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# Synthetic Studies Directed Toward the Phorboxazoles: Preparation of The C3–C15 Bisoxane Segment and Two Stereoisomers

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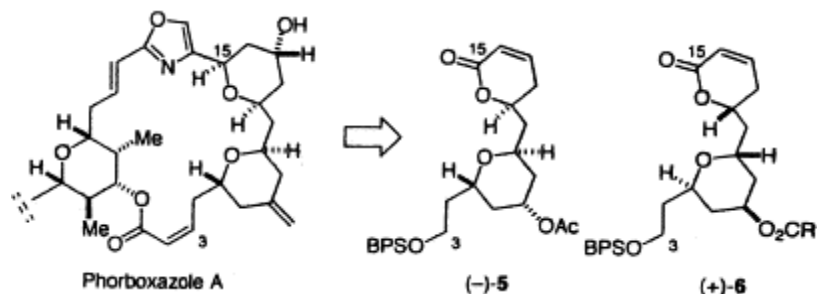
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## Abstract

A synthetic approach to the C3–C15 segment of the cytotoxic marine metabolite phorboxazoles is described. This segment consists of a methylene linked bisoxane structure. The first pyran ring was constructed by a Lewis acid catalyzed diene–aldehyde cyclocondensation. The  $\beta$ -C-glucoside substitution pattern of this ring was established by a stereoselective allylation. Ozonolysis of vinyl group and enantioselective allylation of the racemic aldehyde generated two separable homoallylic alcohols (–)-**22** and (+)-**23**. The Mosher's esters of each alcohol were determined to be >90% de. Reaction of (–)-**22** with acryloyl chloride, followed by ring closing metathesis gave the dihydro-2-pyrone target (–)-**5**. Mitsunobu inversion of (+)-**23** with *p*-nitrobenzoic

acid, hydrolysis, and esterification with acryloyl chloride and ring closing metathesis gave pseudoenantiomeric segment (+)-**6**.

A synthetic approach to the C3–C15 segment of the cytotoxic marine metabolite phorboxazoles is described. The C5–C9 pyran ring was constructed by a Lewis acid catalyzed diene–aldehyde cyclocondensation, while the C11–C15 pyrone ring was constructed by an asymmetric allylation–esterification–ring closing metathesis strategy.

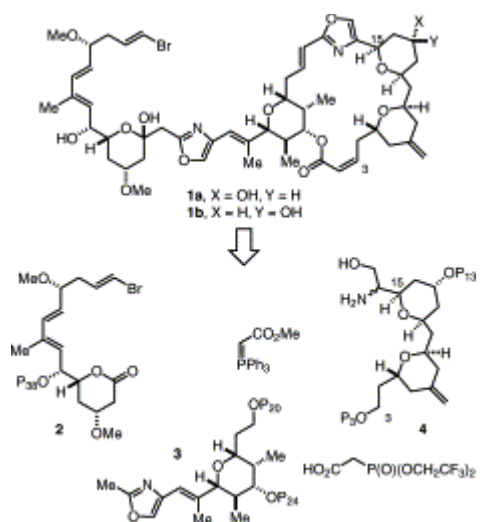


## Keywords

Phorboxazoles, C3–C15 bisoxane segment, stereoisomers, phorboxazoles

The phorboxazoles **A** and **B** (**1a** and **b**) are isomeric macrolides isolated from the marine sponge *Phorbas* sp.<sup>1a</sup> In addition to exhibiting antifungal activity against *Candida albicans*, both phorboxazoles inhibit the growth of most of the 60 tumor cell lines in the NCI panel at concentrations  $<8 \times 10^{-10}$  M. This level of activity places phorboxazole among the most potent cytostatic agents known. While the exact mechanism of action is unknown, the phorboxazoles do not interfere with tubulin polymerization/depolymerization as is the case for many other antitumor agents (e.g. epothilone, taxol). Initial results indicate that **1a** arrests Burkitt lymphoma CA46 cells in the S phase.<sup>1c</sup>

The complex structure of **1** consists of four oxane rings, two oxazole rings, 15 asymmetric centers, and a conjugated diene segment. The complete structure was assigned on the basis of NMR spectral studies, Mosher ester data, degradation, and model synthesis.<sup>1</sup> The outstanding biological activity of **1a/b**, combined with their complex structural architecture, has led to significant activity by a number of research groups,<sup>2</sup> and three total syntheses.<sup>3</sup> The three syntheses are all convergent, with the initial preparation of fragments roughly encompassing the C3–C15 bisoxane portion, the C20–C27 oxane ring, and the C31–C46 diene–oxane fragment. Our retrosynthetic strategy disconnects the target into three major fragments, **2–4** (Scheme 1), with connections similar to those reported by Forsyth<sup>3a</sup> and by Evans.<sup>3b–d</sup> We herein report our detailed study on the enantioselective synthesis of a C3–C15 segment (-)-**5**, its pseudoenantiomer (+)-**6**, and the diastereomer (+)-**7** (Fig. 1).<sup>4</sup>



Scheme 1.

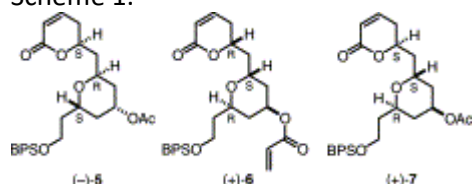


Figure 1.

## 1. Results and discussion

Lewis acid catalyzed diene–aldehyde cyclocondensation<sup>5</sup> of **8** with 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**9**) in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , followed by brief treatment with  $\text{CF}_3\text{CO}_2\text{H}$  gave dihydropyrone *rac*-**10** (Eq. (1), Table 1). In a similar fashion, cyclocondensation in the presence of  $\text{ZnCl}_2$ , or  $\text{TiCl}_4$ , or  $\text{MgBr}_2$  gave the same product. Asymmetric cyclocondensation<sup>6a</sup> of **8** with the chiral auxiliary modified diene 1-*l*-menthyloxy-3-*tert*-butyldimethylsilyloxy-1,3-butadiene (**11**)<sup>6b</sup> in the presence of (+)- $\text{Eu}(\text{hfc})_3$  (hexane), followed by elimination of methanol gave (5*S*)-**10** in good yield. Unfortunately, comparison of the optical rotation of this product with the literature value<sup>2e</sup> indicated that it was only 10% ee. Cyclocondensation of **8** with **9** in the presence of the Keck's *R*-BINOL/ $\text{Ti}(\text{iPrO})_4/\text{CF}_3\text{CO}_2\text{H}$  catalyst<sup>7</sup> likewise gave (5*S*)-**10** with good enantioselectivity (>90% ee) albeit in low isolated yield (19%). Unfortunately in our hands, attempts to optimize the yield of this reaction were unsuccessful.<sup>(1)</sup>

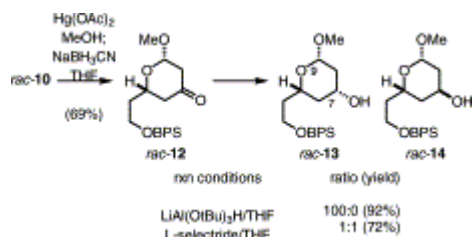
Table 1. Lewis acid catalyzed diene–aldehyde cyclocondensation

Lewis acid/rxn conditions	Yield (%)
$\text{BF}_3 \cdot \text{Et}_2\text{O}/\text{Et}_2\text{O}/-78^\circ\text{C}$ to rt/9 h	71
$\text{ZnCl}_2/\text{Et}_2\text{O}/-78^\circ\text{C}/9$ h, $23^\circ\text{C}/12$ h	70
$\text{TiCl}_4/\text{Et}_2\text{O}/78^\circ\text{C}/9$ h, $23^\circ\text{C}/12$ h	50
$\text{MgBr}_2/\text{Et}_2\text{O}/78^\circ\text{C}/9$ h, $23^\circ\text{C}/12$ h	31
(+)- $\text{Eu}(\text{hfc})_3/\text{hexane}/\text{rt}/24$ h <sup>a</sup>	52 (5 <i>S</i> , 10% ee)
$\text{Ti}(\text{iPrO})_4/\text{R-BINOL}/\text{CF}_3\text{CO}_2\text{H}/\text{Et}_2\text{O}$	19 (5 <i>S</i> , 95% ee)

a1-(1-*l*-Menthyloxy)-3-(*tert*-butyldimethylsilyloxy)-1,3-butadiene (**11**) was used instead of **9**.

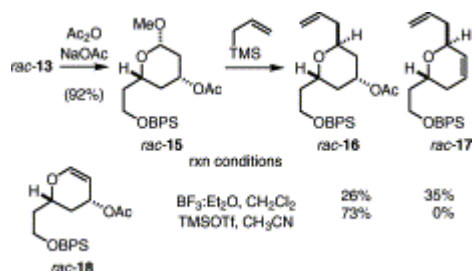
Reaction of *rac*-**10** with mercuric acetate in methanol, followed by treatment with  $\text{NaBH}_3\text{CN}$  gave the methyl glycoside **12** (Scheme 2). Compound **12** was assigned the  $\beta$ -stereochemistry on the basis of the  $^1\text{H}$  NMR signal for the anomeric proton ( $\delta$  4.54, dd,  $J=2.7, 9.0$  Hz). The larger coupling constant is consistent with an axial–axial orientation of the anomeric proton with one on the adjacent carbon. Reduction of **12** with  $\text{LiAlH}(\text{O}t\text{Bu})_3$  gave the

equatorial alcohol **13**, while reduction of **12** with l-selectride gave a mixture of **13** and the axial alcohol **14** (Scheme 2). The structural assignments for **13** and **14** are based on their  $^1\text{H}$  NMR spectral data. In particular, the signals for H9 and H7 (phorbaxazole numbering) of **13** ( $\delta$  4.26, dd,  $J=1.9, 9.5$  Hz and  $\delta$  3.60, br m,  $1/2W=26$  Hz) are consistent with a tetrahydropyran bearing all equatorial substituents, while these signals for **14** ( $\delta$  4.69, dd,  $J=2.1, 9.9$  Hz and  $\delta$  4.31, pentet,  $J=3.0$  Hz) are consistent with a C7 axial hydroxyl group. The diastereoselectivity for reduction of  $\beta$ -pyranoside ketones under these conditions has been previously reported.<sup>8</sup>



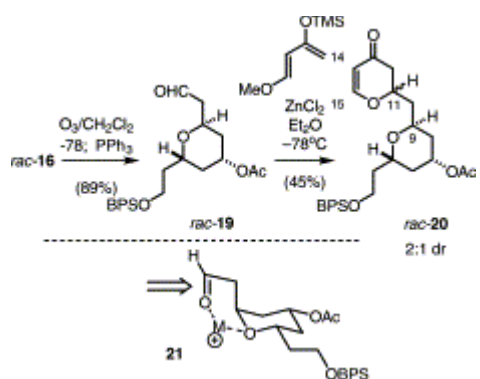
Scheme 2.

Acylation of **13** gave **15** (Scheme 3). Treatment of **15** with allyl trimethylsilane/ $\text{BF}_3 \cdot \text{Et}_2\text{O}$  gave a separable mixture of **16** and **17** (Scheme 3). The  $^1\text{H}$  NMR spectrum of **17** is conspicuous in its absence of a signal for the acetate group and by the presence of signals for 5 olefinic protons. In contrast, the  $^1\text{H}$  NMR spectrum of **16** contains signals at  $\delta$  5.77 (tdd, 1H) and 5.07–4.80 (m, 3H) corresponding to the vinyl group and the C7 proton, and a singlet at  $\delta$  2.04 (3H) corresponding to the acetate methyl. The *trans*- stereochemistry of the allyl substituent in both **16** and **17** was assigned on the basis of the expected<sup>9</sup> axial attack of nucleophiles on the cyclic oxonium ion generated from **15**. The formation of **17** presumably arises from elimination of methanol from **15** to generate the pseudoglycal **18**. A carbon-Ferrier rearrangement of **18** would give the product **17**. Changing the Lewis acid from  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  to  $\text{TMSOTf}$ <sup>10</sup> suppressed the formation of **17**; the desired allylpyran **16** was isolated in 73% yield.



Scheme 3.

Ozonolysis of **16**, followed by treatment of the ozonide with triphenylphosphine, gave the aldehyde *rac*-**19** (Scheme 4). Cyclocondensation of **19** with **9** in the presence of  $\text{TiCl}_4$  gave an *inseparable* mixture of dihydropyrones **20**, which are diastereomeric at C11. The structural assignment for **20** is based on its  $^1\text{H}$  NMR spectral data. In particular, the signals corresponding to the C15 proton of the two diastereomers appear at  $\delta$  7.20 (d) and 7.17 (d), while the signals corresponding to the C14 proton appear at  $\delta$  5.36 (d) and 5.35 (d) ppm. Integration of the C15 signals indicated that the diastereomers were formed in a 2:1 ratio. Cyclocondensation of **19** with **9** in the presence of  $\text{ZnCl}_2$  or  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  in place of  $\text{TiCl}_4$  gave a similar 2:1 mixture of diastereomers **20**. It was not possible to assign the relative stereochemistry of the major diastereomer of **20** at C11.



Scheme 4.

Pyranyl aldehydes similar to **19** are known to undergo cyclocondensation with **9** with modest diastereoselectivity (4:1–5:1).<sup>11</sup> In these cases, the major diastereomer possesses the 9*S*\*,11*R*\* relative stereochemistry. One rationalization for this stereoselectivity is approach of the silyloxydiene **9** to the less hindered face of a chelated structure (c.f. **21**). It should be noted that the 9*S*\*,11*R*\* relative stereochemistry is opposite to that desired for the phorbaxozoles.

Due to the lack of any significant diastereoselectivity in the cyclocondensation of **19**, it was decided to introduce the C11–C15 pyran ring via sequential allylation–esterification–ring-closing metathesis.<sup>12</sup> Toward this end, reaction of *rac*-**19** with *B*-allyldiisopinocampheylborane (prepared from (–)-(IPC)<sub>2</sub>BOMe) under salt-free conditions,<sup>13</sup> followed by oxidative work up with NaBO<sub>3</sub>, gave a separable mixture of the diastereomers (–)-**22** and (+)-**23** (41 and 42%, respectively, Eq. (2)). The *relative* stereochemistry of **22** and **23** were assigned by comparison of their <sup>13</sup>C NMR spectral data with that of the diastereomeric compounds **24** and **25** (Fig. 2), previously reported by Hoffmann's group.<sup>2m</sup> In particular, the spectrum of **22** contains signals at δ 70.6, 69.7, and 67.2 ppm (C5, C9, C11, phorbaxazole numbering, specific assignments not intended) while the spectrum of **23** contains signals at δ 67.6, 67.0, and 66.8 ppm.(2)

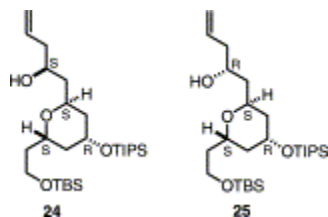


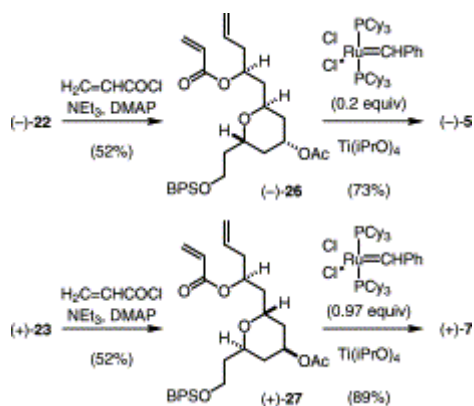
Figure 2.

In comparison, the spectrum of **24** contains signals at δ 71.2, 69.5, and 67.6 ppm, while the spectrum of **25** contains signals at δ 67.8, 67.0, and 66.3 ppm.

Analysis of the <sup>1</sup>H NMR spectra (CDCl<sub>3</sub>) of the (*R*)- and (*S*)-MTPA esters of **22** indicated separation of the H-13 signals; integration of these signals indicated that the Mosher's esters were >90% de. The absolute configuration of **22** at C11 (*S*) is based on the relative chemical shifts for H-13 signals of the (*R*)- and (*S*)-MTPA esters; this signal for the (*R*) ester appears downfield of that for the (*S*) ester.<sup>14</sup> In a similar fashion, integration of the H-13 signals of the (*R*)- and (*S*)-MTPA esters of **23** indicated each to be >90% de. The absolute configuration of **23** at C11 (*S*) is based on the relative chemical shifts of these signals; the signal for the (*R*) ester appears downfield of that for the (*S*) ester.<sup>14</sup>

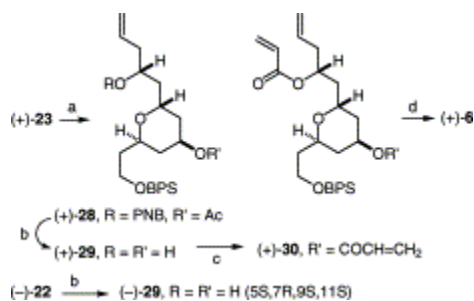
Reaction of the diastereomeric alcohols (–)-**22** or (+)-**23** with acryloyl chloride gave the diastereomeric unsaturated esters (–)-**26** or (+)-**27** (Scheme 5).<sup>15</sup> The structures of acrylate esters **26** and **27** were assigned on

the basis of their NMR spectral data. In particular, doublet of doublets signals present at ca.  $\delta$  6.37, 6.09, and 5.79 ppm in their  $^1\text{H}$  NMR spectra and resonances at ca.  $\delta$  165.5, 130.5, and 128.7 ppm in their  $^{13}\text{C}$  NMR spectra are characteristic of the acrylate group. Ring closing metathesis<sup>16</sup> of (–)-**26** or (+)-**27** in the presence of Grubbs' catalyst gave the dihydropyran-2-ones (–)-**5** or (+)-**7**, respectively.<sup>17</sup> The structures of **5** and **7** were assigned on the basis of their NMR spectral data. In particular, signals present at ca.  $\delta$  6.7–6.8 (ddd) and 6.0–5.9 (dd) ppm in their  $^1\text{H}$  NMR spectra and at ca.  $\delta$  144.9 and 121.4 ppm in their  $^{13}\text{C}$  NMR spectra are characteristic of the olefin of the dihydropyran-2-one ring.



Scheme 5.

The *enantiomers* of certain naturally occurring substances fortuitously exhibit interesting biological activity.<sup>18</sup> It was envisioned that inversion of the C11 stereocenter present in (+)-**23** would generate a molecule enantiomeric with (–)-**22**. To this end, reaction of 2° alcohol (+)-**23** with *p*-nitrobenzoic acid in the presence of DEAD/PPh<sub>3</sub> proceeded with inversion<sup>19</sup> to give (+)-**28** (Scheme 6). Hydrolysis of both the *p*-nitrobenzoate and acetate esters of (+)-**28** gave diol (+)-**29**. In a similar fashion, hydrolysis of (–)-**22** gave the enantiomeric diol (–)-**29**. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of (+)-**29** and (–)-**29** were identical. Reaction of (+)-**29** with 2 equiv. of acryloyl chloride gave the bis-acrylate ester (+)-**30**. Ring closing metathesis of the bis-acrylate (+)-**30** proceeded only via formation of the six-membered dihydropyran-2-one ring to give (+)-**6**.



Scheme 6. Reagents (a) *p*-NO<sub>2</sub>PhCO<sub>2</sub>H, DEAD, PPh<sub>3</sub> (51%); (b) K<sub>2</sub>CO<sub>3</sub>, MeOH (72–88%); (c) H<sub>2</sub>C=CHCOCl, NEt<sub>3</sub>, DMAP (43%); (d) Ru(CHPh)(PCy<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (0.07 equiv.), Ti(*i*PrO)<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub> (79%).

In summary, the C3–C15 segment of the phorbaxozoles (in the form of optically active dihydropyran-2-one (–)-**5**) was prepared in 9 steps from the known aldehyde **8** via the alcohol (–)-**22**. The presence of the  $\alpha,\beta$ -unsaturated lactone should allow for introduction of the requisite C13 hydroxyl substituent<sup>12b</sup> and the C15–C16 bond in a stereoselective fashion. Additionally, the enantiomeric segment (+)-**6** was prepared from (+)-**23**.

## 2. Experimental

### 2.1. General data

Spectrograde solvents were used without purification with the exception of dry ether and dry THF which were distilled from sodium benzophenone ketyl and dichloromethane which was distilled from P<sub>2</sub>O<sub>5</sub> and then stored over molecular sieves. Anhydrous hexane and anhydrous toluene were purchased from Aldrich. Column chromatography was performed on silica gel 60 (60–200 mesh, Aldrich). Melting points were obtained on a Mel-Temp melting point apparatus and are uncorrected. All <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at 300 and 75 MHz, respectively. Elemental analyses were obtained from Midwest Microlabs, Indianapolis, IN and high resolution mass spectra were obtained from the Washington University Resource for Biomedical and Bioorganic Mass Spectrometry.

#### 2.1.1. Dihydropyrone (10)

To a solution of 3-(*tert*-butyldi-phenylsilyloxy)propanal<sup>20</sup> (**8**, 11.42 g, 36.5 mmol) in ether (75 mL) cooled to –78°C was added dropwise 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (**9**, 10.0 g, 5.80 mmol) in ether (25 mL). After stirring for 5 min, BF<sub>3</sub>·Et<sub>2</sub>O (7 mL, 56.9 mmol) was added dropwise over a 5 min period. The mixture was stirred for 9 h during which it was slowly warmed to rt. Saturated aqueous NaHCO<sub>3</sub> was added, the reaction was stirred for 30 min, and then extracted with ether (3×75 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and the solvent evaporated to afford a reddish brown oil. This residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL), trifluoroacetic acid (7 drops) was added, and the mixture stirred for 18 h at rt. Saturated aqueous NaHCO<sub>3</sub> was added, the mixture stirred for 30 min, the layers separated, and the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub> (4×75 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and the solvent evaporated. The residue was purified by chromatography (hexane–ethyl acetate=9:1) to give **10** as a colorless oil (9.879 g, 71%); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.66–7.63 (m, 4H), 7.47–7.37 (m, 6H), 7.29 (d, *J*=6.0 Hz, 1H), 5.40 (d, *J*=6.2 Hz, 1H), 4.67 (tdd, *J*=4.4, 8.6, 12.7 Hz, 1H), 3.90–3.74 (m, 2H), 2.59–2.42 (m, 2H), 2.08–1.97 (m, 1H), 1.93–1.83 (m, 1H), 1.04 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 192.8, 163.3, 135.7, 133.6, 130.0, 127.9, 107.3, 76.6, 59.3, 42.2, 37.4, 27.0, 19.4; FAB-HRMS *m/z* 387.1980 (calcd for C<sub>23</sub>H<sub>28</sub>O<sub>3</sub>SiLi [M+Li]<sup>+</sup> *m/z* 387.1968).

*Effect of Lewis acid: ZnCl<sub>2</sub>.* The reaction of aldehyde **8** with diene **9** in the presence of ZnCl<sub>2</sub> (1.0 M in ether, 1 equiv.) was carried out in ether at –78°C for 9 h, followed by 12 h at room temperature. Reaction of the residue with trifluoroacetic acid in CH<sub>2</sub>Cl<sub>2</sub> was carried out as previously described. Purification of the crude product by chromatography gave **10** as a pale yellow oil (70%).

*Effect of Lewis acid: TiCl<sub>4</sub>.* The reaction of aldehyde **8** with diene **9** in the presence of TiCl<sub>4</sub> (1 equiv.) was carried out in ether at –78°C for 9 h, followed by 12 h at room temperature. Reaction of the residue with trifluoroacetic acid in CH<sub>2</sub>Cl<sub>2</sub> was carried out as previously described. Purification of the crude product by chromatography gave **10** as a pale yellow oil (50%).

*Effect of Lewis acid: MgBr<sub>2</sub>.* The reaction of aldehyde **8** with diene **9** in the presence of MgBr<sub>2</sub> (1 equiv.) was carried out in ether at –78°C for 9 h, followed by 12 h at room temperature. Reaction of the residue with trifluoroacetic acid in CH<sub>2</sub>Cl<sub>2</sub> was carried out as previously described. Purification of the crude product by chromatography gave **10** as a pale yellow oil (31%).

*Effect of chiral Lewis acid and chiral auxillary modified butadiene.* The reaction of aldehyde **8** with 1-(1-*l*-menthyloxy)-3-(*tert*-butyldimethylsilyloxy)-1,3-butadiene<sup>6b</sup> in the presence of (+)-Eu(hfc)<sub>3</sub> (0.05 equiv.) was carried out in anhydrous hexane at room temperature. After 24 h, NEt<sub>3</sub> (4 mL) and methanol (2 mL) were added and the mixture was concentrated under vacuum. Reaction of the residue with trifluoroacetic acid in CH<sub>2</sub>Cl<sub>2</sub> was carried out as previously described. Purification of the crude product by chromatography gave **10** as a pale



yellow oil (52%). The  $^1\text{H}$  NMR spectrum of this product was identical with that of *rac*-**10**:  $[\alpha]_{\text{D}}=-4.1$  (*c* 1.32,  $\text{CHCl}_3$ ) [lit.<sup>2e</sup>  $[\alpha]_{\text{D}}=-35.8$  (*c* 1.0,  $\text{CHCl}_3$ ) 88%ee].

*Effect of Lewis acid: BINOL-Ti(iPrO)<sub>4</sub>*. To a solution of (*R*)-1,1'-binaphthol (75.3 mg, 0.263 mmol) in ether (10 mL) was added 4 Å molecular sieves (526 mg). To this suspension was added dropwise, by syringe,  $\text{Ti}(i\text{PrO})_4$  (0.0374 mL, 0.127 mmol). The reaction mixture turned a reddish-brown in color. To the mixture was added a solution of  $\text{CF}_3\text{CO}_2\text{H}$  in  $\text{CH}_2\text{Cl}_2$  (3  $\mu\text{L}$ , 0.5 M, 0.15 mmol) and the reaction mixture was heated at reflux for 1 h. After the mixture was cooled to room temperature, a solution of **8** (411 mg, 1.32 mmol) in ether (5 mL) was added dropwise. The resultant mixture was cooled to  $-78^\circ\text{C}$  and **9** (0.313 mL) was added dropwise. The reaction mixture was stirred at  $-78^\circ\text{C}$  for 30 min, and then stored in the freezer ( $-5^\circ\text{C}$ ) for 48 h. Saturated aqueous  $\text{NaHCO}_3$  (15 mL) was added and the mixture was stirred for 45 min. The mixture was filtered through filter-aid, the filter bed was washed with ether (4 $\times$ 25 mL) and the combined organic layers dried ( $\text{MgSO}_4$ ) and concentrated. Reaction of the residue with trifluoroacetic acid in  $\text{CH}_2\text{Cl}_2$  was carried out as previously described. Purification of the crude product by chromatography gave **10** as a pale yellow oil (19%).  $[\alpha]_{\text{D}}=-39$  (*c* 0.84,  $\text{CHCl}_3$ ) [lit.<sup>2e</sup>  $[\alpha]_{\text{D}}=-35.8$  (*c* 1.0,  $\text{CHCl}_3$ ) 88%ee].

### 2.1.2. *6*-Methyl glycoside (**12**)

To a solution of dihydro-pyrone **10** (3.00 g, 7.89 mmol) in dry methanol (25 mL) was added, in one portion,  $\text{Hg}(\text{OAc})_2$  (3.1 g, 9.7 mmol). The reaction mixture was stirred at rt for 6 h, and the solvent was evaporated. The residue was dissolved in dry THF (25 mL) and cooled to  $-78^\circ\text{C}$ . To the cooled solution was added, via syringe, a solution of  $\text{NaBH}_3\text{CN}$  (0.2181 g, 3.471 mmol) in THF (2 mL). The reaction mixture was stirred for 4 h, diluted with pentane and the solvent evaporated. The residue was purified by chromatography (hexane–ethyl acetate=19:1) to give **12** as a colorless oil (2.204 g, 69%):  $R_f$  0.49 (hexane–ethyl acetate=4:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.67–7.61 (m, 4H), 7.46–7.34 (m, 6H), 4.54 (dd,  $J=2.7, 9.0$  Hz, 1H), 3.95–3.85 (m, 2H), 3.79 (td,  $J=5.1, 10.2$  Hz, 1H), 3.46 (s, 3H), 2.66 (ddd,  $J=2.6, 3.9, 14.8$  Hz, 1H), 2.43 (dd,  $J=9.7, 14.8$  Hz, 1H), 2.38 (br d,  $J=15.1$  Hz, 1H), 4H), 2.28 (dd,  $J=11.3, 15.1$  Hz, 1H), 1.92–1.84 (m, 2H), 1.04 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  205.9, 135.7, 133.8, 129.9, 127.9, 101.2, 68.2, 59.7, 56.6, 48.1, 47.1, 38.9, 27.1, 19.4; FAB-HRMS  $m/z$  419.2238 (calcd for  $\text{C}_{24}\text{H}_{32}\text{O}_4\text{SiLi}$   $[\text{M}+\text{Li}]^+$   $m/z$  419.2230). Anal. calcd for  $\text{C}_{24}\text{H}_{32}\text{O}_4\text{Si}$ : C, 69.86; H, 7.82. Found: C, 69.85; H, 7.79.

### 2.1.3. Reduction of **12** with $\text{LiAlH}(\text{tBuO})_3$

To a solution of **12** (1.764 g, 4.275 mmol) in dry THF (20 mL) was added, in small portions over a 15 min period, solid  $\text{LiAlH}(\text{OtBu})_3$  (1.358 g, 5.341 mmol). The reaction mixture was stirred at rt for 3 h, at which time TLC analysis indicated complete consumption of **12**. Water (10 mL) was cautiously added dropwise, the mixture was extracted with ether (4 $\times$ 50 mL) and the combined extracts were dried ( $\text{MgSO}_4$ ) and the solvent evaporated. The residue was purified by chromatography (hexane–ethyl acetate=4:1) to give **13** as a colorless oil (1.640 g, 92%):  $R_f$  0.12 (hexane–ethyl acetate=4:1); IR ( $\text{CHCl}_3$ ,  $\text{cm}^{-1}$ ) 3440;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.68–7.63 (m, 4H), 7.46–7.34 (m, 6H), 4.26 (dd,  $J=1.9, 9.5$  Hz, 1H), 3.92–3.73 (m, 3H), 3.60 (br m,  $1/2W=26$  Hz, 1H), 3.42 (s, 3H), 2.17 (tdd,  $J=1.9, 4.6, 12.0$  Hz, 1H), 1.92–1.78 (m, 3H), 1.54 (d,  $J=5.1$  Hz, OH), 1.42–1.33 (m, 2H), 1.05 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  135.7, 134.0, 129.8, 127.8, 101.2, 68.6, 67.2, 60.2, 56.5, 41.1, 40.9, 38.6, 27.0, 19.4; FAB-HRMS  $m/z$  421.2381 (calcd for  $\text{C}_{24}\text{H}_{34}\text{O}_4\text{SiLi}$   $[\text{M}+\text{Li}]^+$   $m/z$  421.2386). Anal. calcd for  $\text{C}_{24}\text{H}_{34}\text{O}_4\text{Si}$ : C, 69.52; H, 8.26. Found: C, 69.45; H, 8.17.

### 2.1.4. Reduction of **12** with *l*-selectride

A solution of *l*-selectride (2 mL, 1.0 M THF, 2.0 mmol) in dry THF (8 mL) was cooled to  $-78^\circ\text{C}$ . To the cooled solution was added dropwise via syringe, over a period of 10 min, a solution of **12** (371 mg, 0.900 mmol) in dry THF (5 mL). The reaction mixture was stirred for 3 h, during which time the mixture was allowed to come to room temperature and TLC analysis indicated completion. Water (8 mL) was cautiously added dropwise, followed by 6N NaOH (0.6 mL), 30%  $\text{H}_2\text{O}_2$  (0.6 mL) and aqueous  $\text{K}_2\text{CO}_3$  (10 mL). The mixture was extracted with

ether (3×15 mL) and the combined extracts were dried (MgSO<sub>4</sub>) and the solvent evaporated. The residue was purified by chromatography (hexane–ethyl acetate=4:1) to give a 1:1 mixture of **13** and **14** as a colorless oil (267 mg, 72%). The axial alcohol **14** was only characterized as a mixture with **13**.

**14**: *R*<sub>f</sub> 0.12 (hexane–ethyl acetate=4:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>, partial) δ 7.68–7.63 (m, 4H), 7.46–7.34 (m, 6H), 4.69 (dd, *J*=2.1, 9.9 Hz, 1H), 4.31 (pentet, *J*=3.0 Hz, 1H), 4.22 (dd, *J*=4.4, 6.3 Hz, 1H), 3.42 (s, 3H), 1.92–1.20 (m, 7H), 1.05 (s, 9H).

#### 2.1.5. Acetoxy β-methyl glycoside (**15**)

To a solution of **13** (1.90 g, 4.582 mmol) in acetic anhydride (20 mL) was added sodium acetate (0.3758 g, 4.582 mmol). The reaction mixture was heated at reflux for 30 min, diluted with water and extracted with ether (4×20 mL). The combined ethereal extracts were repeatedly washed with saturated NaHCO<sub>3</sub>, followed by brine, dried (MgSO<sub>4</sub>) and the solvent evaporated. The residue was purified by chromatography (hexane–ethyl acetate=9:1) to give **15** as a colorless oil (1.924 g, 92%); IR (CHCl<sub>3</sub>, cm<sup>-1</sup>) 1740; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.69–7.64 (m, 4H), 7.46–7.34 (m, 6H), 4.93 (tt, *J*=5.0, 11.5 Hz, 1H), 4.33 (dd, *J*=1.9, 9.8 Hz, 1H), 3.89 (ddd, *J*=5.4, 8.1, 10.1 Hz, 1H), 3.76 (td, *J*=5.1, 10.2 Hz, 1H), 3.68 (br m, 1/2W=21 Hz, 1H), 3.43 (s, 3H), 2.19 (tdd, *J*=2.3, 4.8, 11.8 Hz, 1H), 2.05 (s, 3H), 1.96 (br dd, *J*=5.0, 12.2 Hz, 1H), 1.87–1.79 (m, 2H), 1.43 (dt, *J*=9.7, 11.9 Hz, 1H), 1.29 (q, *J*=12.1 Hz, 1H), 1.06 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 171.0, 135.7, 134.0, 129.8, 127.8, 101.0, 69.1, 68.4, 60.0, 56.5, 38.6, 37.3, 37.0, 27.0, 21.4, 19.4; FAB-HRMS *m/z* 463.2489 (calcd for C<sub>26</sub>H<sub>36</sub>O<sub>5</sub>SiLi [M+Li]<sup>+</sup> *m/z* 463.2492). Anal. calcd for C<sub>26</sub>H<sub>36</sub>O<sub>5</sub>Si: C, 68.38; H, 7.95. Found: C, 68.38; H, 7.92.

#### 2.1.6. Allylation of **15** with TMSOTf

A solution of **15** (0.2244 g, 0.4913 mmol) in anhydrous CH<sub>3</sub>CN (5 mL) was cooled to 0°C. To the cooled solution was added allyltrimethylsilane (5 mL, 3.6 g, 31 mmol). After stirring for 10 min, trimethylsilyl triflate (0.048 mL, 0.055 g, 0.246 mmol) was added dropwise via syringe. The reaction mixture was stirred for ca. 15 min, diluted with water, and extracted with ether. The combined ether extracts were dried (MgSO<sub>4</sub>) and the solvent evaporated. The residue was purified by chromatography (hexane–ethyl acetate=9:1) to give **16** as a pale yellow oil (0.1684 g, 73%): *R*<sub>f</sub> 0.65 (hexane–ethyl acetate=9:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.68–7.64 (m, 4H), 7.46–7.35 (m, 6H), 5.77 (tdd, *J*=7.0, 10.3, 17.0 Hz, 1H), 5.07–4.80 (m, 3H), 4.05–3.92 (m, 2H), 3.84–3.67 (m, 3H), 2.46 (td, *J*=7.2, 14.4 Hz, 1H), 2.23 (td, *J*=7.0, 14.2 Hz, 1H), 2.04 (s, 3H), 1.90–1.78 (m, 2H), 1.72–1.62 (m, 2H), 1.38 (td, *J*=9.3, 13.0 Hz, 1H), 1.05 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 170.8, 135.8, 134.9, 134.1, 129.8, 127.9, 117.3, 70.9, 67.7, 66.0, 60.5, 38.5, 37.1, 36.6, 33.9, 27.0, 21.6, 19.4; FAB-HRMS *m/z* 473.2730 (calcd for C<sub>28</sub>H<sub>38</sub>O<sub>4</sub>SiLi [M+Li]<sup>+</sup> *m/z* 473.2699). Anal. calcd for C<sub>28</sub>H<sub>38</sub>O<sub>4</sub>Si: C, 72.05; H, 8.21. Found: C, 71.65; H, 8.07.

#### 2.1.7. Allylation of **15** with BF<sub>3</sub>·Et<sub>2</sub>O

A solution of **15** (95.4 mg, 0.209 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (3 mL) was cooled to 0°C. To the cooled solution was added allyltrimethylsilane (0.1 mL, 0.63 mmol). After stirring for 10 min, BF<sub>3</sub>·Et<sub>2</sub>O (0.04 mL, 0.4 mmol) was added dropwise via syringe. The reaction mixture was stirred for 20 min at 0°C, and then warmed to room temperature and stirred for 3 h, diluted with saturated aqueous NaHCO<sub>3</sub>, and extracted with CH<sub>2</sub>Cl<sub>2</sub> (2×10 mL). The combined extracts were dried (MgSO<sub>4</sub>) and the solvent evaporated. The residue was purified by chromatography (hexane–ethyl acetate=19:1) to give **17** (30.1 mg, 35%) followed by **16** (25.3 mg, 26%) both as colorless oil.

**17**: *R*<sub>f</sub> 0.78 (hexane–ethyl acetate=19:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.72–7.65 (m, 4H), 7.46–7.35 (m, 6H), 5.91–5.77 (m, 2H), 5.72 (br d, *J*=10.2 Hz, 1H), 5.10–5.00 (m, 2H), 4.16 (br s, 1H), 3.98 (dddd, *J*=4.2, 4.2, 8.4, 8.4 Hz, 1H), 3.89–3.71 (m, 2H), 2.41 (td, *J*=7.2, 14.1 Hz, 1H), 2.24 (td, *J*=7.1, 14.1 Hz, 1H), 2.07–1.65 (m, 4H), 1.06 (s, 9H). This product was not further characterized.

### 2.1.8. Aldehyde (19)

A solution of **16** (0.5200 g, 1.114 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was cooled to -78°C in a dry ice/acetone bath. The system was purged with carrier gas (compressed air) for 20 min, and then ozone (generated from the compressed air with a Welsbach apparatus) was bubbled through the solution until a blue color persisted (ca. 15 min). The system was purged with carrier gas until the blue color disappeared. Triphenylphosphine (1.39 g, 5.31 mmol) was added and the mixture was stirred and allowed to warm to rt over a period of 2.5 h. The reaction mixture diluted with brine and stirred for 10 min. The mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2×10 mL) and the combined extracts dried (MgSO<sub>4</sub>), and concentrated. The residue was purified by chromatography (hexane–acetone, 9:1–4:1 gradient) to give **19** as a colorless oil (0.4632 g, 89%); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.70 (dd, *J*=1.7, 2.4 Hz, 1H), 7.68–7.63 (m, 4H), 7.45–7.35 (m, 6H), 5.07 (br m, 1/2W=26 Hz, 1H), 4.54 (m, 1H), 4.00 (tt, *J*=4.1, 8.1 Hz, 1H), 3.81–3.65 (m, 2H), 2.77 (ddd, *J*=2.5, 8.4, 16.4 Hz, 1H), 2.50 (ddd, *J*=1.7, 5.5, 16.4 Hz, 1H), 2.04 (s, 3H), 2.01–1.90 (m, 2H), 1.80–1.64 (m, 3H), 1.45 (td, *J*=8.3, 14.2 Hz, 1H), 1.04 (s, 9H). Anal. calcd for C<sub>27</sub>H<sub>36</sub>O<sub>5</sub>Si: C, 69.19; H, 7.74. Found: C, 69.07; H, 7.79.

### 2.1.9. Bis-pyran (20)

To a solution of aldehyde **19** (0.2101 g, 0.4489 mmol) in ether (10 mL) cooled to -78°C was added dropwise 1-methoxy-3-trimethylsilyloxy-1,3-butadiene (0.127 g, 0.735 mmol) in ether (5 mL). After stirring for 5 min, a solution of ZnCl<sub>2</sub> (0.73 μL, 1.0 M in ether, 0.73 mmol) was added. The mixture was stirred for 3 h at -78°C, then warmed to room temperature and stirring was continued for 4 h. Saturated aqueous NaHCO<sub>3</sub> was added, the reaction was stirred for 30 min, and then extracted with ether (3×10 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and the solvent evaporated to afford a reddish brown oil. This residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (15 mL), trifluoroacetic acid (3 drops) was added, and the mixture stirred for 8 h at rt. Saturated aqueous NaHCO<sub>3</sub> was added, the mixture stirred for 30 min, the layers separated, and the aqueous layer extracted with CH<sub>2</sub>Cl<sub>2</sub> (4×10 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and the solvent evaporated. The residue was purified by chromatography (hexane–ethyl acetate=9:1) to give **20** as a pale orange oil (0.1092 mg, 45%). Analysis by <sup>1</sup>H NMR spectroscopy indicated that this is a mixture of diastereomers at C11 (ca. 2:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.65–7.60 (m, 4H), 7.46–7.33 (m, 6H), 7.20 (d, *J*=6.1 Hz, 0.65H) and 7.17 (d, *J*=5.7 Hz, 0.35H), 5.36 (d, *J*=6.1 Hz) and 5.35 (d, *J*=6.2 Hz, total 1H), 5.08 (m, 1H), 4.53 (m, 1H), 4.26 (m, 1H), 3.99 (m, 1H), 3.81–3.62 (m, 2H), 2.53–2.32 (m, 2H), 2.05 (s, 3H), 2.01–1.92 (m, 2H), 1.84–1.64 (m, 3H), 1.45 (td, *J*=8.3, 13.1 Hz, 1H), 1.02 (s, 9H); EI-HRMS *m/z* 479.1887 (calcd for C<sub>27</sub>H<sub>31</sub>O<sub>6</sub>Si [M-*t*Bu]<sup>+</sup> *m/z* 479.1890).

### 2.1.10. Chiral allylation of 19

To a solution of (-)-β-methoxydiisopinocampheylborane (4.00 g, 12.6 mmol) in anhydrous toluene (30 mL) at -78°C was added via syringe a solution of allylmagnesium bromide (12.4 mL, 1.0 M in ether, 12.4 mmol). The reaction mixture was stirred at -78°C for 15 min and then warmed to room temperature over 1.5 h. A white precipitate of magnesium salts formed during this time. The reaction mixture was transferred, via syringe, into four equal portions in four centrifuge tubes. After centrifugation, the salt-free solution was transferred into a second flask containing a solution of **19** (2.26 g, 4.81 mmol) and 4 Å molecular sieves in anhydrous toluene (10 mL) at -78°C. The reaction mixture was stirred at -78°C for 6 h, and then slowly warmed to room temperature overnight. Proton NMR monitoring indicated disappearance of the starting aldehyde. Solid sodium perborate (3.4 g) and water (5 mL) were added and the resultant mixture was heated at reflux for 1 h. After cooling to room temperature, brine was added and the reaction mixture stirred for 20 min. The mixture was filtered through filter-aid and the filter bed washed with ether (3×100 mL). The combined organic phases were dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by column chromatography (hexane–ethyl acetate=19:1) to give **22** (1.044 g, 42%) followed by **23** (1.009 g, 41%) both as colorless oils.

(-)-**22**: *R*<sub>f</sub> 0.60 (hexane–ethyl acetate=1:1); [*α*]<sub>D</sub>=-6.9 (*c* 0.94, CHCl<sub>3</sub>); IR (neat) 3483, 3068, 1736, 1639, 989, 912 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.65–7.60 (m, 4H), 7.46–7.33 (m, 6H), 5.82 (tdd, *J*=7.1, 10.8, 16.5 Hz, 1H), 5.15–5.05

(m, 3H), 4.21–4.07 (m, 2H), 3.84–3.67 (m, 3H), 3.16 (OH), 2.23 (t,  $J=6.4$  Hz, 2H), 2.03 and 2.06–1.94 (s and m, 5H), 1.88–1.65 (m, 4H), 1.52 (td,  $J=3.3, 14.2$  Hz, 1H), 1.48 (td,  $J=7.7, 13.2$  Hz, 1H), 1.06 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  170.2, 135.5, 134.7, 133.8, 129.6, 127.6, 117.4, 70.6, 69.7, 67.2, 66.9, 60.4, 41.7, 38.9, 37.5, 35.2, 35.1, 26.8, 21.2, 19.1. Anal. calcd for  $\text{C}_{30}\text{H}_{42}\text{O}_5\text{Si}$ : C, 70.55; H, 8.29. Found: C, 70.51; H, 8.34.

(+)-**23**:  $R_f$  0.55 (hexane–ethyl acetate=1:1);  $[\alpha]_D^{25} +21.9$  (c 1.00,  $\text{CHCl}_3$ ); IR (neat) 3457, 3068, 1736, 1644, 994, 917  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.65–7.60 (m, 4H), 7.46–7.33 (m, 6H), 5.73 (tdd,  $J=7.3, 9.9, 17.4$  Hz, 1H), 5.13–5.02 (m, 3H), 4.27 (m, 1H), 3.98 (tt,  $J=4.2, 8.4$  Hz, 1H), 3.86–3.77 (m, 2H), 3.70 (m, 1H), 2.27–2.10 (m, 2H), 2.04 (s, 3H), 2.00–1.85 (m, 3H), 1.77–1.64 (m, 3H), 1.47–1.35 (m, 2H), 1.04 (s, 9H), OH not observed;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  170.3, 135.5, 134.5, 133.8, 129.6, 127.6, 117.9, 67.6, 67.0, 66.8, 66.1, 60.4, 42.3, 38.8, 37.9, 35.8, 34.9, 26.8, 21.1, 19.1. Anal. calcd for  $\text{C}_{30}\text{H}_{42}\text{O}_5\text{Si}$ : C, 70.55; H, 8.29. Found: C, 70.25; H, 8.35.

#### 2.1.11. (*R*)-MTPA ester of **22**

To a solution of (–)-**22** (52.9 mg, 0.104 mmol) in  $\text{CH}_2\text{Cl}_2$  (8 mL) was added (*R*)- $\alpha$ -methoxy(trifluoromethyl)phenyl acetic acid (73.0 mg, 0.310 mmol), DMAP (5.0 mg, 0.04 mmol) and DCC (0.35 mL, 0.35 mmol). The reaction mixture was stirred for 3 h, and then washed with 3% aqueous HCl, followed by brine, dried ( $\text{MgSO}_4$ ) and concentrated. The residue was purified by column chromatography (hexane–ethyl acetate=19:1) to give a colorless oil (45.4 mg, 60%). Analysis by  $^1\text{H}$  NMR spectroscopy indicated that the product was >90% de:  $R_f$  0.55 (hexane–ethyl acetate=7:3);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.68–7.63 (m, 4H), 7.53–7.50 (m, 2H), 7.41–7.34 (m, 9H), 5.76–5.62 (m, 1H), 5.18–4.99 (m, 4H), 4.01–3.90 (m, 2H), 3.82–3.66 (m, 3H), 3.51 (s, 3H), 2.46–2.39 (m, 2H), 2.03 and 2.12–1.80 (s and m, 5H), 1.76–1.62 (m, 4H), 1.37 (td,  $J=9.0, 13.1$  Hz, 1H), 1.03 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  170.3, 166.0, 135.5, 133.9, 133.8, 132.9, 132.2, 129.6, 128.3, 127.6, 127.4, 118.6, 73.9, 67.2, 66.7, 66.4, 60.4, 55.4, 38.1, 37.5, 36.0, 35.4, 34.1, 26.9, 26.8, 21.3, 21.2, 19.1. This product was not further characterized.

#### 2.1.12. (*S*)-MTPA ester of **22**

The preparation of the (*S*)-MTPA ester of (–)-**22** was carried out in the same fashion as the preparation of the (*R*)-MPTA ester (93%). Analysis by  $^1\text{H}$  NMR spectroscopy indicated that the product was >90% de:  $R_f$  0.55 (hexane–ethyl acetate=7:3);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.68–7.63 (m, 4H), 7.52–7.49 (m, 2H), 7.41–7.33 (m, 9H), 5.62–5.48 (m, 1H), 5.18–4.94 (m, 4H), 4.10–3.92 (m, 2H), 3.84–3.68 (m, 2H), 3.51 (s, 3H), 2.45–2.27 (m, 2H), 2.10 (m, 1H), 2.03 and 2.03–1.82 (s and m, 5H), 1.78–1.55 (m, 4H), 1.45–1.32 (m, 1H), 1.04 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  170.5, 165.9, 135.5, 133.9, 133.8, 132.9, 132.5, 132.2, 129.6, 128.3, 127.6, 127.4, 118.6, 73.8, 67.2, 66.8, 66.5, 60.5, 55.4, 38.0, 37.4, 35.9, 34.2, 26.9, 26.8, 21.2, 19.2. This product was not further characterized.

#### 2.1.13. (*R*)-MTPA ester of **23**

The preparation of the (*R*)-MTPA ester of (+)-**23** was carried out in the same fashion as the preparation of the (*R*)-MPTA ester (–)-**22** (47%). Analysis by  $^1\text{H}$  NMR spectroscopy indicated that the product was >90% de:  $R_f$  0.35 (hexane–ethyl acetate=4:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.68–7.63 (m, 4H), 7.52–7.50 (m, 2H), 7.41–7.34 (m, 9H), 5.71 (tdd,  $J=7.1, 10.0, 17.0$  Hz, 1H), 5.35–5.22 (m, 1H), 5.10–4.95 (m, 3H), 3.93–3.76 (m, 3H), 3.71 (td,  $J=5.3, 10.6$  Hz, 1H), 3.54 (s, 3H), 2.42 (m, 2H), 2.01 and 2.06–1.75 (s and m, 5H), 1.88–1.65 (m, 4H), 1.45–1.20 (m, 2H), 1.06 (s, 9H). This product was not further characterized.

#### 2.1.14. (*S*)-MTPA ester of **23**

The preparation of the (*S*)-MTPA ester of (+)-**23** was carried out in the same fashion as the preparation of the (*R*)-MPTA ester of (–)-**22** (57%). Analysis by  $^1\text{H}$  NMR spectroscopy indicated that the product was >90% de:  $R_f$  0.29 (hexane–ethyl acetate=4:1);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.68–7.63 (m, 4H), 7.52–7.50 (m, 2H), 7.41–7.34 (m, 9H), 5.60 (tdd,  $J=7.2, 10.1, 17.4$  Hz, 1H), 5.35–5.22 (m, 1H), 5.10–4.95 (m, 3H), 4.08 (qd,  $J=3.7, 11.3$  Hz, 1H), 3.99–3.80 (m, 2H), 3.71 (m, 1H), 3.58 (s, 3H), 2.50–2.30 (m, 2H), 2.03 and 2.12–1.90 (s and m, 5H), 1.88–1.50 (m, 6H), 1.07 (s, 9H). This product was not further characterized.

### 2.1.15. Acrylate (-)-26

To a solution of (-)-**22** (105 mg, 0.206 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at 0°C was triethylamine (0.09 mL, 0.62 mmol) and DMAP (2.5 mg, 0.021 mmol). Acryloyl chloride (0.02 mL, 0.25 mmol) was added via syringe and the solution was stirred at 0°C for 20 min, and then warmed to room temperature and stirred for 2 h. The reaction mixture was poured into a separatory funnel with saturated aqueous NaHCO<sub>3</sub>. The layers were separated and the aqueous layer was washed with methylene chloride (3×20 mL). The combined organic layers were dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by column chromatography (hexane–ethyl acetate=4:1) to give (-)-**26** as a colorless oil (60.3 mg, 52%): *R*<sub>f</sub> 0.27 (hexane–ethyl acetate=4:1), [ $\alpha$ ]<sub>D</sub>=-4.0 (*c* 1.26, CHCl<sub>3</sub>); IR 3073, 3042, 1788, 1726, 1636, 1619, 998, 989, 939, 919 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.65–7.60 (m, 4H), 7.46–7.33 (m, 6H), 6.38 (dd, *J*=1.3, 17.4 Hz, 1H), 6.09 (dd, *J*=10.1, 17.4 Hz, 1H), 5.79 (dd, *J*=1.5, 10.1 Hz, 1H), 5.73 (tdd, *J*=6.9, 11.0, 16.5 Hz, 1H), 5.10–4.95 (m, 4H), 4.07 (br m, 1H), 3.97 (dddd, *J*=2.9, 4.9, 7.9, 9.8 Hz, 1H), 3.85–3.67 (m, 2H), 2.37 (m, 2H), 2.03 (s, 3H), 2.10–1.64 (m, 7H), 1.34 (td, *J*=9.4, 12.6 Hz, 1H), 1.05 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  170.3, 165.5, 135.5, 133.7, 133.2, 130.6, 129.5, 128.6, 127.6, 118.1, 70.9, 68.1, 67.3, 66.2, 60.4, 38.3, 38.2, 36.4, 35.7, 34.0, 26.8, 21.2, 19.1; FAB-HRMS *m/z* 507.2187 (calcd for C<sub>29</sub>H<sub>35</sub>O<sub>6</sub>Si [M-tBu]<sup>+</sup> *m/z* 507.2203).

### 2.1.16. Acrylate (+)-27

Reaction of acryloyl chloride with (+)-**23** was carried out in a fashion similar to the preparation of acrylate ester of (-)-**22** (52%): *R*<sub>f</sub> 0.53 (hexane–ethyl acetate=7:3), [ $\alpha$ ]<sub>D</sub>=+30.2 (*c* 1.06, CHCl<sub>3</sub>); IR 3073, 3037, 1739, 1726, 1634, 1614, 983, 917 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.69–7.64 (m, 4H), 7.43–7.34 (m, 6H), 6.37 (dd, *J*=1.8, 17.3 Hz, 1H), 6.09 (dd, *J*=10.2, 17.3 Hz, 1H), 5.78 (dd, *J*=1.8, 10.3 Hz, 1H), 5.70 (tdd, *J*=7.1, 10.4, 17.3 Hz, 1H), 5.14 (m, 1H), 5.08–4.96 (m, 3H), 4.12–4.04 (m, 1H), 3.95–3.80 (m, 2H), 3.67 (td, *J*=5.9, 10.0 Hz, 1H), 2.35 (m, 2H), 2.02 and 2.09–1.90 (s and m, 5H), 1.84–1.55 (m, 5H), 1.33 (td, *J*=9.7, 12.7 Hz, 1H), 1.04 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  170.4, 165.4, 135.5, 133.9, 133.1, 130.4, 129.5, 128.7, 127.6, 118.1, 70.5, 67.6, 67.5, 65.6, 60.2, 39.1, 38.3, 36.4, 35.8, 34.9, 26.8, 21.2, 19.2; FAB-HRMS *m/z* 571.3072 (calcd for C<sub>33</sub>H<sub>44</sub>O<sub>6</sub>SiLi [M+Li]<sup>+</sup> *m/z* 571.3067).

### 2.1.17. Dihydropyran-2-one (-)-5

To a solution of (-)-**26** (57.2 mg, 0.101 mmol) in degassed CH<sub>2</sub>Cl<sub>2</sub> (50 mL) was added, via syringe, Ti(*i*PrO)<sub>4</sub> (0.01 mL, 0.03 mmol). The reaction mixture was heated at reflux for 1 h, and then cooled to room temperature. A solution of 'Grubbs' catalyst' (16.7 mg, 0.020 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added via cannula transfer at room temperature and the reaction mixture was stirred for 20 h. The mixture was filtered through a small bed of silica gel and the filter bed washed with ethyl acetate (3×10 mL). The combined organic layers were washed with brine, dried (MgSO<sub>4</sub>) and concentrated. The residue was purified by column chromatography (hexane–ethyl acetate=7:3) to give (-)-**5** as a colorless oil (39.9 mg, 73%): *R*<sub>f</sub> 0.065 (hexane–ethyl acetate=7:3); [ $\alpha$ ]<sub>D</sub>=-38 (*c* 1.0, CHCl<sub>3</sub>); IR 1731, 704 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.68–7.61 (m, 4H), 7.46–7.32 (m, 6H), 6.77 (ddd, *J*=3.3, 5.3, 9.6 Hz, 1H), 5.97 (br d, *J*=10.1 Hz, 1H), 5.06 (tt, *J*=4.5, 9.0 Hz, 1H), 4.52 (m, 1H), 4.24 (dq, *J*=4.6, 9.1 Hz, 1H), 3.97 (tt, *J*=4.2, 8.4 Hz, 1H), 3.81–3.63 (m, 2H), 2.36 (m, 2H), 2.28 (ddd, *J*=5.5, 9.3, 15.3 Hz, 1H), 2.03 (s, 3H), 1.97 (td, *J*=3.1, 12.7 Hz, 1H), 1.86–1.62 (m, 5H), 1.39 (td, *J*=9.2, 12.9 Hz, 1H), 1.02 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  170.3, 164.1, 144.9, 135.5, 133.8, 129.6, 127.7, 121.4, 75.0, 67.2, 66.4, 65.9, 60.2, 38.1, 36.8, 36.2, 34.4, 28.7, 26.8, 21.2, 19.2; FAB-HRMS *m/z* 479.1882 (calcd for C<sub>27</sub>H<sub>31</sub>O<sub>6</sub>Si [M-tBu]<sup>+</sup> *m/z* 479.1890).

### 2.1.18. Dihydropyran-2-one (+)-7

The reaction of (+)-**27** with Grubbs' catalyst (0.97 equiv.) in methylene chloride was carried out in a fashion similar to the ring closing metathesis of (-)-**26**, except that the reaction was run at room temperature for 20 h. Work-up and purification as before gave (+)-**7** as a colorless oil (89%): *R*<sub>f</sub> 0.14 (hexane–ethyl acetate=7:3); [ $\alpha$ ]<sub>D</sub>=+7.7 (*c* 1.16, CHCl<sub>3</sub>); IR 3067, 1726, 1235 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.64–7.59 (m, 4H), 7.44–7.33 (m, 6H), 6.70 (ddd, *J*=3.0, 5.5, 9.6 Hz, 1H), 5.94 (dd, *J*=2.5, 9.7 Hz, 1H), 5.08 (tt, *J*=4.3, 8.7 Hz, 1H), 4.57 (m, 1H), 4.34 (m, 1H), 4.02 (tt, *J*=4.1, 8.4 Hz, 1H), 3.84 (ddd, *J*=4.0, 9.5, 9.8 Hz, 1H), 3.68 (td, *J*=4.9, 10.2 Hz, 1H), 2.31–2.11 (m, 2H), 2.04 (s, 3H), 2.04–1.62 (m, 7H), 1.44 (td, *J*=8.2, 13.4 Hz, 1H), 1.02 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  170.4, 164.0, 144.8, 135.4,

133.9, 133.6, 129.6, 127.6, 121.3, 74.4, 67.3, 65.5, 65.4, 60.0, 38.0, 37.7, 35.8, 35.0, 29.8, 26.8, 21.3, 19.2. This product was not further characterized.

#### 2.1.19. Mitsunobu inversion of (+)-23

To a stirred slurry of (+)-**23** (358 mg, 0.702 mmol), triphenylphosphine (442 mg, 1.68 mmol), and *p*-nitrobenzoic acid (282 mg, 1.68 mmol) in toluene (5 mL) at  $-30^{\circ}\text{C}$  was added diethyl azodicarboxylate (0.26 mL, 1.7 mmol). The reaction mixture was warmed to rt overnight. Saturated aqueous  $\text{NaHCO}_3$  was added and the layers were separated. The aqueous layer was extracted with ether (4 $\times$ 20 mL) and the combined organic phases were dried ( $\text{MgSO}_4$ ) and concentrated. Excess DEAD was removed by kugelrohr distillation and the residue was purified by column chromatography (hexane–ethyl acetate=7:3), to give (+)-**28** (0.286 g, 51%) as a pale yellow oil:  $R_f$  0.77 (hexane–ethyl acetate=1:1);  $[\alpha]_D^{25} = +8.1$  (c 0.94,  $\text{CHCl}_3$ ); IR 3067, 3048, 1726, 1639, 1608, 1521, 1352, 921  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  8.25 and 8.16 (AA'BB',  $J=9.0$  Hz, 4H), 7.68–7.63 (m, 4H), 7.42–7.34 (m, 6H), 5.78 (tdd,  $J=7.1, 10.1, 17.1$  Hz, 1H), 5.24 (tt,  $J=5.7, 6.7$  Hz, 1H), 5.13–5.01 (m, 3H), 4.16–4.08 (m, 1H), 4.02–3.92 (m, 1H), 3.81–3.64 (m, 2H), 2.57–2.40 (m, 2H), 2.23 (ddd,  $J=7.1, 8.6, 14.5$  Hz, 1H), 2.02 (s, 3H), 1.86–1.64 (m, 5H), 1.43–1.19 (m, 2H), 1.03 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  170.3, 164.0, 150.4, 135.7, 135.5, 133.7, 132.9, 130.6, 129.5, 127.6, 123.4, 118.5, 72.7, 68.1, 67.2, 66.2, 60.3, 38.2, 38.0, 36.3, 35.7, 34.2, 26.7, 21.2, 19.1; FAB-HRMS  $m/z$  666.3054 (calcd for  $\text{C}_{37}\text{H}_{45}\text{O}_8\text{NSiLi}$   $[\text{M}+\text{Li}]^+$   $m/z$  666.3075).

#### 2.1.20. Hydrolysis of (+)-28

A solution of (+)-**28** (78.5 mg, 0.119 mmol) in saturated methanolic  $\text{K}_2\text{CO}_3$  (10 mL) was stirred at rt until TLC monitoring indicated complete consumption of starting material. Aqueous HCl (1% by volume) was added until the solution was neutral. The reaction mixture was extracted with ether (4 $\times$ 25 mL), and the combined organic layers were dried ( $\text{MgSO}_4$ ) and concentrated. The residue was purified by column chromatography (hexane–ethyl acetate=1:1) to give (+)-**29** (40.3 mg, 72%) as a colorless oil:  $R_f$  0.17 (hexane–ethyl acetate=1:1);  $[\alpha]_D^{25} = +9.4$  (c 0.73,  $\text{CHCl}_3$ ); IR 3396, 1107  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.69–7.64 (m, 4H), 7.45–7.36 (m, 6H), 5.89–5.75 (m, 1H), 5.13–5.07 (m, 2H), 4.26–4.21 (m, 1H), 4.05–3.97 (m, 2H), 3.85–3.69 (m, 3H), 3.24 (OH), 2.23 (t,  $J=6.5$  Hz, 1H), 2.00–1.57 (m, 8H), 1.46 (br d,  $J=14.4$  Hz, 1H), 1.35 (td,  $J=7.9, 13.0$  Hz, 1H), 1.05 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  135.5, 134.8, 133.7, 129.6, 127.6, 117.4, 70.8, 70.4, 67.0, 64.2, 60.4, 41.7, 38.9, 38.7, 38.5, 37.7, 26.8, 19.1. This product was used in the next reaction without further characterization.

#### 2.1.21. Hydrolysis of (–)-22

The hydrolysis of (–)-**22** in saturated methanolic  $\text{K}_2\text{CO}_3$  was carried out in a fashion similar to the hydrolysis of (+)-**28** to give (–)-**29** (88%): The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of (–)-**29** were identical with (+)-**29**.  $[\alpha]_D^{25} = -5.7$  (c 0.88,  $\text{CHCl}_3$ ).

#### 2.1.22. Bisacrylate (+)-30

The bisacrylate ester (+)-**30** (43%) of (+)-**29** was prepared in the same fashion as the acrylate ester of (–)-**22**:  $R_f$  0.78 (hexane–ethyl acetate=1:1),  $[\alpha]_D^{25} = +15.5$  (c 0.976,  $\text{CHCl}_3$ ); IR 3068, 1726  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.69–7.64 (m, 4H), 7.43–7.34 (m, 6H), 6.40 and 6.38 (2 $\times$ dd,  $J=1.6, 17.2$  Hz, 2H), 6.09 (2 $\times$ dd,  $J=10.3, 17.3$  Hz, 2H), 5.83 and 5.79 (2 $\times$ dd,  $J=1.6, 10.3$  Hz, 1H), 5.74 (m, 1H), 5.17–5.00 (m, 2H), 4.15–4.05 (m, 1H), 4.03–3.95 (m, 1H), 3.85–3.68 (m, 2H), 2.38 (m, 2H), 2.07 (td,  $J=7.5, 14.5$  Hz, 1H), 2.00 (br d,  $J=12.9$  Hz, 1H), 1.90–1.65 (m, 5H), 1.40 (td,  $J=9.5, 12.7$  Hz, 1H), 1.04 (s, 9H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  165.6, 165.4, 135.5, 133.8, 133.7, 132.2, 130.7, 130.6, 129.5, 128.7, 128.6, 127.6, 118.2, 70.9, 68.0, 67.5, 66.2, 60.3, 38.2, 36.3, 35.8, 34.0, 26.8, 19.1. This product was used in the next reaction without further characterization.

#### 2.1.23. Dihydropyran-2-one (+)-6

The reaction of (+)-**30** with Grubbs' catalyst (0.07 equiv.) in  $\text{CH}_2\text{Cl}_2$  was carried out in a fashion similar to the ring closing metathesis of (–)-**22**, except that the reaction was run at room temperature for 48 h. Work-up and purification as before gave (+)-**6** as a colorless oil (79%):  $R_f$  0.56 (hexane–ethyl acetate=1:1);  $[\alpha]_D^{25} = +45.0$  (c 0.732,

CHCl<sub>3</sub>); IR 1721 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.66–7.61 (m, 4H), 7.45–7.34 (m, 6H), 6.77 (ddd, *J*=3.3, 5.1, 9.5 Hz, 1H), 6.41 (dd, *J*=1.5, 17.4 Hz, 1H), 6.10 (dd, *J*=10.7, 17.4 Hz, 1H), 5.98 (td, *J*=1.9, 9.6 Hz, 1H), 5.85 (dd, *J*=1.6, 10.4 Hz, 1H), 5.16 (tt, *J*=4.8, 8.7 Hz, 1H), 4.53 (m, 1H), 4.25 (dq, *J*=9.6, 4.9 Hz, 1H), 4.00 (tt, *J*=4.1, 8.0 Hz, 1H), 3.81–3.64 (m, 2H), 2.39–2.24 (m, 3H), 2.01 (td, *J*=3.5, 13.0 Hz, 1H), 1.90–1.69 (m, 5H), 1.45 (td, *J*=9.0, 12.9 Hz, 1H), 1.03 (s, 9H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 165.5, 164.2, 144.9, 135.5, 133.7, 133.6, 131.0, 128.5, 127.7, 121.4, 75.0, 67.4, 66.3, 65.8, 60.1, 38.0, 36.8, 36.0, 34.3, 28.6, 26.8, 19.1; FAB-HRMS *m/z* 555.2747 (calcd for C<sub>32</sub>H<sub>40</sub>O<sub>6</sub>SiLi [M+Li]<sup>+</sup> *m/z* 555.2754).

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