(+)-11,11'-Di-O-methylelaiophylidene – Preparation from Elaiophylin and Total Synthesis from (R)-3-Hydroxybutyrate and (S)-Malate

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The macrodiolide antibiotic elaiophylin (6, Scheme 1) is converted into an aglycone 8a by acid-catalysed cleavage of the deoxyfucoses in methanol, with replacement of two lactol OH-groups by OCH3 (C-11 and C-11'). The di-O-methylelaiophylidene (8a), a C2-symmetrical macrodiolide with 2 x 11 stereogenic units, was synthesised from (R)-3-hydroxybutanoate (from the biopolymer PHB) and (S)-malic ester, using diastereoselective steps for the generation of the other stereogenic units. The key intermediates (Scheme 2) are the macrocyclic dialdehyde 10 (cf. 26, 27; 2 x 5 stereogenic units) and the silyl-protected dihydroxy ketone derivative 11 (cf. 34, 35; 3 stereogenic units). These two intermediates almost statistically were subjected to aldol coupling with relative topicality ul, using the Z-boron enolate of the ketone, to give the two C2-symmetrical and the asymmetric aldol (40a, b, c), one of which furnished the aglycone 8a upon acid-catalysed methanolation (Fig. 1 and 2, NMR spectra). The diastereoselective key steps, by which three of the six new asymmetric carbon atoms are created, are α-alkylations of β-hydroxy ester or lactone alkoide-enolates (malic acid → 12 and 15 → 16 in the dialdehyde synthesis, hydroxybutanoic acid → 29 in the ketone preparation).

(+)-11,11'-Di-O-methylelaiophyliden — Herstellung aus Elaiophylin und Totalsynthese aus (R)-3-Hydroxybuttersäure- und (S)-Äpfelsäureester

Das Makrodiodid-Antibiotikum Elaiophylin (6, Schema 1) kann durch säurekatalysierte Abspaltung der Desoxyfucoses-Einheiten in Methanol unter gleichzeitiger Substitution der C-11- und C-11'-Lactol-OH-Gruppen durch OCH3 in das Aglycon 8a umgewandelt werden. Dieses Di-O-methylelaiophyliden genannte C2-symmetrische Makrodiodid 8a enthält 2 x 11 stereogene Einheiten, von denen in der hier beschriebenen Totalsynthese zwei aus (R)-3-Hydroxybuttersäure (aus dem Biopolymer PHB) und (S)-Äpfelsäure stammen, während die anderen durch diastereoselektive Reaktionsschritte erzeugt werden. Die zwei Schlüsselprodukte der konvergenten Synthese (Schema 2) sind der makrocyclische Dialdehyd 10 (vgl. 26, 27; 2 x 5 stereogene Einheiten) und das silygeschützte Dihydroxyketonderivat 11 (vgl. 34, 35; 3 stereogene Einheiten). Aldoladdition des Z-Bor-Enolates des Ketons an den Dialdehyd erfolgte — beinahe statistisch — mit relativer Topizität ul und lieferte zwei C2-symmetrische und ein unsymmetrisches Diaddukt (40a, b, c), von denen eines bei der säurekatalysierten Methanalysis das Aglycon 8a lieferte (Abb. 1 und 2 zeigen die NMR-Spektren). Die diastereoselektiven Schlüsselschritte, mit denen drei der sechs neuen asymmetrischen Kohlenstoffatome erzeugt wurden, sind α-Alkylierungen von β-Hydroxyester oder -lacton-Alkoholat-Enolaten (Äpfelsäure → 12 und 15 → 16 bei der Dialdehydsynthese sowie Hydroxybuttersäure → 29 bei der Herstellung des Ketons).
A) Introduction

Two groups of medium-ring diolides, so-called macrolodiles\textsuperscript{1,2} have been isolated from fungi: the unsymmetrical ones (1, 2) and those with C\textsubscript{2}-symmetry (3–6) (Scheme 1).

Scheme 1

<table>
<thead>
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<th>No.</th>
<th>Name</th>
<th>References</th>
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<tbody>
<tr>
<td>1</td>
<td>Colletoidiol</td>
<td>3, 4, 5</td>
</tr>
<tr>
<td>2</td>
<td>Grahamimycin A\textsubscript{1}</td>
<td>5, 10, 11</td>
</tr>
<tr>
<td>3</td>
<td>Pyrenophorin</td>
<td>14, 15 16–18</td>
</tr>
<tr>
<td>4</td>
<td>Vermiculin</td>
<td>35 18, 22, 36</td>
</tr>
<tr>
<td>5</td>
<td>Conglobatin</td>
<td>39 39, 40 40</td>
</tr>
<tr>
<td>6</td>
<td>Elaiophylin</td>
<td>41 45–50</td>
</tr>
<tr>
<td></td>
<td>Azalomycin 8</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>Antibiotic 255 E</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>Salbomycin</td>
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In a series of papers\textsuperscript{9,11,18,22,28,40} we have described the syntheses of the structurally simpler representatives 1 – 5 of this class of natural products, most of which show antibiotic activity, and of some analogues\textsuperscript{22,28,51,52}. In all cases our strategy was based on the use of readily available chiral building blocks (such as lactic, 3-hydroxybutyric, malic or tartaric acid) which are prepared by biological-chemical methods ("Chiral Pool")\textsuperscript{53,54}. Elaiophylin 6 is the most challenging example of this.
B) Elaiophylin, an aglycone and a strategy

Elaiophylin (6) was isolated, originally, from cultures of Streptomyces melanosporus and exhibits activity against gram-positive bacteria. Compounds which ultimately proved to be identical with elaiophylin were subsequently isolated from other strains of Streptomyces (Scheme 1). The constitution of elaiophylin was first elucidated in 1981, and later the relative and absolute configuration were determined by X-ray analysis and NMR studies.

Despite many attempts to remove the 2,6-deoxyfucose carbohydrate moieties from elaiophylin, the aglycone 7 has never been reported, and treatment with both mild acid and base led to complete decomposition. This observation indicates that the synthesis of elaiophylin from an aglycone would be extremely difficult. We have made extensive studies on the cleavage of elaiophylin under acidic conditions, and it became rapidly clear that only in the presence of methanol (and absence of water) identifiable derivatives, in which the central macrodiolide ring was intact, could be detected. In the presence of p-toluenesulfonic acid, it is pos-
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B: 300-MHz $^1$H NMR spectra of aglycones of elaiophylin 6

A: (+)-11,11'-Di-O-methylelaiophyllidene (8a), by cleavage of 6 with p-toluenesulfonic acid in methanol. — B: Monoaglycone 9 of 11,11'-di-O-methylelaiophyllin, by cleavage of 6 with lanthanum trichloride in methanol. — C: Elaiophyllidene (8a) from the total synthesis.

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sible, however, to isolate the dimethyl aglycone 8a, in which both lactols have been converted into methyl acetals and both deoxyfucose molecules have been removed. The proton NMR spectrum of this aglycone is shown in Figure 1, A. It is clear that there are two molecules of methanol strongly associated with the aglycone. If, on the other hand, p-toluenesulfonic acid is replaced by lanthanum trichloride, which is thought to be less acidic, it is then possible to isolate a monoaglycone 9, in which both of the lactols have been converted into methyl acetals, but only one sugar has been removed. It is apparent from the proton NMR spectrum (Figure 1, B) that this molecule also has two molecules of methanol strongly associated with it. The isolation of the monoaglycone 9 clearly demonstrates that the fastest step in the methanolysis is the conversion of the lactols to methyl acetals (substitution of OH in position 11 by OCH3).

Scheme 2

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The instability of the aglycone 8a under acidic conditions in the presence of water precludes its conversion into elaiophylin itself, since it is clearly impossible to convert a methyl acetal into a free lactol without water. An alternative approach would have required the coupling of a protected derivative of deoxyfucose (e.g., a glycosyl fluoride) with the aglycone 8a (possibly also protected at C-9-OH), followed by removal of all the protecting groups. This would have required both the hydrolysis of the methyl acetal in the presence of the glycosidic bond, and also protecting groups on the deoxyfucose moiety which could be removed under neutral conditions, a formidable set of requirements. We therefore did not investigate this possibility. Thus, our target was the dimethyl aglycone 8a which showed similar biological activity to elaiophylin itself.

Our retrosynthetic analysis is presented in Scheme 2. We proposed firstly to disconnect the masked β-hydroxy ketone function in the aglycone 8a to give a central macrocyclic dialdehyde 10 and two identical side-chain ethyl ketones 11. We proposed to construct the central macrocycle by dimerisation of a suitably monoprotected dihydroxy acid, which may be obtained from malic acid, and to prepare the side chain from 3-hydroxybutyric acid. The final aldol coupling reaction between the dialdehyde 10 and the ketone 11 would, we realised, be hard to control but an alternative strategy involving postponement of the macrodiolide ring formation to the final step, thereby exploiting the C₂-symmetry to its utmost effect, would have required an unmanageable array of protecting groups in such a sensitive molecule.

C) The synthesis of the central ring (10, 27)

The starting material for our synthesis was the benzaldehyde acetal 12, available in five steps from diethyl (S)-malate. Conversion of the free hydroxy group into the triflate using trifluoromethanesulfonic anhydride and pyridine was followed by immediate reaction with sodium cyanide in hexamethylphosphoronic triamide to give the chain-extended nitrile 13 in 57% yield. Hydration of the nitrile function was accomplished using Corey's hydrogen peroxide/1-hexene procedure to give the amide 14 in 97% yield. Hydrogenolysis of the benzylidene acetal, employing 20% palladium hydroxide on charcoal as catalyst, led to the corresponding diol which could not be isolated in pure form, but was instead treated with 1 N hydrochloric acid to give the lactone 15 in 70% yield from 14.

The lactone 15 could be methylated in 75% yield (with 12% recovery of the starting material) and with diastereoselectivity greater than 99 to 1, by treatment with two equivalents of lithium diisopropylamide at -60°C for two hours, addition of n-butyllithium to deprotonate the free diisopropylamine formed, and then quenching of the enolate with methyl iodide. Omission of the n-butyllithium led to significantly lower yields of the methylated product 16, and correspondingly greater recovery of the lactone 15. Opening of the lactone 16 could be achieved using sodium methoxide in methanol to produce a dihydroxy methyl ester which was not purified but instead selectively protected at the primary hydroxy group using Hanessian's tritylpyridinium tetrafluoroborate procedure to give the...
monotrityl ether 17 in 48% overall yield from the lactone 16 (18% recovery). The proton NMR spectrum of the trityl ether 17 indicated that it was contaminated with 3% of a diastereoisomeric product, presumably formed by methoxide-induced epimerisation.

At this stage of our route it was necessary to alter the oxidation states at the terminal carbon atoms of the chain. This process was initiated by reduction of the methyl ester function of 17 using LiAlH₄ in ether to give in 98% yield the diol 18 which was then treated with dimethoxypropane and a catalytic amount of p-toluenesulfonic acid to produce the dioxane 19 in 91% yield. Removal of the trityl protecting group was accomplished using lithium in liquid ammonia to give the alcohol 20 (72%), identical with the compound which we had prepared by our alternative route. 

In Scheme 3 the logistics and overall efficiency of the two routes are compared. The alcohol 20 can be converted into the macrocyclic diol 27 via the intermediates 21 to 26 as we have described previously. Oxidation of the diol 27, using Swern’s conditions, gave the dialdehyde 10 in 91% yield. The dialdehyde was generally used immediately in the aldol reaction.
Scheme 3

Method A: Convergent, using an external chiral auxiliary, 8 steps (35% overall yield) to 20; 3 steps to make the chiral auxiliary from D-valine, yield 82%; recovery of chiral auxiliary after Evans' aldol addition: 78%.

Method B: Linear, starting from the pool of chiral building blocks, 13 steps (7% overall yield) to 20.

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D) Synthesis of the side chain (11, 35)

At first, we synthesised a bis(tert-butyldimethylsilyl)-protected ketone 28a. However, it was shown that the two TBDMS groups could be removed neither prior to nor after the final aldol coupling reaction without extensive decomposition. Studies on the ketone 28b indicated that it was very unstable. We therefore decided that two different protecting groups are necessary at C-5 and C-7 of the ketone (C-13 and C-15 of the final carbon skeleton) to ensure that in the deprotection step the free β-hydroxy ketone function at C-5 (C-13) would not be exposed.

Selective removal of the C-7 (C-15) hydroxy protective group would, we hoped, permit the cyclisation to a δ-lactol which would then not be so prone to elimination.

The side-chain aldol derivative of type 11 which was eventually used in the synthesis, was prepared as follows. Treatment of the ethyl (R)-3-hydroxybutyrate, prepared from the biopolymer PHB, with two equivalents of lithium diisopropylamide and three equivalents of ethyl iodide gave the diastereoisomerically pure ester 29 in 84% yield. Protection of the hydroxy group of 29 using triethylsilyl trifluoromethanesulfonate and lutidine led to the triethylsilyl ether 30 in quantitative yield. Reduction of the ester function to give the alcohol 31 was carried out using diisobutylaluminium hydride in 96% yield. When LiAlH₄ was used for the reduction, substantial amounts of the product of silyl migration from the secondary to the primary oxygen function were observed. Swern oxidation of the alcohol 31 then gave the aldehyde 32 in 84% yield. The partner for the
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projected Mukaiyama aldol reaction, 2-trimethylsilyloxy-1-butene (33), was prepared free of its regiosomer by deprotonation of 2-butanol with lithium 2,2,6,6-tetramethylpiperidide, followed by quenching with trimethylsilyl chloride and fractional distillation.

After a series of experiments to effect the aldol coupling between the aldehyde 32 and the silyl enol ether 33 using various Lewis acids, we found that titanium tetrachloride at \(-75^{\circ}\text{C}\) in dichloromethane led to the formation of a single isolable aldol adduct 34 in 38\% yield. This aldol adduct 34 could be purified by flash chromatography, but the neat compound decomposed very rapidly and so it was protected as the tert-butyldimethylsilyl ether immediately. Initially we tried to use tert-butyldimethylsilyl triflate in the presence of lutidine to effect the silylation. This led, however, to an equimolar mixture of the required silyl ether 35 and its isomer in which the two silyl protecting groups at C-5 and C-7 were interchanged. Presumably, this isomerisation was caused by lutidine-induced silyl transfer via a six-membered transition state. Use of Corey's original procedure, employing imidazole and tert-butyldimethylsilyl chloride in dimethylformamide, gave the required bis-protected diol 35 in rather poor yield (42\%) and very slowly (80 hours).

\[
\begin{align*}
\text{SiEt}_3 & : \text{O} \\
\text{O} & : \text{H} \\
\text{O} & : \text{SiEt}_3 \\
\text{O} & : \text{TBDMS} \\
\text{TBDMSO} & : \text{OH} \\
\text{OH} & : \text{TBDMSO} \\
\text{OMe} & : \text{O} \\
\text{O} & : \text{OMe} \\
\text{H}_a & : \text{OMe} \\
\text{H}_b & : \text{H} \\
J_{ab} & = 10.5 \text{ Hz}
\end{align*}
\]

In order both to establish the configuration of the aldol adduct 34 and to ascertain whether the protected \(\delta\)-hydroxy ketone function could be converted into a cyclic methyl acetal, the bis-protected aldol 35 was treated with water/acetic acid/tetrahydrofuran (3 : 5 : 11) to give the \(\delta\)-lactol 36 (97\%) which was immediately treated with pyridinium \(p\)-toluenesulfonate in methanol to give the methyl acetal 37 in 77\% yield. Removal of the tert-butyldimethylsilyl group was then achieved using tetra-n-butylammonium fluoride in tetrahydrofuran to give the hydroxy compound 38 in 94\% yield. The signal [doublet of triplets \((J = 4.8\) and 10.5 Hz)] due to the hydrogen on C-4 in the proton NMR spectrum of this

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acetal 38 clearly indicates that this proton is trans-diaxial to two protons (3-H$_{ax}$ and 5-H), and therefore the configuration at C-4 is R. The stereochemical course of the aldol addition in which the isolated product is formed according to the open-chain model of Crani's rule, requires some comment. Products which are formed following the open-chain model have been observed in systems with potential chelating groups, which would normally be expected to follow the cyclic model$^{77}$. The low yield in this reaction suggests, perhaps, that the other diasteroisomer may indeed be formed but that it is even more unstable than the product which we isolate (i. e., the reaction might not have been selective at all)

**E) The aldol coupling of the side chain to the macrocyclic dialdehyde**

The crucial step in the synthesis had now been reached. We felt that the best way to ensure that the newly created centres of chirality in the aldol reaction were generated with relative topicity $ul$$^{78}$ (to give a syn product in Masamune's nomenclature) would be to prepare the di-n-butylboron enolate of the ketone 35. It is well-known that it is possible to prepare 2-boron enolates with high stereoselectivity and that these enolates undergo $ul$-addition to aldehydes highly selectively$^{79-81}$. Evans has observed that enolisation of ethyl isobutyl ketone using di-n-butylboron triflate occurs exclusively at the methylene position of the ethyl group, which is analogous to the selectivity which we require$^{81}$. Indeed, treatment of the ketone 35 with di-n-butylboron triflate in ether, and subsequent reaction with benzaldehyde, gave a 51\% yield of an inseparable mixture of two syn-aldol adducts 39 after oxidative work-up, according to the established assignment of configuration by proton NMR spectroscopy. We were therefore confident that we had generated the required 2-enolate. What remained to be determined was the combined diastereofacial selectivities of the dialdehyde 10 and the di-n-butylboron enolate of the ketone 35.

![Molecule 39a](image)

![Molecule 39b](image)

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Treatment of the dialdehyde 10 with four equivalents of the di-\(n\)-butylboron enolate of the ketone 35 led to three stereoisomers 40 (3:5:6 or 21, 37, and 42% d. s., respectively; 42% combined yield) as the only isolable aldol adducts, which were easily separable by flash chromatography. Of these products, two had \(C_2\)-symmetry, whilst the third was unsymmetrical, as evident from the proton NMR spectrum. Assuming that only \(ul\) coupling of the trigonal centres had occurred, the formation of three isomers is indeed expected (see formula 40 and the schematic representations A, B, and C). Thus, the unsymmetrical product (42% d. s.) should have the structure 40b (cf. B). We were unable, at this point, to assign the configurations of the two \(C_2\)-products. The proton NMR spectrum of the unsymmetrical product was a linear combination of the proton NMR spectra of the two \(C_2\) products. After numerous efforts to find conditions which would permit the cleavage of the triethylsilyl ether groups of the aldol adducts 40 including the conditions used in the establishment of the configuration of the ketone 35, we eventually discovered that the use of \(p\)-toluenesulfonic acid in methanol, the conditions used for making the aglycone 8a, effected all the transformations required: cleavage of the triethylsilyl ether, cyclisation to the lactol, methyl acetal formation and cleavage of the tert-butyldimethysilyl ether. This order of steps is mechanistically reasonable (cf. the model series 35→36→37→38). The stereoisomer 40 formed with

\[
40a : (9R,9'S,10S,10'S)
40b : (9R,9'S,10S,10'R)
40c : (9S,9'S,10R,10'R)
\]

A

B

C

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21% d. s. gave, under these conditions, a product (17% yield) which proved to be identical to the dimethyl aglycone 8a, prepared from elaiophylin, by comparison of R_f values, proton NMR (shown in Figure 1, C) and infrared spectra, and of the sense and value of optical rotation. This unambiguously established the configuration of this stereoisomer of 40 to be 40a, as well as establishing the configuration of the other symmetrical aldol adduct (37% d. s.) as 40c. Treatment of 40b and 40c with p-toluenesulfonic acid in methanol led to 8b and 8c, respectively, which were both different from the natural aglycone 8a. Again the proton NMR spectrum of the unsymmetrical compound 8b was a linear combination of the proton NMR spectra of 8a and 8c (see Figure 2).

![Figure 2. Comparison of the 3–7-ppm part of the 300-MHz 1H NMR spectra of the diastereomers 8a, b, and c (cf. A, B, and C below formula 40); for assignment of signals see experimental section](image)

**E) Concluding remarks**

In our synthesis of elaiophylidene (8a) the eleven independent stereogenic units, two double bonds and nine asymmetric carbon atoms, have the following origin: (i) three units are introduced directly from the starting materials methyl (E)-4-bromocrotonate [C(2)–C(3)], ethyl (R)-3-hydroxybutyrate [C(15)] and (S)-malic acid [C(7)]; (ii) three units were generated by coupling of trigonal centres during the Wittig reaction [C(4)–C(5)] and in the final aldol coupling step [C(9), C(10)]; (iii) one centre was created in a nucleophilic addition with 1,2-asymmetric induction subject to Cram's rules [C(13)]; (iv) three centres of chirality were generated...
by electrophilic attack on enolate double bonds with 1,2-asymmetric induction [C(6), C(8), C(14)]; (v) and finally, the methyl acetal centre [C(11)] is formed under the influence of stereoelectronic control \(^{82}\). We have given discussions of the above methods (i), (ii), and (iv) in previous papers, see ref. \(^{54}\), ref. \(^{78,83}\), and ref. \(^{84}\), respectively.

The final attachment of the side-chain ketone 35 to the macrodiolide dialdehyde 10 (cf. also Scheme 2) deserves some additional comments. Although a total yield of 42\%, of which only one fifth is the desired stereoisomer, may appear to be a poor result, it actually demonstrates how powerful a method the aldol addition has recently become \(^ {85}\); the ketone 35 with two methylene groups \(\sigma\) to the carbonyl is added to the aldehyde 10 regio- and diastereoselectively. In principle, three constitutional isomers could have resulted from a non-regioselective reaction, and with unselective \(\sigma k\) and \(\sigma l\) combination of the two trigonal centres nine diastereoisomers of correct constitution could have been formed. Thus, the three isomers which are actually isolated represent a very small selection of all those possible.

Our synthesis emphasises the fact that, at present, there is no method available to control, in an absolute sense, the configurations of asymmetric carbon atoms formed by the coupling of trigonal centres of two complex molecules \(^ {63,86}\). It can therefore be considered fortuitous that the coupling between ketone 35 and di-aldehyde 10 with relative topicity \(\sigma l\) is nearly statistical (compare 1 : 2 : 1 with the observed 1 : 1.7 : 2), and not biased in the undesired direction, to a disastrous degree, by Cram’s rule or by chelation control.

The synthesis described here is yet another demonstration of the fact that “we can now make a few milligrams of anything whose structure we can draw, that is stable, and has fewer than a thousand atoms” \(^ {87}\). The conclusions that we can draw from this synthesis are that we should attempt to find solutions to the problems of coupling complex molecules stereoselectively and of making and breaking glycosidic bonds in molecules as sensitive as elaiophylin and elaiophylin.

We gratefully acknowledge helpful discussions with and receipt of generous samples of elaiophylin from Professor Dr. W. Keller-Schierlein of our Laboratory, Dr. A. von Wartburg, and Dr. W. Pache (Sandoz AG, Basel) for carrying out biological tests, the staff of the analytical department of the ETH organic chemistry institute for obtaining the analytical data, Miss B. Brandenberg for measuring the NMR spectra, and Mr. K. Job (Kilolabor) and Mr. G. Scherpenhuyzen for the preparation of starting materials. This work was supported by a grant from the Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung (Project Nr. 2.306—0.81 and Project Nr. 2.253—0.84) and by the Sandoz AG (Basel). R. F. W. J. thanks the Royal Society for a fellowship in the European Exchange Programme.

**Experimental**

Melting points were determined with a Büchi/Tottoli melting point apparatus and are uncorrected. — The temperature of Kugelrohr distillations is that of the air bath. — Merck Kieselgel 60 (silica, mesh size 0.040—0.063) was used for flash chromatography. — Specific rotations were determined with a Perkin-Elmer 241 polarimeter using CHCl₃ as solvent at
25°C. The concentration is given in g/100 ml. — IR spectra were recorded using a Perkin-
Elmer 297 spectrometer either as KBr discs or in CHCl₃ solution. — ¹H NMR spectra were
obtained with either a Varian EM-390 (90 MHz) or a Bruker WM 300 (300 MHz) instru-
ment. ¹³C NMR spectra were obtained using a Varian CFT-20 instrument. All spectra were
recorded using TMS as internal standard in CDCl₃ as solvent. Signals marked with an
asterisk (*) disappear on addition of D₂O. — Mass spectra were recorded at 70 eV with a
Hitachi-Perkin-Elmer RMV 6M instrument. All reaction solvents, except for tetrahydro-
furan (THF) and hexamethylphosphoric triamide (HMPT) were of purissimum quality. THF
was distilled from potassium/benzophenone ketyl immediately before use. HMPT was dis-
tilled over CaH₂ under reduced pressure. All reactions were carried out in oven-dried glass-
ware under argon. Unless otherwise stated, organic extracts were dried with MgSO₄ and
concentrated using a rotary evaporator. Buffer solution of pH = 7 was prepared by dis-
solving potassium dihydrogen phosphate (85 g) and sodium hydroxide (14.5 g) in water
(950 ml).

The numbering system (IUPAC) in the experimental part is different from that in the text
(trivial nomenclature).

Numbering system according to IUPAC for compounds of type 8 and 40 (this system is
used in the Experimental Part only).

Methanolysis of elaiophylin (6) — Synthesis of the methoxy aglycone 8,16-bis{3-(5-ethyl-
3,4,5,6-tetrahydro-4-hydroxy-2-methoxy-6-methyl-2H-pyran-2-yl)-2-hydroxy-1-methylbut-
yl}-7,15-dimethyl-1,9-dioxacyclohexadeca-3,5,11,13-tetraene-2,10-dione (8a): A mixture of
elaiophylin (50 mg, 0.0488 mmol) and p-toluenesulfonic acid (10 mg) in dry methanol (10 ml)
was stirred at 20°C for 3 h. The mixture was poured into phosphate buffer (pH = 7; 3 ml)
and the methanol evaporated. The residue was dissolved in ether (50 ml), washed with
phosphate buffer (pH = 7), dried, filtered, and evaporated. The residue was chromato-
graphed on Merck silica gel plate (60F₂₅₄) developing with ether/hexane (3 : 1) to give a
homogeneous fraction 8a (20 mg, 49%; Rₚ = 0.28) as an oil; [α]D = +68.0 (c = 0.54,
CCl₄). — IR (CCl₄): 3600-3350 (O-H), 1700 (C=O), 1640 (C=C), 1612 (C=C). —
¹H NMR (300 MHz, C₆H₆) (for numbering see formula above): δ = 0.42* (br., 6H, 4 OH
and 2 MeOH), 0.61 (d, J = 6.7 Hz, 6H, 2 CH₃), 0.84 (d, J = 6.5 Hz, 6H, 2 CH₃), 0.95 (t,
J = 7.6 Hz, 6H, 2 CH₂CH₂CH₃), 1.24 (d, J = 6.2 Hz, 6H, 2 CH₃), 1.25–1.76 (m, 6H,
2 CH₂CH₂Me), 1.32 (d, J = 7.0 Hz, 6H, 2 CH₃), 1.82 [dd, J = 13.2 and 10.7 Hz, 2H,
2H₁₆(C₃')], 1.90–1.97 [m, 2H, 2 HC(1')], 2.18–2.30 [m, 4H, HC(7)], HC(15) and 2 HC(3'),
2.84 [dd, J = 13.2 and 4.6 Hz, 2H, 2H₁₆(C₃')], 3.08 (s, 6H, 2 OMe), 3.13 (s, 6H, 2 MeOH),
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\[
\begin{align*}
3.55 - 3.65 \text{ [m, 4H, 2 HC(4') and 2 HC(6')]}, & \; 3.90 \text{ [dd, J = 9.4 and 3.8 Hz, 2H, 2 HC(2')]}, \\
5.05 \text{ [dd, J = 9.9 and 1.7 Hz, 2H, HC(8) and HC(16)]}, & \; 5.15 \text{ [dd, J = 15.0 and 9.5 Hz, 2H, HC(6) and HC(14)]}, \\
5.39 \text{ [dd, J = 15.4 Hz, 2H, HC(3) and HC(11)]}, & \; 5.73 \text{ [dd, J = 15.1 and 11.2 Hz, 2H, HC(5) and HC(13)]}. \\
\end{align*}
\]

\((3R,4S)-3,5\text{-Benzyldenedioxy}-4\text{-methylpentanenitrile} (13):\) Trifluoromethanesulfonic anhydride (8.8 ml, 54 mmol) was added dropwise to a solution of the alcohol 12 (10 g, 48 mmol) and pyridine (6.5 ml, 80 mmol) in dichloromethane (40 ml) at 0°C over 30 min. The solution was stirred at 0°C for 30 min, and then washed with ice-cold water (2 x 30 ml). The organic phase was dried and added dropwise to a solution of sodium cyanide (2.6 g, 53 mmol) in HMPT (30 ml). The brown solution was stirred for 4 h at 20°C and then water (100 ml) was added. The mixture was extracted with dichloromethane (3 x 80 ml). The combined organic layers were washed with water (100 ml), dried, and evaporated. The residue was purified by flash chromatography (eluants hexane/ethyl acetate, 4 : 1) to give the nitrile 13 (5.9 g, 57%). — M. p. 66-67°C; \([\alpha]_D = +3.2 (c = 1.4, \text{CHCl}_3)\). — IR (KBr): 2980 (m, CH), 2250 (w, C=N). — 1H NMR (300 MHz): \(\delta = 0.86 (d, J = 6.7 Hz, 3H, \text{CH}_3)\), 1.96 - 2.14 (m, 1H, CH\_CH\_3), 2.64 (dd, \(J = 6.4\) and 17.0 Hz, 1H, CH\_CH\_3), 2.75 (dd, \(J = 3.9\) and 17.0 Hz, 1H, CH\_CN), 3.55 (t, \(J = 11.3\) Hz, 1H, CH\_O), 4.16 (dd, \(J = 4.8\) and 11.5 Hz, 1H, CH\_O), 5.02 (dd, \(J = 4.9\) and 11.4 Hz, 1H, CH\_O), 5.25 (s, 1H, O-CH-O), 7.32 - 7.54 (m, 5H, Ar). — 13C NMR (25.2 MHz): \(\delta = 12.1 (q), 24.4 (t), 33.7 (d), 72.3 (t), 78.1 (d), 101.3 (d), 116.9 (s), 126.2 (d), 128.4 (d), 129.1 (d), 137.8 (s). – MS: \(m/z = 217 (24\%), M^+\), 216 (46%, \(M^+ - 1\), 105 (100%), 77 (37%, \(A^+\)).

C\(_{13}\)H\(_{15}\)NO\(_3\) (217.3) Calcd. C 71.84 H 6.96 N 6.45 Found C 71.64 H 6.94 N 6.37

\((3R,4S)-3,5\text{-Benzyldenedioxy}-4\text{-methylpentanenitrile} (14):\) The nitrile 13 (10 g, 46 mmol) was added to hydrogen peroxide (50 ml, 30% in water, 440 mmol), 1-hexene (54 ml, 432 mmol) and sodium carbonate (3.6 g, 34 mmol) in methanol (250 ml). The suspension was stirred for 16 h at 20°C. Sodium metabisulfite (20 g, 117 mmol) in water (200 ml) was added and the solution was extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried and evaporated to give the amide 14 (10.5 g, 97%) which was pure enough for the next step. A sample was recrystallised from toluene. — M. p. 131-132°C; \([\alpha]_D = 27.1 (c = 1.62). – IR (KBr): 3380 and 3200 (m, NH), 2960 (m, C-H). — 1H NMR (300 MHz): \(\delta = 0.84 (d, J = 6.7 Hz, 3H, \text{CH}_3)\), 1.86 - 2.04 (m, 1H, CH\_CH\_3), 2.48 (dd, \(J = 8.12\) and 15.1 Hz, 1H, CH\_CH\_3), 2.64 (dd, \(J = 2.8\) and 15.1 Hz, 1H, CH\_CH\_3), 3.54 (t, \(J = 11.3\) Hz, 1H, CH\_O), 3.82 - 3.92 (m, 1H, CH\_O), 4.14 (dd, \(J = 4.8\) and 11.4 Hz, 1H, CH\_O), 5.55 (s, 1H, O-CH-O), 7.30 - 7.52 (m, 5H, Ar). — 13C NMR: \(\delta = 12.3 (q), 33.5 (d), 39.9 (t), 72.7 (t), 80.1 (d), 101.1 (d), 125.9 (d), 128.3 (d), 128.9 (d), 138.0 (s), 173.1 (s). – MS: \(m/z = 235 (3.1\%, M^+), 234 (13\%, M^+ - 1), 105 (100%), 77 (46\%, A^+)\).}

C\(_{13}\)H\(_{14}\)NO\(_3\) (235.3) Calcd. C 66.36 H 7.28 N 5.95 Found C 66.10 H 7.17 N 5.79

\((3R,4S)-3\text{-Hydroxy}-4\text{-methyl}-5\text{-pentanolide} (15):\) The amide 14 (9.0 g, 38 mmol) was dissolved in ethyl acetate (500 ml). Palladium hydroxide (4.1 g, 20% on charcoal) was added and the suspension was stirred for 10 h under a hydrogen atmosphere at 20°C. The suspension was filtered through celite and the residue was carefully washed with hot ethyl acetate (200 ml). The filtrate was evaporated to give a colourless oil, which was dissolved in hydrochloric acid (60 ml, 1 N) and stirred at 20°C for 18 h. The solution was extracted with ether (200 ml) in a continuous extractor for 10 h. The ether solution was dried and evaporated to give a yellow oil. The residue was purified by flash chromatography (eluants ether) to give the lactone 15 (3.35 g, 68%). A sample was recrystallised from ether/hexane. — M. p. 44.5-46.5°C; \([\alpha]_D = 5.8 (c = 1.22). – IR (KBr): 3400 (br., OH), 2960 (m, C-H), 1620 (m, C=O), 1240 (w, C=O). — 1H NMR: 6 0.86 (d, \(J = 6.7\) Hz, 3H, CH\_3), 1.86 - 2.04 (m, 1H, CH\_CH\_3), 2.48 (dd, \(J = 8.12\) and 15.1 Hz, 1H, CH\_CH\_3), 2.64 (dd, \(J = 2.8\) and 15.1 Hz, 1H, CH\_CH\_3), 3.54 (t, \(J = 11.3\) Hz, 1H, CH\_O), 3.82 - 3.92 (m, 1H, CH\_O), 4.14 (dd, \(J = 4.8\) and 11.4 Hz, 1H, CH\_O), 5.55 (s, 1H, O-CH-O), 7.30 - 7.52 (m, 5H, Ar). — 13C NMR: \(\delta = 12.3 (q), 33.5 (d), 39.9 (t), 72.7 (t), 80.1 (d), 101.1 (d), 125.9 (d), 128.3 (d), 128.9 (d), 138.0 (s), 173.1 (s). – MS: \(m/z = 235 (3.1\%, M^+), 234 (13\%, M^+ - 1), 105 (100\%), 77 (46\%, A^+)\).}
1720 (s, C=O). — 1H NMR (300 MHz): δ = 1.04 (d, J = 6.9 Hz, 3H, CH3), 2.08—2.22 (m, 1H, CHCH3), 2.56 (s, 1H, OH), 2.71 (d, J = 3.9 Hz, 2H, CH2C=O), 4.08—4.16 (m, 1H, CH—O), 4.16—4.24 (m, 1H, CH—O). — 13C NMR (25.2 MHz): δ = 11.87, 32.59, 38.99, 66.22, 70.37, 171.07. — MS: m/z = 149 (21%, M+ + 18), 131 (3%, M' + 1), 130 (2%, M'), 112 (3%, M' — H2O), 89 (100%).

C6H10O3 (130.1) Calcd. C 55.37 H 7.75 Found C 55.79 H 7.85

(2R,3S,4S)-2,4-Dimethyl-3-hydroxy-5-pentanolide (16): n-Butyllithium (4.8 ml, 1.5 N solution in hexane; 7.2 mmol) was added dropwise to a stirred solution of diisopropylamine (1 ml, 7.2 mmol) in THF (10 ml) at 0°C. The mixture was stirred for 15 min and then cooled to −60°C. A solution of the lactone 15 (400 mg, 3 mmol) in THF (16 ml) and HMPT (3 ml) was added over 30 min at −60°C. The solution was stirred at −60°C for 1.5 h and then cooled to −78°C. n-Butyllithium (4 ml, 1.5 N solution in hexane; 6 mmol) was added and the solution stirred for 30 min at −78°C. Methyl iodide (1 ml, 16 mmol) was added and the solution stirred at −78°C for 14 h. The solution was quenched with acetic acid (0.8 ml, 14 mmol) and then allowed to warm up to −20°C. Water (20 ml) was added and the mixture was extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried and evaporated. The residue was purified by flash chromatography (eluant ether) to give the methylated lactone 16 (330 mg, 75%). The starting material (50 mg, 12.5 mmol) was recovered by further elution. — [α]D = 17.9 (c = 1.5). — IR (CHCl3): 3620 (w, 0-H), 1730 (s, C=O). — 1H NMR (300 MHz): δ = 1.04 (d, J = 6.9 Hz, 3H, 2 CH3), 2.16—2.30 (m, 1H, 4-CH), 2.66 (qd, J = 7.4 and 4.8 Hz, 1H, 2 CH), 2.84 (s, 1H, OH), 3.74—3.80 (m, 1H, CH-0), 4.12—4.20 (m, 1H, CH-O).

I3C NMR (25.2 MHz): δ = 10.9, 15.4, 30.7, 42.6, 70.0, 71.7, 174.9. — MS: m/z = 145 (3%, M' + 1), 144 (1%, M+), 126 (10%, M+ — H2O), 56 (100%).

(2R,3S,4S)-3-hydroxy-2,4-dimethyl-5-tert-butyloxy-5-pentanolide (16): The lactone 16 (200 mg; 1.4 mmol) was dissolved in dry methanol (50 ml). Sodium methoxide (160 mg; 3 mmol) was added at 0°C and the suspension was stirred for 16 h at this temperature. Phosphate buffer (pH = 7, 7 ml) was added and the solution was evaporated to a volume of 10 ml. The solution was extracted with dichloromethane (3 x 20 ml) and the combined organic layers were dried and evaporated. The oil was dissolved in acetonitrile (20 ml) and tritylpyridinium tetrafluoroborate (820 mg; 2 mmol) was added. The yellow solution was stirred for 2 h and the solvent was then evaporated. The residue was filtered through flash silica (10 x 2 cm column, eluant hexane/ether, 4:1) to give, after evaporation of the solvent, the monotrityl ether 17 as a colourless oil (285 mg, 70%), homogenous by TLC (ether/hexane, 1:4) though evidently contaminated with about 3% of the epimerised (α to the ester) compound. The lactone 16 (35 mg, 18%) was recovered after further elution with ether. A sample of the ester 17 exhibited the following data: [α]D = 14.3 (c = 1.05). — IR (CHCl3): 3500 (m, OH), 1725 (s, C=O). — 1H NMR (300 MHz): δ = 0.91 (d, J = 6.9 Hz, 3H, CH3), 1.14 (d, J = 7.1 Hz, 3H, CH3), 1.72—1.84 (m, 1H, 4-CH), 2.5 (dq, J = 3.9 and 7.1 Hz, 1H, CH—C=O), 3.20—3.38 (m, 3H, 5-CH2 and OH), 3.68 (s, 3H, OCH3), 3.82—3.92 (m, 1H, CH—O), 7.40—7.68 (m, 15H, Ar). — 13C NMR (25.2 MHz): δ = 9.7, 14.2, 42.3, 51.7, 67.3, 75.4, 87.3, 127.1, 127.8, 128.6, 143.8, 176.1. — MS: m/z = 243 (100%, Tr+), 175 (4%), M+ — Tr), 149 (54%).

C11H32O4 (418.3) Calcd. C 77.48 H 7.22 Found C 77.18 H 7.19

Methyl (2R,3S,4S)-3-hydroxy-2,4-dimethyl-5-tert-butyloxypentanoate (17): The lactone 16 (200 mg; 1.4 mmol) was dissolved in dry methanol (50 ml). Sodium methoxide (160 mg; 3 mmol) was added at 0°C and the suspension was stirred for 16 h at this temperature. Phosphat buffer (pH = 7, 7 ml) was added and the solution was evaporated to a volume of 10 ml. The solution was extracted with dichloromethane (3 x 20 ml) and the combined organic layers were dried and evaporated. The oil was dissolved in acetonitrile (20 ml) and tritylpyridinium tetrafluoroborate (820 mg; 2 mmol) was added. The yellow solution was stirred for 2 h and the solvent was then evaporated. The residue was filtered through flash silica (10 x 2 cm column, eluant hexane/ether, 4:1) to give, after evaporation of the solvent, the monotertrityl ether 17 as a colourless oil (285 mg, 49%), homogenous by TLC (ether/hexane, 1:4) though evidently contaminated with about 3% of the epimerised (α to the ester) compound. The lactone 16 (35 mg, 18%) was recovered after further elution with ether. A sample of the ester 17 exhibited the following data: [α]D = 14.3 (c = 1.05). — IR (CHCl3): 3500 (m, OH), 1725 (s, C=O). — 1H NMR (300 MHz): δ = 0.91 (d, J = 6.9 Hz, 3H, CH3), 1.14 (d, J = 7.1 Hz, 3H, CH3), 1.72—1.84 (m, 1H, 4-CH), 2.5 (dq, J = 3.9 and 7.1 Hz, 1H, CH—C=O), 3.20—3.38 (m, 3H, 5-CH2 and OH), 3.68 (s, 3H, OCH3), 3.82—3.92 (m, 1H, CH—O), 7.40—7.68 (m, 15H, Ar). — 13C NMR (25.2 MHz): δ = 9.7, 14.2, 42.3, 51.7, 67.3, 75.4, 87.3, 127.1, 127.8, 128.6, 143.8, 176.1. — MS: m/z = 243 (100%, Tr+), 175 (4%), M+ — Tr), 149 (54%).

C11H32O4 (418.3) Calcd. C 77.48 H 7.22 Found C 77.18 H 7.19

(2S,3R,4S)-2,4-Dimethyl-5-tert-butyloxy-1,3-pentanediol (18): LiAlH4 (40 mg, 1.05 mmol) was suspended in ether (10 ml) and cooled in an ice/water bath. The methyl ester 17 (120 mg, 1998. D. Seebach et al.

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0.29 mmol) in ether (3 ml) was added dropwise over a period of 30 min. The cooling bath was removed after further 15 min and the mixture was then stirred for 2 h. The cooling bath was replaced and the reaction quenched by the addition of water (0.05 ml), aqueous sodium hydroxide (10%, 0.05 ml), and finally water (0.15 ml). The suspension was stirred for 10 min and then MgSO₄ was added before filtration and washing of the solid with ether (15 ml). The filtrate was evaporated to give the diol 18 (110.2 mg; 98.5%) as an oil which solidified on standing in the refrigerator. A sample was purified by flash chromatography (eluant ether/hexane 1 : 2).

\([\alpha]_D = 23.1\) (c = 3.69).

\(\text{IR (CHCl}_3\text{): 3460 (m, OH).}

\(\text{H NMR (300 MHz): } \delta = 0.74 \text{ (d, } J = 7.0 \text{ Hz, 3H, CH}_3\text{), 0.98 (d, } J = 7.0 \text{ Hz, 3H, CH}_3\text{), 1.66-1.76 (m, 1H, 2-CH or 4-CH), 1.84-1.94 (m, 1H, 2-CH or 4-CH), 2.58 (br. s, 1H, OH), 3.20-3.80 (m, 5H, CH}_2\text{OH, CH}_2\text{OH and CH}_2\text{OTr), 3.88 (br. m, 1H, OH), 7.20-7.48 (m, 15H, Ar).} \)

\(\text{MS: } m/z = 260 (16\%, \text{TrOH}^+), 243 (48\%, \text{Tr}^+), 149 (100\%).\)

1.66-1.76 (m, 1H, 2-CH or 4-CH), 1.84-1.94 (m, 1H, 2-CH or 4-CH), 2.58 (br. s, 1H, OH), 3.20-3.80 (m, 5H, CH₂OH, CH₂OH and CH₂OTr), 3.88 (br. m, 1H, OH), 7.20-7.48 (m, 15H, Ar).

\(\text{M. p. 145-147°C; } [\alpha]_D = -21.4\) (c = 0.5).

\(\text{IR (KBr): 2860 (s, CH).}

\(\text{H NMR (300 MHz): } \delta = 0.74 \text{ (d, } J = 7.0 \text{ Hz, 3H, CH}_3\text{), 0.98 (d, } J = 7.0 \text{ Hz, 3H, CH}_3\text{), 1.66-1.76 (m, 1H, 2-CH or 4-CH), 1.84-1.94 (m, 1H, 2-CH or 4-CH), 2.58 (br. s, 1H, OH), 3.20-3.80 (m, 5H, CH}_2\text{OH, CH}_2\text{OH and CH}_2\text{OTr), 3.88 (br. m, 1H, OH), 7.20-7.48 (m, 15H, Ar).} \)

\(\text{MS: } m/z = 243 (100\%, \text{Tr}^+), 183 (23\%), 165 (36\%), 105 (23\%).\)

\(\text{C}_{29}\text{H}_{34}\text{O}_3\) (430.6) Calcd. C 80.89 H 7.96 Found C 81.09 H 7.89

\(\text{C}_{29}\text{H}_{34}\text{O}_3\) (31 mg, 71%) identical in all respects with the material prepared by the other route.

\(\text{(2S,3S,4S)-1,3-Isopropylidenedioxy-2,4-dimethyl-5-trityloxypentane (19): The diol 18 (58 mg, 0.15 mmol) was dissolved in dimethoxypropane (10 ml) and then p-toluenesulfonic acid (5 mg) was added. The solution was stirred for 2 h until TLC analysis (ether/hexane, 1 : 4) indicated the absence of starting material. The solution was poured into saturated aqueous sodium hydrogen carbonate (5 ml) and then extracted with dichloromethane (3 x 10 ml). The organic extracts were dried and evaporated to give the crude acetonide 19 (58 mg; 91%) which was used without further purification. A sample was recrystallised from hexane.} \)

\(\text{M. p. 145-147°C; } [\alpha]_D = -21.4\) (c = 0.5).

\(\text{IR (KBr): 2860 (s, CH).}

\(\text{H NMR (300 MHz): } \delta = 0.74 \text{ (d, } J = 7.0 \text{ Hz, 3H, CH}_3\text{), 0.98 (d, } J = 7.0 \text{ Hz, 3H, CH}_3\text{), 1.66-1.76 (m, 1H, 2-CH or 4-CH), 1.84-1.94 (m, 1H, 2-CH or 4-CH), 2.58 (br. s, 1H, OH), 3.20-3.80 (m, 5H, CH}_2\text{OH, CH}_2\text{OH and CH}_2\text{OTr), 3.88 (br. m, 1H, OH), 7.20-7.48 (m, 15H, Ar).} \)

\(\text{13C NMR (25.2 MHz): } \delta = 10.3 \text{ (q), 13.1 \text{ (q), 18.9 \text{ (q), 29.6 (d), 35.6 (d), 63.5 (t), 67.3 (t), 71.7 (d), 85.9 (s), 98.5 (s), 126.8 (d), 127.6 (d), 128.9 (d), 144.6 (s).} \)

\(\text{MS: } m/z = 243 (100\%, \text{Tr}^+), 183 (23\%), 165 (36\%), 105 (23\%).\)

\(\text{C}_{29}\text{H}_{34}\text{O}_3\) (430.6) Calcd. C 80.89 H 7.96 Found C 81.09 H 7.89

\(\text{(2S,3S,4S)-3,5-Isopropylidenedioxy-2,4-dimethyl-1-pentanol (20): Lithium (20 mg, 2.9 mmol) was added to liquid ammonia (10 ml) cooled to -78°C. When all the lithium had dissolved, a solution of the trityl ether 19 (100 mg, 0.23 mmol) in dry THF (1 ml) was added over a period of 3 min. The cooling bath was removed and the mixture then stirred at reflux for 30 min. The reaction was then quenched by the careful addition of ammonium chloride (160 mg). Ammonia was allowed to evaporate, and then saturated brine (2 ml) was added. The mixture was diluted with water (5 ml), extracted with ether (3 x 10 ml), then with dichloromethane (3 x 10 ml). The combined organic extracts were dried and evaporated, and the residue was purified by flash chromatography (eluant ether/hexane, 1 : 1) to give the alcohol 20 (31 mg, 71%) identical in all respects with the material prepared by the other route.}\)

\(\text{(3S,5S,7S,8S,11E,13E,15S,16S)-8,16-Bis[(1R)-1-formylethyl]-7,15-dimethyl-1,9-dioxacyclohexadeca-3,5,11,13-tetraene-2,10-dione (10): Oxalyl chloride (50 µl, 0.57 mmol) was dissolved in dichloromethane (3 ml) and cooled to -78°C under an argon atmosphere. Dimethyl sulfoxide (80 µl, 1.1 mmol) was added and, after the solution had been stirred for 2 min, the diol 27 (98 mg, 0.25 mmol), dissolved in dichloromethane (1 ml) and dimethyl sulfoxide (0.2 ml), was then added. The mixture was stirred at -78°C for 15 min and then triethylamine (0.35 ml, 2.5 mmol) was added, and the mixture stirred for further 25 min at -78°C. The cooling bath was removed, and after 15 min the reaction mixture was poured...}\)

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into dilute hydrochloric acid (0.5 N, 5 ml). The organic layer was separated and the aqueous layer re-extracted with dichloromethane (15 ml). The combined organic layers were washed with phosphate buffer (pH 7, 10 ml), dried, and evaporated. The residue was filtered through flash silica (3 cm) in a Pasteur pipette using dichloromethane/ether (1:1) as eluant. The filtrate was evaporated to give the dialdehyde 10 (88 mg, 91%). — IR (CHCl₃): 2990 (CH₃), 1720 (s), 1710 (s). — ¹H NMR (300 MHz): δ = 1.10 (d, J = 6.7 Hz, 6H, 2 CH₃), 1.19 (d, J = 7 Hz, 6H, 2 CH₃), 2.52 (dd, J = 9.5, 10.3, and 6.7 Hz, 2H, 7-H and 15-H). 2.71 (dq, J = 2.5 and 7.0 Hz, 2H, formylethyl 1-H), 5.39 (dd, J = 2.5 and 10.3 Hz, 2H, 8-H and 16-H), 5.57 (d, J = 15.4 Hz, 2H, 3-H and 11-H), 5.65 (dd, J = 9.5 and 15.0 Hz, 2H, 6-H and 14-H), 6.05 (dd, J = 11.2 and 15.0 Hz, 2H, 5-H and 13-H), 6.96 (dd, J = 11.2 and 15.4 Hz, 2H, 4-H and 12-H), 9.67 (s, 2H, 2 CHO). — MS: m/z = 388 (<1%, M⁺), 194 (24%, M⁺/2), 177 (100%, M⁺/2 − OH), 165 (42%, M⁺/2 − CHO).

*Ethyl (2R,3R)-2-ethyl-3-hydroxybutanoate (29):* n-Butyllithium (240 ml, 1.35 N solution in hexane; 324 mmol) was added dropwise to a stirred solution of diisopropylamine (56 ml, 395 mmol) in THF (350 ml) at −50°C. The mixture was stirred for 15 min and a solution of ethyl (R)-3-hydroxybutanoate (17.8 g, 135 mmol) in THF (350 ml) at −50°C. The mixture was stirred for 15 min and a solution of ethyl iodide (40.4 ml, 500 mmol) in THF (20 ml) was added over a period of 20 min and the mixture stirred at −78°C for 8 h. The solution was then warmed to 20°C over a period of 6 h and stirred for another 5 h at 20°C. The mixture was quenched with saturated ammonium chloride solution (100 ml) and extracted with ether/hexane (1:1). The combined organic extracts were washed with saturated ammonium chloride solution (50 ml), dried, filtered, and evaporated to give an oil which was purified by distillation to give 29 (18.1 g, 84%). — B. p. 83−86°C/12 Torr; [α]D = −6.1 (c = 1.0). — IR (CHCl₃): 3620−3350 (OH), 1714 (C=O). — ¹H NMR (300 MHz): δ = 0.93 (t, J = 7.4 Hz, 3H, CCH₂CH₃), 1.22 (d, J = 6.4 Hz, 3H, CH₃CH₂), 1.28 (t, J = 7.2 Hz, 3H, CH₂CH₃), 1.62−1.78 (m, 2H, CCH₂Me), 2.30 (dt, J = 8.4 and 6.0 Hz, 1H, CHCHO), 2.56−2.68* (br., 1H, OH). 3.92 (quint, J = 6.3 Hz, 1H, CHO). 4.19 (q, J = 7.4 Hz, 2H, OCH₂). — ¹³C NMR: δ = 11.8, 14.4, 21.2, 22.2, 55.1, 60.3, 68.3, 175.2. — MS: m/z = 145 (7%, M⁺ − Me), 131 (1%, M⁺ − Et), 116 (72%, M⁺ − MeCHO), 115 (32%, M⁺ − MeCHO or M⁺ − OEt), 101 (71%, M⁺ − MeCHO − Me), 87 (7%, M⁺ − CO₂Et), 73 (100%, CO₂Et), 45 (58%, MeCHO).

C₆H₁₂O₃ (160.2) Calcd. C 59.98 H 10.07 Found C 59.86 H 9.99

*Ethyl (2R,3R)-2-ethyl-3-triethylsiloxybutanoate (30):* Triethylsilyl triflate (30.4 g, 115 mmol) in dichloromethane (180 ml) at −40°C. After 5 min, a solution of 2,6-lutidine (15.6 ml, 134 mmol) in dichloromethane (280 ml) at −40°C. After 5 min, a solution of 2,6-lutidine (15.6 ml, 134 mmol) in dichloromethane (280 ml) was added over 30 min at −40°C. The mixture was stirred at −20°C for 3.5 h and then cooled to −78°C.

The mixture was then stirred at 0°C for 16 h and diluted with dichloromethane (200 ml). The organic solution was washed with distilled hydrochloric acid (0.5 N, 3 × 50 ml) and with saturated brine (50 ml), dried, filtered, and evaporated to give an oil which was purified by distillation to give 30 (29.9 g, 100%). — B. p. 83−84°C/0.1 Torr; [α]D = −19.4 (c = 2.0). — IR (CHCl₃): 1720 (C=O). — ¹H NMR (300 MHz): δ = 0.88 (q, J = 7.7 Hz, 6H, Si(CH₃)₂CH₃), 0.89 (t, J = 7.4 Hz, 3H, CCH₂CH₃), 0.94 (t, J = 7.7 Hz, 9H, Si(CH₃)₂CH₃), 1.15 (d, J = 6.2 Hz, 3H, CH₃CH₂), 1.26 (t, J = 7.2 Hz, 3H, OCH₂CH₃), 1.50−1.58 (m, 2H, CCH₂Me), 2.30 (ddd, J = 9.4, 7.6, and 5.3 Hz, 1H, CHCHO), 4.01 (dq, J = 7.5 and 6.2 Hz, 1H, CH−OCH), 4.13 (q, J = 7.2 Hz, 2H, OCH₂). — MS: m/z = 246 (12%, M⁺ − CH₃), 245 (64%, M⁺ − Et), 159 (21%, MeCHOESiEt₃), 131 (76%, OSiEt₃), 115 (51%, SiEt₃ or MeCH₂CH₂CO₂Et), 103 (100%, HOSiEt₃), 75 (40%, HOSiEt₃ − CH₂), 67 (26%, HOSiEt₃ − CH₂).
(2S,3R)-2-Ethyl-3-trithylsilyloxy-1-butanol (31): Diisobutylaluminium hydride (256 ml, 1.0 N solution in hexane, 256 mmol) was added dropwise to a stirred solution of the ester 30 (24.22 g, 88.4 mmol) at -70°C over 1 h. The mixture was stirred at -70°C for 1 h and at -40°C for 30 min. The mixture was re-cooled to -78°C and quenched by dropwise addition of saturated ammonium chloride solution (100 ml) with vigorous stirring. When the addition was finished the mixture was stirred at 0°C for 30 min. The resulting mixture was poured into a 8-cm flash column (filled with a 2-cm layer of celite at the bottom) and the solvent was eluted by applying pressure from the top. The inorganic salt inside the column was washed with ether (1000 ml) and the combined eluants were washed with saturated ammonium chloride solution (100 ml), dried, filtered, and evaporated to give an oil which was purified by distillation to give 31 (19.63 g, 96%). \( \beta \) p. 79.5-81.5°C/0.08 Torr; \( \delta \) = -10.8 (c = 1.02). -IR (CHCl₃): 3600-3150 (O-H). -\[^1\text{H} \text{NMR} \]): \( \delta = 0.62 \) [q, \( J = 8.0 \) Hz, 6H, Si(CH₂Me₃)], 0.95 [t, \( J = 7.4 \) Hz, 3H, CCH₂CH₃], 0.97 [t, \( J = 8.1 \) Hz, 9H, Si(CH₂CH₂H₃)], 1.26 (d, \( J = 6.3 \) Hz, 3H, CH₂CH₃), 1.16-1.28 (m, 10H, CHCH₂O), 1.36-1.58 (m, 2H, CCH₂Me), 3.13-3.16* (br., 1H, OH), 3.56-3.64 (m, 1H, CH₂H₄O), 3.90-4.00 (m, 2H, CH-OSi and CH₄BO). -MS: \( m/z = 217 \) (10%, \( \text{M}^+ - \text{Me} \)), 203 (14%, \( \text{M}^+ - \text{Et} \)), 159 (23%, MeCHOSiEt₃), 131 (77%, \( \text{SiEt₃} \)), 103 (100%, HOSiEt₂), 75 (70%, HOSiEt₂-C₂H₄). 

\( \text{C}_{12}\text{H}_{26}\text{O}_{2}\text{Si} \) (232.4) Calcd. C 62.01 H 12.14 Found C 62.06 H 12.37

(2R,3R)-2-Ethyl-3-trithylsilyloxybutanal (32): Dimethyl sulfoxide (3.0 ml, 42.2 mmol) was added dropwise to a solution of oxalyl chloride (1.73 ml, 20.1 mmol) in dichloromethane (30 ml) at -78°C. After 1 min, a solution of the alcohol 31 (3.0 g, 12.9 mmol) in dichloromethane (10 ml) was added and the mixture stirred for 5 min. Triethylamine (12.0 ml, 86.6 mmol) was then added over 5 min and the mixture stirred for 15 min. The solution was allowed to warm up to -20°C over a period of 30 min and then poured into saturated ammonium chloride solution (50 ml). The organic layer was separated, dried, filtered, evaporated and distilled to give the aldehyde 32 (1.51 g, 84%). -\( \beta \) p. 68.5-70°C/0.09 Torr; \( \delta = -21.2 \) (c = 1.12). -IR (film): 1720 (H-CO), 1713 (C=O). -\[^1\text{H} \text{NMR} \]): \( \delta = 0.59 \) [q, \( J = 7.6 \) Hz, 6H, Si(CH₂Me₃)], 0.91 [t, \( J = 7.5 \) Hz, 3H, CCH₂CH₃], 0.95 [t, \( J = 7.7 \) Hz, 9H, Si(CH₂CH₂H₃)], 1.22 (d, \( J = 6.3 \) Hz, 3H, CH₂CH₃), 1.48-1.62 (m, 1H, CH₂H₄Me), 1.65-1.80 (m, 1H, CH₂H₄Me), 2.11 (ddt, \( J = 5.2, 3.7 \) and 4.9 Hz, 1H, HCC=O), 4.10 (dq, \( J = 5.2 \) and 6.3 Hz, 1H, CH=O). -MS: \( m/z = 229 \) (1%, \( \text{M}^+ - \text{H} \)), 202 (9%, \( \text{M}^+ - \text{C}_2\text{H}_4 \) or \( \text{M}^+ - \text{CO} \)), 201 (53%, \( \text{M}^+ - \text{CHO} \) or \( \text{M}^+ - \text{Et} \)), 159 (9%, MeCHOSiEt₃), 115 (14%, SiEt₃ or \( \text{M}^+ - \text{SiEt}_3 \)), 103 (100%, HOSiEt₂), 98 (16%, \( \text{M}^+ - \text{SiEt}_2\text{OH} \)), 75 (70%, HOSiEt₂-C₂H₄). 

\( \text{C}_{12}\text{H}_{26}\text{O}_2\text{Si} \) (230.4) Calcd. C 62.55 H 11.37 Found C 62.43 H 11.57

2-Trimethylsilyloxy-1-butene (33): n-Butyllithium (140 ml, 1.6 N solution in hexane, 224 mmol) was added dropwise to a stirred solution of 2,2,6,6-tetramethylpiperidine (38.3 ml, 225 mmol) in THF (300 ml) at -30°C. The solution was stirred at -20°C for 2 h and cooled to -78°C. A solution of 2-butanone (15.1 g, 209 mmol) in THF (20 ml) was added dropwise over 30 min and the mixture was stirred for 15 min. A mixture of chlorotrimethylsilylane (40 ml, 316 mmol) and triethylamine (9.3 ml, 67 mmol) in THF (20 ml) was added over 30 min and the solution was stirred for another 15 min at -78°C. The cooling bath was removed and the solution warmed to 20°C. After 1.5 h the mixture was poured into saturated sodium hydrogen carbonate solution and extracted with pentane (3 x 100 ml). The combined organic extracts were washed with cold saturated ammonium chloride solution (3 x 100 ml) and with saturated sodium hydrogen carbonate solution (100 ml), dried, filtered, and fractionally distilled through a \textit{Vigreux} column (20 cm) to remove the solvents.

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the residue was then fractionally distilled through a spaltrohrkolonne (supplier: Fischer) to
give 33 (13.7 g, 45%) as an oil \( \text{b. p. 115-119°C} \). - IR (CHCl\(_3\)): 1630 (C=CH\(_2\)), 1250
(SiMe\(_3\)). - \(^1\)H NMR (90 MHz): \( \delta = 0.20 \) (s, 9H, SiMe\(_3\)), 1.00 (t, \( J = 7 \) Hz, 3H, CH\(_3\)), 2.00
(t, \( J = 7 \) Hz, 2H, CH\(_2\)=C), 4.03 (br., 2H, C=CH\(_2\)). - MS: \( m/z = 144 \) (17%, M\(^+\)), 129
(33%, M\(^+\) - Me), 73 (24%, SiMe\(_3\)), 28 (100%).

C\(_6\)H\(_{10}\)O\(_3\)Si (144.3) Calcd. C 58.27 H 11.18 Found C 58.19 H 11.13

\((5R,6R,7R)-5-\text{(t}rt\text{-Butyldimethylsilyloxy})-6\text{-ethyl-7-triethylsilyloxy-3-octanone} \) (35): A
solution of titanium tetrachloride (5.0 ml, 1.0 N solution in dichloromethane, 5.0 mmol) was
added dropwise to a stirred mixture of the aldehyde 32 (0.96 g, 4.17 mmol) and 2-trime-
thylsilyloxy-1-butene (33) (1.20 g, 8.32 mmol) in dichloromethane (20 ml) at \(-78°C\). After
10 min, the mixture was poured into vigorously stirred phosphate buffer solution (pH = 7;
50 ml) and the organic layer separated. The aqueous layer was extracted with ether (2 \( \times \) 50 ml) and the combined organic extracts were washed with phosphate buffer (pH = 7;
30 ml). The organic solution was dried, filtered, and evaporated to give an oil which was
chromatographed on silica gel (50 g) eluting with ether/hexane (1 : 4) to give the aldol
34 (482 mg, 38%, \( R_F = 0.18 \)) as an unstable oil. - \(^1\)H NMR (90 MHz): \( \delta = 0.00 \) (s, 3H, SiMe\(_3\)), 0.86 (s, 3H, SiCH\(_3\)), 0.80-1.18 (m, 8H,
CH(CH\(_2\))\(_3\) and COCH\(_2\)CH\(_3\)), 1.28 (d, \( J = 7 \) Hz, 3H, CH\(_2\)CH -O), 1.25-1.60 (m, 1H,
CHCH\(_2\)Me), 2.28-2.73 (m, 4H, CH\(_2\)(C=O)CH\(_2\)), 2.90-3.20 (br., 1H, OH), 4.09 (dq, \( J = 4 \) and 7 Hz, 1H, CH -OSi), 4.38 (ddd, \( J = 7.5 \) and 2 Hz, 1H, HC-OH).

The aldol 34 was immediately dissolved in DMF (10 ml) and added in one portion to a
stirred mixture of imidazole (450 mg, 6.61 mmol) and tert-butyldimethylsilyl chloride
(500 mg, 3.32 mmol) in DMF (6 ml) at 0°C. The mixture was stirred at 25°C for 80 h and
then poured into phosphate buffer (pH = 7; 20 ml). The organic layer was separated and
the aqueous phase extracted with ether/hexane (1 : 1) (5 \( \times \) 50 ml). The combined extracts
were washed with water (50 ml), dried, filtered, and evaporated. The residue was chroma-
tographed on silica gel eluting with ether/hexane (1 : 20) to give the silylated aldol
35 (287 mg, 16% yield from 32; \( R_F = 0.27 \)) as an oil. A sample was kugelrohr-distilled. - B.
\( \text{p. 130-140°C/0.003 Torr; } [\alpha]_D = +27.8 \) (c = 1.89). - IR (film): 1720 (C=O).

\(^1\)H NMR (300 MHz): \( \delta = 0.00 \) (s, 3H, SiCH\(_3\)), 0.08 (s, 3H, SiCH\(_3\)), 0.60 (q, \( J = 8 \) Hz, 6H, Si(CH\(_2\)Me\(_3\))), 0.96 (t, \( J = 8 \) Hz, 9H, Si(CH\(_2\)CH\(_3\))), 0.80-1.18 (m, 8H,
CH\(_2\)CH\(_3\) and COCH\(_2\)CH\(_3\)), 1.28 (d, \( J = 7 \) Hz, 3H, CH\(_2\)CH -O), 1.25-1.60 (m, 1H,
CHCH\(_2\)Me), 2.28-2.73 (m, 4H, CH\(_2\)(C=O)CH\(_2\)), 2.90-3.20* (br., 1H, OH), 4.09 (dq, \( J = 4 \) and 7 Hz, 1H, CH -OSi), 4.38 (ddd, \( J = 7.5 \) and 2 Hz, 1H, HC-OH).

C\(_{22}\)H\(_{48}\)O\(_3\)Siz (416.8) Calcd. C 63.40 H 11.61 Found C 63.28 H 11.49

\((2S,4R,5R,6R,7R)-4\text{-}\text{(t}rt\text{-Butyldimethylsilyloxy})-2,5\text{-diethyl-3,4,5,6-tetrahydro-2-methoxy-6-
methyl-2H-pyran} \) (37): The silylated aldol 35 (150 mg) in THF/acetic acid/water (11 : 5 : 3)
(19 ml) was stirred at 20°C for 15 h. The mixture was poured into excess sodium carbonate
solution, and the solvents were evaporated. The residue was dissolved in ether (50 ml) and
washed with phosphate buffer (pH = 7; 10 ml), dried, filtered, and evaporated to give the
lactol 36 (106 mg, 97%) as an oil. - \(^1\)H NMR (90 MHz): \( \delta = 0.05 \) (s, 6H, SiMe\(_3\)), 0.90 (s,
9H, Si(CH\(_3\))), 1.12 (d, \( J = 6 \) Hz, 3H, CH\(_3\)CH -O), 0.80-2.10 (m, 13H), 2.72-3.10* (br.,
1H, OH), 3.58-4.08 (m, 2H, CH\(_2\)CH -O and CH\(_2\)CH -O).

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The lactol 36 was then dissolved in dry methanol (10 ml) and pyridinium tosylate (15 mg) added. The mixture was stirred at 20 °C for 2.5 h and poured into saturated sodium hydrogen carbonate solution (10 ml). The solvents were evaporated, and the residue was dissolved in ether (50 ml). The ethereal solvents were washed with phosphate buffer (pH = 7; 10 ml), dried, filtered, and evaporated to give the methoxy acetal 37 (68 mg, 0.22 mmol) in THF (1 ml) at 20 °C. The mixture was stirred for 6 h and diluted with ether (50 ml). The residue was chromatographed on silica gel eluting with ether/hexane (1:1) to give 38 (41 mg, 94%; Rf = 0.22) as an oil; [α]D = +64.4 (c = 1.04). - IR (CCl4): 3560-3300 (O−H), - 1H NMR (300 MHz): δ = 0.87 (t, J = 7.6 Hz, 3H, CH3(CH2)3), 1.02 (t, J = 7.6 Hz, 3H, CH3(CH2)3), 1.11 (tt, J = 10.2 and 3.9 Hz, 1H, CHCH2Me), 1.21 (d, J = 6.3 Hz, 3H, CH2CH−O), 1.31 (dd, J = 12.5 and 11.0 Hz, 1H, CH2H5O−CH−O), 1.34−1.41* (br, 1H, OH), 1.47 (dq, J = 14.4 and 7.5 Hz, 1H, (MeO)CCCHH3Me), 1.50−1.70 (m, 2H, CHCH2Me), 1.77 (dq, J = 14.3 and 7.6 Hz, 1H, (MeO)CCCHH3Me), 2.14 (dd, J = 12.4 and 4.9 Hz, 1H, CH2H5O−CH−O), 3.11 (s, 3H, OMe), 3.52 (dq, J = 6.3 and 10.2 Hz, 1H, MeCH−O), 3.90 (dt, J = 4.8 and 10.5 Hz, 1H, HC−OH). - MS: m/z = 185 (1%, M+ − OH), 152 (29%, M+ − MeOH − H2O), 137 (6%, M+ − MeOH − Me − H2O), 123 (21%, M+ − MeOH), 75 (100%), 57 (8%, tBu).

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(2S,4R,5S,6R)-2,5-Diethyl-3,4,5,6-tetrahydro-4-hydroxy-2-methoxy-6-methyl-2H-pyran (38):\]

Tetraphenylboron fluoride (0.66 ml, 1.0 m solution in THF, 0.66 mmol) was added to a stirred solution of the methoxy acetal 37 (68 mg, 0.22 mmol) in THF (1 ml) at 20 °C. The mixture was stirred for 6 h and diluted with ether (50 ml). The resulting solution was washed with saturated sodium hydrogen carbonate solution (10 ml), dried, filtered, and evaporated. The residue was subjected to high-performance liquid chromatography on silica gel eluting with ether/hexane (1:1) to give 39 (78 mg, 77% based on 36) as an oil; [α]D = +42.4 (c = 0.79). - 1H NMR (300 MHz); δ = 0.07 [s, 6H, Si(CH3)2], 0.85 (t, J = 7.5 Hz, 3H, CH3(CH2)3), 0.86 (t, J = 7.6 Hz, 3H, CH3(CH2)3), 0.88 [s, 9H, Si(CH3)2], 1.13 (tt, J = 10.4 and 4.1 Hz, 1H, CH2CH2Me), 1.19 (d, J = 6.3 Hz, 3H, CH2CH−O), 1.30 (dd, J = 12.6 and 10.6 Hz, 1H, CH2H5O−Si), 1.46 [dq, J = 14.3 and 7.5 Hz, 1H, (MeO)CCCHH5Me], 1.48−1.66 (m, 2H, CHCH2Me), 1.73 (dq, J = 14.3 and 7.6 Hz, 1H, (MeO)CCCHH5Me), 2.00 (dd, J = 12.6 and 5.0 Hz, 1H, CH2H5O−Si), 3.09 (s, 3H, OMe), 3.50 (dq, J = 6.2 and 10.3 Hz, 1H, MeCH−O), 3.86 (dt, J = 5.0 and 10.4 Hz, 1H, HCO−Si). - MS: m/z = 227 (1%, M+ − tBu − MeOH), 152 (36%, M+ − HOSitBuMe2 − MeOH), 137 (10%), M+ − HOSitBuMe2 − MeOH − Me), 123 (25%, M+ − HOSitBuMe2 − MeOH − Et), 75 (100%), 57 (8%, tBu).

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[3E,5E,7S,8S(1S,2R,3S,6R,7R,8R),11E,13E,15S,16S,16(1S,2R,3S,6R,7R,8R)]- (40a), [3E,5E,7S,8S(1S,2R,3S,6R,7R,8R),11E,13E,15S,16S,16(1S,2S,3R,6R,7R,8R)]- (40b), [3E,5E,7S,8S(1S,2S,3R,6R,7R,8R),11E,13E,15S,16S,16(1S,2R,3S,6R,7R,8R)]-8,16-Bis(6-tert-butyldimethylsilyloxy-7-ethyl-2-hydroxy-1,3-dimethyl-4-oxo-8- triethylsilyloxy-1-nonyl)-7,15-dimethyl-1,9-dioxacyclohexadeca-3,11,13-tetraene-2,10-dione (40c): Ethyldisopropylamine (148 μl, 0.87 mmol) was added dropwise to a stirred solution of di-n-butylboron triflate (0.75 ml, 1.0 m solution in ether, 0.75 mmol) in ether (4.0 ml) at 0 °C. After 1 min, the solution was cooled to −78 °C and a solution of the ketone 35 (284 mg, 0.68 mmol) in ether (3.0 ml) was added dropwise. The solution was stirred at −78 °C for 30 min and at 0 °C for 10 min. A white precipitate was formed and the solution re-cooled to −78 °C. A solution of the dialdehyde 10 (53 mg, 0.14 mmol) in dichloromethane (1.0 ml) was added dropwise and the mixture stirred at −78 °C for 1 h and at 0 °C for 30 min. The solution was poured into phosphate buffer (pH = 7; 10 ml) and extracted with ether (3 × 15 ml). The combined extracts were dried and evaporated. The residue was dissolved in ether (2.0 ml) and stirred with powdered oxodiperoxymolybdenum (pyridine) (hexamethylphosphoric triamide) (700 mg, 1.61 mmol) at 0°C for 30 min and at 20°C for another 30 min. The solution was diluted with ether (50 ml) and washed with phosphate buffer (pH = 7; 2
10 ml), dried, filtered, and evaporated. The residue was chromatographed on silica gel eluting with hexane/ether (4:1) to give the starting ketone 35 (234 mg, $R_F = 0.95$), 40c (11.2 mg, 15% based on reacted 35, $R_F = 0.62$ in hexane/ether = 2:1), 40b (13.5 mg, 18%; $R_F = 0.55$ in hexane/ether = 2:1), and 40a (6.5 mg, 9%; $R_F = 0.31$ in hexane/ether = 2:1) as oils. – IR (CCl₄) (40a): 3700–3100 (O–H), 1710 (C=O), 1640 (C=C), 1613 (C=C). – ¹H NMR (300 MHz); 40b (for numbering see formula at the beginning of the Experimental Part): $\delta = 0.03$ (s, 6H, 2 SiMe), 0.05 (s, 6H, 2 SiMe), 0.50–0.64 [m, 12H, 2 Si(CH₂Me)₃], 0.83 [s, 18H, 2 Si(CH₃)₃], 0.84–1.48 [m, 36H, 2 Si(CH₂CH₃)₂, 2 CHCH₂CH₃, and 2 CH₂], 1.04 (d, $J = 6.7$ Hz, 6H, 2 CH₃), 1.10 (d, $J = 7.0$ Hz, 6H, 2 CH₃), 1.22 (d, $J = 6.5$ Hz, 6H, 2 CH₃), 1.82–1.96 [m, 2H, 2 CH(1′)], 2.44–2.65 [m, 6H, 2 H₃C(5′)], 2. HC(3′), HC(7) and HC(15)], 2.91 [dd, $J = 17$ and 9 Hz, 2H, 2 H₃C(5′)], 3.70–3.78 [m, 2H, 2 HC(2′)], 3.94–4.04 [m, 2H, 2 HC(8′)], 4.12–4.20 (br., 2H, 2 OH), 4.32–4.45 [m, 2H, 2 HC(6′)], 5.06 [dd, $J = 10$ and 1 Hz, 2H, HC(8) and HC(16)], 5.63 [d, $J = 16$ Hz, 2H, HC(3) and HC(11)], 5.65 [dd, $J = 15$ and 10 Hz, 2H, HC(6) and HC(14)], 6.08 [dd, $J = 15$ and 11 Hz, 2H, HC(5) and HC(13)], 6.97 [dd, $J = 16$ and 11 Hz, 2H, HC(4) and HC(12)].

¹H NMR (300 MHz); 40c (for numbering see formula at the beginning of the Experimental Part): $\delta = 0.06$ (s, 3H, SiMe),−0.03 (s, 3H, SiMe), 0.03 (s, 3H, SiMe), 0.05 (s, 3H, SiMe), 0.50–0.64 [m, 12H, 2 Si(CH₂Me)₃], 0.80 [s, 9H, Si(CH₃)₃], 0.83 [s, 9H, Si(CH₂CH₃)₃], 0.84–1.46 [m, 35H, 2 CHCH₂CH₃, CH₃, 2 OH and 2 Si(CH₂CH₃)₃], 1.04 (d, $J = 6.4$ Hz, 3H, CH₃), 1.04 (d, $J = 6.5$ Hz, 3H, CH₃), 1.11 (d, $J = 7.1$ Hz, 3H, CH₃), 1.12 (d, $J = 6$ Hz, 3H, CH₃), 1.13 (d, $J = 7.1$ Hz, 3H, CH₃), 1.18 (d, $J = 6.4$ Hz, 3H, CH₃), 1.23 (d, $J = 6.5$ Hz, 3H, CH₃), 1.80–2.02 [m, 2H, HC(14) and HC(1′)], 2.40–2.65 [m, 4H, HC(7), HC(15), HC(3′) and H₃C(5′)], 2.65–2.82 [m, 2H, H₃C(5′)], 2.92 [dd, $J = 17$ and 8.2 Hz, 1H, H₃C(5′)], 3.01 [dq, $J = 2$ and 7 Hz, 1H, HC(3′)], 3.70–3.80 [m, 2H, HC(2′) and HC(2′)], 3.90–4.04 [m, 2H, HC(8′) and HC(8′)], 4.34–4.44 [m, 2H, HC(6) and HC(6′)], 4.71 [dd, $J = 9.7$ and 1.1 Hz, 1H, HC(16)], 5.09 [dd, $J = 10$ and 1.2 Hz, 1H, CH(8)], 5.58 [d, $J = 15.4$ Hz, 1H, HC(11)], 5.60 [dd, $J = 15$ and 10.0 Hz, 1H, HC(14)], 5.61 [d, $J = 15.3$ Hz, 1H, HC(3)], 5.65 [dd, $J = 15.0$ and 9.7 Hz, 1H, HC(6)], 6.03 [dd, $J = 15.1$ and 11.1 Hz, 1H, HC(13)], 6.5 [d, $J = 15.0$ and 10.9 Hz, 1H, HC(5)], 6.92 [dd, $J = 15.0$ and 10.9 Hz, 1H, HC(12)], 6.93 [dd, $J = 15.3$ and 11.3 Hz, 1H, HC(4)].

¹H NMR (300 MHz); 40a (for numbering see formula at the beginning of the Experimental Part): $\delta = −0.06$ (s, 6H, 2 SiMe), 0.03 (s, 6H, 2 SiMe), 0.50–0.66 [m, 12H, 2 Si(CH₂Me)₃], 0.80 [s, 18H, 2 Si(CH₃)₃], 0.80–1.50 [m, 30H, 2 CH₂CH₂CH₃ and 2 Si(CH₂CH₃)₂], 1.04 (d, $J = 6.5$ Hz, 6H, 2 CH₃), 1.12 (d, $J = 6.6$ Hz, 6H, 2 CH₃), 1.13 (d, $J = 7.1$ Hz, 6H, 2 CH₃), 1.18 (d, $J = 6.4$ Hz, 6H, 2 CH₃), 1.90–2.02 [m, 2H, HC(1′)], 2.44–2.60 [m, 2H, HC(7) and HC(15)], 2.61–2.82 [m, 4H, 2 H₃C(5′)], 3.01 [dq, $J = 2$ and 7 Hz, 2H, 2 HC(3′)], 3.04–3.10* (br., 2H, 2 OH), 3.70–3.80 [m, 2H, 2 HC(2′)], 3.90–4.02 [m, 2H, 2 HC(8′)], 4.34–4.42 [m, 2H, 2 HC(6′)], 4.72 [dd, $J = 9.9$ and 1.1 Hz, 2H, HC(8) and HC(16)], 5.58 [d, $J = 15.5$ Hz, 2H, HC(3) and HC(11)], 5.61 [dd, $J = 15.0$ and 10.1 Hz, 2H, HC(6) and HC(14)], 6.03 [dd, $J = 15.0$ and 11.3 Hz, 2H, HC(5) and HC(13)], 6.90 [dd, $J = 15.5$ and 11.3 Hz, 2H, HC(4) and HC(12)].

**Methanalysis of 40 to give 8 in the presence of p-toluenesulfonic acid:** A mixture of 40a (6.5 mg, 0.0053 mmol) and p-toluenesulfonic acid (1.0 mg) in methanol (1.0 ml) was stirred at 20°C for 30 min. TLC analysis showed no starting material left. The mixture was poured into phosphate buffer (pH = 7; 5 ml) and extracted with ether (2 × 25 ml). The combined etherol solvents were washed with phosphate buffer (pH = 7; 5 ml), dried, filtered, and evaporated to give an oil which was chromatographed on Merck silica gel plate (60F₂₅₄) developing with ether/hexane (3:1) to give a homogenous fraction 8a (0.7 mg, 16%; $R_F =$...
0.28; [α]D = +86 ± 17 (c = 0.07, CCl₄). This compound is identical by NMR (300 MHz), IR, and TLC with the sample 8a prepared from elaiophylin.

Similar treatment of 40b (3.4 mg, 0.0030 mmol) with p-toluenesulfonic acid in methanol (20°C, 20 min) gave 88b (1.1 mg, 48%; Rf = 0.19, ether/hexane = 3:1) as an oil. – ¹H NMR (300 MHz, C₆D₆); (for numbering see formula at the beginning of the Experimental Part): δ = 0.42* (br., 6H, 4 OH and 2 MeOH), 0.63 (d, J = 6.8 Hz, 3H, CH₃), 0.72 (d, J = 6.6 Hz, 3H, CH₃), 0.87 (d, J = 6.6 Hz, 3H, CH₃). 0.87 (t, J = 7.4 Hz, 3H, CH₂CH₂CH₃), 0.94 (t, J = 7.5 Hz, 3H, CH₂CH₂CH₃), 1.17 (d, J = 5.7 Hz, 3H, CH₃), 1.20–1.75 (m, 6H, 2 CHCH₂Me), 1.23 (d, J = 6.0 Hz, 3H, CH₃), 1.25 (d, J = 5.9 Hz, 3H, CH₃), 1.30 (d, J = 7.0 Hz, 3H, CH₃), 1.70–1.85 [m, 2H, Hα(8) and Hα(C(3′))], 1.90–2.06 [m, 2H, HC(16) and HC(1(1′))], 2.20–2.36 [m, 4H, HC(7), HC(15), HC(3′) and Heq(C(3′))], 2.50 [dq, 1H, HC(4′) and HC(12)], 3.07 (s, 3H, CH₃), 3.52–3.65 [m, 2H, HC(4) and HC(6′)], 3.69 [dq, J = 10 and 10 Hz, 1H, HC(6′)], 3.89–3.95 [m, 2H, HC(4′) and HC(6′)], 3.96 [dd, J = 10.0 and 1.8 Hz, 2H, 2 HC(3′)], 4.13 [dd, J = 10.0 and 1.8 Hz, 2H, 2 HC(3′)], 4.51 (d, J = 15.1 Hz, 1H, HC(3′)], 5.50 (d, J = 15.3 Hz, 1H, HC(11)], 5.73 (dd, J = 15.0 and 11.2 Hz, 1H, HC(5)], 5.81 [dd, J = 15.1 and 11.5 Hz, 1H, HC(13)], 7.05 [dd, J = 16.3 and 11.4 Hz, 1H, HC(4)], 7.11 [dd, J = 15.8 and 11.6 Hz, 1H, HC(12)].

Treatment of 40c (4.6 mg, 0.0041 mmol) with p-toluenesulfonic acid in methanol (20°C, 60 min) gave 8c (1.8 mg, 58%; Rf = 0.15, ether/hexane = 3:1). – ¹H NMR (300 MHz, C₆D₆); (for numbering see formula at the beginning of the Experimental Part): δ = 0.42* (br., 6H, 4 OH and 2 MeOH), 0.73 (d, J = 6.6 Hz, 6H, 2 CH₃), 0.87 (d, J = 6.5 Hz, 6H, 2 CH₃), 0.87 (t, J = 7.5 Hz, 6H, 2 CH₂CH₂CH₃), 1.17 (d, J = 5.5 Hz, 6H, 2 CH₃), 1.20–1.68 (m, 6H, 2 CH₂CH₂Me), 1.26 (d, J = 6.7 Hz, 6H, 2 CH₃), 1.74 [dd, J = 13.0 and 10.6 Hz, 2H, 2 Hα(C(3′))], 1.93–2.06 [m, 2H, 2 HC(1′)], 2.30–2.40 [m, 4H, 2 Hα(C(3′)], HC(7) and HC(15)], 2.49 [dq, J = 1.6 and 6.9 Hz, 2H, 2 HC(3′)], 2.50 (s, 6H, 2 MeOH), 3.20 (s, 6H, 2 MeO), 3.44 [dt, J = 4.5 and 11.0 Hz, 2H, 2 HC(4′)], 3.69 [dd, J = 10.1 and 6.3 Hz, 2H, 2 HC(6′)], 4.13 [dd, J = 1.5 and 8.1 Hz, 2H, 2 HC(2′)], 4.96 [dd, J = 10.0 and 1.8 Hz, 2H, HC(8) and HC(16)], 5.46 [dd, J = 15.2 and 10.2 Hz, 2H, HC(6) and HC(14)], 5.52 [dd, J = 15.4 Hz, 2H, HC(3) and HC(11)], 5.79 [dd, J = 14.9 and 11.0 Hz, 2H, HC(5) and HC(13)], 7.15 [dd, J = 15.4 and 11.0 Hz, 2H, HC(4) and HC(12)].


5) There is a whole family of macrolactones structurally related to Colletoladiol and Grahimmycin A9. They have been named: Colletol, Colletoketol, and Colletolactol, see ref.6b, and Grahimmycin A and B; see S. Gurusiddiuh, R. C. Ronald, J. A. Magnanum, and B. A. McFadden, U. S. Patent 4,220,718 (1980) [Chem. Abstr. 94, 28879h (1981)].


43. E. I. Khlebarova, I. Kh. Georgieva-Borisova, G. N. Sheikova, and N. O. Blinov, Farmatsiya (Sofia) 22, 3 (1972).
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Total Synthesis of (+)-11,11'-Di-O-methylelaiophylidene

56 R. F. W. Jackson, M. A. Sutter, and D. Seebach, Liebigs Ann. Chem. 1985, 2313. The systematic name for the macrodiolide building block in this paper is not in accordance with the IUPAC rules.

57 For a preliminary communication in which most of the work is mentioned which is described here in full detail see: D. Seebach, H.-F. Chow, R. F. W. Jackson, K. Lawson, M. A. Sutter, S. Thatsiravongs, and J. Zimmermann, J. Am. Chem. Soc. 107, 5292 (1985).


59 Methanol was also present in the crystals used for X-ray analysis and could be located as being hydrogen-bonded to OH-groups of the sugar moiety.


61 We are not sure whether LaC13 acts as a Lewis acid or whether it is just a very special source of HCl:

\[ \text{LaC}13 + n\text{CH}_3\text{OH} \rightleftharpoons \text{La(OCH}_3)_n\text{C}1_3 - n + n\text{HCl} \]

62 Biological-chemical methods for attaching or removing the sugars have not yet been tested.


64 Part of the projected Ph. D. thesis of J. Zimmermann, ETH Zürich. Using the same method, products of type 12-20 with substituents other than methyl are accessible.


67 The β-oxygen effect [A. C. Richardson, Carbohydr. Res. 10, 395 (1969)] may be responsible for the fact that using less good leaving groups and solvents other than HMPT gave yields of 20% or less. — It is also conceivable that too good a leaving group or too drastic conditions lead to ionisation of the C—O bond and thus to pinacol-type rearrangements or hydride shift. — Finally, low yields may be due to competing elimination or acetal cleavage. Unpublished results by K. Lawson and R. Jakob (ETH Zürich 1982 and 1983/84, respectively).


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CAS Registry Numbers

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