The Stereochemistry of the Nozaki-Hiyama-Kishi Reaction and the Construction of 10-Membered Lactones. The Enantioselective Total Synthesis of (-)-Decarestrictine D.

Ronaldo A. Pilli* and Mauricio M. Victor

Instituto de Química, Universidade Estadual de Campinas, CP 6154, 13083-970 Campinas - SP, Brazil

The use of the intramolecular Nozaki-Hiyama-Kishi reaction to construct 10-membered lactones is described. The influence of the nature of the protecting groups at C4 and C5 on the stereochemistry of the newly formed stereogenic center at C7 was investigated. The utility of this methodology has been demonstrated in the stereoselective total synthesis of (-)-decarestrictine D from 1,3-propanediol and polyhydroxybutyrate (PHB) in 13 steps and 6.3% overall yield.

Keywords: decarestrictine D, decanolide, Nozaki-Hiyama-Kishi reaction, lactone

Introduction

Decarestrictine D (1) is a 10-membered lactone isolated from Penicillium corylophilum, simplicissimum1a-c and independently from the Canadian Tuckahoe fungi Polyporus tuberaster1d and named as tuckolide. A general panel of whole cell screening demonstrated that decarestrictine D inhibits cholesterol biosynthesis in HEP-G2 liver cells and this beneficial effect was corroborated by in vivo studies with normolipidemic rats. In addition, it appears that decarestrictine D is highly selective in that it exhibits no significant antibacterial, antifungal, antiprotozoal, or antiviral activity. However, recent studies2 revealed DNA-binding activity for decarestrictine D and the corresponding bisglycosylated derivatives, disclosing new avenues of opportunities in structure-activity relationship. Such significant biological properties exhibited by decarestrictine D contributed much to the interest in devising synthetic approaches to this family of natural products.

While the relative stereochemistry was provided by X-ray analysis3b, its absolute configuration has been recently established by total synthesis3 and X-ray analysis of a chiral derivative3. Other members of the 10-membered lactone family4 include decarestrictines A (2) and B (3), phoracantholide I (4)5 and pyrenolide A (5)6.

The synthetic approach to lactones has traditionally focused mainly on the use of fragmentation/ring expansion reactions and on lactonization strategies in order to build the lactone ring7. Recently, examples of the construction of lactones through the formation of C-C bond appeared8 and the intramolecular Nozaki-Hiyama-Kishi (NHK) coupling reaction9 stands as a promising protocol10. Moreover, the factors controlling the stereochemical outcome of the C-C bond forming step are unknown which prompted us to investigate how the conformational bias in the acyclic precursor influences the stereochemical course of the reaction.
According to our synthetic plan, the construction of the decanolide ring would arise from the formation of the C6-C7 bond. The stereogenic centers at C3 and C4 could conceivably come from the chiral pool by de novo construction through asymmetric methodology such as Sharpless asymmetric dihydroxylation (Scheme 1). The C7-C10 fragment 8 was planned to be prepared from natural biopolymer polyhydroxybutyrate (PHB) while the C1-C6 fragment 7 could be obtained either from tartaric acid (path A) or through Sharpless asymmetric dihydroxylation (path B). The choice of fragment 7 poses the additional opportunity to investigate the influence of the protecting groups at C3 and C4 (cyclic or acyclic) on the stereochemical outcome of the Nozaki-Hiyama-Kishi cyclization. The different local conformations that might be enforced by the protecting groups at C3 and C4 were expected to impart changes on the geometry of the transition state as proposed by Kishi and Schreiber.

Results and Discussion

The C1-C6 fragment 7

Our first choice for the preparation of optically pure 7 was to employ (2R,3R)-diethyl tartrate protected as the corresponding isopropylideneacetal (Scheme 2). After treating (2R,3R)-diethyl tartrate 9 with 2,2-dimethoxypropane (DMP) in acetone as solvent, a mixture of dimethyl, acetone:DMP 1:1, PTSA (87%); b) NaBH₄, EtOH, 0 °C (60%); c) NaH, THF, 0 °C then TBSCl (90%).

Scheme 2. Preparation of threitol 14 from (2R,3R) diethyl tartrate (9).
diethyl and methylethyl esters 12a-c, as determined by GC and NMR analyses, was formed which was reduced with NaBH₄ in ethanol to afford threitol 13 in 60% overall yield. Monoprotection of diol 13 was accomplished under the conditions described by McDougal and Oh¹⁵ and uneventfully afforded primary alcohol 14 in 90% yield.

Concomitantly, the preparation of fragment 7 along path B (Scheme 1) was investigated. Monosilylation of 1,3-propanediol 15 with TBSCl led to 16 in 91% yield. Swern oxidation afforded aldehyde 17 which was employed in the next step without further purification (Scheme 3). Horner-Emmons-Wadsworth reaction with the lithium anion of ketophosphonate 18 afforded α,β-insaturated esters 10E and 10Z (22:1 ratio). Flash chromatography on silica gel allowed separation of the geometric isomers which were isolated in 70% (major isomer 10E) and 3% (minor isomer 10Z). Dihydroxylation of 10E with AD-mix® α led to (2R,3S)-19 in 94% yield and 91% enantiomeric excess after analysis by GC on chiral stationary phase¹⁶. Diol (-)-19 was fully protected as the corresponding TBS-ether (-)-20 in quantitative yield with TBSCl, imidazole and DMF as solvent.

At this stage we faced the preparation of the corresponding vinylic iodides from alcohol 14 and/or ester 20 and the Takai protocol was elected as our first choice¹⁷. This method employs the addition of organochromium species to an aldehyde and for that purpose alcohol 14 was oxidized to aldehyde 21 under Swern conditions (Scheme 4). When aldehyde 21 was treated with iodoform (2.0 equiv.) and CrCl₂ (6.0 equiv.) at 0 °C iodide 22 was isolated in low yield (23%, 2 steps) as a 3:1 mixture of the E and Z isomers, as determined by ¹H NMR analyses¹⁸, while no reaction was observed when a mixture of 1,4-dioxane-THF (6:1) was employed¹⁹.

In another attempt, ester (-)-20 was reduced with DIBAL-H to aldehyde 23 (Scheme 5) which was treated under the conditions mentioned above for aldehyde 21 but even after a large reaction time, iodide 24 was obtained in low yield (12% overall and 24% yield based on recovered aldehyde) but fortunately a single stereoisomer was formed²¹. In summary, due to the low selectivity observed in the olefination of aldehyde 21 and the need of homologation imposed by route A we decided to concentrate our efforts on route B.
Upon changing the amounts of CrCl$_2$ (12 equiv.) and iodoform (4 equiv.), iodide was obtained in 53% yield when the reaction was carried out at 55 °C (Table 1).

The reason for the high diastereoselectivity in the Takai olefination of aldehyde is not totally clear at this point but it can be rationalized through the intervention of the geminal organochromium species, as proposed by Hodgson. The addition of this species to the aldehyde would be followed by $\text{syn}$ elimination. The preferential formation of olefin $E$-28 would arise from the relief of steric interactions between the R group in 23 and the iodine atom upon changing conformation $27a$ to $27b$. The corresponding $Z$ olefin would be less favoured due to the expected higher steric energy associated to conformer $27a$ which displays staggered R group and iodine (Scheme 6). The presence of bulky TBS groups in the aldehyde would not only enforce conformation $27b$ but could conceivably slow down the reaction.

With the preparation of the key intermediate 24 secured, we focused on its conversion to carboxylic acid 7. The primary OTBS group was removed with HF-pyridine to afford the primary alcohol in 64% yield which was converted to the corresponding carboxylic acid with Jones reagent (79% yield). Considering that partial deprotection of the OTBS group in 24 was observed during column chromatography on silica gel and the report by Evans e coworkers on the one-pot primary OTBS deprotection-Jones oxidation sequence, we decided to carry out the oxidation step directly from crude iodide 24.

Scheme 5. Preparation of vinylic iodide 24.

Table 1. Takai olefination of aldehyde 23.

<table>
<thead>
<tr>
<th>Entry</th>
<th>CrCl$_2$ (equiv.)</th>
<th>CHI$_3$ (equiv.)</th>
<th>Time (h)</th>
<th>Temp. (°C)</th>
<th>Yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>2</td>
<td>18</td>
<td>0</td>
<td>12 (24)</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>2</td>
<td>48</td>
<td>Rt</td>
<td>18 (50)</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>4</td>
<td>66</td>
<td>Rt</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>4</td>
<td>66</td>
<td>55</td>
<td>53</td>
</tr>
</tbody>
</table>

$^a$ yield in parenthesis based on recovered aldehyde.

Scheme 6. Mechanistic rationale for the stereoselective formation of $(E)$-vinylic iodide 28.

Scheme 7. Preparation of fragment C1-C6 7.
**The C7-C10 fragment 8**

The preparation of this moiety began with the reduction of PHB (11) with LiAlH$_4$ to afford diol (-)-29, in 85% yield. Selective silylation of the primary hydroxyl group afforded (+)-8, in 83% yield. The enantiomeric excess of this intermediate was determined to be >99% ee by GC analysis with chiral column (Scheme 8).

**Coupling of the C1-C6 and C7-C10 fragments**

Our expectation to control the stereogenic center to be created at C7 was based on the interplay of transannular interactions, known to be proeminent in medium-size rings, and on the proposal by Overman and coworkers of a well organized arrangement in the transition state of the Nozaki-Hiyama-Kishi reaction. During the synthesis of (-)-7-deacetoxyalcionine, Overman and coworkers proposed the chelation of the vinylic chromium species to the carbonyl of the aldehyde to explain the outstanding diastereoselectivity observed in the formation of the 9-membered ring (>20:1). Carbonyl facial selection would then be dictated by a preferential *endo* positioning of the hydrogen in the formyl group of the aldehyde to minimize transannular interactions.

As applied to our case, the ideas above allow one to expect that:

i) the methyl group at C9 would adopt a pseudo-equatorial orientation in the transition state thus determining the relative position of the C9-C7 moiety and influencing carbonyl facial selection;

ii) the judicious choice of the protecting group at the oxygens atoms at C3 and C4 could dictate the relative positioning of the C5-C6 and C2-O-C7 fragments (Figure 1): OTBS protecting groups which are bound to adopt *anti* relative orientation would enforce *gauche* orientation (conformation A) while isopropylideneacetal as protecting group would keep the side chains apart (conformation B).

The coupling of the C1-C6 and C7-C10 fragments was carried out with Yamaguchi protocol: carboxylic acid (-)-7 was previously treated with 2,4,6-trichlorobenzoyl chloride and the mixed anhydride formed was reacted with alcohol (+)-8. Ester (-)-30 was isolated in 83% yield (Scheme 9).

In order to test our working hypothesis, alcohol (-)-35 was prepared from (-)-30: removal of the primary OTBS group afforded unstable alcohol 31 which was immediately protected as the PMB ether to afford (-)-32 in 74% overall yield (two steps). The secondary hydroxyl groups at C3 e C4 were removed with a large excess of HF-pyridine complex and the unstable diol 33 was immediately protected as the corresponding isopropylidene acetal with dimethoxypropane and catalytic PPTS in DMF to afford (-)-34 in 85% overall yield (two steps). Oxidative cleavage of the PMB ether provided alcohol (-)-35, in 70% yield. Surprisingly, alcohol (-)-35 turned out to be rather stable as compared to alcohol 31 as no sign of transesterification was detected by $^1$H-NMR even after monitoring the same sample in CDCl$_3$ for 7 days. Such behaviour was assigned to conformational changes upon changing from a sterically demanding protecting group (OTBS) to a conformationally constrained one (isopropylidene acetal).

![Conformation A and Conformation B](image)

**Scheme 8.** Preparation of the C7-C10 fragment 8 from polyhydroxybutyrate (11).

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a) LiAlH$_4$, THF, reflux, 5h (85%); b) TBSCI, Et$_3$N, DMAP, CH$_2$Cl$_2$, 0 °C, 1h (83%)

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**The macrolactonization step: stereoselective Nozaki-Hiyama-Kishi cyclization (NHK)**

At this point we were ready to apply the intramolecular NHK reaction to the aldehydes derived from conformationally biased alcohols \(31\) and \(35\). Due to the labile nature of alcohol \(31\), a method was sought to oxidize it as soon as it was liberated from \((-)\)-\(30\): our first choice was the use of Swern conditions [i] \((\text{COCl})_2, \text{DMSO}, \text{CH}_2\text{Cl}_2, -78 \, ^\circ\text{C}; \) ii) \(\text{Et}_3\text{N}, \text{rt}\) which led mainly to carboxylic acid \((-)\)-\(7\) through base-promoted elimination, probably at the aldehyde stage. We were then forced to try Dess-Martin periodinane\(34\) which only circumvented the formation of \((-)\)-\(7\) and efficiently provided aldehyde \(36\) when the modified conditions described by Meyer and Schreiber\(34c\) were employed (Scheme 10).

Aldehyde \(36\) was not purified but immediately used in the NHK step. After extensive experimentation the best

**Scheme 9.** The coupling of fragments \((-)\)-\(7\) and \((+)\)-\(8\).

\[\text{Scheme 10. The Nozaki-Hiyama-Kishi coupling and the formation of decanoides}\]
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In the spectra of the isopropylidene derivatives 39a and 39b, H-7 appeared as a multiplet and the information on the relative configuration of this stereogenic center had to be retrieved from the data of H-8 and H-6: in the major diastereoisomer 39b, H-8ax appeared as a doublet at δ 1.87 with two large (J 14.9 and J(H8ax-H7) 7.3 Hz) and a small one (J(H8eq-H9eq) 3.7 Hz) while H-6 displayed a doublet at δ 5.69 with two large coupling constants in 39b (J 16.4 and 7.3 Hz) and appeared as a multiplet in minor 39a. Additionally, isomers 39a and 39b could not be separated by chromatography on silicagel and only circumstantial evidence on the stereochemical assignment at C-7 could be provided at this stage for 39a and 39b.

The final proof of the 7S configuration of (-)-38a came from its conversion to (-)-decarestrictine D (1). Tetrabutylammonium fluoride (TBAF) and acetic acid in THF led to recovery of (-)-38a even after 24 h at room temperature while the use of hydrofluoric acid in acetonitrile-water mixture led to extensive decomposition. We reasoned that the acid lability of 1 would call for a buffered medium. We turned our attention to the HF-pyridine complex which provided 1 but only in 10% yield after 24 h at room temperature with recovery of (-)-38a and, finally, to a mixture of TBAF-HF in acetonitrile-water which successfully provided 1 in 83% yield, after 2.5 h at room temperature (Scheme 11).

The authenticity of synthetic (-)-decarestrictine D ([α]D _25_ −70.9 (c 0.24, CHCl₃; lit.[14] ([α]D _25_ −67.0 (c 0.26, CHCl₃)) was secured after comparison of its spectroscopic data with those described by Zeeck[16] and Andrus[1].

In conclusion, the total synthesis of 1 was achieved in 13 steps and 6.3% overall yield from 1,3-propanediol and provided the opportunity to uncover the effect of local conformations on the stereochemical outcome of the Nozaki-Hiyama-Kishi intramolecular cyclization as applied to the formation of 10-membered lactones. Further studies are underway in order to collect more data on such effects.

protocol required the use of 15 equiv. of CrCl₂ in degassed DMF at room temperature which afforded decanolide (-)-38a as a single isomer in 30% overall yield (3 steps) from ester (-)-30. Attempts to improve the yield without decrease of the diastereoselectivity were not successful as the use of DMSO as solvent afforded similar overall yield (35%) but a 2:1 mixture of (-)-38a and 38b (C-7 epimer), as determined by ¹H NMR of the crude mixture. Modification in the workup of the reaction (use of triethanolamine or ethylenediamine to complex chromium salts) or the use of modified conditions for the chromium-mediated Reformatsky reaction[35] were not successful. The above reaction condition was applied to alcohol (-)-35 and decanolides 39a and 39b were isolated in 41% yield (two steps) as a 1:2 mixture (¹H NMR).

At this point we were not able to carry out an unambiguous assignment of (-)-38a but its ¹H-NMR data suggested the 7S configuration: H-7 appeared as a triple doublet at δ 4.21 with two large coupling constants (10.8 and 8.4 Hz) and a small one (3.4 Hz). The two large coupling constants were assigned to its trans orientation to H-6 and H-8 in chair-chair-chair conformation of (-)-38a while the small one was due to H-8. Such assignment was supported by some nOe experiments: a 4.3% increment at H-7 was observed upon irradiation of H-9 (δ 5.08).

![Figure 2. Chair-chair-conformation and nOe increments for decanolide 38a.](image_url)

In the spectra of the isopropylidene derivatives 39a and 39b, H-7 appeared as a multiplet and the information on the relative configuration of this stereogenic center had to be retrieved from the data of H-8 and H-6: in the major diastereoisomer 39b, H-8ax appeared as a doublet at δ 1.87 with two large (J 14.9 and J(H8ax-H7) 7.3 Hz) and a small one (J(H8eq-H9eq) 3.7 Hz) while H-6 displayed a doublet at δ 5.69 with two large coupling constants in 39b (J 16.4 and 7.3 Hz) and appeared as a multiplet in minor 39a. Additionally, isomers 39a and 39b could not be separated by chromatography on silicagel and only circumstantial evidence on the stereochemical assignment at C-7 could be provided at this stage for 39a and 39b.

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![Scheme 11. Final step in the total synthesis of (-)-decarestrictine D (1).](image_url)

a) TBAF, 40% aq. HF, CH₃CN, rt (83%).
Experimental

General

Melting points are uncorrected. Unless otherwise stated, all reactions were carried out under a nitrogen atmosphere. Anhydrous solvents were freshly distilled before use: diethyl ether and tetrahydrofuran (THF) from sodium benzophenone ketyl, benzene from sodium and stored over 4 Å molecular sieves, methylene chloride and triethylamine from CaH₂. Dimethylformamide was treated with P₂O₅, distilled from CaH₂ and stored over 4 Å molecular sieves. CrCl₂ containing 0.5% mol NiCl₂ was activated 4 h at 250°C under vacuum (1 mmHg) and weighted under argon atmosphere in a glovebox. The remaining reagents were purchased from commercial suppliers and used without further purification. ¹H NMR spectra were recorded at 300 or 500 MHz; ¹³C NMR spectra were recorded at 75 or 125 MHz. Residual CHCl₃ (0.01 %) was used as an internal standard in ¹H NMR spectra. ¹³C NMR spectra were referenced to CDCl₃ at δ 77.0. Optical rotations were measured at 25°C in a Polamat A (Carl Zeiss) polarimeter at 546 nm (mercury line). Infrared spectra were recorded as films in KBr cells on with Nicolet Impact 410 spectrophotometer, unless otherwise stated. GC-MS analyses were performed on a Hewlett-Packard 5890 seriesII gas chromatograph coupled to a MSD 5970 mass spectrometer. High resolution mass spectra were obtained via electron impact (70 eV) on a VG Autospec spectrometer. Column chromatography was performed using silica gel (70-230 Mesh), except when stated otherwise. Gradients of EtOAc and n-hexane were used as eluents and reactions were monitored by TLC (plates from Macherey-Nagel, Germany).

3-tert-Butyldimethylsilyloxy-1-propanol (16)

NaH (0.785 g, 32.7 mmol; 60% in mineral oil), previously washed with hexane, was suspended in THF (70 cm³). A solution of 1,3-propanediol (5.67 g, 91%) as a colorless oil. IR νmax/cm⁻¹ 3355; ¹H NMR (300 MHz, CDCl₃) δ 3.84 (t, J 5.5 Hz, 2H), 3.81 (t, J 5.5 Hz, 2H), 2.60 (s, br, 1H), 1.77 (quint, J 5.5 Hz, 2H), 0.89 (s, 9H), 0.07 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 62.8, 62.2, 34.2, 25.8, -5.5 (x2).

Ethyl (E)-5-(tert-butyldimethylsilyloxy)-2-pentenoate (10E)

To a stirred solution of oxalyl chloride (0.60 cm³, 6.9 mmol) in CH₂Cl₂ (10.3 cm³) at -78°C was added dropwise. A solution of crude aldehyde in THF (10.4 cm³) was added dropwise. The reaction was allowed to reach room temperature and stirred for additional 2.5 h, diluted with Et₂O (60 cm³) and successively washed with water (10 cm³), brine (10 cm³), dried over MgSO₄ and concentrated. The crude aldehyde (0.370 g) was used in the next step without further purification.

To a stirred suspension of NaH (0.125 g; 5.20 mmol; 60% in mineral oil previously washed with hexane) in THF (10.4 cm³) at 0°C was added dropwise triethylphosphonoacetate (18) (1.03 cm³). After 15 min, a solution of crude aldehyde in THF (10.4 cm³) was added dropwise. The reaction was allowed to reach room temperature and stirred for additional 2.5 h, diluted with Et₂O (60 cm³) and successively washed with water (10 cm³), brine (10 cm³), dried over MgSO₄ and concentrated. Silica gel chromatography (EtOAc/hexane 1:99, v/v) furnished 10E (0.614 g, 69%) and its isomer 10Z (0.034 g, 4%). (10E): IR νmax/cm⁻¹ 1724, 1657; ¹H NMR (300 MHz, CDCl₃) δ 6.96 (dt, J 16.0, 7.0 Hz, 1H), 5.86 (dt, J 16.0, 1.5 Hz, 1H), 4.19 (q, J 7.2 Hz, 2H), 3.73 (t, J 6.5 Hz, 2H), 2.41 (dq, J 6.5, 1.5 Hz, 2H), 1.28 (t, J 7.2 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 166.4, 145.8, 122.9, 61.5, 60.1, 35.7, 25.8, 18.3, 14.2, -5.4 (x2); MS (EI) m/z 73 (100%), 201 (86 %, [M-C₄H₉]⁺); HRMS (EI): found 201.0925; calc. for C₅H₆O₃Si [M-C₄H₉]⁺ 201.09470; (10Z): IR νmax/cm⁻¹ 1722; ¹H NMR (300 MHz, CDCl₃) δ 6.34 (dt, J 11.5, 7.0 Hz, 1H), 5.83 (dt, J 11.5, 1.7 Hz, 1H), 4.16 (q, J 7.1 Hz, 2H), 3.71 (dt, J 9.0, 6.0 Hz, 2H), 2.87 (dq, J 7.0, 1.7 Hz, 2H), 1.29 (t, J 7.1 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 166.4, 147.1, 120.8, 62.0, 59.8, 32.5, 25.9, 18.3, 14.2, -5.4 (x2).

Ethyl (2R,3S)-5-(tert-butyldimethylsilyloxy)-2,3-dihydroxy-pentanoate (19)

To a vigorously stirred mixture containing t-BuOH (14.8 cm³), water (14.8 cm³) and AD-mix Zα (4.16 g) was added at room temperature metanesulfonamide (0.283 g, 2.97 mmol). The orange mixture was cooled at 0°C and olefin
Ethyl (2R,3S)-2,3,5-tris-(tert-butyldimethylsilyloxy)-pentanoate (20)

To a solution of diol (-)-19 (0.799 g, 2.73 mmol) in DMF (1.60 cm³) were added imidazole (0.930 g, 13.7 mmol) and TBSCI (0.988 g, 6.55 mmol). The reaction was stirred 48 h at room temperature, diluted with Et₂O (10 cm³) and quenched by the addition of brine (20 cm³). After phase separation, the aqueous phase was washed with the addition of 3H NMR (75 MHz, CDCl₃)  δ 4.28 (q, J 7.1 Hz, 2H), 4.17 (dd, J 9.0, 3.5, 2.0 Hz, 1H), 4.05 (d, J 2.0 Hz, 1H), 3.87 (m, 2H), 3.19-3.25 (br s 2H), 1.95 (dd, J 14.5, 9.0, 4.5 Hz, 1H), 1.73 (dd, J 14.5, 5.5, 3.5 Hz, 1H), 1.31 (t, J 7.1 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 6H); 13C NMR (75 MHz, CDCl₃) δ 173.1, 73.6, 72.1, 61.8, 61.6, 35.2, 25.8, 18.1, 14.1, -5.6 (x2); MS (EI) m/z 75 (100%), 235 (30%, [M-C₄H₉]⁺); HRMS (EI): found 235.10014; calc. for C₁₂H₂₀O₅Si₃: [M-C₄H₉]⁺ 235.10018.

(3S,4S,5E)-3,4-bis-(tert-Butyldimethylsilyloxy)-6-iodo-5-hexenoic acid (7)

To a solution of ester (-)-20 (0.582 g, 1.12 mmol) in toluene (2.3 cm³) at -95°C (liquid N₂/hexane bath) was added dropwise a 1.0 mol L⁻¹ DIBAL-H soln. in hexane (2.3 cm³, 2.3 mmol). The reaction mixture was stirred for 1 h at -95°C, quenched with ethyl acetate (3.96 cm³), followed by addition of a saturated solution of sodium and potassium tartrate (4.0 cm³). The reaction mixture was allowed to warm to room temperature and stirred 2 h at this temperature. Addition of Et₂O (10 cm³) was followed by phase separation. The aqueous phase was further extracted with Et₂O (4 x 5 cm³), the combined organic layers were concentrated under reduced pressure, and the residue was filtered through Celite. Evaporation under reduced pressure afforded crude aldehyde 23 which was used in the next step without further purification.

To a suspension of CrCl₂ (1.62 g, 13.2 mmol) in THF (36 cm³) were added via cannula a solution of iodoform (1.76 g, 4.47 mmol) and crude aldehyde 23 in THF (12 cm³). The reaction mixture was stirred and warmed at 55-60°C for 48 h. The reaction was quenched with brine (60 cm³), and diluted with Et₂O (60 cm³). The organic layer was separated, and the aqueous one was extracted with Et₂O until all iodoform has been extracted. The combined organic layers were washed with a 1 mol L⁻¹ Na₂S₂O₃ (30 cm³), brine (30 cm³), and dried over MgSO₄. Evaporation under reduced pressure afforded crude iodide 24 which was used in the next step without further purification.

A stirred ice-cold acetone solution (43 cm³) of crude iodide 24 was treated dropwise with 8 mol L⁻¹ Jones reagent. The excess of the Jones reagent was quenched by the addition of 2-propanol and the mixture was allowed to reach room temperature. The clear greenish solution was decanted and the remaining chromium salts were extracted with Et₂O (4 x 10 cm³). The combined extracts were washed with brine (20 cm³) and dried over MgSO₄. The solvents were removed in vacuum and the remaining crude product was purified by column chromatography (EtOAc/hexane 10:90, v/v) to give carboxylic acid (-)-7 (0.299 g, 53% overall) as a viscous oil. [α]Dₑ 56 –52.9 (c 1.7, EtOH); IR νmax/cm⁻¹ 3500-2500, 1716, 1608; 1H NMR (300 MHz, CDCl₃) δ 6.67 (dd, J 14.5, 4.0 Hz, 1H), 6.30 (dd, J 14.5, 1.5 Hz, 1H), 4.18-4.08 (m, 2H), 2.63 (dd, J 16.0, 3.0 Hz, 1H), 2.25 (dd, J 16.0, 8.0 Hz, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.09 (s, 6H), 0.07 (s, 3H), 0.06 (s, 3H); 13C NMR (75 MHz, CDCl₃) δ 178.5, 144.2, 77.1, 76.2, 71.8, 36.6, 25.5 (x2), 17.8, 17.7, -5.0, -5.2, -5.3, -5.4; MS (EI): m/z 463 (100%, [M-C₄H₉]⁺); HRMS (EI): found 443.05715; calc. for C₁₄H₂₈O₄Si₂: [M-C₄H₉]⁺ 443.05709.

(R)-1,3-Butanediol (29)

To a suspension of LiAlH₄ (0.200 g, 5.27 mmol) in THF (9.2 cm³) at 15°C was added portionwise poly-hydroxybutyrate (PHB) 11 (0.600 g, 6.97 mmol). The...
reaction mixture was stirred for 2 h at room temperature, refluxed 5 h and allowed to stir overnight at room temperature. The reaction mixture was cooled at 0°C and successively treated with water (0.2 cm³), 10% aqueous NaOH (0.2 cm³) and water (0.6 cm³). The inorganic solids were filtered, washed with EtOAc (3 x 10 cm³) and extracted with boiling Et₂O. The combined organic layers were dried over MgSO₄ and concentrated to afford (-)-29 (0.599 g, 85%) as a colorless oil. [ε]₂⁰ –60.0 (c 1.0, CHCl₃); IR νmax/cm⁻¹ 1735, 1606; ¹H NMR (300 MHz, CDCl₃) δ 6.67 (dd, J 14.0, 3.5 Hz, 1H), 6.27 (dd, J 14.0, 1.5 Hz, 1H), 5.00 (sex, J 6.6 Hz, 1H), 4.18-4.08 (m, 2H), 3.64 (t, J 6.6 Hz, 2H), 2.57 (dd, J 16.0, 2.5 Hz, 1H), 2.16 (dd, J 16.0, 8.0 Hz, 1H), 1.90-1.76 (m, 1H), 1.76-1.60 (m, 1H), 1.24 (d, J 6.0 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 76.7, 76.2, 72.6, 59.4, 38.9, 37.0, 25.7, 25.6, 25.5, 19.9, 18.0, 17.9, 17.6, -5.0, -5.1, -5.2, -5.3, -5.7, -5.8; MS (EI): m/z 73 (100%), 629 (1%, [M-C₄H₉⁺]); HRMS (EI): found 629.20055; calc. for C₂₄H₅₀O₅Si₃I [M-C₄H₉⁺] 629.20109.

(R)-1-(tert-Butyldimethylsilyloxy)-3-butanol (8)

To a solution of diol (-)-29 (0.453 g, 5.03 mmol) in CH₂Cl₂ (10 cm³) at 0°C was added triethylamine (0.85 cm³, 5.31 mmol). After 1 h the solution was diluted with Et₂O (2 cm³) was added one drop of a solution of triflic acid (0.05 cm³) in Et₂O (10 cm³). After 1 h the reaction mixture was stirred for 2 h at room temperature, which was taken up in benzene (1.4 cm³). A solution of diol (-)-29 (0.453 g, 5.03 mmol) in CH₂Cl₂ (10 cm³) at 0°C was added to a stirred THF (1.43 cm³) solution of acid (-)-30 (0.114 g, 0.165 mmol) and Et₃N (0.85 cm³, 0.59 mmol). After 1 h the solution was diluted with Et₂O (2 cm³) and washed with brine (5 cm³) and washed over MgSO₄. Evaporation under reduced pressure afforded crude alcohol which was used in the next step without further purification.

To a stirred solution of crude alcohol and p-methoxybenzyl chloroacetimidate (0.061 g, 0.22 mmol) in Et₂O (2 cm³) was added one drop of a solution of triflic acid (0.05 cm³) in Et₂O (10 cm³). After 1 h the reaction mixture was taken up in benzene (1.4 cm³). A solution of alcohol (+)-8 (0.098 g, 0.48 mmol) and DMAP (0.117 g, 0.96 mmol) in benzene (4.6 cm³) was added to the above solution, and stirring was continued 1.5 h at room temperature. The reaction mixture was diluted with Et₂O (25 cm³) and washed with saturated aqueous NaHCO₃ (10 cm³) and brine (10 cm³), dried over MgSO₄ and concentrated to leave an oil, which was flash chromatographed on silica gel (hexane) to give ester (-)-30 (0.260 g, 83%) as a colorless viscous oil.[ε]₂⁰ –60.0 (c 1.0, CHCl₃); IR νmax/cm⁻¹ 1735, 1606; ¹H NMR (300 MHz, CDCl₃) δ 6.67 (dd, J 14.0, 3.5 Hz, 1H), 6.27 (dd, J 14.0, 1.5 Hz, 1H), 5.00 (sex, J 6.6 Hz, 1H), 4.18-4.08 (m, 2H), 3.64 (t, J 6.6 Hz, 2H), 2.57 (dd, J 16.0, 2.5 Hz, 1H), 2.16 (dd, J 16.0, 8.0 Hz, 1H), 1.90-1.76 (m, 1H), 1.76-1.60 (m, 1H), 1.24 (d, J 6.0 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 38.2, 38.1, 30.1, 29.8, 26.7, 23.5, 17.9, -5.9, -6.0; MS (EI): m/z 73 (100%), 629 (1%, [M-C₄H₉⁺]); HRMS (EI): found 629.20055; calc. for C₂₄H₄₄O₅Si₃I [M-C₄H₉⁺] 629.20109.

(R)-3-(4-Methoxybenzoyloxy)-1-methyl-propyl (3S,4S,5E)-3,4-bis-(tert-butyl(dimethyl)silyloxy)-6-iodo-5-hexenoate (32)

To a solution of diol (-)-30 (0.114 g, 0.165 mmol) in THF (2.52 cm³) in a Nalgene® tube was added freshly prepared buffered pyridinium hydrofluoride (stock solution prepared from:0.208 g HF/pyridine complex, 0.47 cm³ pyridine and 1.65 cm³ of THF). After 3 h at room temperature the reaction was diluted with Et₂O (3 cm³) and neutralized by the dropwise addition of saturated NaHCO₃ (6 cm³). The layers were separated, the aqueous layer was extracted with Et₂O (3 x 5 cm³), the combined organic layers were washed with brine (5 cm³) and dried over MgSO₄. Evaporation under reduced pressure afforded crude alcohol which was used in the next step without further purification.

To a stirred solution of crude alcohol and p-methoxybenzyl chloroacetimidate (0.061 g, 0.22 mmol) in Et₂O (2 cm³) was added one drop of a solution of triflic acid (0.05 cm³) in Et₂O (10 cm³). After 1 h the reaction mixture was taken up in benzene (1.4 cm³). A solution of alcohol (+)-8 (0.098 g, 0.48 mmol) and DMAP (0.117 g, 0.96 mmol) in benzene (4.6 cm³) was added to the above solution, and stirring was continued 1.5 h at room temperature. The reaction mixture was diluted with Et₂O (25 cm³) and washed with saturated aqueous NaHCO₃ (10 cm³) and brine (10 cm³), dried over MgSO₄ and concentrated to leave an oil, which was flash chromatographed on silica gel (hexane) to give ester (-)-30 (0.260 g, 83%) as a colorless viscous oil.[ε]₂⁰ –60.0 (c 1.0, CHCl₃); IR νmax/cm⁻¹ 1735, 1606; ¹H NMR (300 MHz, CDCl₃) δ 6.67 (dd, J 14.0, 3.5 Hz, 1H), 6.27 (dd, J 14.0, 1.5 Hz, 1H), 5.00 (sex, J 6.6 Hz, 1H), 4.18-4.08 (m, 2H), 3.64 (t, J 6.6 Hz, 2H), 2.57 (dd, J 16.0, 2.5 Hz, 1H), 2.16 (dd, J 16.0, 8.0 Hz, 1H), 1.90-1.76 (m, 1H), 1.76-1.60 (m, 1H), 1.24 (d, J 6.0 Hz, 3H), 0.89 (s, 9H), 0.88 (s, 9H), 0.87 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 38.2, 38.1, 30.1, 29.8, 26.7, 23.5, 17.9, -5.9, -6.0; MS (EI): m/z 73 (100%), 629 (1%, [M-C₄H₉⁺]); HRMS (EI): found 629.20055; calc. for C₂₄H₄₄O₅Si₃I [M-C₄H₉⁺] 629.20109.
To a solution of (-)-32 (0.059 g, 0.085 mmol) in THF (1.2 cm³) in a Nalgene® tube was added freshly prepared buffered pyridinium hydrofluoride (stock solution prepared from 0.534 g HF:pyridine complex, 1.20 cm³ pyridine and 0.81 cm³ THF). After 20 h at room temperature the reaction was diluted with Et₂O (10 cm³) and neutralized by the dropwise addition of saturated NaHCO₃ solution (2 cm³), brine (2 cm³), and dried over Na₂SO₄. The solvent was evaporated and the residue was chromatographed on a silica gel column (EtOAc:hexane 15:85, v/v) to give alcohol (-)-33 (0.0204 g, 70%) as a colorless oil. [α]D²⁰⁻¹⁸.⁷ (c 1.87, CHCl₃); IR νmax/cm⁻¹ 3469, 1738, 1608; ¹H NMR (500 MHz, CDCl₃) δ 6.63-6.53 (m, 2H), 5.15 (dd, J 13.0, 6.3, 4.4 Hz, 1H), 4.14-4.07 (m, 2H), 2.70-2.56 (m, 2H), 1.90-1.81 (m, 3H), 1.68 (s, 6H), 1.40 (s, 6H), 1.32 (s, 3H), 1.21 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.4, 141.8, 109.7, 82.7, 81.4, 76.2, 69.4, 58.9, 38.9, 37.4, 27.0, 26.8, 20.4; MS (EI): m/z 97 (100%), 369 (35%, [M-CH₃]⁺); HRMS (EI): found 369.02082; calc. for C₁₂H₁₈O₅I [M-CH₃]⁺ 369.01990.

(R)-3-(4-Methoxybenzoyloxy)-1-methyl-propyl 2-{[(E)-2-iodo-1-ethenyl]-2,2-dimethyl-1,3-dioxolan-4-yl}acetate (34)

To a solution of (-)-32 (0.059 g, 0.085 mmol) in THF (1.2 cm³) in a Nalgene® tube was added freshly prepared buffered pyridinium hydrofluoride (stock solution prepared from 0.092 g HF:pyridine complex, 0.20 cm³ pyridine and 0.73 cm³ THF). After 3 h at room temperature the reaction was diluted with Et₂O (4 cm³) and neutralized by the dropwise addition of saturated NaHCO₃. The layers were separated, the aqueous layer was extracted with Et₂O (3 x 5 cm³), the combined organic layers were washed with brine (5 cm³), and dried over MgSO₄. Evaporation under reduced pressure afforded crude diol which was used in the next step without further purification.

To a stirred solution of crude diol and 2,2-dimethoxypropane (0.523 cm³, 4.25 mmol) in DMF (1 cm³) was added PPTS (0.002 g). After 20 h the reaction was quenched by addition of EtOAc (6 cm³) and successively washed with saturated NaHCO₃ solution (2 cm³), brine (2 cm³), dried over MgSO₄ and concentrated. Column chromatography (EtOAc:hexane 15:85, v/v) gave cetal (R)-34 (0.365 mg, 77% for 2 steps) as a colorless oil. [α]D²⁰⁺⁻³⁴.⁶ (c 0.002, CHCl₃); IR νmax/cm⁻¹ 1738, 1614; ¹H NMR (500 MHz, CDCl₃) δ 7.26-7.23 (m, 2H), 6.89-6.86 (m, 2H), 6.58-6.54 (m, 2H), 5.14-5.08 (m, 1H), 4.41 (s, 2H), 4.13-4.05 (m, 2H), 3.80 (s, 3H), 3.52-3.46 (m, 2H), 2.56-2.48 (m, 2H), 2.42-2.34 (m, 2H), 1.90 (ddt, J 14.1, 8.1, 6.0 Hz, 1H), 1.81 (dtt, J 14.1, 6.9, 5.1 Hz, 1H), 1.40 (s, 6H), 1.25 (d, J 6.3 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 169.6, 159.1, 142.0, 130.3, 129.3, 113.7, 109.5, 82.7, 81.2, 76.0, 72.7, 69.4, 66.2, 55.2, 37.3, 35.9, 27.1, 26.8, 20.2; MS (EI): m/z 121 (100%), 489 (2.0%, [M-CH₃]⁺); HRMS (EI): found 489.07787; calc. for C₂₀H₂₆O₆I [M-CH₃]⁺ 489.07742.

13 C NMR (125 MHz, CDCl₃)

14.1, 6.9, 5.1 Hz, 1H), 1.40 (s, 6H), 1.25 (d, J 6.3 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 6.63-6.53 (m, 2H), 5.15 (dd, J 13.0, 6.3, 4.4 Hz, 1H), 4.14-4.07 (m, 2H), 2.70-2.56 (m, 2H), 1.90-1.81 (m, 3H), 1.68 (s, 6H), 1.40 (s, 6H), 1.32 (s, 3H), 1.21 (s, 3H), 1.21 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.4, 141.8, 109.7, 82.7, 81.4, 76.2, 69.4, 58.9, 38.9, 37.4, 27.0, 26.8, 20.4; MS (EI): m/z 97 (100%), 369 (35%, [M-CH₃]⁺); HRMS (EI): found 369.02082; calc. for C₁₂H₁₈O₅I [M-CH₃]⁺ 369.01990.

(4S,5S,8S,10R)-8-Hydroxy-4,5-bis-(tert-butylidimethylsilyloxy)-10-methyl-3,4,5,8,9,10-hexahydro-2H-2-oxecinone (38a)

To a solution of (-)-30 (0.0503 g, 0.073 mmol) in THF (1.13 cm³) in a Nalgene® tube was added freshly prepared buffered pyridinium hydrofluoride (stock solution prepared from 0.092 g HF:pyridine complex, 0.20 cm³ pyridine and 0.73 cm³ THF). After 3 h at room temperature the reaction was diluted with Et₂O (4 cm³) and neutralized by the dropwise addition of saturated NaHCO₃. The layers were separated, the aqueous layer was extracted with Et₂O (4 x 3 cm³), the combined organic layers were washed with brine (5 cm³), and dried over MgSO₄. Evaporation under reduced pressure afforded crude alcohol 31 which was used in the next step without further purification.

To a suspension of Dess Martin periodinane (0.176 g, 0.42 mmol) in CH₂Cl₂ (1.83 cm³) containing water (0.008 cm³) was added a solution of the alcohol above in CH₂Cl₂ (0.50 cm³). The reaction mixture was stirred 1 h, and it was diluted with EtOAc (12 cm³). After the addition of saturated NaHCO₃ (12 cm³), the organic layer was separated and aqueous layer was extracted with EtOAc (2 x 5 cm³). The combined organic layer was washed with aqueous 1M L⁻¹ NaHSO₃ (10 cm³), brine (10 cm³) and dried over MgSO₄. Concentration produced the crude aldehyde 6 that was used in next step without further purification.

To a suspension of CrCl₂ (0.130 g, 1.06 mmol) containing 0.5 mol of NiCl₂ in degassed DMF (12 cm³) was added via cannula and under ice bath cooling a solution of aldehyde 6 (previously dried with 2 x 0.5 cm³ benzene in vacuo) in degassed DMF (2.6 cm³). The reaction mixture was stirred overnight at room temperature, and the solvent was distilled off under vacuum (0.1 mmHg). The residue was dissolved in saturated NH₄Cl (10 cm³) and extracted with Et₂O (4 x 10 cm³) and EtOAc (2 x 10 cm³). The organic layer was washed with brine (40 cm³) and dried over MgSO₄. The crude product was purified by flash...
chromatography (EtOAc:hexane 10:90, v/v) to yield (−)-38a (0.010 g, 31% for 3 steps) as a colorless oil. [α]$_{D}^{13}$ = −35.0 (c 1.0, CHCl$_3$); IR ν$_{max}$/cm$^{-1}$ 3435, 1738; $^1$H NMR (300 MHz, CDCl$_3$) δ 0.92-0.72 (m, 2H), 5.08 (dd, J 11.0, 6.2, 2.2 Hz, 1H), 4.26-4.14 (m, 2H), 3.91 (ddd, J 6.2, 4.4, 1.8 Hz, 1H), 2.57 (dd, J 3.2, 1.8 Hz, 1H), 2.17 (dd, J 13.2, 6.2 Hz, 1H), 1.86 (ddd, J 13.9, 4.0, 2.3 Hz, 1H), 1.76 (dt, J 13.9, 10.6 Hz, 1H), 1.63 (s, br, 1H), 1.20 (d, J 6.6 Hz, 3H), 0.95 (s, 3H), 0.94 (s, 3H), 0.13 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 170.6, 134.8, 129.2, 74.4, 73.4, 72.8, 67.1, 42.7, 35.2, 25.7, 25.5, 21.2, 18.0, 17.8, -5.1, -5.2, -5.3 (x2); MS (EI): m/z 73 (100%), 387 (3%), [M-C$_6$H$_4$]$^+$; HRMS (EI): found 387.20234; calc. for C$_{18}$H$_{34}$O$_3$Si$_2$ [M-C$_4$H$_g$]$: 387.20321$.

(3aS,7R,9RS,11aS)-9-Hydroxy-2,2,7-trimethyl-4,5,7,8,9,11a-hexahydro-3aH-[1,3]-dioxolof[4,5-d]oxecin-5-one (39a/39b)

To a suspension of Dess Martin periodinane (0.0286 g, 0.068 mol) in CH$_2$Cl$_2$ (1.0 cm$^3$) containing water (0.002 cm$^3$) was added a solution of alcohol (−)-35 in CH$_2$Cl$_2$ (0.27 cm$^3$). The reaction mixture was stirred 1 h, and it was diluted with AcOEt (7 cm$^3$). After the addition of saturated NaHCO$_3$ (7 cm$^3$), the organic layer was separated and aqueous layer was extracted with EtOAc (2 x 5 cm$^3$). The combined organic layer was washed with aqueous 1 mol L$^{-1}$ NaHCO$_3$ (5 cm$^3$), brine (5 cm$^3$) and dried over MgSO$_4$. Concentration produced the crude aldehyde 37 that was used in next step without further purification.

To a suspension of CrCl$_3$ (0.077 g, 0.63 mmol) containing 0.5% mol of NiCl$_2$ in degassed DMF (7 cm$^3$) was added via cannula and under ice bath cooling a solution of the aldehyde 37 (azetroped 2 x 0.5 cm$^3$ benzene in vacuo) in degassed DMF (1.6 cm$^3$). The reaction mixture was stirred overnight at room temperature, and the solvent was destilled off under vacuum (0.1 mmHg). The residue was dissolved in saturated NH$_4$Cl (15 cm$^3$) and extracted with Et$_2$O (4 x 10 cm$^3$) and EtOAc (2 x 10 cm$^3$). The organic layer was washed with brine (20 cm$^3$) and dried over MgSO$_4$. The crude product was purified by flash chromatography (EtOAc:hexane 20:80, v/v) to yield 39a/39b (0.006 g, 54% for 2 steps) as a 2:1 unseparable mixture of diastereoisomers. Major 39a$^+$: $^1$H NMR (500 MHz, CDCl$_3$) δ 5.69 (dd, J 16.4, 7.3 Hz, 1H), 5.57 (dd, J 16.6, 8.5, 1.1 Hz, 1H), 5.26 (qd, J 6.8, 2.2 Hz, 1H), 4.62-4.49 (m, 1H), 4.12 (t, J 8.6 Hz, 1H), 3.93 (ddd, J 10.9, 8.6, 5.2 Hz, 1H), 3.06 (dd, J 15.2, 5.2 Hz, 1H), 2.43 (dd, J 15.3, 11.1 Hz, 1H), 2.08 (dd, J 14.9, 5.6, 2.2 Hz, 1H), 1.44 (s, 3H), 1.42 (s, 3H), 1.29 (d, J 6.9 Hz, 3H). Minor 39a$^-$: $^1$H NMR (500 MHz, CDCl$_3$) δ 6.00-5.90 (m, 2H), 5.05 (ddq, J 9.5, 6.7, 1.3 Hz, 1H), 4.39-4.34 (m, 1H), 4.24-4.20 (m, 1H), 3.96 (dd, J 10.8, 8.7, 5.5 Hz, 1H), 3.09 (dd, J 14.8, 5.5 Hz, 1H), 2.44 (dd, J 14.8, 10.8 Hz, 1H), 2.15 (dd, J 14.2, 4.6, 1.2 Hz, 1H), 1.71 (dd, J 4.2, 9.4 Hz, 1H), 1.46 (s, 3H), 1.42 (s, 3H), 1.27 (d, J 6.9 Hz, 3H).

Decaerstrictine D ([−]−)

To a solution of (−)-38a (0.0062 g, 0.014 mmol) and TBAF (0.011 g, 0.042 mmol) in CH$_2$CN (0.85 cm$^3$) was added HF 40% (0.14 cm$^3$). The solution was stirred at room temperature 2.5 h and diluted with EtOAc (3 cm$^3$). Neutralization with saturated NaHCO$_3$ solution allowed phase separation, and the aqueous layer was extracted with EtOAc (3 x 2 cm$^3$). The combined organic layers were washed with brine (5 cm$^3$), and dried over MgSO$_4$. Silica-gel chromatography (EtOAc) afforded the (−)-decaerstrictin D ([−]−) (0.0025 g, 83%) as a white solid. [α]$_{D}^{13}$ −70.9 (c 0.24, CHCl$_3$); [α]$_{D}^{13}$ −83.3 (c 0.24, CHCl$_3$); lit.$^{15}$ [α]$_{D}^{13}$ −67.0 (c 0.26, CHCl$_3$); $^1$H NMR (500 MHz, CD$_2$OD) δ 5.83 (dd, J 15.9, 9.3, 1.5 Hz, 1H), 5.74 (dd, J 15.9, 3.1 Hz, 1H), 5.17 (ddq, J 11.3, 6.5, 1.6 Hz, 1H), 4.19 (dd, J 4.5, 3.2, 1.5 Hz, 1H), 4.07 (dd, J 10.7, 9.3, 3.4 Hz, 1H), 3.94 (dd, J 6.8, 4.6, 2.4 Hz, 1H), 2.59 (dd, J 14.0, 2.3 Hz, 1H), 2.31 (dd, J 14.1, 6.9 Hz, 1H), 1.85 (ddd, J 13.9, 3.6, 1.5 Hz, 1H), 1.72 (dt, J 13.9, 11.2 Hz, 1H), 1.21 (d, J 6.7 Hz, 3H); $^{13}$C NMR (75 MHz, CD$_2$OD) δ 175.3, 133.9, 130.1, 73.9, 72.5, 72.2, 68.2, 42.9, 33.0, 21.0.

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References


16. Column: heptakis-(2,6-methyl-3-pentyl)-α-cyclo-


18. Major isomer (E): δ 6.48 (dd, J 14.5, 0.8 Hz, H5), 6.59 (dd, J 14.5, 5.8 Hz, H4); minor isomer: δ 6.29 (t, J 8.0 Hz, H4), 6.53 (J 8.0, 0.8 Hz, H5).


20. Attempts to reduce the ester with LiAlH₄ followed by oxidation of the aldehyde did not provide better yields.

21. 24E: δ 6.22 (dd, J 14.5, 1.8 Hz, H6) and 6.69 (dd, J 14.5, 4.0 Hz, H5).

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31. Secondary to primary acyl migration was observed for alcohol 31.

32. During chromatographic purification and/or storing formation of the corresponding butyrolactone was observed from diol 33.


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