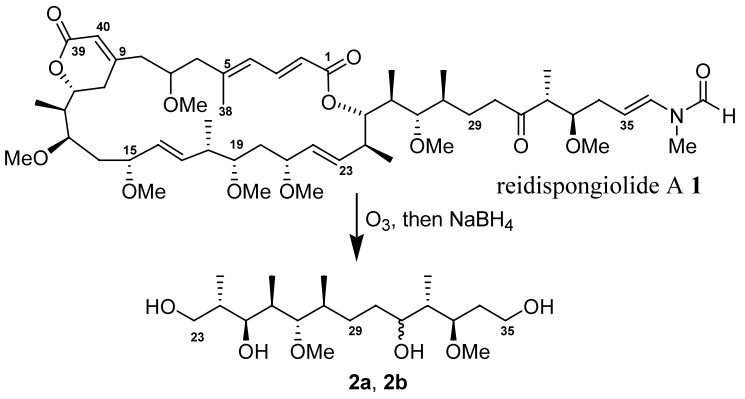


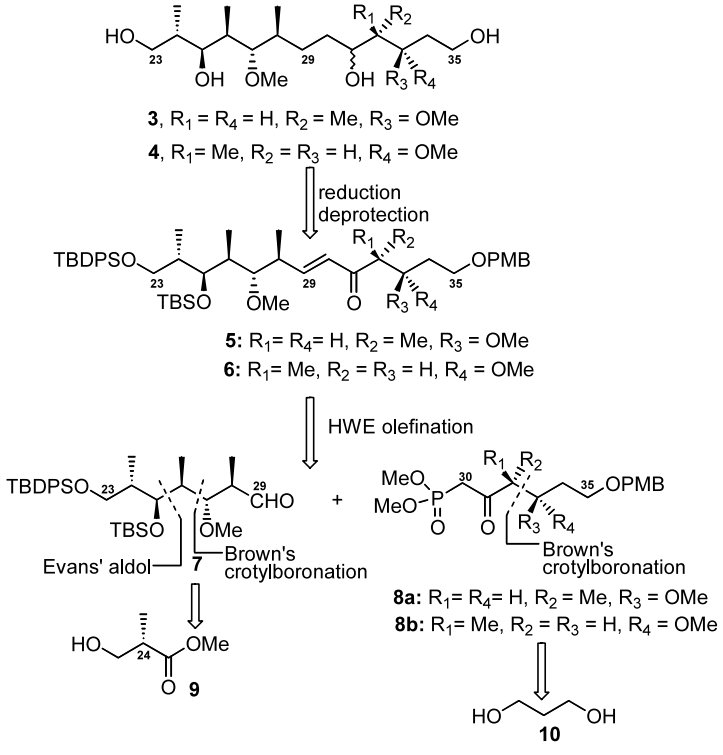
Figure 1. Structure of reidispongiolide A **1** and of the degradation fragments **2a** and **2b**.

the stereochemistry of C22–C26 region of mycalolides and ulapualides is enantiomeric with that of scytophycins and aplyronins, while identical in the C30–C33 region.

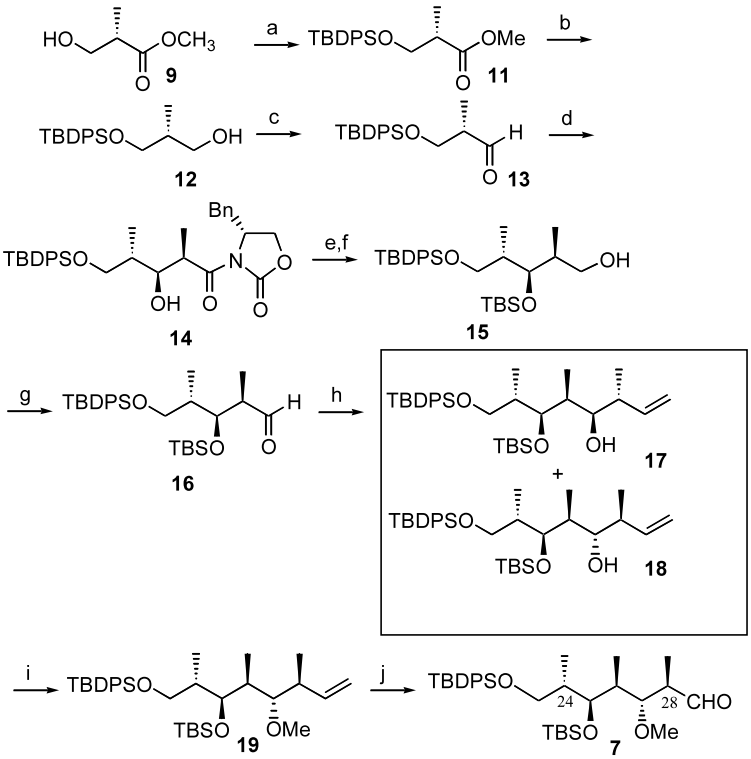
Therefore, in order to establish the relative stereochemistry between the C24–C28 and the C32–C33 parts in reidispongiolide **1** and to determine the absolute stereochemistry we have synthetized the two possible diastereoisomers **3a**–**b** and **4a**–**b** in a stereocontrolled manner for comparison with the natural fragments **2a** and **2b**.

2. Results and discussion

Our first disconnection, summarized in Scheme 1 involved cleavage of the C29–C30 bond leaving two subunits **7** and **8** to be coupled through a Horner–Wadsworth–Emmons coupling procedure. This approach, previously used for the construction of the side chain of halichondramides[14] and scytophycins[15] would allow a straightforward access to both diastereoisomers of the natural fragment **3** and **4** simply using the enantiomeric ketophosphonates **8a** and **8b**.



Scheme 1.



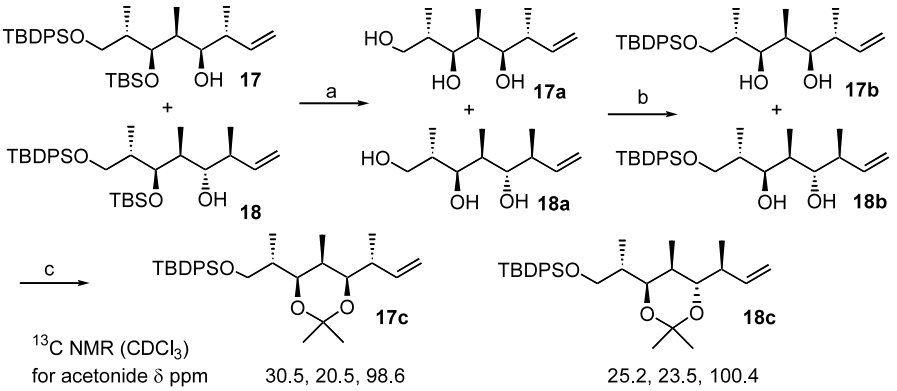
Scheme 2. *Reagents and conditions*: (a) TDPSCl, DMAP, Et_3N (99%); (b) $LiBH_4$, MeOH, 0°C (99%); (c) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, −78→0°C (95%); (d) Bu_2BOTf, *R*-4-benzyl-3-propionyloxazolidinone, −78°C, 1 h, then **13**, −78→−10°C, 2 h, 98%; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, (97%); (f) $LiBH_4$, MeOH, rt, (75%); (g) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, −78→0°C, (98%); (h) *tert*-BuOK, *trans*-2-butene, *n*-BuLi, −78→−45°C, (+)-Ipc_2BOMe, $BF_3{\cdot}OEt_2$, aldehyde **16**, −78°C, 8 h, NaOH, H_2O_2, overnight, rt (70%); (i) MeOTf, di-*t*-Bu-Pyr, (78%); (j) OsO_4, NMO acetone/H_2O 3:1, then H_5IO_6 (97%).

The synthetic strategy for accessing to aldehyde **7** relies upon Evans' aldol procedure to introduce C25–C26 stereocenters followed by a Brown's crotylboronation for the construction of C27–C28 propionate unit. Analogously Brown's crotylboronation was selected as key synthetic step to access to ketophosphonates **8a**–**b**.

The synthesis of aldehyde **7** commences with addition under Evans' condition of the boron enolate derived from (*R*)-4-benzyl-3-propionyloxazolidinone to protected aldehyde **13** easily prepared from commercially available methyl (2*S*)-3-hydroxy-2-methylpropionate **9** (Scheme 2).[16] The aldol adduct **14** was obtained in 98% yield (> 97% de)[17] and was converted to primary alcohol **15** after protection of the OH-function as its TBS ether followed by removal of the oxazolidinone auxiliary with $LiBH_4$ in MeOH (73% yield, two steps).

Primary alcohol **15** was submitted to oxidation under standard Swern condition and the unpurified aldehyde **16** was reacted with (+)-(*E*)-crotyldiisopinocampheylborane under Brown's condition to give a 7:3 diastereomeric mixture of homoallylic alcohols **17** and **18**.

The stereochemistry of the newly generated stereocenters in **17** and **18** was determined on the basis of the ^{13}C NMR analysis of 1,3 diol acetonides **17c** and **18c** derived from the 1,3 diols **17b** and **18b** (Scheme 3). Surprisingly, we



Scheme 3. *Reagents and conditions*: (a) MeOH/HCl, rt; (b) TDPSCl, Et_3N, DMAP, rt; (c) dimethoxypropane dry, *p*-TsOH (cat.).

found that the major distereoisomer **17** has a C25–C27 *syn* relationship based on the resonances 30.5 and 20.5 observed in the ^{13}C NMR spectrum of the acetonide **17c**.

Evidently, the existing chirality in the aldehyde **16** played a significant role in the asymmetric induction, which overrode the induction predicted for the Brown crotylboronation.[18] In spite of the observed undesired stereochemical outcome, we continued the synthetic sequence on the minor stereoisomer **18**, leaving the problem of the optimization of this unfavourable step until after the definition of the absolute stereochemistry of the C25–C35 region of reidispongiolide A.

Methylation of desired homoallylic alcohol **18** under mild conditions afforded **19** in 78% yield. Quantitative oxidative cleavage of the terminal double bond completed the synthesis of the C23–C29 aldehyde **7**.

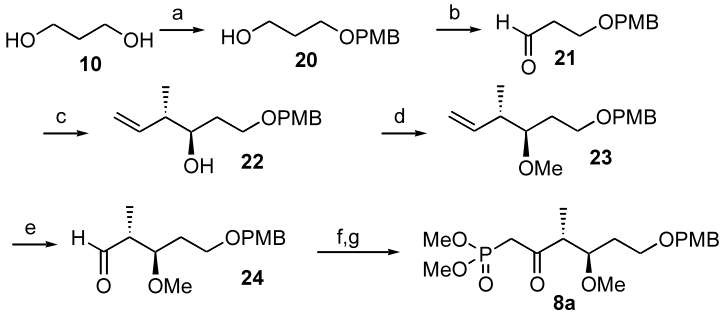
The two enantiomeric β-keto phosphonates **8a** and **8b**, required for the projected coupling reaction with aldehyde **7**, were obtained in a straightforward manner using the seven steps sequence depicted in Scheme 4 for the preparation of **8a**.[†]

Thus the monoprotected propane diol **20**[19] was oxidised to the aldehyde **21**. The homoallylic alcohol **22** was obtained (de >98%, ee 95%) through addition of (–)-(*E*)-crotyldiisopinocampheylborane to the above aldehyde. The diastereoisomeric purity of **22** was >98% as judged by the ^1H NMR spectra of the isolated homoallylic alcohol, whereas the enantiomeric excess and the absolute stereochemistry at C33 were determined by the application of the modified Mosher's method.

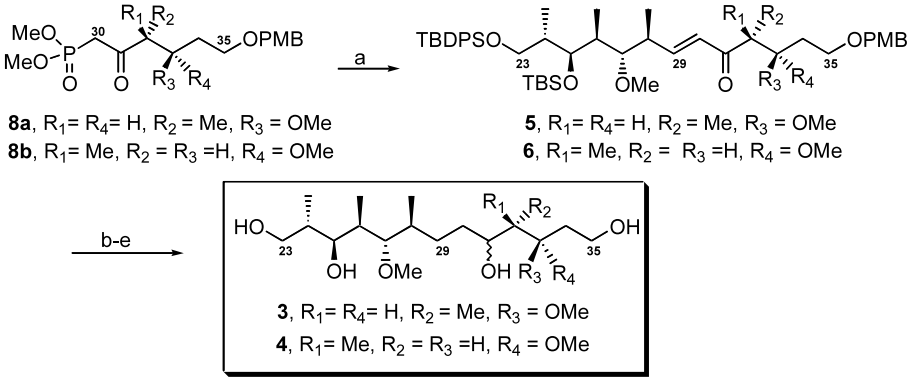
Methylation of the secondary hydroxy group (NaH, CH_3I, 80% yield) followed by oxidative cleavage of the terminal double bond, gave the aldehyde **24**.

Finally, treatment of **24** with methyl dimethylphosphonate in the presence of *n*BuLi, followed by oxidation of the resulting alcohol with PDC/DMF then produced the phosphonate **8a**.

A Wadsworth–Emmons coupling between aldehyde **7** and **8a** or **8b** using activated barium hydroxide[20] in wet THF as base next gave the *E*-alkene **5** and **6** in 76 and 78% yield, respectively (Scheme 5). Completion of the synthesis of the natural fragments **3** and **4** required a



Scheme 4. *Reagents and conditions*: (a) NaH, Bu_4NI, PMBCl, 0°C→rt (70%); (b) $(COCl)_2$, DMSO, TEA, CH_2Cl_2, –78→0°C, (99%); (c) *tert*-BuOK, *trans*-2-butene, *n*-BuLi, –78→–45°C, (–)-Ipc_2BOMe, $BF_3{\cdot}OEt_2$, aldehyde **21**, –78°C, 3 h, NaOH, H_2O_2, overnight, rt (70%); (d) NaH, CH_3I, THF (80%); (e) OsO_4, NMO, acetone/H_2O 3:1, then H_5IO_6 (95%); (f) $(MeO)_2POCH_3$, *n*BuLi, THF, –78°C (85%); (g) PDC, DMF (65%).



Scheme 5. *Reagents and conditions*: (a) activated $Ba(OH)_2$, then **7**, rt; (b) Pt(C), H_2, ethanol; (c) $NaBH_4$, MeOH, rt; (d) DDQ, CH_2Cl_2, rt; (e) MeOH/HCl, rt.

[†] The synthesis of **8b** from **10** was carried out under the same conditions except (+)-Ipc_2BOMe used instead of (–)-Ipc_2BOMe.

Table 1. ^{1}H NMR data for compounds **2**–**4** (CD_3OD, 500 MHz)

No.	**2a**[a]	**2b**[a]	**3a**	**3b**	**4a**	**4b**
23	3.77 dd (10.3, 5.1)	3.77 dd (10.3, 5.1)	3.77 dd (10.6, 5.2)	3.77 dd (10.3, 4.4)	3.77 dd (10.3, 5.1)	3.77 dd (10.3, 4.3)
	3.57 dd (10.3, 6.0)	3.57 dd (10.3, 6.0)	3.57 dd (10.6, 6.0)	3.57 dd (10.3, 5.9)	3.57 dd (10.3, 6.1)	3.57 dd (10.3, 6.0)
24	1.77 m	1.77 m	1.77 m	1.77 m	1.77 m	1.77 m
25	3.75 dd	3.75 dd	3.75 dd	3.75 dd	3.75 dd	3.75 dd
26	1.88 m	1.88 m	1.88 m	1.88 m	1.88 m	1.88 m
27	3.14 dd (6.9, 4.3)	3.14 dd (6.9, 4.3)	3.14 dd (7.0, 4.0)	3.14 dd (7.3, 4.4)	3.14 dd (7.7, 5.1)	3.15 dd (6.9, 4.3)
28	1.76 m	1.76 m	1.76 m	1.76 m	1.76 m	1.76 m
29	1.72 m, 1.14 m	1.62 m, 1.39 m	1.72 m, 1.14 m	1.62 m, 1.39 m	1.78 m, 1.14 m	1.78 m, 1.19 m
30	1.60 m, 1.40 m	1.76 m, 1.53 m	1.60 m, 1.40 m	1.76 m, 1.53 m	1.60 m, 1.40 m	1.81 m, 1.64 m
31	3.41 m	3.47 m	3.41 m	3.47 ddd (11.0, 8.1, 3.7)	3.41 m	3.43 m
32	1.72 m	1.97 m	1.72 m	1.97 m	1.75 m	1.94 m
33	3.74 m	3.63 m	3.74 m	3.63 m	3.70 m	3.63 m
34	1.86 m, 1.65 m	1.86 m, 1.65 m	1.86 m, 1.65 m	1.86 m, 1.65 m	1.86 m, 1.70 m	1.78 m, 1.60 m
35	3.70 m	3.70 m	3.70 m	3.70 m	3.70 m	3.70 m
Me-24	0.87 d (6.6)	0.87 d (6.6)	0.87 d (6.8)	0.87 d (7.3)	0.87 d (6.9)	0.87 d (7.6)
Me-26	0.92 d (6.7)	0.92 d (6.7)	0.92 d (7.0)	0.92 d (6.6)	0.92 d (7.1)	0.92 d (6.9)
Me-28	1.03 d (6.6)	1.03 d (6.6)	1.03 d (6.9)	1.03 d (6.9)	1.03 d (6.9)	1.04 d (6.9)
Me-32	0.92 d (6.7)	0.85 d (6.7)	0.92 d (6.7)	0.85 d (6.6)	0.93 d (7.1)	0.86 d (6.9)
OMe-27	3.54 s	3.54 s	3.54 s	3.54 s	3.54 s	3.55 s
OMe-33	3.42 s	3.36 s	3.42 s	3.36 s	3.41 s	3.38 s

[a] Assignment was inferred from 2D-COSY experiment

four-step sequence involving: a) catalytic hydrogenation of the double bond (Pt/C, H_2); b) $NaBH_4$ reduction of carbonyl at C31 position; c) oxidative cleavage of thePMB group; d) complete removal of the silyl protecting groups.

NMR data of both epimers at C-31 of the synthetic triol **3** were superimposable with those of the corresponding fragments derived from the natural reidispongiolide, whereas small but significant differences were observed for some protons in **4** when compared with the natural fragments **2a** and **2b** as shown in Tables 1 and 2. In particular, the NMR data of the two C31 epimers of the compound **4** differed in the chemical shifts for the OMe at C33, for the methyl groups at C28 and C32 and for the resonances of the C30 methylene protons.

The absolute configuration of the C23–C35 segment of reidispongiolides/sphinxolides was then determined through Mosher's analysis.[‡] The C23,C35-di-Mosher esters were prepared from the natural fragment **2b**. Importantly, the ^{1}H NMR spectra of C23,C35-di-(*S*)-Mosher ester and C23,C35-di-(*R*)-Mosher ester were distinctly different. The synthetic fragment **3** was then converted to the corresponding C23,C35-di-(*S*)-Mosher ester, and its ^{1}H NMR spectrum was found to be superimposable on the ^{1}H NMR spectrum of the natural C23,C35-di-(*S*)-Mosher ester, thereby establishing the absolute configuration of the C23–C35 portion of

Table 2. ^{13}C NMR data for compounds **2** and **3** (CD_3OD, 125 MHz)

No.	**2a**[a,b]	**2b**[a,b]	**3b**	**4b**
23	67.2	67.2	67.2	67.0
24	39.6	39.6	39.6	39.7
25	73.7	73.7	73.7	74.3
26	37.7	37.7	37.7	37.7
27	91.0	91.0	91.0	90.8
28	36.6	36.6	36.6	36.8
29	27.7	27.7	27.7	27.9
30	33.9	33.2	33.2	33.5
31	73.1	74.4	74.4	74.6
32	42.0	41.7	41.7	41.9
33	81.8	80.7	80.7	80.6
34	33.6	33.6	33.6	33.8
35	60.4	60.4	60.4	60.4
Me-24	13.7	13.7	13.7	13.7
Me-26	10.0	10.4	10.4	10.4
Me-28	17.4	17.4	17.4	17.7
Me-32	10.0	10.7	10.7	10.5
OMe-27	62.1	62.1	62.1	62.1
OMe-33	57.0	57.0	57.0	57.1

[a] Assignment based on analysis of HMQC and HMBC data.
[b] In the original paper (see ref. 12) the ^{13}C NMR values for natural fragments **2a** and **2b** were inferred from HMBC experiments and are not correct for calibration problems. The revised values are reported in the table.

[‡] The $[\alpha]_D$ value of synthetic fragment was found to be of the same sign and similar absolute value [synthetic $[\alpha]_D = +5.0$ (*c* 0.5), natural $[\alpha]_D = +3.6$ (*c* 0.4)]. However, we were concerned that the value might be too small to draw an unambiguous conclusion.

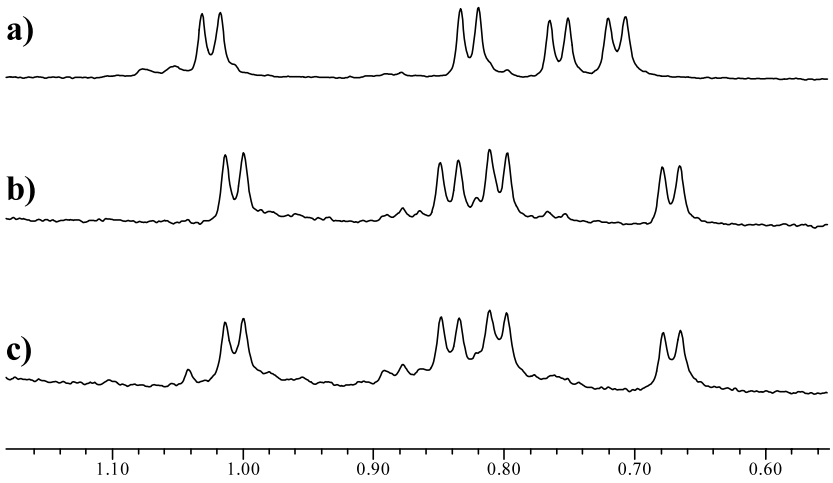


Figure 2. The methyl region of ^{1}H NMR (500 MHz, $CDCl_3$) of di-Mosher esters. (a) Di-(*R*)-Mosher ester derived from the natural C23–C35 fragment **2b**. (b) Di-(*S*)-Mosher ester derived from the natural C23–C35 fragment **2b**. (c) Di-(*S*)-Mosher ester derived from the synthetic C23–C35 fragment **3b**.

reidispongiolide A to be the same of the synthetic fragment **3** (Fig. 2).

3. Conclusion

In conclusion, the stereochemistry of the C23–C35 portion of reidispongiolide A was unambiguously determined as 24*S*,25*S*,26*S*,27*S*,28*S*,32*R*,33*R* by enantioselective synthesis and Mosher's analysis.

4. Experimental

NMR spectra were obtained on a Bruker AMX 500 MHz recorded in $CDCl_3$ ($\delta_H = 7.26$ and $\delta_C = 77.0$ ppm) and CD_3OD ($\delta_H = 3.30$ and $\delta_C = 49.0$ ppm). J are in hertz and chemical shifts (δ) are reported in ppm and referred to $CHCl_3$ and CHD_2OD as internal standards. Where ^{1}H NMR data for a mixture of diasteroisomers is presented, an asterix (*) follows the assignment of a resolved resonance that correspond to a proton of the minor diasteroisomer. Where ^{13}C NMR data for a mixture of diasteroisomers is presented, resolved resonances that correspond to the minor diasteroisomer are indicated in brackets. FAB MS spectra were obtained with glycerol as matrix on a VG Prospec (Fisons) mass spectrometer. Optical rotations were measured with a Perkin–Elmer 141 polarimeter operating at 589 nm. Infrared (IR) spectra were recorded on a Bruker IFS 48 FT-IR apparatus and only selected and characteristic IR absorption data are provided for each compound. Methyl (2*S*)-(+)-3-hydroxy-2-methylpropionate was purchased from Fluka. Solvents and reagents were used as supplied from commercial sources with the following exceptions. Tetrahydrofuran, toluene, dichloromethane and triethylamine were distilled from calcium hydride immediately prior to use. All reactions were monitored by TLC on silica gel plates (Machery, Nagel). Crude products were purified by column chromatography on silica gel 70–230 mesh. All reactions were carried out under argon atmosphere using flame-dried glassware.

14.1. (4*R*,2′*R*,3′*S*,4′*S*)-4-Benzyl-3-(5′-*tert*-butyldiphenylsilyloxy-3′-hydroxy-2′,4′-dimethylpentanoyl)-2-oxazolidinone 14

Bu_2BOTf (13.4 mL, 1 M in CH_2Cl_2, 13.4 mmol) and Et_3N (2.3 mL, 16.8 mmol) were added to a solution of (*R*)-4-benzyl-3-propionyloxazolidinone (3.1 g, 13.4 mmol) in dry dichloromethane (70 mL) at −78°C under argon and the resulting pale yellow solution was stirred for 1 h at −78°C and then at 0°C for 30 min before being re-cooled to −78°C. A solution of the aldehyde **13** (4.0 g, 12.2 mmol) in dry CH_2Cl_2 was cannulated to the solution which was stirred at −78°C for 1 h and then warmed to −10°C, stirred for 1 h and then quenched with pH 7 potassium phosphate monobasic-sodium hydroxide buffer (14 ml). A solution of 30% H_2O_2 in MeOH (1:2, 32 ml) was added to the mixture that was stirred overnight at room temperature and concentrated. The residue was diluted with CH_2Cl_2 and the resulting layers separated. The aqueous phase was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$, water, and brine. The organic phase was then dried (Na_2SO_4), concentrated, chromatographed on silica gel (8:2 *n*-hexane:ethyl acetate) to give **14** (6.8 g, 98%) as a colorless oil. $[\alpha]_D^{24} = -25.3$ (*c* 16, $CHCl_3$); IR (thin film): 3690, 1790, 1695 cm^{-1}; HR FABMS *m*/*z* 560.2812 $(M+H)^+$, calcd for $C_{33}H_{42}NO_5Si$: 560.2832; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.91 (3H, d, $J = 6.9$ Hz, CH_3-4′); 1.07 (9H, s, *t*Bu-Si); 1.29 (3H, d, $J = 6.7$ Hz, CH_3-2′); 1.88 (1H, m, H-4′), 2.79 (1H, m, CH_2-Bn); 3.31 (1H, dt, $J = 2.6$ and 12.8 Hz, CH_2-Bn); 3.73 (1H, dd, $J = 6.0$ and 10.3 Hz, H-5′a); 3.82 (1H, dd, $J = 4.3$ and 10.3 Hz, H-5′b); 3.99 (2H, m, H-2′ and H-3′); 4.18 (2H, m, H-5); 4.70 (1H, m, H-4); 7.20–7.44 (11H, m, Ph); 7.65 (4H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 9.4, 13.2, 19.3, 26.9 (3C), 37.7, 40.6, 53.4, 55.6, 66.2, 68.4, 75.0, 127.2, 127.7 (4C), 128.9 (2C), 129.4 (2C), 129.7 (2C), 133.2, 135.4 (2C), 135.6 (4C), 153.1, 176.4.

4.2. (4*R*,2′*R*,3′*S*,4′*S*)-4-Benzyl-3-(5′-*tert*-butyldiphenylsilyloxy-3′-*tert*-butyldimethylsilyloxy-2′,4′-dimethylpentanoyl)-2-oxazolidinone

2,6-Lutidine (3.5 mL, 24.3 mmol) and TBSOTf (3.0 mL, 12.1 mmol)) were added sequentially to a solution of the alcohol **14** (3.4 g, 6.1 mmol) in dry CH_2Cl_2 at 0°C under argon atmosphere. The mixture was allowed to warm at room temperature where stirring was continued for 2 h. Saturated $NaHCO_3$ was added and the organic phase was washed with water, dried ($MgSO_4$) and then concentrated in vacuo. Purification by column chromatography on silica gel using *n*-hexane:ethyl acetate (98:2) as eluent gave the silyl ether as a colorless oil (4.0 g, 97% yield). $[\alpha]_D^{24} = -37.3$ (*c* 5, $CHCl_3$); IR (thin film): 1789, 1700, 1200, 1100 cm^{-1}; HR FABMS *m*/*z* 674.3679 $(M+H)^+$, calcd for $C_{39}H_{56}NO_5Si_2$: 674.3697; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): −0.1 (3H, s, CH_3-Si); 0.03 (3H, s, CH_3-Si); 0.82 (9H, s, *t*Bu-Si); 1.03 (3H, d, $J=7.1$ Hz, CH_3-4′); 1.04 (9H, s, *t*Bu-Si); 1.20 (3H, d, $J=6.7$ Hz, CH_3-2′); 1.96 (1H, m, H-4′); 2.72 (1H, m, CH_2-Bn); 3.33 (1H, dt, $J=2.6$ and 12.8 Hz, CH_2-Bn); 3.73 (1H, dd, $J=6.0$ and 10.3 Hz, H-3′a); 3.95 (2H, H-5′a and H2′); 4.08 (2H, m, H-5′b and H-5a); 4.18 (1H, m, H-5b); 4.45 (1H, m, H-4); 7.18–7.41 (11H, m, Ph); 7.64 (4H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): −4.6, −3.2, 8.2, 13.4, 18.1, 19.2, 25.8 (3C), 26.9 (3C), 37.5, 40.9, 41.9, 55.6, 65.9, 66.1, 73.7, 127.3, 127.7 (4C), 128.9 (2C), 129.4 (2C), 129.5 (2C), 132.9, 135.4 (2C), 135.6 (4C), 152.8, 175.5.

4.3. (2*S*,3*R*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylpentanol 15

Dry methanol (567 μl, 17.7 mmol) and $LiBH_4$ (8.85 mL, 2 M in THF, 17.7 mmol) were added to a solution of the previous silyl alcohol (4.0 g, 5.9 mmol) in dry THF at 0°C under argon and the resulting mixture was stirred for 1 h at 0°C. The mixture was quenched by addition of NaOH (1 M, 11.8 mL) and then allowed to warm to room temperature. Ethyl acetate was added and the separated aqueous phase was extracted with ethyl acetate (3×30 mL). The combined organic phases were washed with water, dried (Na_2SO_4) and concentrated. Purification by silica gel (*n*-hexane:ethyl acetate 85:15) gave the alcohol **15** as a colorless oil (2.2 g, 75%). $[\alpha]_D^{24} = +0.6$ (*c* 15, $CHCl_3$); IR (thin film): 3630, 3520, 1200, 1100 cm^{-1}; HR FABMS *m*/*z* 501.3232 $(M+H)^+$, calcd for $C_{29}H_{49}O_3Si_2$: 501.3220; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): −0.1 (3H, s, CH_3-Si); 0.03 (3H, s, CH_3-Si); 0.82 (9H, s, *t*Bu-Si); 0.86 (3H, d, $J=6.7$ Hz, CH_3-2), 0.95 (3H, d, $J=6.9$ Hz, CH_3-4), 1.08 (9H, s, *t*Bu-Si); 1.84 (1H, m, H-2); 1.99 (1H, m, H-4); 3.43 (2H, m, H-1); 3.51 (1H, dd, $J=6.0$ and 9.5 Hz, H-5a); 3.78 (2H, m, H-5b and H-3); 7.41 (6H, m, Ph); 7.64 (4H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): −4.4, −4.2, 11.7, 14.0, 18.2, 19.2, 25.9 (3C), 26.9 (3C), 38.6, 40.4, 66.5, 66.6, 74.2, 127.6 (4C), 129.6 (2C), 133.8 (2C), 135.6 (4C).

4.4. (2*R*,3*S*,4*S*)-3-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)-2,4-dimethylpentanal 16

A solution of DMSO (1.1 mL, 16 mmol) in dry dichloromethane (50 mL) was cooled at −78°C and oxalyl chloride (698 μL, 8 mmol) was added dropwise over 15 min. After 30 min a solution of the alcohol **15** (2.0 g, 4 mmol) in dry CH_2Cl_2 was added via cannula and the mixture was stirred at −78°C for 1 h. Et_3N (2.8 mL, 20 mmol) was added dropwise and the mixture was allowed to warm to room temperature. The reaction was quenched by addition of aqueous $NaHSO_4$ (1 M, 50 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with $NaHSO_4$, water, saturated aqueous $NaHCO_3$, and brine. The organic phase was then dried, concentrated to give the corresponding aldehyde **16** (1.95 g, 98%) as a colorless oil which was used immediately without any further purification. HR FABMS *m*/*z* 499.3078 $(M+H)^+$, calcd for $C_{29}H_{47}O_3Si_2$: 499.3064; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): −0.06 (3H, s, CH_3-Si); −0.04 (3H, s, CH_3-Si); 0.81 (9H, s, *t*Bu-Si); 0.92 (3H, d, $J=6.7$ Hz, CH_3-4); 1.08 (9H, s, *t*Bu-Si); 1.09 (3H, d, $J=6.9$ Hz, CH_3-2), 1.99 (1H, m, H-4); 2.50 (1H, m, H-2); 3.50 (1H, dd, $J=6.8$ and 10.3 Hz, H-5a); 3.71 (1H, dd, $J=6.0$ and 10.3 Hz, H-5b); 4.2 (1H, br dd, $J=6.1$ Hz); 7.41 (6H, m, Ph); 7.70 (4H, m, Ph), 9.70 (1H, s, H-1); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): −4.4, −4.2, 8.2, 13.4, 18.1, 19.2, 25.8 (3C), 26.9 (3C), 40.9, 49.6, 65.9, 71.8, 127.4 (4C), 129.5 (2C), 133.9 (2C), 135.9 (4C), 205.0.

4.5. (3*S*,4*S*,5*S*,6*S*,7*S*)-6-(*tert*-Butyldimethylsilyloxy)-8-(*tert*-butyldiphenylsilyloxy)-3,5,7-trimethyl-1-octen-4-ol 18

To a cloudy solution of potassium *tert*-butoxide (4.8 mL, 1 M in THF, 4.8 mmol) and *trans*-2-butene (excess) in THF (2 mL) at −78°C was added dropwise *n*BuLi (3 mL, 1.6 M in hexane, 4.8 mmol). The resulting yellow mixture was allowed to stir at −45°C for 20 min. The reaction mixture was recooled to −78°C and a solution of (+)-*B*-methoxydiisopinocampheylborane (1.85 g, 5.8 mmol) in THF (1 mL) was added. The resulting colorless reaction mixture was stirred at −78°C for 35 min. $BF_3{\cdot}Et_2O$ (715 mL, 5.8 mmol) was added rapidly followed immediately by a solution of the crude aldehyde **16** (1.04 g, 2.09 mmol) in THF (2.5 mL). The resulting cloudy reaction was stirred at −78°C for 4 h. The reaction was quenched by addition of 3N aqueous NaOH (5 mL) followed by 30% aqueous H_2O_2 (5 mL). The reaction mixture was warmed to 25°C and stirred overnight. The mixture was diluted with ethyl acetate and saturated aqueous NaCl. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic extracts were dried ($MgSO_4$) and then concentrated in vacuo. Purification by silica gel (*n*-hexane:ethyl acetate 994:6) gave the mixture of homoallylic alcohols **17** and **18** (810 mg, 70%).

The mixture was separated by HPLC chromatography performed on a Macherey-Nagel Nucleosil column (3.9 mm i.d.×30 cm) with a 99.5% hexane/ethyl acetate solvent as eluent to obtain 600 mg of pure **17** and 220 mg of pure **18**.

Data for **17**: $[\alpha]_D^{24}=-3.8$ (*c* 3, $CHCl_3$); IR (thin film): 3375, 2930, 1640, 1230, 1089 cm^{-1}; HR FABMS *m*/*z* 555.3695 $(M+H)^+$, calcd for $C_{33}H_{55}O_3Si_2$: 555.3690; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): −0.09 (3H, s, CH_3-Si); 0.01 (3H, s, CH_3-Si); 0.93 (9H, s, *t*Bu-Si); 0.99 (6H, d, $J=6.6$ Hz, CH_3-5 and CH_3-7), 1.05 (3H, d, $J=6.9$ Hz, CH_3-3), 1.15 (9H, s, *t*Bu-Si); 1.88 (1H, m, H-7); 2.17 (1H, m, H-5); 2.37 (1H, m, H-3); 3.43 (1H, dd, $J=3.7$ and 5.9 Hz, H-4); 3.59 (1H, t, $J=9.6$ Hz H-8a); 3.81 (1H, dd, $J=9.6$, 6.6 Hz, H-8b); 3.98 (1H, t, $J=4.4$ Hz, H-6); 5.12 (1H, s, H-1a); 5.15 (1H, d, $J=5.9$ Hz, H-1b); 5.84 (1H, m, H-2); 7.41 (6H, m, Ph); 7.68 (4H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ −4.0, −3.7, 9.1, 13.9, 16.8, 18.3, 19.2, 26.2 (3C), 27.0 (3C), 37.5, 40.9, 41.8, 66.2, 76.1, 76.5, 115.6, 127.6 (4C), 129.5 (2C), 133.8 (2C), 135.6 (4C), 141.0.

Data for **18**: $[\alpha]_D^{24}=-4.1$ (*c* 7, $CHCl_3$); IR (thin film): 3350, 2950, 1640, 1230, 1100 cm^{-1}; HR FABMS *m*/*z* 555.3679 $(M+H)^+$, calcd for $C_{33}H_{55}O_3Si_2$: 555.3690; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): −0.1 (3H, s, CH_3-Si); 0.02 (3H, s, CH_3-Si); 0.77 (9H, s, *t*Bu-Si); 0.78 (3H, d, $J=6.7$ Hz, CH_3-7), 0.96 (3H, d, $J=6.9$ Hz, CH_3-5), 1.06 (9H, s, *t*Bu-Si); 1.08 (3H, d, $J=6.9$ Hz, CH_3-8), 1.71 (1H, m, H-7); 2.04 (1H, m, H-5); 2.29 (1H, m, H-3); 3.43 (1H, t, $J=8.8$ Hz, H-4); 3.76 (2H, m, H-8a and H-6); 3.87 (1H, dd, $J=10.3$, 5.1 Hz, H-8b); 5.01 (1H, d, $J=10$ Hz, H-1a); 5.05 (1H, d, $J=4.5$ Hz, H-1b); 5.88 (1H, m, H-2); 7.41 (6H, m, Ph); 7.64 (4H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): −4.4, −4.2, 12.4, 15.1, 17.9, 18.1, 19.2, 25.8 (3C), 26.9 (3C), 39.6, 40.3, 40.6, 66.8, 76.6, 77.0, 115.3, 127.5 (4C), 129.5 (2C), 134.6 (2C), 135.6 (4C), 139.0.

4.6. (3*S*,4*S*,5*S*,6*S*,7*S*)-4-*O*-Methyl-6-*O*-(*tert*-butyldimethylsilyl)-8-*O*-(*tert*-butyldiphenylsilyl)-3,5,7-trimethyl-1-octen-4,6,8-triol 19

2,6-Di-*tert*-butylpyridine (1.8 ml, 8.1 mmol) and methytrifluoromethansulfonate (888 μl, 8.1 mmol) were added sequentially to a solution of alcohol **18** (150 mg, 0.27 mmol) in CH_2Cl_2 at 0°C under argon atmosphere. The mixture was allowed to warm at room temperature where stirring was continued for 14 h. Saturated $NaHCO_3$ was added and the organic phase was washed with water, dried ($MgSO_4$) and then concentrated in vacuo. Purification by column chromatography on silica using *n*-hexane:ethyl acetate (998:2) as eluent gave the methyl ether **19** (120 mg, 78%) as a colorless oil. $[\alpha]_D^{24}=+10.9$ (*c* 1.4, $CHCl_3$); IR (thin film): 2930, 1640, 1463, 1255, 1094, 835 cm^{-1}; HR FABMS *m*/*z* 569.3858 $(M+H)^+$, calcd for $C_{34}H_{57}O_3Si_2$: 569.3846; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): −0.05 (3H, s, CH_3-Si); 0.04 (3H, s, CH_3-Si); 0.74 (3H, d, $J=6.9$ Hz, CH_3-5); 0.82 (9H, s, *t*Bu-Si); 0.89 (3H, d, $J=6.9$ Hz, CH_3-7), 1.05 (9H, s, *t*Bu-Si); 1.11 (3H, d, $J=6.9$ Hz, CH_3-3), 1.70 (1H, m, H-5); 1.87 (1H, m, H-7); 2.46 (1H, m, H-3); 2.93 (1H, dd, $J=8.6$, 1.7 Hz, H-4); 3.39 (1H, dd, $J=10.3$, 7.7 Hz H-8a); 3.41 (3H, s, OCH_3); 3.72 (1H, dd, $J=10.3$, 6.0 Hz, H-8b); 3.96 (1H, d, $J=6.0$ Hz, H-6); 4.99 (1H, s, H-1a); 5.01 (1H, d, $J=5.1$ Hz, H-1b); 5.88 (1H, m, H-2); 7.39 (6H, m, Ph); 7.67 (4H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): −4.4, −3.6, 11.3, 13.6, 18.0, 18.4, 19.2, 26.1 (3C), 26.9 (3C), 38.6, 39.8, 42.6, 60.3, 66.4, 72.6, 87.2, 114.2, 127.5 (4C), 129.4 (2C), 134.0, 134.1, 135.7 (4C), 140.4.

4.7. (2*R*,3*R*,4*S*,6*S*,7*S*)-5-(*tert*-Butyldimethylsilyloxy)-7-(*tert*-butyldiphenylsilyloxy)-3-methoxy-2,4,6-trimethylheptanal 7

To a solution of alkene **19** (120 mg, 0.21 mmol) in acetone/water (8:1, 2 mL) at room temperature was added OsO_4 (30 μl, 0.0042 mmol) followed, after 10 min, by NMO (30 mg, 0.25 mmol). The mixture was stirred overnight, and H_5IO_6 (95 mg, 0.42 mmol) was added. After 30 min the resulting mixture was extracted with ethyl acetate and the organic layer was washed with water, brine, dried (Na_2SO_4), filtered and concentrated to afford aldehyde **7** (116 mg, 97%) that was used for the next step without further purification. HR FABMS *m*/*z* 571.3650 $(M+H)^+$, calcd for $C_{33}H_{55}O_4Si_2$: 571.3639; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): −0.04 (3H, s, CH_3-Si); 0.05 (3H, s, CH_3-Si); 0.70 (3H, d, $J=6.9$ Hz, CH_3-4); 0.83 (9H, s, *t*Bu-Si); 0.89 (3H, d, $J=6.9$ Hz, CH_3-6), 1.06 (9H, s, *t*Bu-Si); 1.14 (3H, d, $J=6.9$ Hz, CH_3-2), 1.89 (2H, m, H-4 and H-6); 2.73 (1H, m, H-2); 3.34 (3H, s, OCH_3); 3.43 (2H, m, H-3 and H-7a); 3.69 (1H, dd, $J=10.3$, 5.2 Hz, H-7b); 4.06 (1H, d, $J=6.1$ Hz, H-5); 7.37 (6H, m, Ph); 7.67 (4H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): −3.9, 9.8, 11.3, 13.2, 18.4, 19.2, 26.0 (3C), 26.8 (3C), 37.7, 42.3, 47.8, 58.2, 66.3, 72.0, 84.2, 127.5 (4C), 129.5 (2C), 133.9 (2C), 135.6 (4C), 203.8.

4.8. 3-(4′-Methoxybenzyloxy)propanal 21

A solution of DMSO (1.7 mL, 24 mmol) in dry dichloromethane (40 mL) was cooled at −78°C and oxalyl chloride (2 M in CH_2Cl_2, 6 mL, 12 mmol) was added dropwise over 15 min. After 30 min a solution of the alcohol **20** (1.2 g, 6 mmol) in dry CH_2Cl_2 was added via cannula and the mixture was stirred at −78°C for 1 h. Et_3N (4.2 mL, 30 mmol) was added dropwise and the mixture was allowed to warm to room temperature. The reaction was quenched by addition of aqueous $NaHSO_4$ (1 M, 40 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×40 mL). The combined organic layers were washed with $NaHSO_4$, water, saturated aqueous $NaHCO_3$, and brine. The organic phase was then dried, concentrated to give the corresponding aldehyde **21** (1.15 g, 99%) as a colorless oil which was used immediately without any further purification. HR FABMS *m*/*z* 195.1040 $(M+H)^+$, calcd for $C_{11}H_{15}O_3$: 195.1021; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 2.65 (2H, t, $J=7.0$ Hz, H-2); 3.74 (2H, overlapped, H-3); 3.76 (3H, s, OCH_3); 4.45 (2H, s, $ArCH_2O$-); 6.85 (2H, d, $J=8.5$ Hz, ArH); 7.32 (2H, d, $J=8.5$ Hz, ArH); 9.73 (1H, s, H-1).

4.9. (3*R*,4*S*)-1-(4′-Methoxybenzyloxy)-4-methyl-5-hexen-3-ol 22

To a cloudy solution of potassium *tert*-butoxide (8.8 mL, 1 M in THF, 8.8 mmol) and *trans*-2-butene (excess) in THF (2 mL) at −78°C was added dropwise *n*BuLi (5.5 mL, 1.6 M in hexane, 8.8 mmol). The resulting yellow mixture was allowed to stir at −45°C for 20 min. The reaction mixture was recooled to −78°C and a solution of (−)-*B*-methoxydiisopinocampheylborane (3.6 g, 11.4 mmol) in THF (1 mL) was added. The resulting colorless reaction mixture was stirred at −78°C for 35 min. $BF_3{\cdot}Et_2O$ (1.4 mL, 11.33 mmol) was added rapidly followed immediately by a solution of the crude aldehyde **21** (1.0 g, 5.2 mmol) in THF (2.5 mL). The resulting cloudy reaction was stirred at −78°C for 4 h. The reaction was quenched by addition of 3N aqueous NaOH (30 mL) followed by 30% aqueous H_2O_2 (30 mL). The reaction mixture was warmed to 25°C and stirred overnight. The mixture was diluted with ethyl acetate and saturated aqueous NaCl. The layers were separated and the aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic extracts were dried ($MgSO_4$) and then concentrated in vacuo. Purification by silica gel (*n*-hexane:ethyl acetate 92:8) gave the homoallylic alcohol **22** (914 mg, 70%). $[\alpha]_D^{24}=-0.38$ (*c* 2.6, $CHCl_3$); IR (thin film): 3455, 2955, 2931, 1613, 1513, 1256, 1089 cm^{-1}; HR FABMS *m*/*z* 251.1630 $(M+H)^+$, calcd for $C_{15}H_{23}O_3$: 251.1647; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.02 (3H, d, $J=6.8$ Hz, CH_3-4); 1.71 (2H, m, H-2); 2.22 (1H, m, H-4); 3.65 (3H, m, H-1 and H-3); 3.76 (3H, s, OCH_3); 4.45 (2H, s, $ArCH_2O$-); 5.05 (1H, d, $J=4.8$ Hz, H-6a); 5.08 (1H, bs, H-6b); 5.80 (1H, m, H-5); 6.87 (2H, d, $J=8.7$ Hz, ArH); 7.25 (2H, d, $J=8.7$ Hz, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 15.8, 33.5, 44.0, 55.2, 69.0, 73.0, 74.3, 113.7 (2C), 115.4, 129.3 (2C), 130.1, 140.5, 158.9.

The characterization data recorded for *ent*-**22** (IR, ^1H NMR, ^{13}C NMR, HRMS) was identical to that listed above for enantiomer **22**; $[\alpha]_D^{24}=+0.5$ (*c* 2.0, $CHCl_3$).

4.10. (3*R*,4*S*)-1-*O*-(4′-Methoxybenzyl)-3-*O*-methyl-4-methyl-5-hexen-1,3-diol 23

Sodium hydride (1.28 g, 60% suspension in oil, 32 mmol) was added in one portion to a stirred solution of the alcohol **22** (800 mg, 3.2 mmol) in THF dry at 0°C under nitrogen. The mixture was stirred at 0°C for 5 min and then methyl iodide (4 ml, 64 mmol) was added in one portion. The resulting mixture was left at room temperature for 2 h and then quenched with MeOH, diluted with water and extracted with ethyl acetate. The combined organic extracts were dried ($MgSO_4$) and then concentrated in vacuum. Purification by silica gel (*n*-hexane:ethyl acetate 99:1) gave **23** (676 mg, 80%). $[\alpha]_D^{24}=+5.6$ (*c* 3, $CHCl_3$); IR (thin film): 3031, 1612, 1513 cm^{-1}; HR FABMS *m*/*z* 265.1825 $(M+H)^+$, calcd for $C_{16}H_{25}O_3$: 265.1804; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.01 (3H, d, $J=6.9$ Hz, CH_3-4); 1.69 (2H, m, H-2); 2.44 (1H, m, H-4); 3.25 (1H, m, H-1); 3.34 (3H, s, OCH_3-4); 3.53 (2H, m, H-1 and H-3); 3.80 (3H, s, OCH_3); 4.42 (2H, m, $ArCH_2O$-); 5.01 (1H, d, $J=4.8$ Hz, H-6a); 5.04 (1H, bs, H-6b); 5.78 (1H, m, H-5); 6.88 (2H, d, $J=8.7$ Hz, ArH); 7.26 (2H, d, $J=8.7$ Hz, ArH). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 14.5, 31.1, 40.2, 55.2, 58.0, 67.0, 72.6, 81.6, 113.7 (2C), 114.7, 129.2 (2C), 130.1, 140.5, 158.9.

The characterization data recorded for *ent*-**23** (IR, ^1H NMR, ^{13}C NMR, HRMS) was identical to that listed above for enantiomer **23**; $[\alpha]_D^{24}=-8.8$ (*c* 1.8, $CHCl_3$).

4.11. (2*R*,3*R*)-3-Methoxy-5-(4′-methoxybenzyloxy)-2-methylpentanal 24

To a solution of alkene **23** (520 mg, 2.0 mmol) in acetone/water (8:1) at room temperature was added OsO_4 (251 μL, 0.04 mmol) followed, after 10 min by NMO (281 mg, 2.4 mmol). The mixture was stirred overnight and H_5IO_6 (912 mg, 4.0 mmol) was added. After 30 min the resulting mixture was extracted with ethyl acetate and the organic layer was washed with water, brine, dried (Na_2SO_4), filtered and concentrated to afford aldehyde **24** (505 mg, 95%) that was used for the next step without further purification. HR FABMS *m*/*z* 267.1575 $(M+H)^+$, calculated for $C_{15}H_{23}O_4$: 267.1596; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.09 (3H, d, $J=6.9$ Hz, CH_3-2); 1.78 (2H, m, H-4); 2.64 (1H, m, H-2); 3.35 (3H, s, OCH_3); 3.54 (2H, m, H-3 and H-5b); 3.67 (1H, m, H-5a); 3.80 (3H, s, OCH_3); 4.42 (2H, m, $ArCH_2O$-); 6.88 (2H, d, $J=8.7$ Hz, ArH); 7.25 (2H, d, $J=8.7$ Hz, ArH); 9.71 (1H, s, H-1); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 9.7, 31.5, 49.7, 55.2, 57.8, 65.9, 72.7, 78.7, 113.8 (2C), 129.3 (2C), 130.4, 159.2, 204.0.

The characterization data recorded for *ent*-**24** (IR, ^1H NMR, ^{13}C NMR, HRMS) was identical to that listed above for enantiomer **24**.

4.12. Dimethyl (3*S*,4*R*)-2-hydroxy-4-methoxy-6-(4′-methoxybenzyloxy)-3-methylhexyl phosphonate

A solution of *n*-butyllithium (3.04 mL, 2.5 M in hexane, 7.6 mmol) was added dropwise over 5 min to a stirred solution of dimethyl methylphosphonate (864 μL, 7.98 mmol) in dry THF at −78°C under nitrogen and the resulting solution was stirred for 0.5 h at −78°C. A solution of the aldehyde **24** (500 mg, 1.9 mmol) in dry THF was added dropwise over 20 mins and the mixture was stirred for an additional hour. It was then quenched with aqueous saturated $NaHCO_3$ solution and allowed to come to room temperature. The mixture was extracted with ethyl acetate (3×50 ml) and the combined organic extracts were dried (Na_2SO_4) and then concentrated in vacuo. Purification by silica gel (*n*-hexane:ethyl acetate 2:8) gave the hydroxyphosphonate (617 mg, 85%, 65:35 diasteromeric mixture) as a colorless oil. HR FABMS *m*/*z* 391.1901 $(M+H)^+$, calcd for $C_{18}H_{32}O_7P$: 391.1886; ^1H NMR (500 MHz, CD_3OD) δ (ppm): 0.92–0.86* (d's, $J=6.9$ Hz, CH_3-3); 1.69–1.63* (1H, m, H-1a); 1.76 (1H, m, H-5a); 1.93–1.86* (1H, m, H-1b); 2.04 (2H, m, H-3 and H-5b); 3.36–3.32* (s's, OCH_3); 3.58–3.50* (3H, m, H-4 and

H-6); 3.75–3.72 (s's CH_3O-P); 3.76–3.78 (s's CH_3O-P); 3.80 (3H, s, OCH_3); 4.21–4.22* (1H, m, H-2); 4.45 (2H, m, $ArCH_2O$-); 6.91 (2H, d, $J=8.7$ Hz, ArH); 7.28 (2H, d, $J=8.7$ Hz, ArH); ^{13}C NMR (125 MHz, CD_3OD) δ (ppm): 9.6 (10.8), 31.2 (31.0), 32.0 (32.1), 42.8 (42.9), 52.9, 53.2, 55.7, 58.0 (57.9), 67.2, 67.4, (67.9), 76.3, 81.6 (80.1), 114.7 (2C), 130.4 (130.5) (2C), 131.7, 160.7.

The characterization data recorded for *ent*-hydroxyphosphonate (IR, ^1H NMR, ^{13}C NMR, HRMS) was identical to that listed above 3*S*,4*R* hydroxyphosphonate.

4.13. Dimethyl (3*R*,4*R*)-4-methoxy-6-(4′-methoxybenzyloxy)-3-methyl-2-oxohexyl phosphonate 8a

Pyridinium dichromate (2.0 g, 5.2 mmol) was added in one portion to a solution of the hydroxyphosphonate (500 mg, 1.3 mmol) in dry DMF and the resulting solution was stirred at room temperature under nitrogen for 5 h. The mixture was diluted with water and then extracted with ether. The combined ether extracts were washed with water and brine, then dried (Na_2SO_4) and evaporated to dryness in vacuo to leave **8a** as a colorless oil (328 mg, 65%). $[\alpha]_D^{24}=-1.7$ (*c* 4.5, $CHCl_3$); HR FABMS *m*/*z* 389.1740 $(M+H)^+$, calcd for $C_{18}H_{30}O_7P$: 389.1729; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.98 (3H, d, $J=6.9$ Hz, CH_3-3); 1.65 (1H, m, H-5a), 1.78 (1H, m, H-5b), 3.00 (2H, m, H-1a and H-3), 3.20 (1H, m, H-1b), 3.25 (3H, s, OCH_3), 3.26 (1H, m, H-6a), 3.45 (2H, m, H-4 and H-6b), 3.68–3.69, 3.70–3.72 (6H, CH_3O-P), 3.80 (3H, s, OCH_3), 4.38 (2H, m, $ArCH_2O$-), 6.78 (2H, d, $J=8.7$ Hz, ArH), 7.22 (2H, d, $J=8.7$ Hz, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 11.8, 31.2, 41.5, 50.3, 52.2, 52.9, 57.8, 60.3, 65.9, 72.7, 80.3, 113.7 (2C), 129.1 (2C), 131.4, 159.2, 204.9.

The characterization data recorded for **8b** (IR, ^1H NMR, ^{13}C NMR, HRMS) was identical to that listed above for enantiomer **8a**; $[\alpha]_D^{24}=+1.4$ (*c* 5.0, $CHCl_3$).

4.14. (3*R*,4*R*,8*S*,9*S*,10*S*,11*S*,12*S*)-11-(*tert*-Butyldimethylsilyloxy)-13-(*tert*-butyldiphenylsilyloxy)-3,9-dimethoxy-1-(4′-methoxybenzyloxy)-4,8,10,12-tetramethyl-6-tridecen-5-one 5

A solution of the ketophosphonate **8a** (23.3 mg, 0.06 mmol) in dry THF was stirred in the presence of activated barium hydroxide octahydrate (10 mg, 0.054 mmol) at room temperature for 30 min, and then a solution of the aldehyde **7** (20 mg, 0.035 mmol) in 40:1 THF/water was added. The inhomogeneous mixture was stirred vigorously at room temperature for 3.5 h and then diluted with dichloromethane. The organic extract was washed with saturated $NaHCO_3$ and brine and then dried (Na_2SO_4) and concentrated in vacuo. Purification by silica gel (*n*-hexane:ethyl acetate 98:2) gave the compound **5** as a colorless oil (22.1 mg, 76%); IR (thin film): 2930, 1693, 1620, 1230, 1089, 834 cm^{-1}; HR FABMS *m*/*z* 833.5220 $(M+H)^+$, calcd for $C_{49}H_{77}O_7Si_2$: 832.5208; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): −0.01 (3H, s, CH_3-Si); 0.02 (3H, s, CH_3-Si); 0.73 (3H, d, $J=6.8$ Hz, CH_3), 0.77 (9H, s, *t*Bu-Si); 0.84 (3H, d, $J=7.1$ Hz, CH_3), 1.02 (3H, d, $J=6.9$ Hz, CH_3); 1.06 (9H, s, *t*Bu-Si); 1.15 (3H, d, $J=6.9$ Hz, CH_3), 1.67 (2H, m); 1.71 (1H, m); 1.76 (1H, m); 1.85 (2H, m); 2.65 (1H, m); 3.06 (1H, d, $J=8.1$ Hz); 3.13 (1H, t, $J=8.0$ Hz); 3.27 (3H, s, OCH_3); 3.31 (3H, s, OCH_3); 3.38 (1H, m); 3.54 (2H, m); 3.62 (2H, m); 3.80 (3H, s, OCH_3); 3.92 (1H, m); 4.42 (2H, m); 6.14 (1H, d, $J=15.6$ Hz); 6.86 (2H, d, $J=8.7$ Hz), 6.94 (1H, dd, $J=15.6$, 6.1 Hz); 7.24 (2H, d, $J=8.7$ Hz); 7.40 (6H, m, Ph); 7.65 (4H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): −3.9, −3.6, 11.5, 12.3, 13.7, 17.0, 18.4, 19.2, 26.1 (3C), 26.9 (3C), 29.7, 31.3, 38.3, 38.7, 42.2, 46.9, 55.2, 58.1, 60.2, 66.2, 66.3, 72.4, 72.5, 79.8, 86.8, 113.7 (2C), 127.6 (6C), 129.5 (2C), 129.6 (2C), 130.7, 133.9 (3C), 135.6 (4C), 149.4, 159.2, 202.4.

4.15. (3*S*,4*S*,8*S*,9*S*,10*S*,11*S*,12*S*)-11-(*tert*-Butyldimethylsilyloxy)-13-(*tert*-butyldiphenylsilyloxy)-3,9-dimethoxy-1-(4′-methoxybenzyloxy)-4,8,10,12-tetramethyl-6-tridecen-5-one 6

A solution of the ketophosphonate **8b** (23.3 mg, 0.06 mmol) in dry THF was stirred in the presence of activated barium hydroxide octahydrate (10 mg. 0.054 mmol) at room temperature for 30 min, and then a solution of the aldehyde **7** (20 mg, 0.035 mmol) in 40:1 THF/water was added. The inhomogeneous mixture was stirred vigorously at room temperature for 3.5 h and then diluted with dichloromethane. The organic extract was washed with saturated $NaHCO_3$ and brine and then dried (Na_2SO_4) and concentrated in vacuo. Purification by silica gel (*n*-hexane:ethyl acetate 98:2) gave the compound **6** as a colorless oil (22.7 mg, 78%); IR (thin film): 2930, 1695, 1615, 1230, 1089, 834 cm^{-1}. HR FABMS *m*/*z* 833.5218 $(M+H)^+$, calcd for $C_{49}H_{77}O_7Si_2$: 832.5208; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): −0.01 (3H, s, CH_3-Si); 0.02 (3H, s, CH_3-Si); 0.74 (3H, d, $J=6.7$ Hz, CH_3), 0.77 (9H, s, *t*Bu-Si); 0.84 (3H, d, $J=6.9$ Hz, CH_3), 1.06 (9H, s, *t*Bu-Si); 1.01 (3H, d, $J=6.9$ Hz, CH_3), 1.16 (3H, d, $J=7.1$ Hz, CH_3), 1.66 (2H, m); 1.70 (1H, m); 1.76 (1H, m); 1.87 (2H, m); 2.66 (1H, m); 3.06 (1H, d, $J=8.2$ Hz); 3.12 (1H, t, $J=7.8$ Hz); 3.27 (3H, s, OCH_3); 3.32 (3H, s, OCH_3); 3.38 (1H, m); 3.54 (2H, m); 3.63 (2H, m); 3.80 (3H, s, OCH_3); 3.91 (1H, m); 4.42 (2H, m); 6.13 (1H, d, $J=15.4$ Hz); 6.86 (2H, d, $J=8.8$ Hz), 6.94 (1H, dd, $J=15.4$, 5.8 Hz); 7.24 (2H, d, $J=8.8$ Hz); 7.41 (6H, m, Ph); 7.64 (4H, m, Ph); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm): −3.9, −3.6, 11.7, 12.4, 13.7, 17.7, 18.4, 19.2, 26.1 (3C), 26.8 (3C), 29.7, 31.3, 38.5, 38.6, 42.2, 47.8, 55.2, 58.1, 60.2, 65.4, 66.2, 72.4, 72.5, 79.8, 86.9, 113.8 (2C), 127.9 (4C), 129.1 (2C), 129.3 (2C), 129.5 (2C), 130.6, 133.9 (3C), 135.7 (4C), 151.9, 159.1, 202.3.

4.16. (2*S*,3*S*,4*R*,5*S*,6*S*,10*S*,11*R*)-5,11-Dimethoxy-2,4,6,10-tetramethyltridecane-1,3,9,13-tetraol 3

Enone **5** was subjected to the following four step sequence:

(a) 10 mg sample was dissolved in ethanol and hydrogenated in the presence of Pt/C catalyst (2 mg) for 2 h. The mixture was filtered through Celite and the filtrate was concentrated in vacuo to leave the ketone as a liquid (9.0 mg, 90%).
(b) $NaBH_4$ was added in one portion to a stirred solution of this latter in MeOH at room temperature. The mixture was stirred for 1 h and then was concentrated in vacuo and then diluted with NH_4Cl and ethyl acetate. The aqueous phase was extracted with ethyl acetate and then the combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo to leave 8.2 mg of pure alcohol (90%).
(c) To a solution of the alcohol in CH_2Cl_2 and MS was added DDQ. The reaction was stirred at 25°C overnight and then filtered through Celite and the filtrate was washed with aqueous NaOH (1N, 20 mL) and brine and then dried (Na_2SO_4) and concentrated in vacuo (6.6 mg, 95%).
(d) A solution of HCl in MeOH (2N, 5 mL) was added to a solution of the silyl alcohol in methanol (1 mL) at room temperature. The reaction was stirred for 2 h and Ag_2CO_3 was added. The mixture was treated with a stream of N_2 to eliminate the CO_2, and concentrated in vacuo to obtain 3.3 mg (98%) of mixture of C31 epimers of compound **3**. The residue was purified by HPLC (water:methanol 55:45) on a μ-Bondapak C-18 (3.9 mm×30 cm) to afford the two epimers at C-31 of tetrol **3**: **3a** (0.8 mg, t_R 6.9 mim) and **3b** (2 mg, t_R 9.6 min).

Compound **3a**: $[\alpha]_D^{24}=+3.3$ (*c* 0.3, $CHCl_3$); HR FABMS *m/z* 365.2912 $(M+H)^+$, calcd for $C_{19}H_{41}O_6$: 365.2903; ^1H NMR (500 MHz, CD_3OD) δ (ppm): Table 1.

Compound **3b**: $[\alpha]_D^{24}=+5.0$ (*c* 0.5, $CHCl_3$); HR FABMS *m/z* 365.2908 $(M+H)^+$, calcd for $C_{19}H_{41}O_6$: 365.2903; ^1H NMR (500 MHz, CD_3OD) δ (ppm): Table 1; ^{13}C NMR (125 MHz, CD_3OD): Table 2.

4.17. (2*S*,3*S*,4*R*,5*S*,6*S*,10*R*,11*S*)-5,11-Dimethoxy-2,4,6,10-tetramethyltridecane-1,3,9,13-tetraol 4

The synthesis of tetrol **4** from enone **6** was carried out under the same conditions used to obtain tetrol **3**. The residue was purified by HPLC (water:methanol 52:48) on a C-18 column LUNA (3 μ, 250×4.6 mm) to afford the two epimers at C-31 of tetrol **4**: **4a** (0.5 mg, t_R 15 min), **4b** (1.7 mg, t_R 25.5 min)

Compound **4a**: $[\alpha]_D^{24}=+16.7$ (*c* 0.3, $CHCl_3$); HR FABMS *m/z* 365.2907 $(M+H)^+$, calcd for $C_{19}H_{41}O_6$: 365.2903; ^1H NMR (500 MHz, CD_3OD) δ (ppm): Table 1.

Compound **4b**: $[\alpha]_D^{24}=-3.0$ (*c* 0.6, $CHCl_3$); HR FABMS *m/z* 365.2908 $(M+H)^+$, calcd for $C_{19}H_{41}O_6$: 365.2903; ^1H NMR (500 MHz, CD_3OD) δ (ppm): Table 1; ^{13}C NMR (125 MHz, CD_3OD): Table 2.

4.18. General procedure to prepare MTPA ester

0.5–1.0 mg sample was dissolved in freshly distilled CH_2Cl_2 and treated with triethylamine (10 μL), (−)- or (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl) (5 μL) and a catalytic amount of 4-(dimethylamino)pyridine. The mixture was left to stand at room temperature for 12 h, with the resulting mixture purified by silica gel column.

[(*S*)-MTPA ester of **22**]: $[\alpha]_D^{24}=-22$ (*c* 10, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.91 (3H, d, $J=6.9$ Hz, CH_3-4); 1.87 (2H, m, H-2); 2.47 (1H, m, H-4); 3.39–3.29 (2H, m, H-1); 3.50 (3H, s, OCH_3); 3.78 (3H, s, OCH_3); 4.37 (2H, s, $ArCH_2O$-); 5.02 (1H, d, $J=5.1$ Hz, H-6b); 5.04 (1H, bs, H-6a); 5.27 (1H, m, H-3); 5.67 (1H, m, H-5); 6.88 (2H, d, $J=8.6$ Hz, ArH); 7.25 (2H, d, $J=8.6$ Hz, ArH); 7.38–7.53 (5H, m, ArH).

[(*R*)-MTPA ester of **22**]: $[\alpha]_D^{24}=+13$ (*c* 13, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 1.01 (3H, d, $J=7.0$ Hz, CH_3-4); 1.82 (2H, m, H-2); 2.51 (1H, m, H-4); 3.30–3.25 (2H, m, H-1); 3.50 (3H, s, OCH_3); 3.78 (3H, s, OCH_3); 4.31 (2H, s, $ArCH_2O$-); 5.04 (1H, d, $J=4.8$ Hz, H-6b); 5.07 (1H, bs, H-6a); 5.27 (1H, m, H-3); 5.71 (1H, m, H-5); 6.88 (2H, d, $J=8.7$ Hz, ArH); 7.25 (2H, d, $J=8.7$ Hz, ArH); 7.38–7.53 (5H, m, ArH).

[(*S*)-MTPA ester of **3b**]: $[\alpha]_D^{24}=-14.0$ (*c* 0.6, $CHCl_3$); HR FABMS *m/z* 712.3405 $(M+H)^+$, calcd for $C_{35}H_{50}F_6O_8$: 712.3410; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.67 (3H, d, $J=6.6$ Hz); 0.80 (3H, d, $J=7.1$ Hz); 0.84 (3H, d, $J=6.6$ Hz); 1.00 (3H, d, $J=6.6$ Hz); 1.43 (1H, m); 1.63 (2H, m); 1.73 (1H, m); 1.82 (3H, m); 1.94 (2H, m); 2.14 (1H, m,); 2.80 (1H, dd, $J=8.8$, 2.2 Hz); 3.12 (1H, m); 3.23 (3H, s); 3.40 (3H, s); 3.48 (3H, s); 3.54 (3H, s); 3.63 (d, $J=10.3$ Hz); 4.29 (2H, m); 4.43 (2H, m); 5.17 (1H, m); 7.40 (5H, m, ArH); 7.51 (5H, m, ArH).

[(*S*)-MTPA ester of **2b**]: $[\alpha]_D^{24}=-14.4$ (*c* 0.6, $CHCl_3$); HR FABMS *m/z* 712.3420 $(M+H)^+$, calcd for $C_{35}H_{50}F_6O_8$: 712.3410; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.67 (3H, d, $J=6.6$ Hz); 0.80 (3H, d, $J=7.3$ Hz); 0.84 (3H, d, $J=6.6$ Hz); 1.00 (3H, d, $J=6.6$ Hz); 1.44 (1H, m); 1.61 (2H, m); 1.73 (1H, m); 1.82 (3H, m); 1.94 (2H, m); 2.13 (1H, m); 2.80 (1H, dd, $J=8.8$, 2.2 Hz); 3.13 (1H, m); 3.23 (3H, s); 3.41 (3H, s); 3.48 (3H, s); 3.54 (3H, s); 3.63 (d, $J=9.6$ Hz); 4.29 (2H, m); 4.43 (2H, m); 5.17 (1H, m); 7.40 (5H, m, ArH); 7.52 (5H, m, ArH).

[(*R*)-MTPA ester of **2b**]: $[\alpha]_D^{24}=-10$ (*c* 0.1, $CHCl_3$); HR FABMS *m/z* 712.3415 $(M+H)^+$, calcd for $C_{35}H_{50}F_6O_8$: 712.3410; ^1H NMR (500 MHz, $CDCl_3$) δ (ppm): 0.71 (3H, d, $J=6.6$ Hz); 0.76 (3H, d, $J=6.6$ Hz); 0.83 (3H, d, $J=7.2$ Hz); 1.02 (3H, d, $J=6.6$ Hz); 1.48 (1H, m); 1.66 (2H, m); 1.71 (1H, m); 1.81 (3H, m); 1.93 (2H, m); 2.11 (1H, m), 2.85 (1H, dd, $J=8.1$, 2.2 Hz); 3.12 (1H, m); 3.18 (3H, s); 3.42 (3H, s); 3.51 (3H, s); 3.54 (3H, s); 3.71 (d, $J=9.6$ Hz); 4.30 (1H, m); 4.36 (1H, m); 4.43 (1H, dd, $J=10.3$, 5.1 Hz); 4.48 (1H, dd, $J=10.3$, 2.9 Hz); 5.13 (1H, m); 7.39 (5H, m, ArH); 7.52 (5H, m, ArH).

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