Stereochemistry of Sphinxolides and Reidispongiolides. Asymmetric Synthesis of the C17−C22 Fragment of Reidispongiolide A

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Five fragments, **2a**–**4b**, embedding all the stereogenic centers of reidispongiolide A (**1**), have been prepared by a controlled ozonolysis of the natural compound. The absolute stereochemistry of the asymmetric centers of fragment **3**, corresponding to the C17–C22 portion of reidispongiolide A, was determined by enantioselective synthesis and application of the advanced Mosher method.

Introduction

Sphinxolides[1,2] and reidispongiolides[3,4] are macrocyclic lactones belonging to an emerging class of marine natural products. These molecules contain an unusual polymethylated, polymethoxylated 26-membered lactone ring joined to an 11-carbon, stereochemically complex, acyclic chain. These metabolites, isolated in our laboratories from two New Caledonian marine sponges, *Neosiphonia superstes* and *Reidispongia coerulea*, exhibit a nanomolar in vitro cytotoxic activity against various human tumor cell lines. The mechanism of action was recently clarified:[5] they interact with organized filaments of actin causing a permanent change in their reticular structure and preventing their depolymerization. In addition, they circumvent the multidrug resistance mediated by overexpression of P-glycoprotein. Whereas the gross structure was determined on the basis of spectroscopic data, no information regarding the stereochemistry of these compounds (15 to 17 stereogenic centers) was available.

More recently, the application of *J*-based configurational analysis[6] allowed us to determine the relative configuration of the C7−C8, C10−C15, C24−C28, C32−C34 subunits of sphinxolide.[7] Even if fruitful information could be obtained by the application of the aforementioned spectroscopic approach, neither the total relative configuration of these metabolites, nor their absolute configuration could be determined.

To address this issue we undertook a chemical approach involving the controlled degradation of the natural product and the enantioselective synthesis of the obtained fragments.

In this paper we describe the preparation of the five fragments **2a**−**4b** from reidispongiolide A (**1**) together with their spectral characterization and report the stereochemical findings with respect to the fragment **3**.

Results and Discussion

Degradation of Reidispongiolide A (1)

Initial attempts to use the degradative methods reported for aplyronine,[8] scytophycins,[9] and mycalolides,[10] which contain a very similar array of functional groups, failed due to the formation of very complex mixtures. Good results were eventually obtained, however, by a controlled ozonolysis of the double bonds of reidispongiolide A (**1**), selected among the reidispongiolide and sphinxolide family as the major metabolite available in our laboratories.

Ozonolysis of reidispongiolide A (**1**), followed by reductive workup, afforded a mixture that was chromatographed by reversed phase HPLC (μ-Bondapak C-18, 50% MeOH/H_2O) to obtain the C5−C16 fragments (**2a** and **2b**) as a mixture of two inseparable epimers at C-5, the C17−C22 fragment (**3**) and the C23−C35 fragments (**4a** and **4b**), diastereoisomeric at C-31 (Figure 1). The structures of these fragments (**2a**−**4b**) were firmly established on the basis of their spectroscopic data (cf. Exp. Sect.).

Enantioselective Synthesis of Model Compounds 14−17

As depicted in Scheme 1, all possible diastereoisomers (**14**−**17**) of the C17−C22 fragment (**3**) were obtained starting from L-malate dimethyl ester, which is commercially available in high optical purity. Regioselective reduction of

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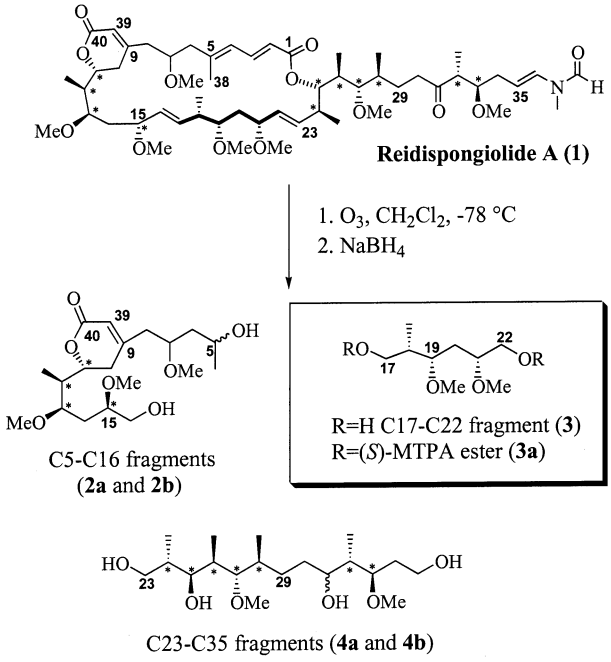
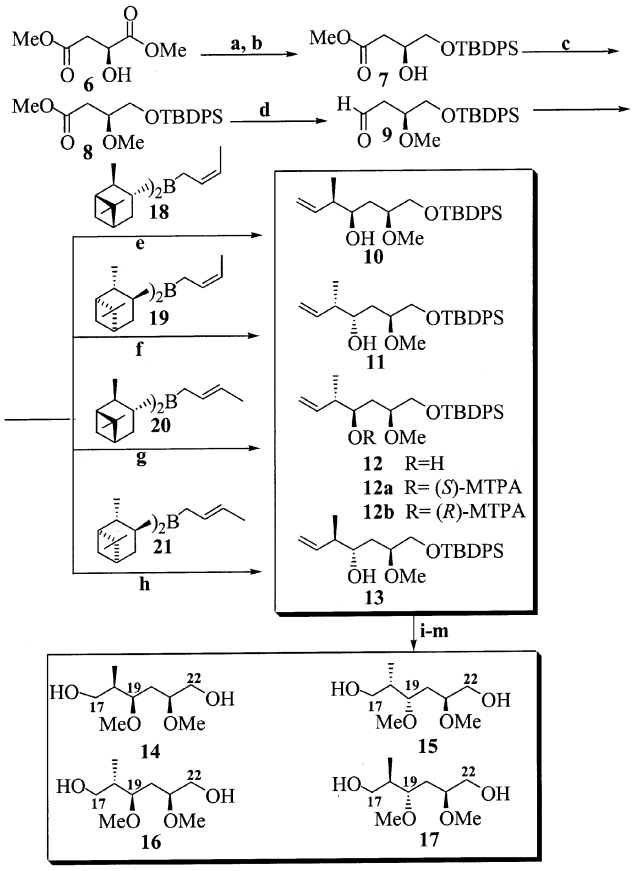


Figure 1. Chemical degradation of reidispongiolide A (1); asterisks (*) label the structural domains of which only the relative configuration was determined



Scheme 1. a) $BH_3{\cdot}SMe_2$, THF, −78 °C, 20 min, $NaBH_4$, 0−25 °C, 4 h; b) TBDPSCl, Et_3N, DMAP, CH_2Cl_2, 25 °C, 14 h, 72% for two steps; c) $CF_3SO_3CH_3$, Di-*t*BuPyr, CH_2Cl_2, 25 °C, 14 h, 87%; d) DIBAL-H, CH_2Cl_2, −80 °C, 2 h; 85%; e) 18, THF −78 °C 4 h, NaOH, H_2O_2, 70%; f) 19, THF −78 °C 4 h, NaOH, H_2O_2, 72%; g) 20, THF −78 °C 4 h, NaOH, H_2O_2, 75%; h) 21, THF −78 °C 4 h, NaOH, H_2O_2, 73%; i) $CF_3SO_3CH_3$, Di-*t*BuPyr, CH_2Cl_2, 25 °C, 24 h, 75−85%; l) O_3, CH_2Cl_2, −78 °C, then $NaBH_4$ overnight, 70−80%; m) MeOH/HCl 2 N, 2 h, room temperature, 75−80%. TBDPS = *tert*-butyldiphenylsilyl, DMAP = 4-(dimethylamino)pyridine, Di-*t*BuPyr = 2,6-di-*tert*-butylpyridine, DIBAL-H = diisobutylaluminum hydride

one of the two methyl ester groups with $BH_3{\cdot}SMe_2$ [11] afforded a 1,2-diol in which the primary hydroxyl group was selectively protected with TBDPSCl (72% yield over two steps). Whereas strongly basic conditions (e.g. NaH, MeI, THF, 0 °C) led to a massive decomposition of the starting material **7**, the use of methyl triflate[12] (1.5 equiv.) and 2,6-di-*tert*-butylpyridine (2.6 equiv.) at 25 °C gave the methyl ether **8** in 87% isolated yield. Reduction of **8** with DIBAL-H gave the aldehyde **9** in 80% yield. This latter was reacted with the organoborane reagents (**18**−**21**) prepared from (+)- or (−)-*B*-methoxydiisopinocampheylborane and (*Z*)- and (*E*)-2-butene under Brown's conditions[13] to afford the diastereoisomeric homoallylic alcohols **10**−**13**.

The diastereomeric purity of **10**−**13** was judged as >95% by HPLC analysis. In some cases[14] it has been reported that the diastereofacial selectivity of the chiral β-alkoxy aldehydes can change the induction predicted for the Brown crotylboration reaction. Thus, the absolute configuration of the newly generated carbinol center in **12** was independently determined by the advanced Mosher method,[15] which confirmed the expected stereochemical outcome according to the Brown crotylboration reaction (see Exp. Sect.).

The homoallylic alcohols **10**−**13** were transformed into the corresponding methyl ethers with methyl triflate (1.5 equiv.) and 2,6-di-*tert*-butyl pyridine (2.6 equiv.) at 25 °C. Finally, ozonolysis of the terminal double bonds followed by reductive workup and deprotection of the TBDPS group by treatment with dilute HCl afforded the diastereoisomeric derivatives **14**−**17**.

A comparison of the ^1H and ^{13}C NMR chemical shifts of the synthetic derivatives **14**−**17** with the corresponding fragment **3** arising from the degradation of the natural reidispongiolide (Table 1 and 2) clearly indicates that **3** has the same relative configuration (18*R*,19*R*,21*S*, or its enantiomer) as the synthetic fragment **14**.

Determination of the Absolute Stereochemistry of the C17−C22 Region of Reidispongiolide A

Although the measured optical rotations of fragment **3** and compound **14** suggested their enantiomeric relationship (see Exp. Sect.), the observed value for **3** is too low for an unambiguous assignment of its absolute stereochemistry. To solve this problem, the ^1H NMR spectrum of the bis(*S*)-MTPA ester **3a** of the C17−C22 segment obtained from natural reidispongiolide A (**1**) was compared with those of the bis(*S*)- and (*R*)-MTPA esters (**14a** and **14b**, respectively) of the synthetic fragment **14**.

Compounds **14a** and **14b** show very similar NMR profiles, although significant differences were observed for the signals of the methylene protons at C-17 (**14a:** δ_H = 4.36 and 4.52; **14b:** δ_H = 4.36 and 4.42) and the methylene pro-

Table 1. Selected NMR spectroscopic data for compounds **10−13**

	10		**11**		**12**		**13**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	3.71 dd (11.0, 4.4)[a] 3.59 dd (11.0, 5.0)	65.0	3.74 dd (11.3, 5.1)[a] 3.65 dd (11.3, 5.8)	65.3	3.75 dd (11.0, 5.1)[a] 3.65 dd (11.0, 5.1)	65.3	3.74 dd (10.3, 5.1)[a] 3.67 dd (10.3, 5.2)	65.3
2	3.64 m	74.8	3.71 m	71.6	3.70 m	74.4	3.71 m	71.3
3	1.79 d (8.0) 1.49 m	35.6	1.73 ddd (14.2, 8.0, 2.2) 1.61 ddd (14.2, 9.6, 3.7)	35.2	1.73 dd (14.7, 1.5) 1.58 m	35.2	1.70 m 1.61 m	35.6
4	3.47 m	82.9	3.58 m	79.7	3.51 m	82.5	3.58 m	79.4
5	2.24 m	44.1	2.26 m	44.1	2.26 m	43.8	2.20 m	44.3
6	5.79 m	141.1	5.77 m	140.8	5.82 m	140.3	5.81 m	140.5
7	5.07 d (11.0) 5.04 d (5.9)	114.9	5.09 d (16.0) 5.05 d (8.8)	115.1	5.09 d (10.0) 5.08 d (16.1)	114.9	5.09 d (16.1) 5.08 d (10.0)	115.6
OMe-2	3.37 s	57.8	3.38 s	58.1	3.40 s	57.5	3.38 s	58.2
Me-5	1.04 d (6.6)	15.1	1.05 d (6.6)	15.2	1.07 d (6.6)	15.3	1.04 d (6.6)	15.9

[a] Coupling constants are given in Hz and enclosed in parentheses.

Table 2. Selected NMR spectroscopic data for compounds **14−17**

	14		**15**		**16**		**17**	
	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
17	3.61 dd (11.0, 6.6)[a] 3.44 d (11.0)	64.6	3.63 dd (10.3, 6.0)[a] 3.41 dd (10.3, 4.3)	65.1	3.52 dd overlapped 3.47 dd overlapped	65.3	3.51 dd (12.0, 6.0)[a] 3.45 dd	65.4
18	1.90 m	38.9	1.90 m	40.2	2.03 m	39.0	2.03 m	39.0
19	3.44 m	79.3	3.52 m	80.3	3.47 m	80.9	3.51 m	80.9
20	1.67 m 1.77 m	32.0	1.59 br t	34.9	1.68 t (6.9)	32.1	1.57 m 1.49 m	33.9
21	3.32 m	80.0	3.39 m	80.4	3.40 m	80.9	3.45 m	80.3
22	3.67 dd (11.7, 4.4) 3.54 dd (11.7, 5.1)	63.1	3.66 dd (11.1, 4.3) 3.53 dd	64.3	3.69 dd (12.0, 3.4) 3.54 dd overlapped	64.3	3.68 dd (11.1, 3.4) 3.54 dd (11.1, 6.0)	64.5
Me-18	0.98 d (6.6)	10.4	0.93 d (6.5)	12.3	0.94 d (6.5)	12.3	0.91 d (6.9)	12.1
OMe-19	3.38 s	56.5	3.46 s	58.8	3.41 s	57.3	3.46 s	57.9
OMe-21	3.43 s	56.3	3.44 s	57.7	3.35 s	57.3	3.40 s	57.8

[a] Coupling constants are given in Hz and enclosed in parentheses.

tons at C-22 (**14a:** δ_H = 4.28 and 4.57; **14b:** δ_H = 4.35 and 4.57). As shown in Figure 2, the ^{1}H NMR spectroscopic data of the bis(*S*)-MTPA ester **3a** were identical with those of the bis(*R*)-MTPA ester **14b**, and therefore the natural fragment **3** is enantiomeric with respect to the synthetic fragment **14**. Therefore, the absolute configurations at C18, C19 and C21 in reidispongiolide A (**1**) were determined to be *S*, *S*, and *R*, respectively.

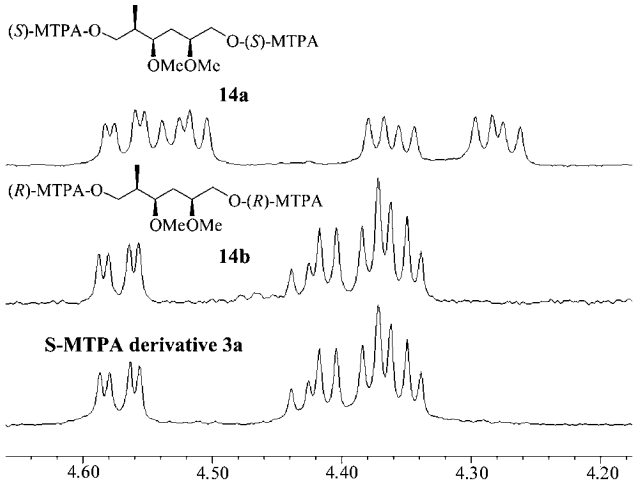


Figure 2. ^{1}H NMR spectra (partial) of (*S*)- and (*R*)-MTPA esters of the synthetic C17−C22 fragment (**14a** and **14b**) and (*S*)-MTPA ester **3a** derived from reidispongiolide A (**1**)

It should be pointed out that the determination of the absolute configuration of the C17−C22 portion of reidispongiolide A (**1**) does not imply the definition of the total absolute configuration of the natural compound because the spatial interconnection between the individual structural domains cannot be determined by spectroscopic methods.

Experimental Section

General: NMR spectra were measured at 500 MHz (^{1}H) and 125 MHz (^{13}C), and referenced to the residual solvent signal ($CDCl_3$; δ_H = 7.26 and δ_C= 77.0; CD_3OD; δ_H = 3.34 and δ_C = 49.0). FAB-MS spectra were performed in a glycerol matrix on a VG Prospec-Autospec (Fisons) mass spectrometer. IR spectroscopy was performed on a IFS 48 Bruker instrument. HPLC was achieved on a Waters model 6000 A pump equipped with a U6 K injector and a differential refractometer, model 401. Optical rotations were measured with a Perkin−Elmer 141 polarimeter operating at 589 nm.

Reidispongiolide A was isolated from the CH_2Cl_2 extract of the sponge *Reidispongia coerulea*.[3]

L-malate dimethyl ester was purchased from Fluka. Solvents and reagents were used as supplied from commercial sources, except for tetrahydrofuran, toluene, dichloromethane and triethylamine, which were distilled from calcium hydride immediately prior to use. All reactions were performed under an argon atmosphere. All reaction were monitored by TLC on silica gel plates (Macherey−Nagel). Products were purified by open or flash chromatography on Macherey−Nagel silica gel (70−230 and 230−400 mesh, respectively).

Degradation Procedure to Obtain Fragments 2a−4b: Ozone was bubbled through a solution of reidispongiolide A **1** (30 mg) in CH_2Cl_2 (5 mL) at −78 °C for 60 s. The excess of ozone was purged with a stream of N_2. The solution was then diluted with MeOH, $NaBH_4$ was added and the resulting mixture was stirred at room temperature overnight. The reaction was quenched by addition of water and the resulting mixture was partitioned with CH_2Cl_2. The layers were separated and the aqueous one was extracted with CH_2Cl_2 (3 × 20 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated to give 27 mg of residue. Reversed-phase HPLC chromatography of this residue [C_{18} μ-Bondapak, 3.9 mm i.d. × 30 cm, flow rate 1.5 mL min^{-1}, 50% aqueous MeOH], afforded fragments **2a** and **2b** as an inseparable mixture (5.0 mg, t_R 4.1 min), fragment **3** (2.5 mg, t_R 2.8 min), fragment **4a** (3.1 mg, t_R 5.6 min) and **4b** (4.5 mg, t_R 7.2 min).

Fragments 2a and 2b: Mixture of two epimers at C-5, $C_{19}H_{34}O_7$, colorless oil. $[\alpha]_D^{25} = 0$ ($c = 0.3$, MeOH). IR (KBr): $\tilde{\nu}$ = 3300, 1725, 1200 cm^{-1}. ^1H NMR (500 MHz, CD_3OD):[16] δ = 5.85 (s, 1 H, 39-H), 4.53 (m, 1 H, 11-H), 3.90/3.92 (m, 1 H, 5-H), 3.68 (m, overlapped, 2 H, 7-H and 16-H_a), 3.53 (m, overlapped, 1 H, 16-H_b), 3.49 (m, 1 H, 13-H), 3.45 (s, 3 H, 15-OMe), 3.40 (s, 3 H, 7-OMe), 3.40 (m, 1 H, 15-H), 3.37 (s, 3 H, 13-OMe), 2.61 (dd, overlapped, 1 H, 8-H_a), 2.54 (dd, overlapped, 1 H, 8-H_b), 2.57 (dd, overlapped, 1 H, 10-H_a), 2.52 (dd, overlapped, 1 H, 10-H_b), 2.15 (m, 1 H, 12-H), 1.80 (m, 1 H, 6-H_a), 1.73 (m, 1 H, 14-H_a), 1.65 (m, 1 H, 14-H_b), 1.50 (m, 1 H, 6-H_b), 1.22/1.20 (d, J = 6.6 Hz, 3 H, 5-Me), 1.06 (d, J = 6.6 Hz, 3 H, 12-Me). ^{13}C NMR (125 MHz, CD_3OD): δ = 168.5 (s, C-40), 157.0 (s, C-9), 117.3 (d, C-39), 80.5 (d, C-13), 79.9 (d, C-15), 79.2 (d, C-11), 77.7 (d, C-7), 65.5 (d, C-5), 63.9 (t, C-16), 57.5 (q's, OMe-7 and OMe-15), 56.3 (q, OMe-13), 43.7 (t, C-6), 41.3 (t, C-8), 39.8 (d, C-12), 34.2 (t, C-14), 33.0 (t, C-10), 23.7 (q, Me-5); 10.7 (q, Me-12). HRMS FAB (positive ion) for $C_{19}H_{35}O_7$ $[M + H]^+$: calcd. 374.2305; found 374.2310

Fragment 3: $C_9H_{20}O_4$, colorless oil. $[\alpha]_D^{25} = +1.0$ ($c = 0.2$, MeOH). IR (KBr): $\tilde{\nu}$ = 3300, 1200 cm^{-1}. ^1H NMR (500 MHz, CD_3OD):[16] δ = 3.67 (dd, J = 11.7, 3.8 Hz, 1 H, 22-H_a), 3.61 (dd, J = 10.3, 6.6 Hz, 1 H, 17-H_a), 3.54 (dd, J = 11.7, 4.6 Hz, 1 H, 22-H_b), 3.44 (m's, 2 H, 17-Hb and 19-H), 3.43 (s, 3 H, 21-OMe), 3.38 (s, 3 H, 19-OMe), 3.32 (m, 1 H, 21-H), 1.90 (m, 1 H, 18-H), 1.77 (m, 1 H, 20-H_a), 1.67 (m, 1 H, 20-H_b), 0.98 (d, J = 6.6 Hz, 3 H, 18-Me). ^{13}C NMR (125 MHz, CD_3OD): δ = 79.9 (d, C-21), 79.3 (d, C-19), 64.6 (t, C-17), 63.1 (t, C-22), 56.6 (q, OMe-19), 56.3 (q, OMe-21), 38.9 (d, C-18), 32.0 (t, C-20), 10.4 (q, Me-18). HRMS (FAB positive) for $C_9H_{21}O_4$ $[M + H]^+$: calcd. 193.1440; found 193.1444.

Fragments 4a and 4b (epimers at C-31): $C_{19}H_{40}O_6$, colorless oil. IR (KBr): $\tilde{\nu}$ = 3300, 1200 cm^{-1}. ^1H NMR (500 MHz, CD_3OD):[16] δ = 3.77 (dd, J =10.3, 5.1 Hz,1 H, 23-H_a), 3.75 (dd, overlapped, 1 H, 25-H), 3.74/3.63 (dd, overlapped, 1 H, 33-H), 3.70 (m, 2 H, 35-H), 3.57 (dd, J = 10.3, 6.0 Hz, 1 H, 23-H_b), 3.54 (s, 3 H, 27-OMe), 3.42/3.36 (s, 3 H, 33-OMe), 3.41/3.47 (m, overlapped, 1 H, 31-H), 3.14 (dd, J = 6.9, 4.3 Hz, 1 H, 27-H), 1.88 (dd, overlapped, 1 H, 26-H), 1.86 (m, 1 H, 34-H_a), 1.77 (m, 1 H, 24-H), 1.76 (dd, overlapped, 1 H, 28-H), 1.72/1.97 (m, 1 H, 32-H), 1.72/1.62 (m, 1 H, 29-H_a), 1.65 (m, 1 H, 34-H_b), 1.60/1.76 (m, 1 H, 30-H_a), 1.40/1.53 (m, 1 H, 30-H_b), 1.14/1.39 (m, 1 H, 29-H_b), 1.03 (d, J = 6.6 Hz, 3 H, 28-Me), 0.92/0.85 (d, J = 6.7 Hz, 3 H, 32-Me) 0.92 (d, J = 6.7 Hz, 3 H, 26-Me), 0.87 (d, J = 6.6 Hz, 3 H, 24-Me). ^{13}C NMR (125 MHz, CD_3OD): δ = 87.0 (d, C-27), 78.2/77.1 (d, C-33), 71.0 (d, C-25), 69.0/70.3 (d, C-31), 63.5 (t, C-23), 58.8 (q, OMe-27), 56.3 (t, C-35), 54.5 (q, OMe-33), 38.4/38.1 (d, C-32), 36.4 (d, C-24), 34.4 (d, C-26), 33.5 (d, C-28), 31.4 (t, C-34), 30.8/30.0 (t, C-30), 24.9 (t, C-29), 14.3 (q, Me-28), 10.2 (q, Me-24), 6.6/7.3 (q, Me-32) 6.9 (q, Me-26). HRMS (FAB positive) for $C_{19}H_{41}O_6$ $[M + H]^+$: calcd. 365.2903; found 365.2909.

Methyl (3*S*)-4-(*tert*-Butyldiphenylsilyloxy)-3-hydroxybutanoate (7): The chemoselective reduction of the L-malate dimethyl ester was performed according to the published procedure.[11] The obtained diol was silylated as follows: triethylamine (2.7 mL, 19.4 mmol) was added at 0 °C to a solution of the alcohol (1.3 g, 9.7 mmol) in CH_2Cl_2 (10 mL). After stirring for 10 min at this temperature, *tert*-butylchlorodiphenylsilane (3.1 mL, 11.7 mmol) and 4-dimethylaminopyridine (239 mg, 1.96 mmol) were added to the mixture. The resulting solution was stirred at room temperature for 14 h. The reaction was quenched with 1.2 N HCl and extracted with three 50 mL portions of CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and then concentrated. The residue was purified by column chromatography (15 g silica gel, *n*-hexane/EtOAc 98:2) to afford the silyl ether **7** (3.3 g, 72% for two steps) as a colorless oil. $[\alpha]_D^{25} = -9.0$ ($c = 0.8$, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3500, 1725, 1230, 1110, 720 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.58 (m, 4 H, Ph-H), 7.20−7.35 (m, 6 H, Ph-H), 4.18 (m's, 2 H, 3-H and 4-H_a), 3.55 (4 H, COO*Me* and 4-H_b), 2.98 (s, 1 H, OH), 2.48 (dd, J = 16.1, 4.4 Hz, 1 H, 2-H_a), 2.42 (dd, J = 16.1, 8.8 Hz, 1 H, 2-H_b), 0.99 (s, 9 H, *t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.7 (s, C-1), 135.8 (Ph), 133.3 (Ph), 130.1 (Ph), 128.1(Ph), 68.9 (d, C-3), 67.2 (t, C-4), 52.0 (q, COO*Me*), 38.2 (t, C-2), 27.1 (q, CH_3-*t*Bu), 19.1 (s, *t*Bu). HRMS (FAB positive) for $C_{21}H_{29}O_4Si$ $[M + H]^+$: calcd. 373.1835; found 373.1830.

Methyl (3*S*)-4-(*tert*-Butyldiphenylsilyloxy)-3-methoxybutanoate (8): 2,6-Di-*tert*-butylpyridine (2.9 mL, 13 mmol) and methyl trifluoromethanesulfonate (1.5 mL, 13 mmol) were added sequentially to a solution of alcohol **7** (1.7 g, 4.6 mmol) in CH_2Cl_2 at 0 °C under an argon atmosphere. The mixture was allowed to warm to room temperature where stirring was continued for 14 h. A saturated solution of $NaHCO_3$ was then added and the organic phase washed with water, dried ($MgSO_4$) and then concentrated in vacuo. Purification by column chromatography on silica with *n*-hexane/EtOAc (99:1) as eluent gave the methyl ether **8** (1.5 g, 87%) as a colorless oil. $[\alpha]_D^{25} = -15$ ($c = 1.0$, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1725, 1230, 1110, 720 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.68 (m, 4 H, Ph-H), 7.38−7.48 (m, 6 H, Ph-H), 3.81 (m, 1 H, 3-H), 3.77 (dd, J = 10.3, 5.1 Hz, 1 H, 4-H_a), 3.71 (s, 3 H, COO*Me*), 3.67 (dd, J = 10.3, 5.1 Hz, 1 H, 4-H_b), 3.37 (s, 3 H, 3-OMe), 2.70 (dd, J = 16.2, 4.4 Hz, 1 H, 2-H_a), 2.58 (dd, J = 16.2, 8.1 Hz, 1 H, 2-H_b), 0.99 (s, 9 H, *t*Bu). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.0 (s, C-1), 135.5 (Ph), 133.2 (Ph), 129.7 (Ph), 127.6 (Ph), 72.3 (d, C-3), 64.4 (t, C-4), 58.0 (q, OMe), 51.5 (q, COO*Me*), 37.0 (t, C-2), 26.7 (q, *t*Bu), 19.1 (s, *t*Bu). HRMS (FAB positive) for $C_{22}H_{31}O_4Si$ $[M + H]^+$: calcd. 387.1992; found 387.1990.

(3*S*)-4-(*tert*-Butyldiphenylsilyloxy)-3-methoxybutanal (9): A solution of DIBAL-H (1 M in dichloromethane, 3.8 mL) was added dropwise over 15 min to a stirred solution of methyl ester **8** (1.4 g,

3.6 mmol) in dry CH_2Cl_2 under an argon atmosphere at −80 °C, and the resulting solution was stirred at −80 °C for 2 h. It was then quenched by addition of ethyl acetate (20 mL) and aqueous sodium potassium tartrate (30 mL, 0.5 M). The mixture was stirred for 3 h and the layers were separated. The aqueous layer was extracted with two 40 mL portions of ethyl acetate. The combined organic layers were dried, filtered and concentrated to give the aldehyde **9** (1.1 g, 85%) which was used immediately without purification in the next reaction.

General Procedure for the Enantioselective Brown's Crotylation of Aldehyde 9: *n*BuLi (1.6 M in hexane, 1.7 equiv.) was added dropwise to a cloudy solution of potassium *tert*-butoxide (1 M in THF, 1.7 equiv.) and *cis*- or *trans*-2-butene (excess) in THF (2 mL) at −78 °C. The resulting yellow mixture was stirred at −45 °C for 20 min. The reaction mixture was recooled to −78 °C and a solution of (+)- or (−)-*B*-methoxydiisopinocampheylborane (2.2 equiv.) in THF (1 mL) was added. The resulting colorless reaction mixture was stirred at −78 °C for 35 min. $BF_3{\cdot}Et_2O$ (2.2 equiv.) was added rapidly followed immediately by a solution of the crude aldehyde **9** (about 200 mg, 0.55 mmol) in THF (2.5 mL). The resulting cloudy reaction mixture was stirred at −78 °C for 4 h. The reaction was then quenched by addition of 3 N 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 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and then concentrated in vacuo. The crude homoallylic alcohols were purified by flash column chromatography on silica gel to obtain a 70−80% yield. The diastereomeric purity of **10−13** was judged as >95% by HPLC analysis performed on a Macherey−Nagel Nucleosil column (3.9 mm i.d. × 30 cm) with a 94% hexane/ethyl acetate solvent mixture as eluent.

(2*S*,4*R*,5*R*)-1-*O*-(*tert*-Butyldiphenylsilyl)-5-methyl-2-*O*-methyl-6-hepten-1,2,4-triol (10): Compound **9** (200 mg, 0.55 mmol) was reacted with the organoborane reagent **18** derived from *cis*-2-butene and (−)-*B*-methoxydiisopinocampheylborane according to the general procedure to give **10** (158 mg, 70%). $[\alpha]_D^{25} = -14.7$ (c = 0.5, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3300, 1230, 1110, 720 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): see Table 1. ^{13}C NMR (125 MHz, $CDCl_3$): see Table 1. HRMS (FAB positive) for $C_{25}H_{36}O_3Si$ [M + H]$^+$: calcd. 413.2512; found 413.2515.

(2*S*,4*S*,5*S*)-1-*O*-(*tert*-Butyldiphenylsilyl)-5-methyl-2-*O*-methyl-6-hepten-1,2,4-triol (11). Reaction of aldehyde **9** (210 mg, 0.57 mmol) with the organoborane reagent **19** derived from *cis*-2-butene and (+)-*B*-methoxydiisopinocampheylborane was performed according to the general procedure to give **11** (170 mg, 72%). $[\alpha]_D^{25} = -5.8$ (c = 0.17, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3300, 1230, 1110, 720 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): see Table 1. ^{13}C NMR (125 MHz, $CDCl_3$): see Table 1. HRMS (FAB positive) for $C_{25}H_{36}O_3Si$ [M + H]$^+$: calcd. 413.2512; found 413.2517.

(2*S*,4*R*,5*S*)-1-*O*-(*tert*-Butyldiphenylsilyl)-5-methyl-2-*O*-methyl-6-hepten-1,2,4-triol (12): Reaction of aldehyde **9** (220 mg, 0.60 mmol) with the organoborane reagent **20** derived from *trans*-2-butene and (−)-*B*-methoxydiisopinocampheylborane was performed according to the general procedure to give **12** (186 mg, 75%). $[\alpha]_D^{25} = -11.5$ (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3300, 1230, 1110, 720 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): see Table 1. ^{13}C NMR ($CDCl_3$): see Table 1. HRMS (FAB positive) for $C_{25}H_{36}O_3Si$ [M + H]$^+$: calcd. 413.2512; found 413.2508.

(2*S*,4*S*,5*R*)-1-*O*-(*tert*-Butyldiphenylsilyl)-5-methyl-2-*O*-methyl-6-hepten-1,2,4-triol (13): Reaction of aldehyde **9** (207 mg, 0.56 mmol) with the organoborane reagent **21** derived from *trans*-2-butene and (+)-*B*-methoxydiisopinocampheylborane was performed according to the general procedure to give **13** (170 mg, 73%). $[\alpha]_D^{25} = -9.4$ (c = 1.0, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 3300, 1230, 1110, 720 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): see Table 1. ^{13}C NMR (125 MHz, $CDCl_3$): see Table 1. HRMS (FAB positive) for $C_{25}H_{36}O_3Si$ [M + H]$^+$: calcd. 413.2512; found 413.2515.

General Procedure for Methylation of Homoallylic Alcohols 10−13: 2,6-Di-*tert*-butylpyridine (3 equiv.) and methyl trifluoromethanesulfonate (3 equiv.) were added sequentially to a solution of the appropriate homoallylic alcohol in CH_2Cl_2 at 0 °C under an argon atmosphere. The mixture was allowed to warm to room temperature where stirring was continued for 14 h. A saturated solution of $NaHCO_3$ was then added and the organic phase was washed with water, dried ($MgSO_4$) and then concentrated in vacuo. Purification by column chromatography on silica with *n*-hexane/EtOAc (997:3) as eluent gave the dimethyl ethers as colorless oils (75−85% yields).

General Procedure for the Reductive Ozonolysis: A solution of the appropriate alkene (about 50 mg, 0.12 mmol) in dichloromethane (3 mL) was ozonized at −78 °C until a light blue color persisted. The excess of ozone was purged with a stream of argon (until colorless) and the solution was then diluted with methanol and $NaBH_4$ added. The mixture was stirred at room temperature overnight. The reaction was quenched by addition of water and the resulting mixture was partitioned with ethyl acetate. The layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated to give the required alcohol (35−40 mg, 70−80%) which was used directly in the final step.

General Procedure to Obtain Diols 14−17: A solution of HCl in MeOH (2 N, 5 mL) was added to a solution of the appropriate protected alcohol (about 35 mg) 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. The residue was purified by silica gel chromatography (chloroform/methanol 98:2) to afford the diol (**14−17**) as a colorless oil (11.7−12.5 mg, 75−80%).

(2*S*,4*R*,5*R*)-2,4-Di-*O*-methyl-5-methyl-1,2,4,6-hexanetetraol (14): $[\alpha]_D^{25} = -6.4$ (c = 0.3, MeOH). IR (KBr): $\tilde{\nu}$ = 3300, 1230 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): see Table 2. ^{13}C NMR (125 MHz, $CDCl_3$): see Table 2. HRMS (FAB positive) for $C_9H_{21}O_4$ [M + H]$^+$: calcd. 193.1440; found. 193.1443.

(2*S*,4*S*,5*S*)-2,4-Di-*O*-methyl-5-methyl-1,2,4,6-hexanetetraol (15): $[\alpha]_D^{25} = -23.2$ (c = 0.5, MeOH). IR (KBr): $\tilde{\nu}$ = 3300, 1230 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): see Table 2. ^{13}C NMR (125 MHz, $CDCl_3$): see Table 2. HRMS (FAB positive) for $C_9H_{21}O_4$ [M + H]$^+$: calcd. 193.1440; found. 193.1445.

(2*S*,4*R*,5*S*)-2,4-di-*O*-methyl-5-methyl-1,2,4,6-hexanetetraol (16): $[\alpha]_D^{25} = +12.5$ (c = 1.2, MeOH). IR (KBr): $\tilde{\nu}$ = 3300, 1230 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): see Table 2. ^{13}C NMR (125 MHz, $CDCl_3$): see Table 2. HRMS (FAB positive) for $C_9H_{21}O_4$ [M + H]$^+$: calcd. 193.1440; found. 193.1439.

(2*S*,4*S*,5*R*)-2,4-di-*O*-methyl-5-methyl-1,2,4,6-hexanetetraol (17): $[\alpha]_D^{25} = -20.3$ (c = 0.3, MeOH). IR (KBr): $\tilde{\nu}$ = 3300, 1230 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): see Table 2. ^{13}C NMR (125 MHz, $CDCl_3$): see Table 2. HRMS (FAB positive) for $C_9H_{21}O_4$ [M + H]$^+$: calcd. 193.1440; found. 193.1444.

Standard Procedure for the Preparation of the MTPA Derivatives: The appropriate alcohol (5.0 mg) 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, and the resulting mixture was then purified on a silica gel column.

Compound 3a [(*S*)-MTPA ester of 3]: $[\alpha]_D^{25} = -14.0$ ($c = 0.05$, MeOH). − ^{1}H NMR ($CDCl_3$): see Figure 2. HRMS (FAB positive) for $C_{30}H_{36}F_6O_6$: calcd. 638.2314; found 638.2310.

Compound 12a [(*S*)-MTPA ester of 12]: $[\alpha]_D^{25} = -12.3$ ($c = 0.7$, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.72−7.30 (m, 15 H, Ar-H), 5.62 (m, 1 H, 6-H), 5.21 (m, 1 H, 4-H), 5.03 (br. s, 1 H, 7-H_a), 5.00 (d, J = 16.0 Hz, 1 H, 7-H_b)), 3.68 (dd, J = 10.8, 5.2 Hz, 1 H, 1-H), 3.59 (dd, J = 10.8, 5.1 Hz, 1 H, 1-H), 3.55 (s, 3 H, OMe), 3.48 (m, 1 H, 2-H), 3.21 (s, 3 H, 2-OMe), 2.42 (m, 1 H, 5-H), 1.95 (dd, J = 14.5, 2.6 Hz, 1 H, 3-H_a), 1.90 (dd, J = 14.5, 4.8 Hz, 1 H, 3-H_b), 0.99 (s, 9 H, *t*Bu), 0.94 (d, J = 6.7 Hz, 3 H, 5-Me). HRMS (FAB positive) for $C_{35}H_{43}F_3O_5Si$: calcd. 628.2832; found 628.2829.

Compound 12b [(*R*)-MTPA ester of 12]: $[\alpha]_D^{20} = -5.1$ ($c = 0.4$, $CHCl_3$). −^{1}H NMR ($CDCl_3$): δ = 7.70−7.32 (m, 15 H, Ar-H), 5.72 (m, 1 H, 6-H), 5.20 (m, 1 H, 4-H), 5.08 (br. s, 1 H, 7-H_a), 5.05 (d, J = 16.0 Hz, 1 H, 7-H_b), 3.57 (m, 2 H, 1-H), 3.53 (s, 3 H, OMe), 3.47 (m, 1 H, 2-H), 3.12 (s, 3 H, 2-OMe), 2.52 (m, 1 H, 5-H), 1.86 (dd, J = 14.5, 2.6 Hz, 1 H, 3-H_a), 1.78 (dd, J = 14.5, 4.8 Hz, 1 H, 3-H_b), 1.04 (d, J = 6.7 Hz, 3 H, 5-Me), 0.99 (s, 9 H, *t*Bu),. HRMS (FAB positive) for $C_{35}H_{43}F_3O_5Si$: calcd. 628.2832; found 628.2829.

Compound 14a [(*S*)-MTPA ester of 14]: $[\alpha]_D^{20} = -34.0$ ($c = 0.7$, MeOH). ^{1}H NMR ($CDCl_3$): see Figure 2. HRMS (FAB positive) for $C_{30}H_{36}F_6O_6$: calcd. 638.2314; found. 638.2310.

Compound 14b [(*R*)-MTPA ester of 14]: $[\alpha]_D^{20} = +14.0$ ($c = 0.05$, MeOH). ^{1}H NMR ($CDCl_3$): see Figure 2. HRMS (FAB positive) for $C_{30}H_{36}F_6O_6$: calcd. 638.2314; found 638.2310.

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