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*. 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).

\[ \text{synargentolide A} \]

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. In the case of 5, a similar analysis leads to 2,6-dideoxy-L-xylohexose (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. 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-\textit{iso}pinocampheylborane prepared from (+)-di-\textit{iso}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 di-\textit{iso}pinocampheylborane prepared from (−)-di-\textit{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-Blpc₂ [from (+)-DIP-Cl and allylmagnesium bromide], Et₂O, −78°C, 1 h (single diastereoisomer, 58% overall yield after the ozonolysis–allylation sequence, see ref. 9); (b) TBSOTf, 2,6-lutidine, CH₂Cl₂, RT, 1 h (92%); (c) O₃, −78°C, then PPh₃, RT, 2 h; (d) (EtO)₂POCH₂COOEt, LiCl, DIPEA, MeCN, RT, 3 h (65% overall yield after the ozonolysis–olefination sequence); (e) DIBAL, 0°C, 1 h, 75%; (f) MnO₂, CH₂Cl₂, reflux, 2 h; (g) allyl-Blpc₂ [from (+)-DIP-Cl and allylmagnesium bromide], Et₂O, −78°C, 1 h (9:1 mixture of diastereoisomers, 60% overall yield after the oxidation-allylation sequence); (h) acryloyl chloride, DIPEA, CH₂Cl₂, −78°C, 2 h (69% of the epimer mixture); (i) 10% PhCH=RuCl₂(PCy₃)₂, CH₂Cl₂, reflux, 3 h (78% of the epimer mixture); (j) PPTS, aq. MeOH, reflux, 2 d; (k) Ac₂O, Et₃N, DMAP, CH₂Cl₂, RT, 1 h (60% overall yield of the 9:1 epimer mixture after the two steps). *Abbreviations:* DIP-Cl, di-isopinocampheylboron chloride; TBSOTf, t-butyldimethylsilyl triflate; DIPEA, ethyl N,N-di-isopropylamine; DIBAL, di-isobutylaluminum hydride; Cy, cyclohexyl; PPTS, pyridinium p-toluenesulfonate; DMAP, N,N-dimethylaminopyridine.

Scheme 3. Synthesis of lactone 6. *Reagents and conditions:* (a) allyl-Blpc₂ [from (−)-DIP-Cl and allylmagnesium bromide], Et₂O, −78°C, 1 h (85:15 mixture of diastereoisomers, 61% after the oxidation–allylation two-step sequence); (b) acryloyl chloride, DIPEA, CH₂Cl₂, −78°C, 2 h (70% of the epimeric mixture); (c) PhCH=RuCl₂(PCy₃)₂ (10%), CH₂Cl₂, reflux, 3 h (77%); (d) PPTS, aq. MeOH, reflux, 2 days; (e) Ac₂O, Et₃N, DMAP, CH₂Cl₂, 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

<table>
<thead>
<tr>
<th>Carbon</th>
<th>5</th>
<th>6</th>
<th>Synargentolide A</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-2</td>
<td>163.8</td>
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<td>C-3</td>
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<td>121.6</td>
</tr>
<tr>
<td>C-4</td>
<td>144.5</td>
<td>144.4</td>
<td>144.5</td>
</tr>
<tr>
<td>C-5</td>
<td>29.8</td>
<td>29.4</td>
<td>29.4</td>
</tr>
<tr>
<td>C-6</td>
<td>77.7</td>
<td>77.2</td>
<td>77.2</td>
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<tr>
<td>C-1’</td>
<td>131.4</td>
<td>131.0</td>
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<tr>
<td>C-2’</td>
<td>128.6</td>
<td>128.1</td>
<td>128.3</td>
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<tr>
<td>C-3’</td>
<td>34.2</td>
<td>34.0</td>
<td>34.0</td>
</tr>
<tr>
<td>C-4’</td>
<td>70.7</td>
<td>70.5</td>
<td>69.7</td>
</tr>
<tr>
<td>C-5’</td>
<td>74.4</td>
<td>74.3</td>
<td>73.8</td>
</tr>
<tr>
<td>C-6’</td>
<td>69.0</td>
<td>68.7</td>
<td>67.4</td>
</tr>
<tr>
<td>C-7’</td>
<td>16.6</td>
<td>16.5</td>
<td>16.0</td>
</tr>
<tr>
<td>OAc (C=O)</td>
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<td>170.1 (x 2), 170.0</td>
<td>170.2, 170.1, 170.0</td>
</tr>
<tr>
<td>OAc (Me)</td>
<td>21.2, 21.0, 20.8</td>
<td>21.0, 20.8, 20.6</td>
<td>21.0, 20.9, 20.8</td>
</tr>
</tbody>
</table>
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). 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 13C-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.

**Experimental Section**

**General Procedures.** RT denotes room temperature. NMR spectra were measured at 500 MHz in CDCl3 solution at 25 °C. The signals of the deuterated solvent (CDCl3) were taken as the reference (the singlet at δ 7.25 for 1H-NMR and the triplet centered at 77.00 ppm for 13C NMR data). The multiplicities of the 13C-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 N2, in flame-dried glassware. Et2O was freshly distilled from sodium-benzophenone ketyl. Dichloromethane was freshly distilled from CaH2. 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. NaHCO3 (if acids had been used in the reaction) or into satd. aq. NH4Cl (if bases had been utilized), then washing the organic layer again with brine, drying over anhydrous Na2SO4 or MgSO4 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.

**Scheme 2**

(4R,5S,6S)-5,6-Bis-(tert-butyldimethylsilyloxy)-hept-1-en-4-ol (8)
Ethyl (2E,4S,5S)-dihydroxy-2-enoate (A) was obtained as reported, by asymmetric dihydroxylation of ethyl sorbate. The dihydroxy ester (1.74 g, ca. 10 mmol) was then dissolved in dry CH₂Cl₂ (50 mL) under N₂ 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 CH₂Cl₂). Column chromatography on silica gel (hexanes-CHCl₃, 9:1) afforded the expected disilylated derivative (B) (3.42 g, 85%): colorless oil, [α]D −47.9 (c 1.25; CHCl₃); 1H 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), 0.92 (s, 9H), 0.90 (s, 9H), 0.07 (3H, s), 0.06 (6H, s), 0.05 (3H, s); 13C NMR (125 MHz) δ 166.6, 18.1, 18.0 (C), 147.7, 121.4, 74.9, 71.1 (CH), 60.2 (CH₂), 25.9 (x 6), 17.4, 14.3, −4.7, −4.8, −4.9, −5.0 (CH₃). IR ν 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 C₂₀H₄₂O₄Si₂−Me, M = 387.2386.

The disilylated derivative from above was dissolved in dry CH₂Cl₂ (125 mL) and cooled to −78°C. A stream of ozone–oxygen was bubbled through the solution until persistence of the blue color. Dry N₂ was then bubbled through the solution for 10 min. at the same temperature. After addition of PPh₃ (3.94 g, ca. 15 mmol), the solution was left to stir at RT for 2 h, then worked up (extraction with CH₂Cl₂). Removal of solvent gave a solid material, which was washed three times with cold pentane (3 x 10 mL). The solid (Ph₃PO) 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 1M solution in Et₂O, 10 mL, 10 mmol) was added dropwise under N₂ via syringe to a solution of (+)-DIP-Cl (3.85 g, 12 mmol) in dry Et₂O (50 mL) cooled in a solid-CO₂–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 Et₂O (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% H₂O₂ (25 mL). After stirring for 30 min., the mixture was poured onto satd. aq. NaHCO₃ and extracted with Et₂O. Column chromatography on silica gel (hexanes-EtOAc, 95:5) afforded 8 (1.87 g, 58% overall yield for the ozonolysis/allylation sequence): colorless oil, [α]D −2.2 (c 1.3; CHCl₃); 1H 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); 13C NMR (125 MHz) δ 18.1, 18.0 (C), 135.6, 75.3, 70.2, 68.1 (CH), 116.7, 40.6 (CH₂), 25.8 (x 6), 17.7, −4.2, −4.6 (x 2), −4.8 (CH₃). IR ν max. (cm⁻¹) 3560 (br., OH); HR EIMS, Found m/z (% rel. int.) 333.2238 [M⁺−C₃H₅] (1), 303 (8), 185 (45), 159 (60), 73 (100). Calcd. for C₁₉H₄₀O₃Si₂−C₃H₅, M = 333.2281.
(4R,5R,6S)-4,5,6-Tris-(tert-butyldimethylsilyloxy)-hept-1-ene (9). Alcohol 8 (1.87 g, ca. 5 mmol) was dissolved in dry CH₂Cl₂ (20 mL) under N₂ 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 CH₂Cl₂). Column chromatography on silica gel (hexanes-EtOAc, 19:1) afforded 9 (2.25 g, 92%): colorless oil, [α]D +18 (c 1; CHCl₃); 1H-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); 13C-NMR (125 MHz) δ 18.2 (x 2), 18.1 (C), 137.3, 77.3, 74.0, 68.4 (CH), 116.2, 37.3 (CH₂), 25.9 (x 9), 21.1, –3.0, –4.0, –4.2 (x 4) (CH₃). HR EIMS, Found m/z (% rel. int.) 447.3215 [M⁺−C₃H₅] (3), 329 (11), 303 (25), 259 (26), 185 (72), 159 (100), 73 (90); Calcd. for C₂₅H₅₆O₃Si₃−C₃H₅, M = 447.3146.

Ethyl (2E,5R,6R,7S)-5,6,7-Tris-(tert-butyldimethylsilyloxy)-oct-2-enoate (11). Alkene 9 (2.25 g, 4.6 mmol) was dissolved in dry CH₂Cl₂ (75 mL) and cooled to −78°C. A stream of ozone-oxygen was bubbled through the solution until persistence of the blue color. Dry N₂ was then bubbled through the solution for 10 min. at the same temperature. After addition of PPh₃ (2.36 g, ca. 9 mmol), the solution was stirred at RT for 2 h, then worked up (extraction with CH₂Cl₂). Removal of solvent gave a solid material, which was washed with cold pentane (3 x 10 mL). The solid (Ph₃PO) 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)CH₂CO₂Et (1.8 mL, ca. 9 mmol) were dissolved in dry acetonitrile (20 mL) under N₂. 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 Et₂O) 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, [α]D +21.3 (c 1.26; CHCl₃); 1H-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); 13C 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 (CH₂), 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) (CH₃). IR, νmax. (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 C₂₈H₆₀O₅Si₃−t-Bu, M = 503.4132.

(2E,5R,6R,7S)-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 N₂ with DIBAL (1M solution in hexanes, 6 mL, 6 mmol). The solution was then stirred at RT. for 1 h. Satd aq. NH₄Cl 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%) as a colorless oil, \([\alpha]_D +15.1\) (c 1.45; CHCl₃); ¹H NMR (500 MHz) \(\delta 5.65\) (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); ¹³C NMR (125 MHz) \(\delta 18.1\) (x 2), 18.0 (C), 131.7, 130.8, 77.3, 74.1, 68.1 (CH), 63.9, 35.6 (CH₂), 26.0 (x 3), 25.9 (x 3), 25.8 (x 3), 21.1, −4.0 (x 3), −4.3 (x 3) (CH₃). IR νmax. (cm⁻¹) 3350 (br., OH); HR EIMS, \(m/z\) (% rel. int.) 447.3145 [M⁺−C₄H₇] (3), 303 (14), 215 (28), 159 (100), 73 (68). Calcd. for C₂₆H₅₈O₄Si₃ −C₄H₇, M = 447.3146.

(5E,4R,8R,9R,10S)-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 CH₂Cl₂ (35 mL) and treated with MnO₂ (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 CH₂Cl₂. 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 1M solution in Et₂O, 2.5 mL, 2.5 mmol) was added dropwise via syringe, under N₂, to a solution of (+)-DIP-Cl (0.96 g, 3 mmol) in dry Et₂O (15 mL) cooled in a solid CO₂–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 Et₂O (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% H₂O₂ (7 mL). After stirring for 30 min., the mixture was poured onto satd. aq. NaHCO₃ and worked up (extraction with Et₂O). 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, ¹H- NMR (500 MHz) \(\delta 5.82\) (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), 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); ¹³C NMR (125 MHz) \(\delta 18.1, 18.0, 17.9\) (C), 134.4, 133.8, 130.3, 77.1, 74.1, 72.1, 68.3 (CH), 117.7, 42.0, 35.6 (CH₂), 25.9 (x 6), 25.8 (x 3), 20.9, −4.0, −4.1 (x 2), −4.3 (x 3) (CH₃). IR νmax. (cm⁻¹) 3350 (br., OH). FABMS, m/z 559 [M+H⁺]; calcd. for C₂₉H₆₃O₄Si₃, M = 559. The NMR signals are those of the major component 14.

(2E,1R,5R,6R,7S)-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 CH₂Cl₂ (50 mL) under N₂, 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 CH₂Cl₂). 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) $\delta$ 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 (dd, $J = 8, 4, 4$ 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) $\delta$ 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 $\nu_{\text{max.}}$ (cm$^{-1}$) 1728 (C=O). EIMS, $m/z$ (% rel. int.) 555 [M–t-Bu –t-Bu] (1), 303 (11), 159 (100), 73 (48). Calcd. for C$_{32}$H$_{64}$O$_5$Si$_3$–t-Bu, M = 555. The NMR signals are those of the major component 15.

(6R)-6-[(1E,4R,5R,6S)-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$_2$Cl$_2$ (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) $\delta$ 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 (dd, $J = 8, 4, 4$ 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) $\delta$ 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 $\nu_{\text{max.}}$ (cm$^{-1}$) 1738 (C=O). EIMS, $m/z$ (% rel. int.) 527 [M–t-Bu –t-Bu] (8), 483 (23), 159 (100), 73 (98). Calcd. for C$_{30}$H$_{60}$O$_5$Si$_3$–t-Bu, M = 527. The NMR signals are those of the major component 16.

(6R)-6-[(1E,4R,5R,6S)-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$_2$Cl$_2$ (20 mL) and treated with Et$_3$N (700 $\mu$L, ca. 5 mmol), DMAP (6 mg, 0.05 mmol), and acetic anhydride (375 $\mu$L, ca. 4 mmol). The mixture was stirred under N$_2$ at RT for 1 h. Work-up (extraction with CH$_2$Cl$_2$) 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) $\delta$ 6.82 (dd, $J = 9.8, 5, 3.3$ 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) $\delta$ 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 $\nu_{\text{max.}}$ (cm$^{-1}$) 1740 (C=O). The NMR signals are those of the major component 5.
(5E,4S,8R,9R,10S)-8,9,10-Tris-(tert-butyl(dimethyl)silyloxy)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) \(\delta\) 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) \(\delta\) 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 \(\nu_{\text{max}}\) (cm\(^{-1}\)) 3350 (br., OH). The NMR signals are those of the major component 17.

(2E,1S,5R,6R,7S)-1-Allyl-5,6,7-tris-(tert-butyl(dimethyl)silyloxy)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) \(\delta\) 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 (dd, \(J = 8, 4, 4\) 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) \(\delta\) 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 6), 25.9 (x 3), 21.0, –4.0, –4.1 (x 2), –4.3 (x 3) (CH\(_3\)). IR \(\nu_{\text{max}}\) (cm\(^{-1}\)) 1728 (C=O). The NMR signals are those of the major component 18.

(6S)-6-[(1E,4R,5R,6S)-4,5,6-Tris-(tert-butyl(dimethyl)silyloxy)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\(_2\)(PC\(_3\))\(_2\) under the same reaction conditions described above. Column chromatography on silica gel furnished lactone 19 as an inseparable 9:1 mixture (77%): colorless oil, \(^1^H\)-NMR (500 MHz) \(\delta\) 6.83 (dt, \(J = 9.8, 1.8\) Hz, 1H), 6.02 (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), 0.06 (6H, s), 0.03 (3H, s), 0.02 (3H, s); \(^{13}C\) NMR (125 MHz) \(\delta\) 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 \(\nu_{\text{max}}\) (cm\(^{-1}\)) 1738 (C=O). The NMR signals are those of the major component 19.

(6R)-6-[(1E,4R,5R,6S)-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) \(\delta\)
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 = 9.8, 1 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); 13C 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 (CH2), 21.0, 20.8, 20.6, 16.5 (CH3). IR νmax. (cm⁻¹) 1740 (C=O). The NMR signals are those of the major component 6.

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References and Notes


10. The chiral allylborationes used in this paper were prepared as described in the literature from allylmagnesium bromide and the appropriate enantiomer of the commercially available diiso-pinocampheylboron chloride. See: Ramachandran, P. V.; Chen, G.-M.; Brown, H. C. *Tetrahedron Lett.* **1997**, *38*, 2417. For a recent review on asymmetric allylborationes, see: Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23.

11. The relative configuration of the three stereocenters was checked by desilylation of 8 to a known xylo-1,2,3-triol: Roush, W. R.; Brown, R. *J. J. Org. Chem.** **1983**, *48*, 5093.


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. 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) \(\delta\) 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) \(\delta\) 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.

![Diagram](image-url)