Stereoselective synthesis of the published structure of synargentolide A and of one of its stereoisomers

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This paper is dedicated to Prof. P. Molina on the occasion of his 60th birthday

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Abstract

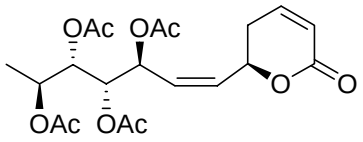
A stereoselective synthesis is described of the structure published for the naturally occurring synargentolide A, an α,β-unsaturated lactone. The key steps of the synthesis were a Brown´s asymmetric allylation and a ring closing metathesis. The spectroscopic data of the synthetic product were very close to those of the natural product but did not exactly match them. An epimer of the published structure was then synthesized according to a similar strategy. Again, the data of the synthetic product did not match those reported for the natural product. It is thus likely that the actual structure of synargentolide A differs from the published one in more than mere stereochemical aspects.

Keywords: Synargentolide A, ring-closing metathesis, asymmetric allylboration, asymmetric dihydroxylation

Introduction

Lactone rings constitute structural features of a broad range of natural products.[1] Many of these, most particularly the α, β-unsaturated lactones,[1a] display pharmacologically relevant properties. In recent times, we have been interested in the synthesis of natural lactones of such structural type. Among them, the conjugated δ-lactones spicigerolide **1**, anamarine **2**, hyptolide **3** and synrotolide **4** have been isolated from species of *Hyptis*, *Syncolostemon*, and related genera of the family Lamiaceae.[2] All these molecules possess a Michael acceptor moiety, a feature which potentially endows them with cytotoxic properties.[1a,3] While this makes these products attractive synthetic goals, efforts in this direction have been limited for many years to the syntheses of **2** and its unnatural enantiomer.[4] Recently, we have published stereoselective syntheses of **1**, **2** and **3**.[5] We describe a stereoselective synthesis of a lactone with structure **5**, which was proposed for

synargentolide A, a compound isolated in 1998 from extracts of *Syncolostemon argenteus*.[6] In addition, for reasons we will comment on later, we have also synthesized lactone **6**, an epimer of **5** at the lactone ring-attachment carbon atom (C-6 in heterocycle pyrone numbering).



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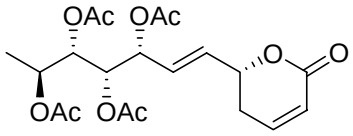

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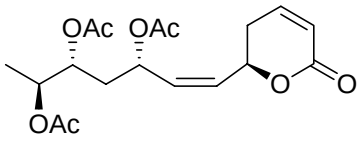

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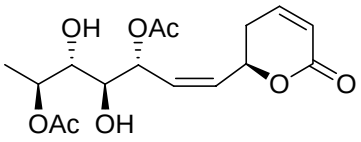

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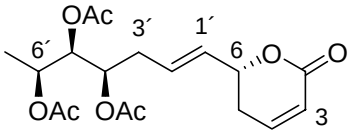

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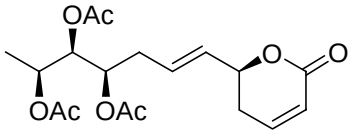

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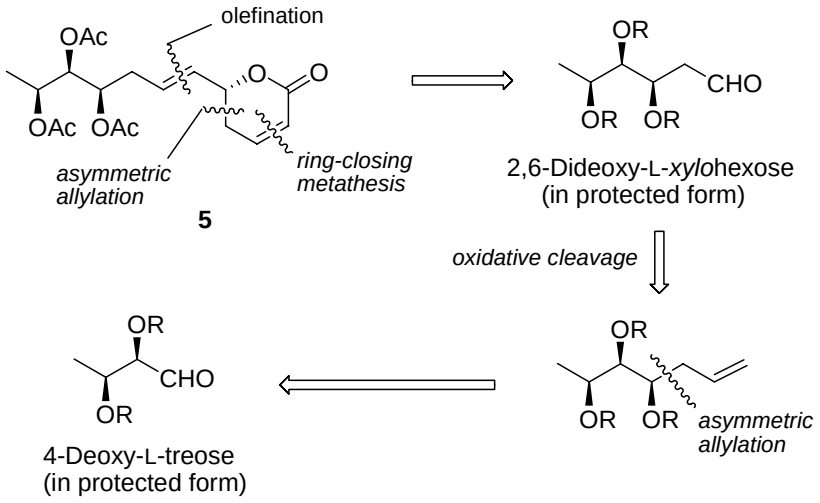
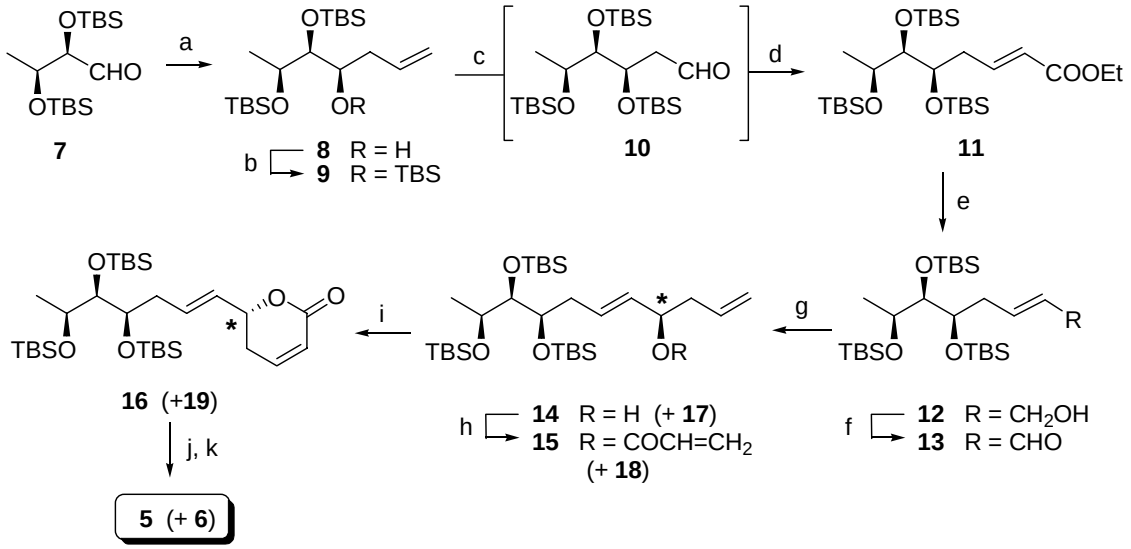
Results and Discussion

For the retrosynthetic analysis of both **5** and **6**, we relied on the same concept as used in our syntheses of lactones **1**–**3**, where asymmetric allylations and ring-closing metatheses played a key role in the construction of the 6-alkenyl-2-pyrone moiety.[5,7] In the case of **5**, a similar analysis leads to 2,6-dideoxy-L-*xylo*hexose (L-boivinose), a monosaccharide which is not available commercially (Scheme 1). Several syntheses of this and related 2,6-dideoxyhexoses have been previously reported in the literature.[8] In the present case, however, we have selected a different approach based on the sequential asymmetric allylation/oxidative cleavage of a suitably protected 4-deoxy-L-treose.

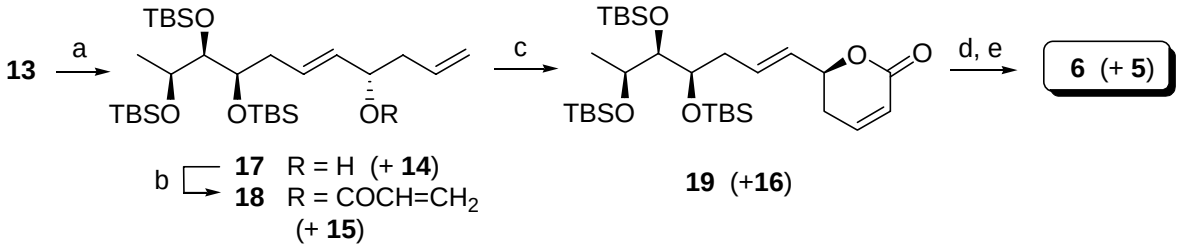


Scheme 1. Retrosynthetic analysis of lactone **5**.

The known aldehyde **7** [9] (Scheme 2) was subjected to Brown's asymmetric allylation with the B-allyl di-*iso*pinocampheylborane prepared from (+)-di-i*so*pinocampheylboron chloride and allylmagnesium bromide.[10] This provided compound **8** as a single diastereoisomer,[11] which was then silylated to **9**. Ozonolytic cleavage of the double bond in **9** was followed by Wittig–Horner olefination of the intermediate aldehyde **10** under mild conditions[12] to yield the conjugated ester **11**. The latter was reduced via alcohol **12** to the corresponding aldehyde **13**, which was then subjected to a new Brown allylation with the same reagent as above. This gave a 9:1 mixture of the homoallyl alcohol **14** and its epimer (Scheme 3) at the starred carbon **17**. The mixture proved inseparable in our hands, even when using HPLC. We thus carried it over to the end of the synthesis. Reaction of **14** (+**17**) with acryloyl chloride provided the mixture of **15** and its epimer **18**, again inseparable, which was then subjected to the conditions of ring-closing metathesis with the standard Grubbs' ruthenium catalyst $PhCH{=}RuCl_2(PCy_3)_2$ (Cy = cyclohexyl).[13] The resulting lactone **16** in admixture with its epimer **19** was finally deprived of its three silyl protecting groups and peracetylated to yield lactone **5**, still containing about 10% of its C-6 epimer **6**.[14] Unexpectedly, however, the NMR data of the major lactone **5**, while very similar to those of the natural product,[15] were sufficiently different to prove their non-identity (Figure 1 and Table 1). The aspect and position of the NMR signals of the minor lactone **6** also suggested its non-identity with the natural product. However, we decided to synthesize this stereoisomer in order definitively to confirm this conclusion. The previous synthetic strategy was used again in this case (Scheme 3). Thus, aldehyde **13** was subjected to Brown allylation with the B-allyl d*i*-i*so*pinocampheylborane prepared from (–)-di-*iso*pinocampheylboron chloride and allylmagnesium bromide. Unfortunately, an inseparable 9:1 mixture of **17** and **14** was formed once again. Acryloylation as above, followed by ring-closing metathesis, furnished lactone **19** containing about 10% of its epimer **16**. Removal of all protecting groups and peracetylation finally yielded lactone **6**, contaminated with **5**. We were then able to confirm that synthetic **6** is also different from the natural product (Figure 1 and Table 1).



Scheme 2. Synthesis of lactone **5**. *Reagents and conditions*: (a) allyl-$BIpc_2$ [from (+)-DIP-Cl and allylmagnesium bromide], Et_2O, −78°C, 1 h (single diastereoisomer, 58% overall yield after the ozonolysis–allylation sequence, see ref. 9); (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, RT, 1 h (92%); (c) O_3, −78°C, then PPh_3, RT, 2 h; (d) $(EtO)_2POCH_2COOEt$, LiCl, DIPEA, MeCN, RT, 3 h (65% overall yield after the ozonolysis–olefination sequence); (e) DIBAL, 0°C, 1 h, 75%; (f) MnO_2, CH_2Cl_2, reflux, 2 h; (g) allyl-$BIpc_2$ [from (+)-DIP-Cl and allylmagnesium bromide], Et_2O, −78°C, 1 h (9:1 mixture of diastereoisomers, 60% overall yield after the oxidation-allylation sequence); (h) acryloyl chloride, DIPEA, CH_2Cl_2, −78°C, 2 h (69% of the epimer mixture); (i) 10% $PhCH{=}RuCl_2(PCy_3)_2$, CH_2Cl_2, reflux, 3 h (78% of the epimer mixture); (j) PPTS, aq. MeOH, reflux, 2 d; (k) Ac_2O, Et_3N, DMAP, CH_2Cl_2, RT, 1 h ((60% overall yield of the 9:1 epimer mixture after the two steps). Abbreviations: DIP-Cl, di-*iso*pinocampheylboron chloride; TBSOTf, *t*-butyldimethylsilyl triflate; DIPEA, ethyl N,N-di-*iso*propylamine; DIBAL, di-*iso*butylaluminum hydride; Cy, cyclohexyl; PPTS, pyridinium *p*-toluenesulfonate; DMAP, N,N-dimethylaminopyridine.



Scheme 3. Synthesis of lactone **6**. *Reagents and conditions*: (a) allyl-$BIpc_2$ [from (−)-DIP-Cl and allylmagnesium bromide], Et_2O, −78°C, 1 h (85:15 mixture of diastereoisomers, 61% after the oxidation–allylation two-step sequence); (b) acryloyl chloride, DIPEA, CH_2Cl_2, −78°C, 2 h (70% of the epimeric mixture); (c) $PhCH{=}RuCl_2(PCy_3)_2$ (10%), CH_2Cl_2, reflux, 3 h (77%); (d) PPTS, aq. MeOH, reflux, 2 days; (e) Ac_2O, Et_3N, DMAP, CH_2Cl_2, RT, 1 h (50% overall for the two steps).

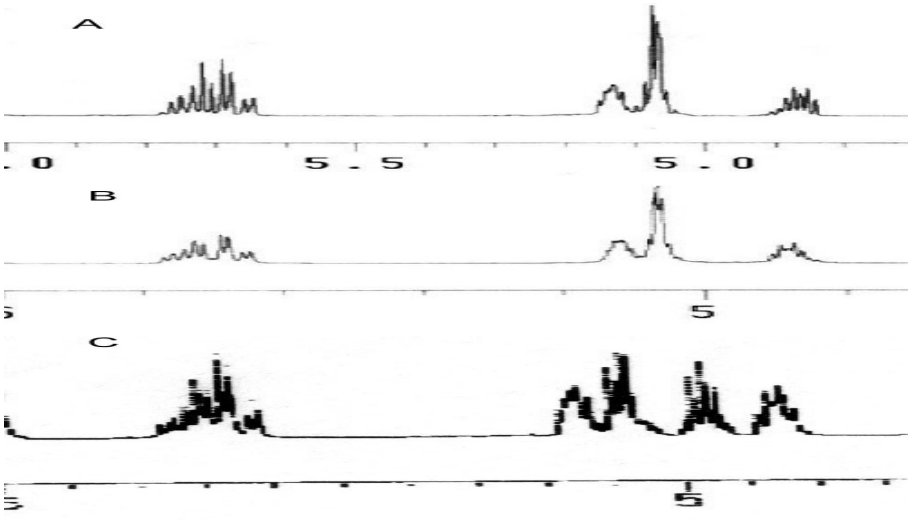


Figure 1. Comparison of the δ 6.00–4.70 range of the ^{1}H- NMR spectra of the synthetic lactones **5** (A) and **6** (B) with that of natural synargentolide A (C).

Table 1. ^{13}C- NMR data of synthetic lactones **5** and **6** and of natural synargentolide A

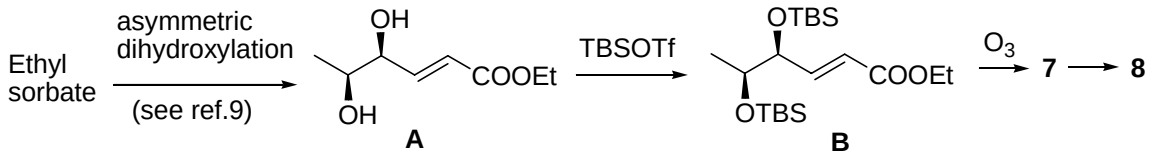
	Compound		
Carbon	5	6	Synargentolide A
C-2	163.8	163.8	163.8
C-3	121.9	121.7	121.6
C-4	144.5	144.4	144.5
C-5	29.8	29.4	29.4
C-6	77.7	77.2	77.2
C-1′	131.4	131.0	130.9
C-2′	128.6	128.1	128.3
C-3′	34.2	34.0	34.0
C-4′	70.7	70.5	69.7
C-5′	74.4	74.3	73.8
C-6′	69.0	68.7	67.4
C-7′	16.6	16.5	16.0
OAc (C=O)	170.3, 170.2 (x 2)	170.1 (x 2), 170.0	170.2, 170.1, 170.0
OAc (Me)	21.2, 21.0, 20.8	21.0, 20.8, 20.6	21.0, 20.9, 20.8

It turns out, therefore, that the structure published for the natural lactone synargentolide A is not correct. The authors established the relative configuration of the C-4′/C-5′/C-6′ carbon chain of synargentolide A by NMR examination of the two acetonides formed between the hydroxyl pairs at C-4′/C-5′ (1,3-dioxolane) and C-4′/C-6′ (1,3-dioxane).[6] The five-membered acetonide was found to be *trans* on the basis of 2D- NOE correlations, whereas the six-membered acetonide was found to be *cis* on the basis of the ^{13}C- NMR chemical shifts of the methyl signals. Furthermore, the absolute configurations at C-6 and C-6′ were determined by CD measurements and NMR studies of the Mosher esters, respectively. Assuming the correctness of the authors' stereochemical conclusions, it appears that the proposed structure differs from the actual one in more than mere configurational aspects.[16]

Experimental Section

General Procedures. RT denotes room temperature. NMR spectra were measured at 500 MHz in $CDCl_3$ solution at 25 °C. The signals of the deuterated solvent ($CDCl_3$) were taken as the reference (the singlet at δ 7.25 for ^{1}H- NMR and the triplet centered at 77.00 ppm for ^{13}C NMR data). The multiplicities of the ^{13}C- NMR signals were determined with the DEPT pulse sequence. Mass spectra were run by the electron impact (EIMS, 70 eV) or with the fast atom bombardment mode (FABMS, *m*-nitrobenzyl alcohol matrix). IR data are given only for relevant functions (OH, C=O) and were recorded as films on NaCl plates (for oils) or as KBr pellets (solids). Optical rotations were measured at 25 °C. Reactions which required an inert atmosphere were carried out under N_2, in flame-dried glassware. Et_2O was freshly distilled from sodium-benzophenone ketyl. Dichloromethane was freshly distilled from CaH_2. Tertiary amines were freshly distilled from KOH. Hexane was freshly distilled from sodium wire. Commercially available reagents were used as received. Unless detailed otherwise, "work-up" means pouring the reaction mixture into 5% aq. $NaHCO_3$ (if acids had been used in the reaction) or into satd. aq. NH_4Cl (if bases had been utilized), then washing the organic layer again with brine, drying over anhydrous Na_2SO_4 or $MgSO_4$ and evaporation of the solvent *in vacuo*. When solutions were filtered through a Celite pad, the pad was washed again with the same solvent, and the washing liquids added to the main organic layer. The obtained material was then chromatographed on a silica gel column (60-200 μ) with the indicated eluent. Reagent acronyms are explained in the caption of Scheme 2.

(4*R*,5*S*,6*S*)-5,6-Bis-(*tert*-butyldimethylsilyloxy)-hept-1-en-4-ol (**8**)



Ethyl (2*E*,4*S*,5*S*)-dihydroxyhex-2-enoate (**A**) was obtained as reported, by asymmetric dihydroxylation of ethyl sorbate.[9] The dihydroxy ester (1.74 g, ca. 10 mmol) was then dissolved in dry CH_2Cl_2 (50 mL) under N_2 and treated sequentially with 2,6-lutidine (3.5 mL, 30 mmol) and TBSOTf (5.75 mL, 25 mmol). The mixture was stirred overnight at reflux and worked up (extraction with CH_2Cl_2). Column chromatography on silica gel (hexanes-EtOAc, 9:1) afforded the expected disilylated derivative (**B**) (3.42 g, 85%): colorless oil, $[\alpha]_D$ –47.9 (*c* 1.25; $CHCl_3$); ^{1}H- NMR (500 MHz) δ 7.09 (dd, *J* = 15.7, 3.5 Hz, 1H), 6.04 (dd, *J* = 15.7, 2 Hz, 1H), 4.27 (m, 1H), 4.20 (m, 2H), 3.84 (quint., *J* = 6 Hz, 1H), 1.30 (t, *J* = 7 Hz, 3H), 1.00 (d, *J* = 6 Hz, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.07 (3H, s), 0.06 (6H, s), 0.05 (3H, s); ^{13}C NMR (125 MHz) δ 166.6, 18.1, 18.0 (C), 147.7, 121.4, 74.9, 71.1 (CH), 60.2 (CH_2), 25.9 (x 6), 17.4, 14.3, –4.7, –4.8, –4.9, –5.0 (CH_3). IR $\nu_{max.}$ (cm^{-1}) 1725 (C=O); HR EIMS, *m/z* (% rel. int.) 387.2374 [M^+–Me] (5), 358 (43), 345 (84), 244 (38), 159 (100), 147 (66), 73 (67); calcd. for $C_{20}H_{42}O_4Si_2$–Me, M = 387.2386.

The disilylated derivative from above was dissolved in dry CH_2Cl_2 (125 mL) and cooled to –78°C. A stream of ozone–oxygen was bubbled through the solution until persistence of the blue color. Dry N_2 was then bubbled through the solution for 10 min. at the same temperature. After addition of PPh_3 (3.94 g, ca. 15 mmol), the solution was left to stir at RT for 2 h, then worked up (extraction with CH_2Cl_2). Removal of solvent gave a solid material, which was washed three times with cold pentane (3 x 10 mL). The solid (Ph_3PO) was discarded, and the organic phase evaporated in vacuo to yield crude aldehyde **7** which was used as such in the asymmetric allylation (for weight calculations, the yield of the ozonolysis step was assumed to be quantitative).

Allylmagnesium bromide (commercial 1*M* solution in Et_2O, 10 mL, 10 mmol) was added dropwise under N_2 via syringe to a solution of (+)-DIP-Cl (3.85 g, 12 mmol) in dry Et_2O (50 mL) cooled in a solid-CO_2–acetone bath. After replacing the latter by an ice bath, the mixture was stirred for 1 h. The solution was then allowed to stand, which caused precipitation of magnesium halide. The supernatant solution was then transferred carefully to another flask via cannula. After cooling at –78°C, a solution of crude **7** from above, in dry Et_2O (25 mL), was added dropwise via syringe, and the resulting solution stirred further at the same temp. for 1 h. The mixture was then quenched by addition of phosphate pH 7 buffer solution (50 mL), MeOH (50 mL), then 30% H_2O_2 (25 mL). After stirring for 30 min., the mixture was poured onto satd. aq. $NaHCO_3$ and extracted with Et_2O. Column chromatography on silica gel (hexanes-EtOAc, 95:5) afforded **8** (1.87 g, 58% overall yield for the ozonolysis/allylation sequence): colorless oil, $[\alpha]_D$ –2.2 (*c* 1.3; $CHCl_3$); ^{1}H- NMR (500 MHz) δ 5.82 (ddt, *J* = 17, 10.2, 7 Hz, 1H), 5.08 (br. d, *J* = 17 Hz, 1H), 5.06 (br. d, *J* = 10.2 Hz, 1H), 3.89 (qd, *J* = 8, 2.3 Hz, 1H), 3.80 (dq, *J* = 4.4, 6.5 Hz, 1H), 3.50 (dd, *J* = 4.4, 2.3 Hz, 1H), 2.50 (d, *J* = 8 Hz, 1H, OH), 2.25 (m, 2H), 1.16 (d, *J* = 6.5 Hz, 3H), 0.92 (s, 9H), 0.88 (s, 9H), 0.12 (3H, s), 0.10 (3H, s), 0.05 (3H, s), 0.03 (3H, s); ^{13}C NMR (125 MHz) δ 18.1, 18.0 (C), 135.6, 75.3, 70.2, 68.1 (CH), 116.7, 40.6 (CH_2), 25.8 (x 6), 17.7, –4.2, –4.6 (x 2), –4.8 (CH_3). IR $\nu_{max.}$ (cm^{-1}) 3560 (br., OH); HR EIMS, Found *m/z* (% rel. int.) 333.2238 [M^+–C_3H_5] (1), 303 (8), 185 (45), 159 (60), 73 (100). Calcd. for $C_{19}H_{42}O_3Si_2$ –C_3H_5, M = 333.2281.

(4*R*,5*R*,6*S*)-4,5,6-Tris-(*tert*-butyldimethylsilyloxy)-hept-1-ene (9). Alcohol **8** (1.87 g, ca. 5 mmol) was dissolved in dry CH_2Cl_2 (20 mL) under N_2 and treated sequentially with 2,6-lutidine (1.2 mL, ca. 10 mmol) and TBSOTf (1.72 mL, 7.5 mmol). The reaction mixture was then stirred for 1 h at RT and worked up (extraction with CH_2Cl_2). Column chromatography on silica gel (hexanes-EtOAc, 19:1) afforded **9** (2.25 g, 92%): colorless oil, $[\alpha]_D$ +18 (*c* 1; $CHCl_3$); ^{1}H- NMR (500 MHz) δ 5.80 (ddt, *J* = 17, 10.2, 7 Hz, 1H), 5.04 (br. d, *J* = 17 Hz, 1H), 5.00 (br. d, *J* = 10.2 Hz, 1H), 4.02 (m, 1H), 3.79 (m, 1H), 3.40 (m, 1H), 2.54 (m, 1H), 2.25 (m, 1H), 1.20 (br. d, *J* = 6.5 Hz, 3H), 0.92 (br. s, 9H), 0.91 (br. s, 9H), 0.90 (br. s, 9H), 0.09 (6H, br. s), 0.07 (6H, br. s), 0.05 (6H, br. s); ^{13}C- NMR (125 MHz) δ 18.2 (x 2), 18.1 (C), 137.3, 77.3, 74.0, 68.4 (CH), 116.2, 37.3 (CH_2), 25.9 (x 9), 21.1, –3.0, –4.0, –4.2 (x 4) (CH_3). HR EIMS, Found *m/z* (% rel. int.) 447.3215 [M^+–C_3H_5] (3), 329 (11), 303 (25), 259 (26), 185 (72), 159 (100), 73 (90); Calcd. for $C_{25}H_{56}O_3Si_3$–C_3H_5, M = 447.3146.

Ethyl (2*E*,5*R*,6*R*,7*S*)-5,6,7-Tris-(*tert*-butyldimethylsilyloxy)-oct-2-enoate (11). Alkene **9** (2.25 g, 4.6 mmol) was dissolved in dry CH_2Cl_2 (75 mL) and cooled to −78°C. A stream of ozone-oxygen was bubbled through the solution until persistence of the blue color. Dry N_2 was then bubbled through the solution for 10 min. at the same temperature. After addition of PPh_3 (2.36 g, *ca*. 9 mmol), the solution was stirred at RT for 2 h, then worked up (extraction with CH_2Cl_2). Removal of solvent gave a solid material, which was washed with cold pentane (3 x 10 mL). The solid (Ph_3PO) was discarded, and the organic phase evaporated *in vacuo* to yield crude aldehyde **10** as an oil which was used as such in the olefination (for weight calculations, the yield of the ozonolysis step was assumed to be quantitative).

Anhydrous lithium chloride (424 mg, 10 mmol), DIPEA (1.22 mL, 7 mmol) and $(EtO)_2P(O)CH_2CO_2Et$ (1.8 mL, *ca*. 9 mmol) were dissolved in dry acetonitrile (20 mL) under N_2. The mixture was stirred at RT for 5 min. A solution of crude **10** from above in dry acetonitrile (20 mL) was then added to the mixture, and stirred for 3 h at RT. Work-up (extraction with Et_2O) and column chromatography on silica gel (hexanes-EtOAc, 99:1) yielded **8** (1.68 g, 65% overall yield for the ozonolysis/olefination sequence): colorless oil, $[\alpha]_D$ +21.3 (*c* 1.26; $CHCl_3$); ^{1}H-NMR (500 MHz) δ 6.94 (dt, *J* = 15.7, 7.5 Hz, 1H), 5.80 (d, *J* = 15.7 Hz, 1H), 4.18 (m, 2H), 4.08 (dq, *J* = 3.5, 6.5 Hz, 1H), 3.78 (dt, *J* = 4, 5 Hz, 1H), 3.37 (t, *J* = 4 Hz, 1H), 2.66 (dddd, *J* = 14.5, 7.5, 4, 1.3 Hz, 1H), 2.45 (dt, *J* = 14.5, 7.5 Hz, 1H), 1.28 (t, *J* = 7 Hz, 3H), 1.18 (d, *J* = 6.5 Hz, 3H), 0.92 (br. s, 9H), 0.90 (br. s, 9H), 0.89 (br. s, 9H), 0.07 (12H, s), 0.04 (3H, s), 0.03 (3H, s); ^{13}C NMR (125 MHz) δ 166.5, 18.1, 18.0 (x 2) (C), 148.2, 122.9, 77.4, 73.6, 67.6 (CH), 60.0, 35.6 (CH_2), 26.0 (x 3), 25.9 (x 3), 25.8 (x 3), 21.3, 14.3, –4.0 (x 2), –4.1 (x 2), –4.5 (x 2) (CH_3). IR, $\nu_{max.}$ (cm^{-1}) 1725 (C=O); HR EIMS, *m/z* (% rel. int.) 503.4200 [M^+–*t*-Bu] (16), 401 (16), 371 (22), 331 (50), 303 (44), 257 (100), 159 (96), 73 (70). Calcd. for $C_{28}H_{60}O_5Si_3$ – *t*-Bu, M = 503.4132.

(2*E*,5*R*,6*R*,7*S*)-5,6,7-Tris-(*tert*-butyldimethylsilyloxy)-oct-2-en-1-ol (12). Ester **11** (1.68 g, *ca*. 3 mmol) was dissolved in dry hexane (15 mL), cooled to 0°C, and treated dropwise under N_2 with DIBAL (1*M* solution in hexanes, 6 mL, 6 mmol). The solution was then stirred at RT. for 1 h. Satd aq. NH_4Cl was then added and the stirring continued for 30 min. The reaction mixture

was then filtered through Celite, and the Celite pad washed with EtOAc. Solvent removal gave an oily material, which was chromatographed on silica gel (hexanes-EtOAc, 95:5) to afford **12** (1.17 g, 75%): colorless oil, $[\alpha]_D$ +15.1 (*c* 1.45; $CHCl_3$); ^{1}H- NMR (500 MHz) δ 5.65 (m, 2H), 4.10 (br. s, 1H, OH), 4.00 (dq, *J* = 4.2, 6.5 Hz, 1H), 3.73 (ddd, *J* = 8, 4, 4 Hz, 1H), 3.38 (t, *J* = 4.2 Hz, 1H), 2.52 (m, 2H), 2.24 (m, 2H), 1.17 (d, *J* = 6 Hz, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.07 (12H, s), 0.05 (3H, s), 0.03 (3H, s); ^{13}C NMR (125 MHz) δ 18.1 (x 2), 18.0 (C), 131.7, 130.8, 77.3, 74.1, 68.1 (CH), 63.9, 35.6 (CH_2), 26.0 (x 3), 25.9 (x 3), 25.8 (x 3), 21.1, –4.0 (x 3), –4.3 (x 3) (CH_3). IR $\nu_{max.}$ (cm^{-1}) 3350 (br., OH); HR EIMS, *m/z* (% rel. int.) 447.3145 [M^+–C_4H_7] (3), 303 (14), 215 (28), 159 (100), 73 (68). Calcd. for $C_{26}H_{58}O_4Si_3$ –C_4H_7, M = 447.3146.

(5*E*,4*R*,8*R*,9*R*,10*S*)-8,9,10-Tris-(*tert*-butyldimethylsilyloxy)undeca-1,5-dien-4-ol (14). The alcohol **12** (1.17 g, 2.25 mmol) was dissolved in CH_2Cl_2 (35 mL) and treated with MnO_2 (3 g, *ca*. 35 mmol). The reaction mixture was then stirred at reflux until consumption of the starting material (*ca*. 2 h, TLC monitoring), then filtered through Celite and washed with CH_2Cl_2. Solvent removal gave crude aldehyde **13**, which was used as such in the asymmetric allylation (for weight calculations, the yield of the oxidation step was assumed to be quantitative).

Allylmagnesium bromide (commercial 1*M* solution in Et_2O, 2.5 mL, 2.5 mmol) was added dropwise via syringe, under N_2, to a solution of (+)-DIP-Cl (0.96 g, 3 mmol) in dry Et_2O (15 mL) cooled in a solid CO_2–acetone bath. After replacing the latter by an ice bath, the mixture was stirred for 1 h. Upon standing, magnesium halide precipitated. The supernatant solution was then carefully transferred to another flask via cannula. After cooling at −78°C, the solution of crude **13** from above, in dry Et_2O (5 mL), was added dropwise via syringe, then stirred further at the same temperature for 1 h. The reaction mixture was then quenched by addition of pH 7 phosphate buffer solution (15 mL), MeOH (15 mL) and 30% H_2O_2 (7 mL). After stirring for 30 min., the mixture was poured onto satd. aq. $NaHCO_3$ and worked up (extraction with Et_2O). Column chromatography on silica gel (hexanes-EtOAc, 95:5) afforded **14** (755 mg as an inseparable 9:1 mixture with **17**, 60% overall yield for the oxidation/allylation sequence): colorless oil, ^{1}H- NMR (500 MHz) δ 5.82 (ddt, *J* = 17, 10.2, 7 Hz, 1H), 5.66 (dt, *J* = 15.5, 6.5 Hz, 1H), 5.50 (dd, *J* = 15.5, 6.8 Hz, 1H), 5.15-5.10 (m, 2H), 4.12 (dt, *J* = 6.8, 6.8 Hz, 1H), 4.00 (dq, *J* = 4, 6.5 Hz, 1H), 3.73 (ddd, *J* = 8, 4, 4 Hz, 1H), 3.36 (dd, *J* = 4, 4 Hz, 1H), 2.50 (m, 1H), 2.35-2.20 (m, 3H), 1.60 (br. s, 1H, OH), 1.17 (d, *J* = 6.5 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 18H), 0.07 (9H, s), 0.06 (3H, s), 0.05 (6H, s); ^{13}C NMR (125 MHz) δ 18.1, 18.0, 17.9 (C), 134.4, 133.8, 130.3, 77.1, 74.1, 72.1, 68.3 (CH), 117.7, 42.0, 35.6 (CH_2), 25.9 (x 6), 25.8 (x 3), 20.9, –4.0, –4.1 (x 2), –4.3 (x 3) (CH_3). IR $\nu_{max.}$ (cm^{-1}) 3350 (br., OH). FABMS, *m/z* 559 [M+H^+]; calcd. for $C_{29}H_{63}O_4Si_3$, M = 559. The NMR signals are those of the major component **14**.

(2*E*,1*R*,5*R*,6*R*,7*S*)-1-Allyl-5,6,7-tris-(*tert*-butyldimethylsilyloxy)oct-2-enyl acrylate (15). The mixture of alcohols **14**/**17** (755 mg, 1.35 mmol) was dissolved in dry CH_2Cl_2 (50 mL) under N_2, cooled to −78°C, and treated with DIPEA (3.5 mL, 20 mmol) and acryloyl chloride (1.1 mL, 13.5 mmol). The reaction mixture was then stirred for 2 h at the same temp. and worked up (extraction with CH_2Cl_2). Column chromatography on silica gel (hexanes-EtOAc, 95:5) afforded

15 (571 mg as an inseparable 9:1 mixture with **18**, 69%): colorless oil, ^{1}H- NMR (500 MHz) δ 6.40 (dd, *J* = 17.3, 1.5 Hz, 1H), 6.10 (dd, *J* = 17.3, 10.5 Hz, 1H), 5.80 (dd, *J* = 10.5, 1.5 Hz, 1H), 5.80–5.70 (m, 2H), 5.50 (dt, *J* = 15.5, 7 Hz, 1H), 5.40 (m, 1H), 5.10-5.05 (m, 2H), 4.00 (dq, *J* = 4, 6.5 Hz, 1H), 3.73 (ddd, *J* = 8, 4, 4 Hz, 1H), 3.36 (dd, *J* = 4, 4 Hz, 1H), 2.50 (m, 1H), 2.40 (m, 2H), 2.20 (m, 1H), 1.17 (d, *J* = 6.5 Hz, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.07 (12H, s), 0.04 (3H, s), 0.02 (3H, s); ^{13}C-NMR (125 MHz) δ 165.3, 18.1 (x 2), 18.0 (C), 133.4, 132.9, 129.3, 129.0, 77.2, 74.0 (x 2), 68.3 (CH), 130.3, 117.8, 39.3, 35.7 (CH_2), 26.0 (x 9), 21.1, –4.0 (x 2), –4.3 (x 3), –4.4 (CH_3). IR $\nu_{max.}$ (cm^{-1}) 1728 (C=O). EIMS, *m/z* (% rel. int.) 555 [M^+–*t*-Bu] (1), 303 (11), 159 (100), 73 (48). Calcd. for $C_{32}H_{64}O_5Si_3$–*t*-Bu, M = 555. The NMR signals are those of the major component **15**.

(6*R*)-6-[(1*E*, 4*R*, 5*R*, 6*S*)-4,5,6-Tris-(*tert*-butyldimethylsilyloxy)hept-1-enyl]-5, 6-dihydropyran-2-one (16). The mixture of acrylates **15**/**18** (552 mg, 0.9 mmol) was dissolved under N_2 in dry, degassed CH_2Cl_2 (80 mL) and treated with Grubbs' ruthenium catalyst $PhCH{=}RuCl_2(PCy_3)_2$ (74 mg, 0.09 mmol). The mixture was then stirred at reflux until consumption of the starting material (*ca*. 2.5 h, TLC monitoring). After removal of solvent under reduced pressure, and column chromatography of the residue on silica gel (hexanes-EtOAc, 95:5), lactone **16** was obtained (410 mg as an inseparable 9:1 mixture with **19**, 78%): colorless oil, ^{1}H- NMR (500 MHz) δ 6.82 (dt, *J* = 9.8, 4.3 Hz, 1H), 5.98 (dt, *J* = 9.8, 1.8 Hz, 1H), 5.75 (dt, *J* = 15.5, 7 Hz, 1H), 5.55 (dd, *J* = 15.5, 7 Hz, 1H), 4.80 (q, *J* = 7 Hz, 1H), 4.00 (dq, *J* = 4, 6.5 Hz, 1H), 3.70 (ddd, *J* = 8, 4, 4 Hz, 1H), 3.32 (dd, *J* = 4, 4 Hz, 1H), 2.50 (m, 1H), 2.35 (m, 2H), 2.25 (m, 1H), 1.12 (d, *J* = 6.5 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.84 (s, 9H), 0.02 (12H, s), 0.00 (6H, s); ^{13}C- NMR (125 MHz) δ 163.8, 18.0 (x 2), 17.9 (C), 144.4, 133.6, 128.4, 121.6, 78.0, 77.2, 73.8, 67.8 (CH), 35.5, 29.6 (CH_2), 25.9 (x 9), 21.0, –4.1, –4.2 (x 2), –4.3, –4.4, –4.5 (CH_3). IR $\nu_{max.}$ (cm^{-1}) 1738 (C=O). EIMS, *m/z* (% rel. int.) 527 [M^+–*t*-Bu] (8), 483 (23), 159 (100), 73 (98). Calcd. for $C_{30}H_{60}O_5Si_3$–*t*-Bu, M = 527. The NMR signals are those of the major component **16**.

(6*R*)-6-[(1*E*,4*R*,5*R*,6*S*)-4,5,6-Triacetoxyhept-1-enyl]-5,6-dihydropyran-2-one (5). The mixture of lactones **16**/**19** (292 mg, 0.5 mmol) was dissolved in MeOH (50 mL), treated with PPTS (12 mg, 0.05 mmol) and water (0.1 mL) and heated at reflux for 2 days. Solid $NaHCO_3$ (100 mg) was then added to the mixture, which was then stirred for 5 min. and filtered. Solvent removal under reduced pressure gave an oily residue which was dissolved in dry CH_2Cl_2 (20 mL) and treated with Et_3N (700 μL, ca. 5 mmol), DMAP (6 mg, 0.05 mmol), and acetic anhydride (375 μL, *ca*. 4 mmol). The mixture was stirred under N_2 at RT for 1 h. Work-up (extraction with CH_2Cl_2) and column chromatography of the residue on silica gel (hexanes-EtOAc, 95:5) provided lactone **5** contaminated with about 10% of **6** (110 mg, 60% overall for the two steps): colorless oil, ^{1}H- NMR (500 MHz) δ 6.82 (ddd, *J* = 9.8, 5, 3.3 Hz, 1H), 6.02 (dt, *J* = 9.8, 2 Hz, 1H), 5.75–5.65 (m, 2H), 5.12 (m, 1H), 5.06 (m, 2H), 4.85 (dt, *J* = 10, 5.5 Hz, 1H), 2.45–2.30 (m, 4H), 2.12 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 1.20 (d, *J* = 6 Hz, 3H); ^{13}C NMR (125 MHz) δ 170.3, 170.2 (x 2), 163.8 (C), 144.5, 131.4, 128.6, 121.9, 77.7, 74.4, 70.7, 69.0 (CH), 34.2, 29.8 (CH_2), 21.2, 21.0, 20.8, 16.6 (CH_3). IR $\nu_{max.}$ (cm^{-1}) 1740 (C=O). The NMR signals are those of the major component **5**.

(5*E*,4*S*,8*R*,9*R*,10*S*)-8,9,10-Tris-(*tert*-butyldimethylsilyloxy)undeca-1,5-dien-4-ol (17). Aldehyde **13** was prepared as reported above and allowed to react in crude form with the allylating reagent prepared from (–)-DIP-Cl and allylmagnesium bromide. Under the same conditions as above, column chromatography on silica gel (hexanes–EtOAc, 95:5) afforded **17** in 61% overall yield after the two steps as an inseparable 9:1 mixture with **14**: colorless oil, ^{1}H- NMR (500 MHz) δ 5.82 (ddt, *J* = 17, 10.2, 7 Hz, 1H), 5.66 (dt, *J* = 15.5, 7 Hz, 1H), 5.52 (dd, *J* = 15.5, 6.3 Hz, 1H), 5.15–5.10 (m, 2H), 4.12 (dt, *J* = 6.3, 6.3 Hz, 1H), 4.00 (dq, *J* = 4, 6.5 Hz, 1H), 3.75 (ddd, *J* = 8, 4, 4 Hz, 1H), 3.37 (dd, *J* = 4, 4 Hz, 1H), 2.50 (m, 1H), 2.35-2.20 (m, 3H), 1.60 (br. s, 1H, OH), 1.17 (d, *J* = 6.5 Hz, 3H), 0.92 (s, 9H), 0.90 (s, 18H), 0.06 (12H, s), 0.04 (6H, s); ^{13}C NMR (125 MHz) δ 18.1, 18.0 (x 2) (C), 134.5, 133.8, 130.3, 77.2, 74.0, 71.7, 68.3 (CH), 118.0, 42.0, 35.6 (CH_2), 26.0 (x 6), 25.8 (x 3), 21.0, –4.0, –4.1 (x 2), –4.3 (x 3) (CH_3). IR $\nu_{max.}$ (cm^{-1}) 3350 (br., OH). The NMR signals are those of the major component **17**.

(2*E*,1*S*,5*R*,6*R*,7*S*)-1-Allyl-5,6,7-tris-(*tert*-butyldimethylsilyloxy)oct-2-enyl acrylate (18). The **17**/**14** alcohol mixture was allowed to react with DIPEA and acryloyl chloride under the same reaction conditions as described above. Column chromatography on silica gel gave **18** and **15** as an inseparable 9:1 mixture (70%): colorless oil, ^{1}H- NMR (500 MHz) δ 6.38 (dd, *J* = 17.3, 1.5 Hz, 1H), 6.10 (dd, *J* = 17.3, 10.5 Hz, 1H), 5.78 (dd, *J* = 10.5, 1.5 Hz, 1H), 5.78-5.70 (m, 2H), 5.48 (dd, *J* = 15.5, 6.5 Hz, 1H), 5.38 (m, 1H), 5.10-5.05 (m, 2H), 3.98 (dq, *J* = 4, 6.5 Hz, 1H), 3.75 (ddd, *J* = 8, 4, 4 Hz, 1H), 3.35 (dd, *J* = 4, 4 Hz, 1H), 2.50 (m, 1H), 2.40 (m, 2H), 2.23 (m, 1H), 1.17 (d, *J* = 6.5 Hz, 3H), 0.92 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.05 (9H, s), 0.04 (6H, s), 0.03 (3H, s); ^{13}C NMR (125 MHz) δ 165.2, 18.1 (x 2), 18.0 (C), 133.3, 132.3, 129.2, 129.0, 77.1, 73.8, 73.5, 68.3 (CH), 130.2, 117.7, 39.1, 35.6 (CH_2), 26.0 (x 3), 25.9 (x 6), 20.9, –4.0 (x 2), –4.3 (x 3), –4.4 (CH_3). IR $\nu_{max.}$ (cm^{-1}) 1728 (C=O). The NMR signals are those of the major component **18**.

(6*S*)-6-[(1*E*,4*R*,5*R*,6*S*)-4,5,6-Tris-(*tert*-butyldimethylsilyloxy)hept-1-enyl]-5,6-dihydropyran--2-one (19). The **18**/**15** mixture of acrylates was subjected to ring-closing metathesis in the presence of Grubbs' ruthenium catalyst, $PhCH{=}RuCl_2(PCy_3)_2$ under the same reaction conditions described above. Column chromatography on silica gel furnished lactone **19** as an inseparable 9:1 mixture with **16** (77%): colorless oil, ^{1}H- NMR (500 MHz) δ 6.83 (dt, *J* = 9.8, 4.3 Hz, 1H), 6.02 (dt, *J* = 9.8, 1.8 Hz, 1H), 5.80 (dt, *J* = 15.5, 7 Hz, 1H), 5.60 (dd, *J* = 15.5, 7 Hz, 1H), 4.85 (q, *J* = 7 Hz, 1H), 4.02 (dq, *J* = 4, 6.5 Hz, 1H), 3.72 (ddd, *J* = 8, 4, 4 Hz, 1H), 3.36 (dd, *J* = 4, 4 Hz, 1H), 2.56 (m, 1H), 2.40 (m, 2H), 2.30 (m, 1H), 1.16 (d, *J* = 6.5 Hz, 3H), 0.88 (s, 9H), 0.87 (s, 9H), 0.84 (s, 9H), 0.07 (6H, s), 0.06 (6H, s), 0.03 (3H, s), 0.02 (3H, s); ^{13}C NMR (125 MHz) δ 164.0, 18.1 (x 2), 18.0 (C), 144.4, 134.2, 128.4, 121.7, 78.3, 77.3, 74.0, 67.8 (CH), 35.4, 29.7 (CH_2), 26.0 (x 3), 25.9 (x 6), 21.3, –4.0, –4.2 (x 2), –4.3, –4.4, –4.5 (CH_3). IR $\nu_{max.}$ (cm^{-1}) 1738 (C=O). The NMR signals are those of the major component **19**.

(6*R*)-6-[(1*E*,4*R*,5*R*,6*S*)-4,5,6-Triacetoxyhept-1-enyl]-5,6-dihydropyran-2-one (6). The **19**/**16** lactone mixture was subjected to sequential desilylation/acetylation under the reaction conditions described above. Column chromatography of the residue on silica gel provided lactone **6** contaminated with about 10% of **5**, in 50% overall yield: colorless oil, ^{1}H- NMR (500 MHz) δ

6.85 (dt, *J* = 9.8, 4.5 Hz, 1H), 6.02 (dt, *J* = 9.8, 1 Hz, 1H), 5.75–5.65 (m, 2H), 5.12 (m, 1H), 5.06 (m, 2H), 4.87 (dt, *J* = 10, 5.5 Hz, 1H), 2.45–2.25 (m, 4H), 2.11 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 1.20 (d, *J* = 6 Hz, 3H); ^{13}C NMR (125 MHz) δ 170.1 (x 2), 170.0, 163.8 (C), 144.4, 131.0, 128.1, 121.7, 77.2, 74.3, 70.5, 68.7 (CH), 34.0, 29.4 (CH_2), 21.0, 20.8, 20.6, 16.5 (CH_3). IR $\nu_{max.}$ (cm^{-1}) 1740 (C=O). The NMR signals are those of the major component **6**.

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10. The chiral allylboranes used in this paper were prepared as described in the literature from allylmagnesium bromide and the appropriate enantiomer of the commercially available di-*iso*-pinocampheylboron chloride. See: Ramachandran, P. V.; Chen, G.-M.; Brown, H. C. *Tetrahedron Lett*. **1997**, *38*, 2417. For a recent review on asymmetric allylborations, see: Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23.
11. The relative configuration of the three stereocenters was checked by desilyation of **8** to a known *xylo*-1,2,3-triol: Roush, W. R.; Brown, R. J. *J. Org. Chem*. **1983**, *48*, 5093.
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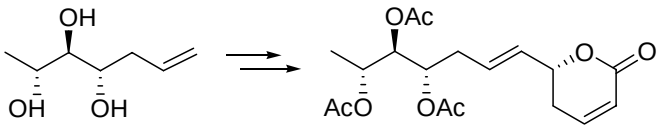
14. As with the other pairs of epimers, our efforts to separate these two lactones via HPLC were unsuccessful.
15. No authentic sample of synargentolide A was available to us for a direct comparison. NMR spectra of the natural compound were sent to us by M. T. Davies-Coleman (see Acknowledgments).
16. The assignment of a *syn, syn*-relative configuration within the C-4′/C-5′/C-6′ chain seems well founded on the basis of the presented data.[6] However, and in order to definitively exclude the possibility of a mis-assignment in this fragment, we also synthesized lactone **ii**,

which shows the *anti, anti* arrangement within the aforementioned carbon chain. The known *ribo*-1,2,3-triol **I** [11] was the starting material, and the synthetic strategy was identical to that depicted in Scheme 2. This provided lactone **ii** as a colorless oil (contaminated with about 10% of its C-6 epimer): ^{1}H- NMR (500 MHz) δ 6.85 (ddd, *J* = 9.8, 5, 3.5 Hz, 1H), 6.02 (dt, *J* = 9.8, 1 Hz, 1H), 5.74 (dt, *J* = 15.5, 7 Hz, 1H), 5.65 (dd, *J* = 15.5, 6.5 Hz, 1H), 5.13 (dd, *J* = 5.5, 4.5 Hz, 1H), 5.08 (m, 2H), 4.87 (dt, *J* = 10, 5.5 Hz, 1H), 2.50-2.30 (m, 4H), 2.10 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.23 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz) δ 170.0, 169.9, 169.8, 163.8 (C), 144.5, 130.7, 129.0, 121.6, 77.6, 73.3, 70.6, 68.6 (CH), 33.3, 29.5 (CH_2), 21.1, 20.9, 20.8, 15.2 (CH_3). Lactone **ii** therefore also proved different from the natural product. Note the diagnostic ^{13}C chemical shift value of the terminal methyl group at about 15 ppm. Lactones **5**, **6**, and synargentolide A show this signal above 16 ppm. This supports the conclusion that synargentolide A does not have an *anti, anti* relative configuration in its side chain as has lactone **ii**.



i **ii**