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(+)-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 OCH_3 (C-11 and C-11′). The di-*O*-methylelaiophylidene (**8a**), a C_2-symmetrical macrodiolide with 2 × 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 × 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 topicity *ul*, using the *Z*-boron enolate of the ketone, to give the two C_2-symmetrical and the asymmetric aldol (**40a, b, c**), one of which furnished the aglycone **8a** upon acid-catalysed methanolysis (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 alkoxide-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 Makrodiolid-Antibiotikum Elaiophylin (**6**, Schema 1) kann durch säurekatalysierte Abspaltung der Desoxyfucose-Einheiten in Methanol unter gleichzeitiger Substitution der C-11- und C-11′-Lactol-OH-Gruppen durch OCH_3 in das Aglycon **8a** umgewandelt werden. Dieses Di-*O*-methylelaiophyliden genannte C_2-symmetrische Makrodiolid **8a** enthält 2 × 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 × 5 stereogene Einheiten) und das silylgeschützte 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 C_2-symmetrische und ein unsymmetrisches Diaddukt (**40a, b, c**), von denen eines bei der säurekatalysierten Methanolyse 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).

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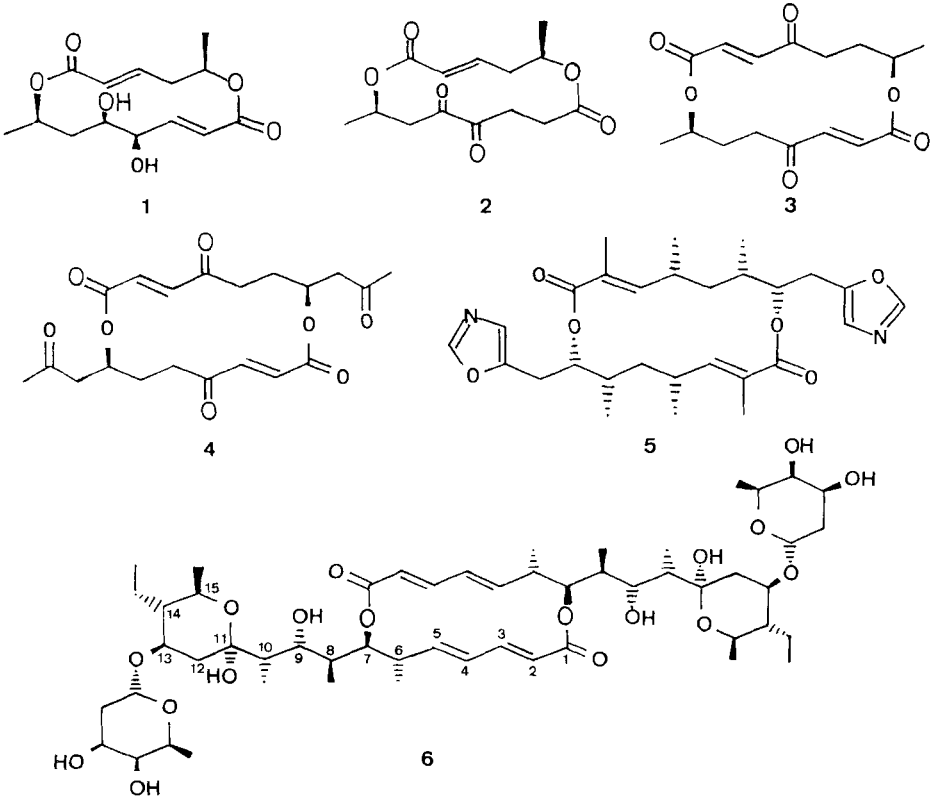
A) Introduction

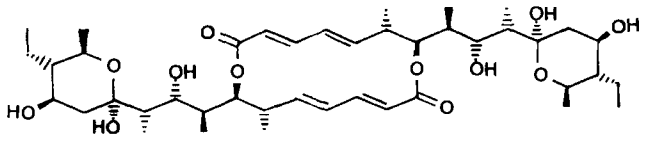
Two groups of medium-ring diolides, so-called macrodiolides[1,2] have been isolated from fungi: the unsymmetrical ones (**1, 2**) and those with C_2-symmetry (**3**–**6**) (Scheme 1).

Scheme 1



No.	Name	References		
		Isolation	Structure Elucidation	Synthesis
1	Colletodiol	3, 4, 5	5, 6, 7	8, 9
2	Grahamimycin A_1	5, 10	5, 10, 11	11–13
3	Pyrenophorin	14, 15	16–18	18–34
4	Vermiculin	35	18, 22, 36	18, 22, 37, 38
5	Conglobatin	39	39, 40	40
6	Elaiophylin	41	45–50	
	Azalomycin 8	42		
	Antibiotic 255 E	43		
	Salbomycin	44		

In a series of papers[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[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")[53,54]. Elaiophylin **6** is the most challenging example of this



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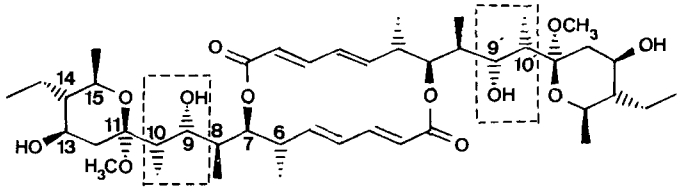
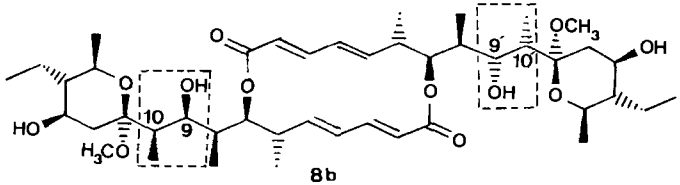


8a



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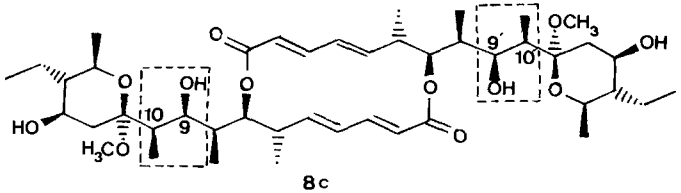
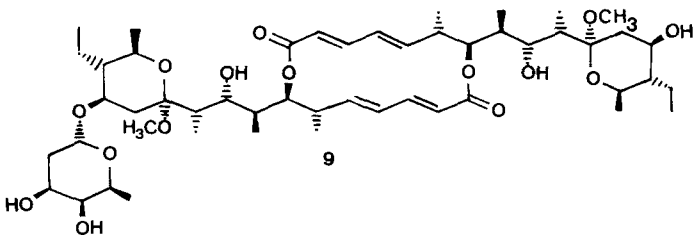


8c



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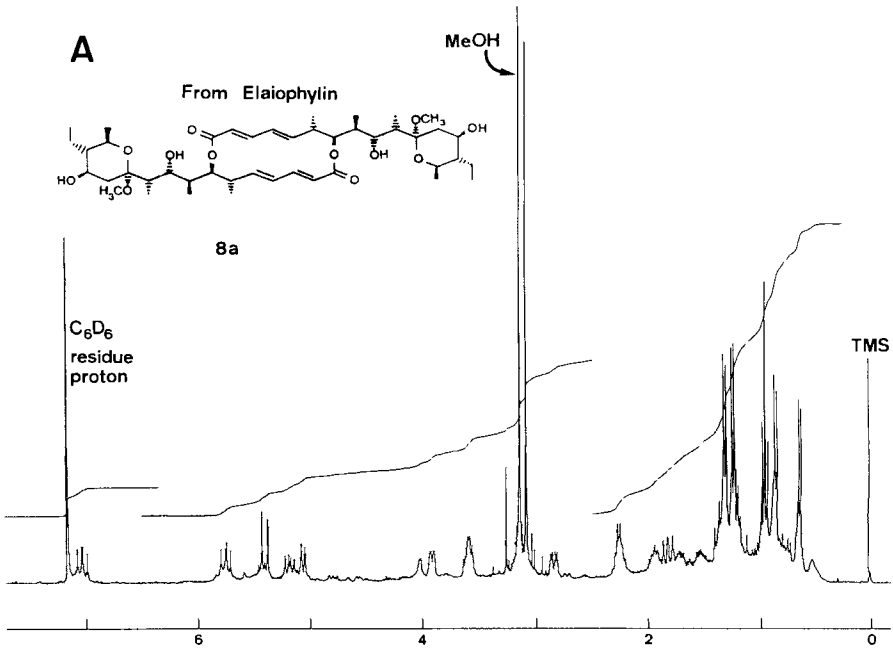
class of natural products to a synthetic organic chemist, and some years ago we started an effort towards a synthesis of this compound[55]. This led to the preparation of a model system[52] and to the synthesis of a key diolide intermediate which employed *Evans'* aldol methodology (using an external auxiliary) to create two of the chirality centres in the target[56]. We describe here, in full[57], the total synthesis of an aglycone of elaiophylin (dimethylelaiophylidene) from (*R*)-3-hydroxybutyrate and (*S*)-malate.

B) Elaiophylin, an aglycone and a strategy

Elaiophylin (**6**) was isolated, originally, from cultures of *Streptomyces melanosporus*[41] 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)[42–44]. The constitution of elaiophylin was first elucidated in 1981[46], and later the relative and absolute configuration were determined by X-ray analysis[47–49] and NMR studies[48,50].

Despite many attempts to remove the 2,6-deoxyfucose carbohydrate moieties from elaiophylin, the aglycone **7** has never been reported[45,58], 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-



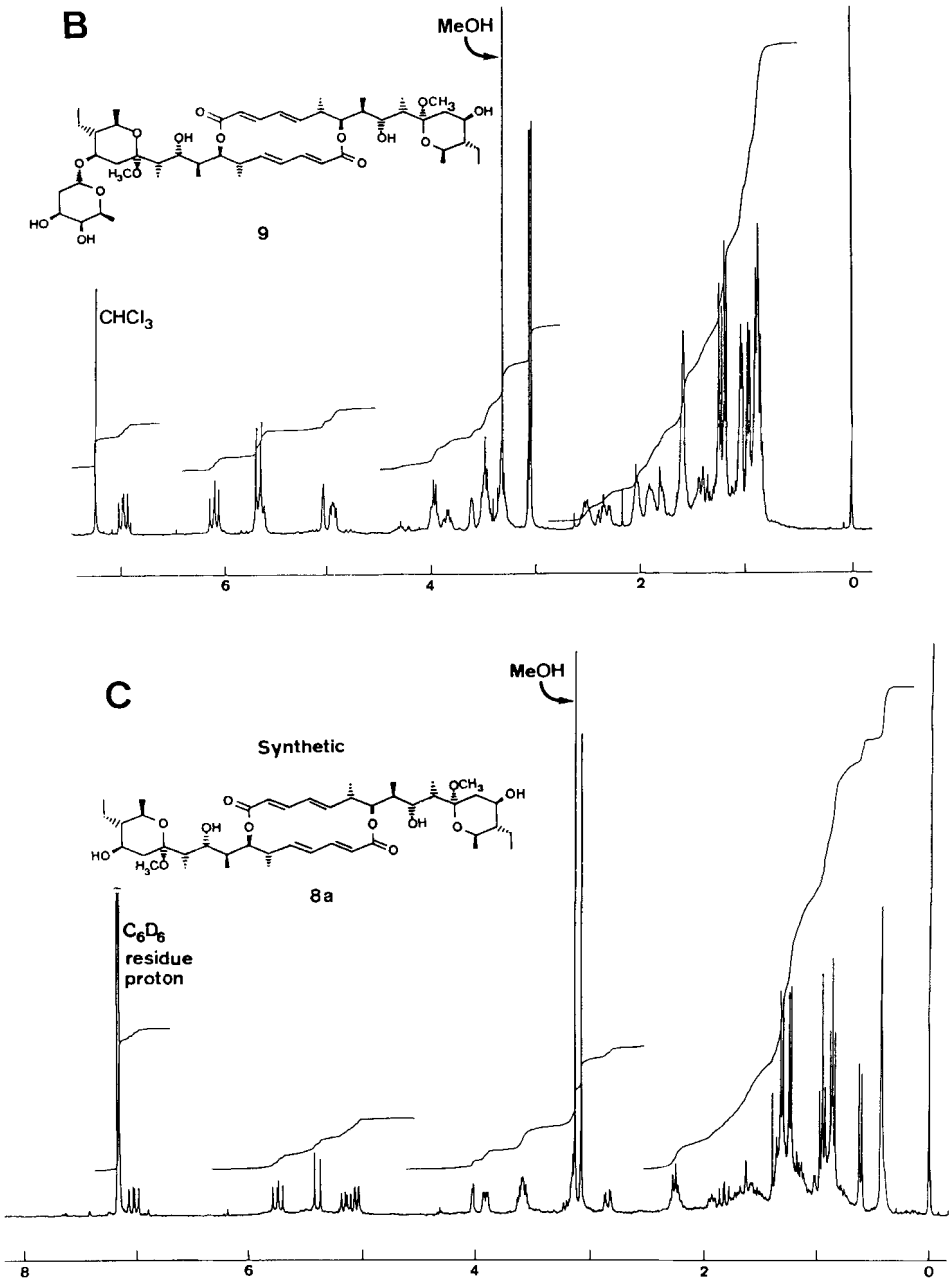
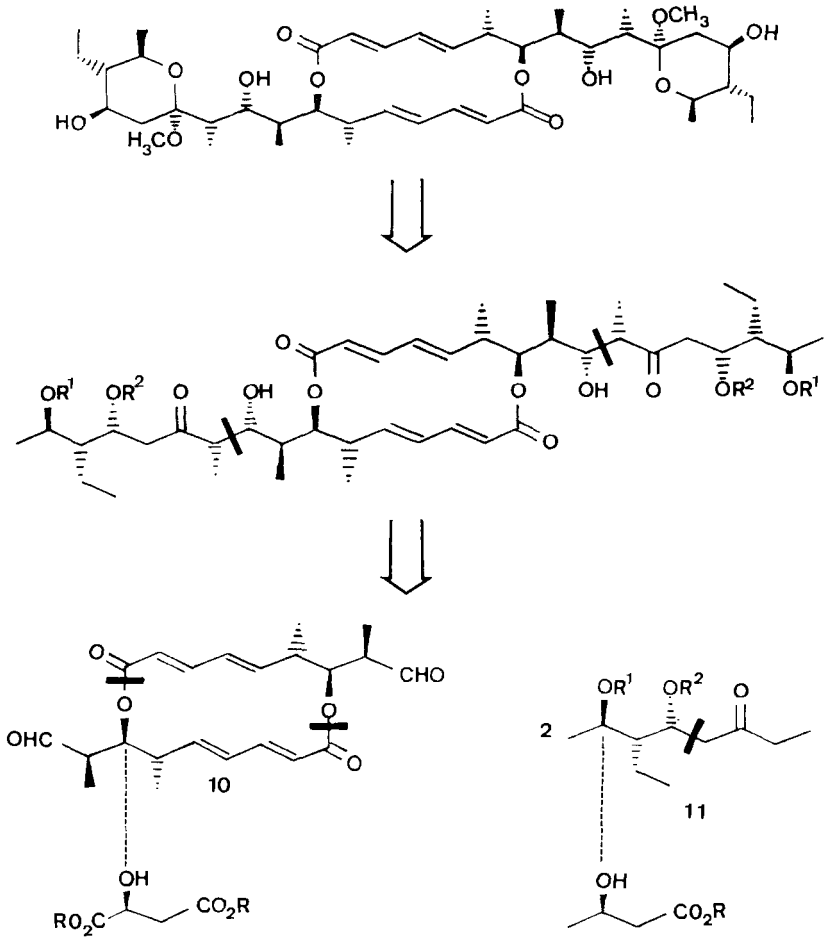


Figure 1. 300-MHz ^{1}H NMR spectra of aglycones of elaiophylin **6**

A: (+)-11,11′-Di-*O*-methylelaiophylidene (**8a**), by cleavage of **6** with *p*-toluenesulfonic acid in methanol. — **B**: Monoaglycone **9** of 11,11′-di-*O*-methylelaiophylin, by cleavage of **6** with lanthanum trichloride in methanol. — **C**: Elaiophylidene (**8a**) from the total synthesis.

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[59]. If, on the other hand, *p*-toluenesulfonic acid is replaced by lanthanum trichloride, which is thought to be less acidic[60,61], 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 OCH_3).

Scheme 2



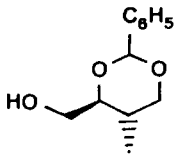
The instability of the aglycone **8a** under acidic conditions in the presence of water precludes its conversion into elaiophylin itself, since it is clearly impossible to convert a methyl acetal into a free lactol without water[62]. An alternative approach would have required the coupling of a protected 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[63] but an alternative strategy involving postponement of the macrodiolide ring formation to the final step, thereby exploiting the C_2-symmetry to its utmost effect, would have required an unmanageable array of protecting groups in such a sensitive molecule[45,58].

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

The starting material[64] for our synthesis was the benzaldehyde acetal **12**, available in five steps from diethyl (*S*)-malate[65]. Conversion of the free hydroxy group into the triflate using trifluoromethanesulfonic anhydride and pyridine[66] was followed by immediate reaction with sodium cyanide in hexamethylphosphoric triamide to give the chain-extended nitrile **13** in 57% yield[67]. Hydration of the nitrile function was accomplished using *Corey's* hydrogen peroxide/1-hexene procedure[68] 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[69,70] 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**[71]. 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 *Hanessians's* tritylpyridinium tetrafluoroborate procedure[72] to give the



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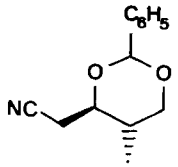

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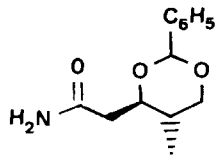

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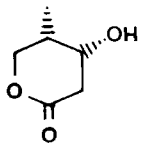

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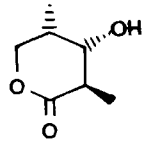

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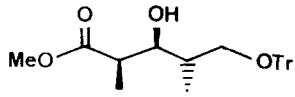

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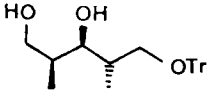
monotrityl ether **17** in 48% overall yield from the lactone **16** (18% recovery). The proton NMR spectrum of the trityl ether **17** indicated that it was contaminated with 3% of a diastereoisomeric product, presumably formed by methoxide-induced epimerisation.



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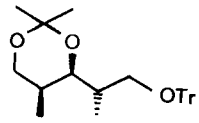

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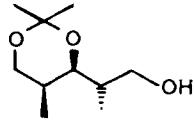

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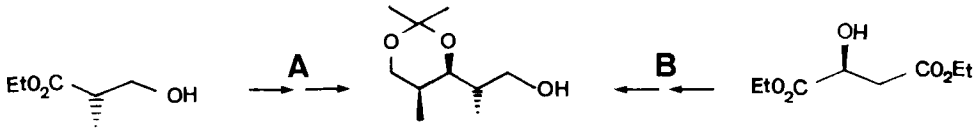
At this stage of our route it was necessary to alter the oxidation states at the termial carbon atoms of the chain. This process was initiated by reduction of the methyl ester function of **17** using $LiAlH_4$ in ether to give in 98% yield the diol **18** which was then treated with dimethoxypropane 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[56].

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[56]. 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



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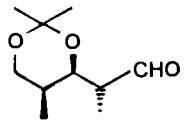
Method A: Convergent, using an external chiral auxiliary. 8 steps (35% overall yield) to **20**; 3 steps to make the chiral auxiliary from D-valine, yield 82%; recovery of chiral auxiliary after *Evans*' aldol addition: 78%.

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



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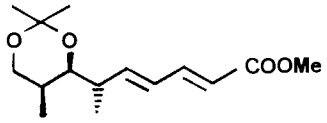

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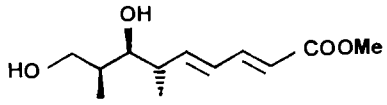

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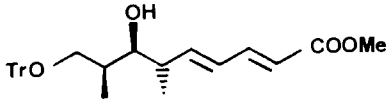

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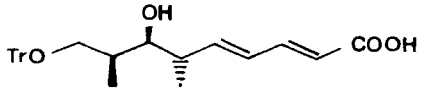

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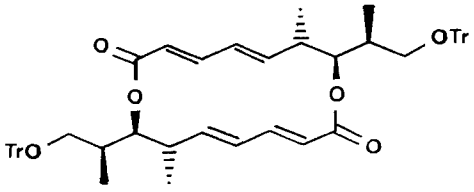

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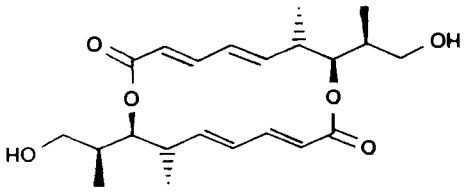

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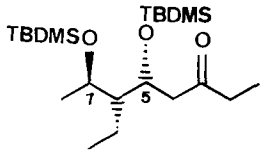
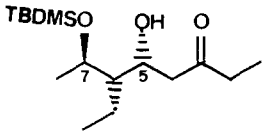
D) Synthesis of the side chain (11, 35)

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[55]. 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.



28a



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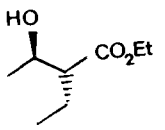

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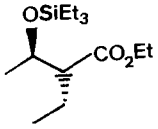

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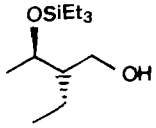

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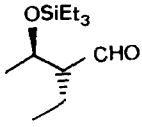

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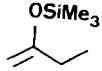

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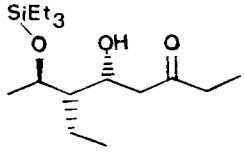
The side-chain aldol derivative of type **11** which was eventually used in the synthesis, was prepared as follows. Treatment[69,70] of the ethyl (*R*)-3-hydroxybuyrate, prepared from the biopolymer PHB[73], with two equivalents of lithium diisopropylamide and three equivalents of ethyl iodide gave the 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 $LiAlH_4$ 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

projected *Mukaiyama* aldol reaction, 2-trimethylsilyloxy-1-butene (**33**), was prepared free of its regioisomer by deprotonation of 2-butanone 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 °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[74]. Use of *Corey*'s original procedure, employing imidazole and *tert*-butyldimethylsilyl chloride in dimethylformamide[75], gave the required *bis*-protected diol **35** in rather poor yield (42%) and very slowly (80 hours).



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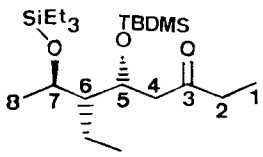

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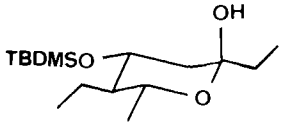

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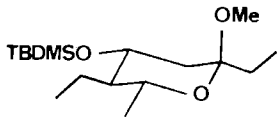

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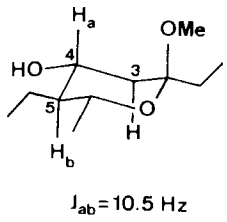


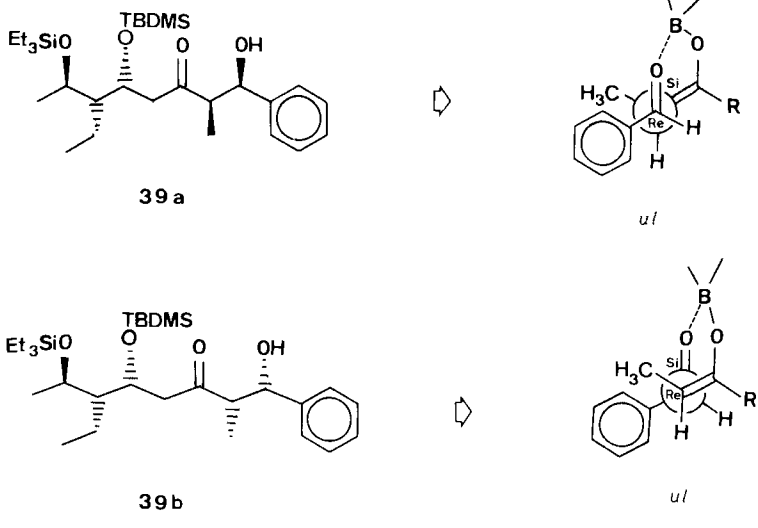
38

In order both to establish the configuration of the aldol adduct **34** and to ascertain whether the protected δ-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)[76] to give the δ-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

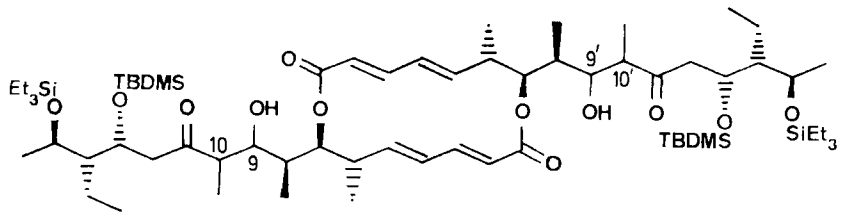
acetal **38** clearly indicates that this proton is *trans*-diaxial to two protons (3-H_{ax} and 5-H), and therefore the configuration at C-4 is *R*. The stereochemical course of the aldol addition in which the isolated product is formed according to the open-chain model of *Cram*'s rule, requires some 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 diastereoisomer 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

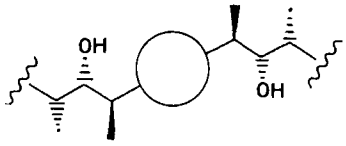
The crucial step in the synthesis had now been reached. We felt that the best way to ensure that the newly created centres of chirality in the aldol reaction were generated with relative topicity *ul*[78] (to give a *syn* product in *Masamune*'s nomenclature) would be to prepare the di-*n*-butylboron enolate of the ketone **35**. It is well-known that it is possible to prepare *Z*-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 *Z*-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**.



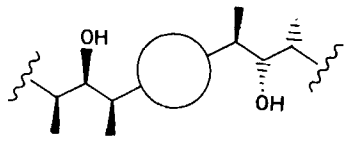
Treatment of the dialdehyde **10** with four equivalents of the di-*n*-butylboron enolate of the ketone **35** led to three stereoisomers **40** (3 : 5 : 6 or 21, 37, and 42% d. s., respectively; 42% combined yield) as the *only* isolable aldol adducts, which were easily separable by flash chromatography. 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*-butyldimethylsilyl ether. This order of steps is mechanistically reasonable (*cf.* the model series **35**→**36**→**37**→**38**). The stereoisomer **40** formed with



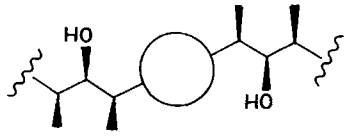
40a : (9R,9′R,10S,10′S)
40b : (9R,9′S,10S,10′R)
40c : (9S,9′S,10R,10′R)



A



B



C

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).

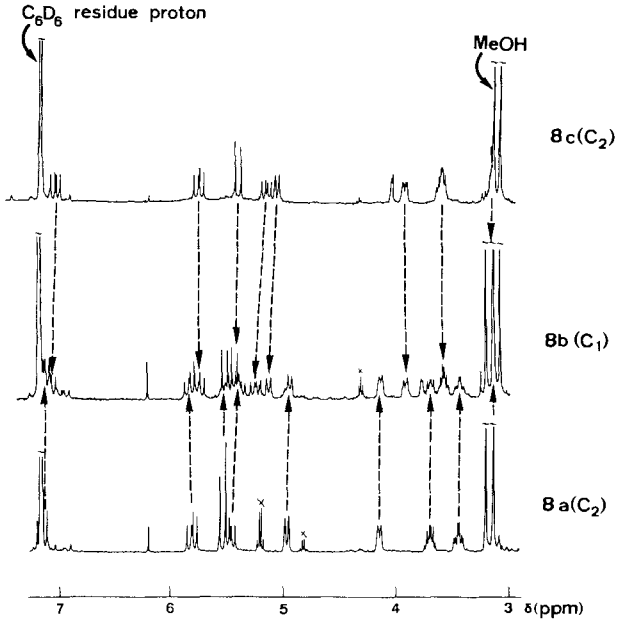


Figure 2. Comparison of the 3–7-ppm part of the 300-MHz ^{1}H NMR spectra of the diastereomers **8a, b,** and **c** (cf. **A, B,** and **C** below formula **40**); for assignment of signals see experimental section

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 α 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 *lk* and *ul* 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 dialdehyde **10** with relative topicity *ul* is nearly statistical (compare 1 : 2 : 1 with the observed 1 : 1.7 : 2), and not biased in the undesired direction, to a disasterous 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 elaiophylidene and elaiophylin.

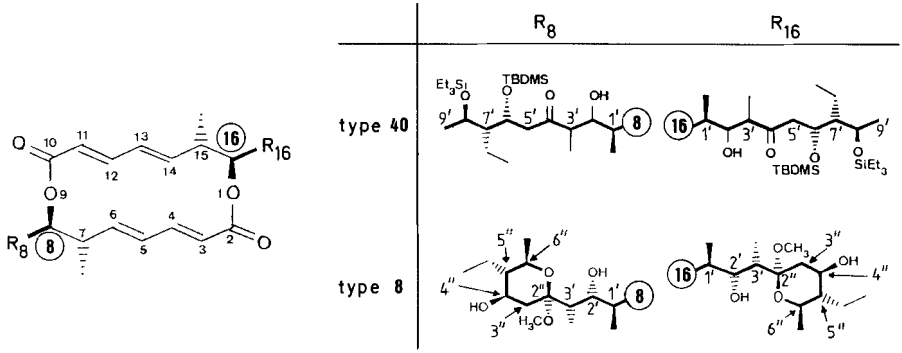
We gratefully acknowledge helpful discussions with and receipt of generous samples of elaiophylin from Professor Dr. *W. Keller-Schierlein* of our Laboratory, Dr. *A. von Wartburg*, and Dr. *W. Pache* (Sandoz AG, Basel) for carrying out biological tests, the staff of the analytical department of the 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 $CHCl_3$ 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 $CHCl_3$ solution. – ^1H NMR spectra were obtained with either a Varian EM-390 (90 MHz) or a Bruker WM 300 (300 MHz) instrument. ^{13}C NMR spectra were obtained using a Varian CFT-20 instrument. All spectra were recorded using TMS as internal standard in $CDCl_3$ as solvent. Signals marked with an asterisk (*) disappear on addition of D_2O. – Mass spectra were recorded at 70 eV with a Hitachi-Perkin-Elmer RMV 6M instrument. All reaction solvents, except for tetrahydrofuran (THF) and hexamethylphosphoric triamide (HMPT) were of *purissimum* quality. THF was distilled from potassium/benzophenone ketyl immediately before use. HMPT was distilled over CaH_2 under reduced pressure. All reactions were carried out in oven-dried glassware under argon. Unless otherwise stated, organic extracts were dried with $MgSO_4$ and concentrated using a rotary evaporator. Buffer solution of pH = 7 was prepared by dissolving 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-methylbutyl]-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 chromatographed on Merck silica gel plate ($60F_{254}$) developing with ether/hexane (3 : 1) to give a homogeneous fraction **8a** (20 mg, 49%; R_F = 0.28) as an oil; $[\alpha]_D$ = +68.0 (c = 0.54, CCl_4). – IR (CCl_4): 3600–3350 (O–H), 1700 (C=O), 1640 (C=C), 1612 (C=C). – ^1H NMR (300 MHz, C_6H_6) (for numbering see formula above): δ = 0.42* (br., 6H, 4 OH and 2 MeO*H*), 0.61 (d, J = 6.7 Hz, 6H, 2 CH_3), 0.84 (d, J = 6.5 Hz, 6H, 2 CH_3), 0.95 (t, J = 7.6 Hz, 6H, 2 $CHCH_2CH_3$), 1.24 (d, J = 6.2 Hz, 6H, 2 CH_3), 1.25–1.76 (m, 6H, 2 $CHCH_2Me$), 1.32 (d, J = 7.0 Hz, 6H, 2 CH_3), 1.82 [dd, J = 13.2 and 10.7 Hz, 2H, $2H_{ax}C(3'')$], 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, $2H_{eq}C(3'')$], 3.08 (s, 6H, 2 OMe), 3.13 (s, 6H, 2 MeOH),

3.55–3.65 [m, 4H, 2 HC(4″) and 2 HC(6″)], 3.90 [dd, J = 9.4 and 3.8 Hz, 2H, 2 HC(2′)], 5.05 [dd, J = 9.9 and 1.7 Hz, 2H, HC(8) and HC(16)], 5.15 [dd, J = 15.0 and 9.5 Hz, 2H, HC(6) and HC(14)], 5.39 [d, J = 15.4 Hz, 2H, HC(3) and HC(11)], 5.73 [dd, J = 15.1 and 11.2 Hz, 2H, HC(5) and HC(13)], 7.02 [dd, J = 15.3 and 11.2 Hz, 2H, HC(4) and HC(12)].

(3R,4S)-3,5-Benzylidenedioxy-4-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 × 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 × 80 ml). The combined organic layers were washed with water (100 ml), dried, and evaporated. The residue was purified by flash chromatography (eluant 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, $CHCl_3$). – IR (KBr): 2980 (m, CH), 2250 (w, C≡N). – ^{1}H NMR (300 MHz): δ = 0.86 (d, J = 6, 7 Hz, 3H, CH_3), 1.96–2.14 (m, 1H, C*H*CH_3), 2.64 (dd, J = 6.4 and 17.0 Hz, 1H, CH_ACN), 2.75 (dd, J = 3.9 and 17.0 Hz, 1H, CH_BCN), 3.55 (t, J = 11.3 Hz, 1H, CH_AO), 3.68–3.78 (m, 1H, CH–O), 4.16 (dd, J = 4.8 and 11.5 Hz, 1H, CH_BO), 5.52 (s, 1H, O–CH–O), 7.32–5.54 (m, 5H, Ar). – ^{13}C NMR (25.2 MHz): δ = 12.1 (q), 22.4 (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%, Ar^+).

$C_{13}H_{15}NO_2$ (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-Benzylidenedioxy-4-methylpentanamide (**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 × 200 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), 1650 (s, C=O), 1620 (m, C=O). – ^{1}H NMR (300 MHz): δ = 0.84 (d, J = 6.7 Hz, 3H, CH_3), 1.86–2.04 (m, 1H, C*H*CH_3), 2.48 (dd, J = 8.12 and 15.1 Hz, 1H, CH_AC=O), 2.64 (dd, J = 2.8 and 15.1 Hz, 1H, CH_BC=O), 3.54 (t, J = 11.3 Hz, 1H, CH_AO), 3.82–3.92 (m, 1H, CH–O), 4.14 (dd, J = 4.8 and 11.4 Hz, 1H, CH_BO), 5.55 (s, 1H, O–CH–O), 7.30–7.52 (m, 5H, Ar). – ^{13}C NMR: δ = 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%, Ar^+).

$C_{13}H_{17}NO_3$ (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-Hydroxy-4-methyl-5-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 (eluant 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),

1720 (s, C=O). – ^{1}H NMR (300 MHz): δ = 1.04 (d, *J* = 6.9 Hz, 3H, CH_3), 2.08–2.22 (m, 1H, C*H*CH_3), 2.56 (s, 1H, OH), 2.71 (d, *J* = 3.9 Hz, 2H, CH_2C=O), 4.08–4.16 (m, 1H, CH–O), 4.16–4.24 (m, 1H, CH–O), 4.31–4.39 (m, 1H, CH–O). – ^{13}C 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^+ – H_2O), 89 (100%).

$C_6H_{10}O_3$ (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 × 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 %) was recovered by further elution. – $[\alpha]_D$ = 17.9 (*c* = 1.5). – IR ($CHCl_3$): 3620 (w, O–H), 2980 (w, C–H), 1730 (s, C=O). – ^{1}H NMR (300 MHz): δ = 1.04 (d, *J* = 6.9 Hz, 3H, 4 CH_3), 1.33 (d, *J* = 7.4 Hz, 3H, 2 CH_3), 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–O), 4.12–4.20 (m, 1H, CH–O), 4.22–4.32 (m, 1H, CH–O). – ^{13}C NMR (25.2 MHz): δ = 10.9, 15.4, 30.7, 42.6, 70.0, 71.7, 174.9. – MS: *m/z* = 145 (2%, M^+ + 1), 144 (1%, M^+), 126 (10%, M^+ – H_2O), 56 (100%).

$C_7H_{12}O_3$ (144.2) Calcd. C 58.32 H 8.39 Found C 58.36 H 8.23

Methyl (2R,3S,4S)-3-hydroxy-2,4-dimethyl-5-trityloxypentanoate (**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. 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 × 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 × 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, 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: $[\alpha]_D$ = 14.3 (*c* = 1.05). – IR ($CHCl_3$): 3500 (m, OH), 1725 (s, C=O). – ^{1}H NMR (300 MHz): δ = 0.91 (d, *J* = 6.9 Hz, 3H, CH_3), 1.14 (d, *J* = 7.1 Hz, 3H, CH_3), 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-CH_2 and OH), 3.68 (s, 3H, OCH_3), 3.82–3.92 (m, 1H, 3-CH), 7.40–7.68 (m, 15H, Ar). – ^{13}C 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%).

$C_{27}H_{30}O_4$ (418.3) Calcd. C 77.48 H 7.22 Found C 77.18 H 7.19

(2S,3R,4S)-2,4-Dimethyl-5-trityloxy-1,3-pentanediol (**18**): $LiAlH_4$ (40 mg, 1.05 mmol) was suspended in ether (10 ml) and cooled in an ice/water bath. The methyl ester **17** (120 mg,

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 $MgSO_4$ 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). – IR ($CHCl_3$): 3460 (m, OH). – ^{1}H NMR (300 MHz): δ = 0.74 (d, J = 7.0 Hz, 3H, CH_3), 0.98 (d, J = 7.0 Hz, 3H, CH_3), 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_2OH, $CHOH$ and CH_2OTr), 3.88 (br. m, 1H, OH), 7.20–7.48 (m, 15H, Ar). – MS: m/z = 260 (16%, $TrOH^+$), 243 (48%, Tr^+), 149 (100%).

(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 × 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. – M. p. 145–147°C; $[\alpha]_D$ = –21.4 (c = 0.5). – IR (KBr): 2860 (s, CH). – ^{1}H NMR (300 MHz): δ = 0.98 (d, J = 6.9 Hz, 3H, CH_3CH), 1.02 (d, J = 6.9 Hz, 3H, CH_3CH), 1.25 (s, 3H, CH_3C), 1.34 (s, 3H, CH_3C), 1.52–1.60 (m, 1H, 2-CH or 4-CH), 1.64–1.77 (m, 1H, 2-CH or 4-CH), 3.04 (dd, J = 2.7 and 8.5 Hz, 1H, CH_AOTr), 3.24 (dd, J = 4.3 and 8.5 Hz, 1H, CH_BOTr), 3.61 (dd, J = 1.6 and 11.5 Hz, 1H, 1-CH_A), 3.96 (dd, J = 2.4 and 10.2 Hz, 1H, 3-CH), 4.14 (dd, J = 2.7 and 11.5 Hz, 1H, 1-CH_B), 7.20–7.48 (m, 15H, Ar). – ^{13}C NMR (25.2 MHz): δ = 10.3 (q), 13.1 (q), 18.9 (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). – MS: m/z = 243 (100%, Tr^+), 183 (23%), 165 (36%), 105 (23%).

$C_{29}H_{34}O_3$ (430.6) Calcd. C 80.89 H 7.96 Found C 81.09 H 7.89

(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 × 10 ml), then with dichloromethane (3 × 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[56].

(3E,5E,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**[56] (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

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 ($CHCl_3$): 2990 (CH), 1720 (s), 1710 (s). – ^{1}H NMR (300 MHz): δ = 1.10 (d, *J* = 6.7 Hz, 6H, 2 CH_3), 1.19 (d, *J* = 7 Hz, 6H, 2 CH_3), 2.52 (ddq, *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 (40 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. 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, 2 × 100 ml). 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; $[\alpha]_D$ = −6.1 (*c* = 1.0). – IR ($CHCl_3$): 3620–3350 (O–H), 1714 (C=O). – ^{1}H NMR (300 MHz): δ = 0.93 (t, *J* = 7.4 Hz, 3H, CCH_2CH_3), 1.22 (d, *J* = 6.4 Hz, 3H, CH_3CH), 1.28 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.62–1.78 (m, 2H, CCH_2Me), 2.30 (dt, *J* = 8.4 and 6.0 Hz, 1H, $CHCO_2$), 2.56–2.686* (br., 1H, OH), 3.92 (quint, *J* = 6.3 Hz, 1H, CHOH), 4.19 (q, *J* = 7.4 Hz, 2H, OCH_2). – ^{13}C 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^+ – MeCHOH or M^+ – OEt), 101 (71%, M^+ – MeCHO – Me), 87 (7%, M^+ – CO_2Et), 73 (100%, CO_2Et), 45 (58%, MeCHOH).

$C_8H_{16}O_3$ (160.2) Calcd. C 59.98 H 10.07 Found C 59.86 H 9.99

Ethyl (2R,3R)-2-ethyl-3-triethylsilyloxybutanoate (**30**): Triethylsilyl triflate (30.4 g, 115 mmol) was added dropwise to a stirred solution of the alcohol **29** (17.36 g, 109 mmol) in dichloromethane (180 ml) at −40 °C. After 5 min, a solution of 2,6-lutidine (15.6 ml, 134 mmol) in dichloromethane (20 ml) was added over a period of 20 min at −40 °C. The mixture was then stirred at 0 °C for 16 h and diluted with dichloromethane (200 ml). The organic solution was washed with diluted 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 distillaton to give **30** (29.9 g, 100%). – B. p. 83–84 °C/0.1 Torr; $[\alpha]_D$ = −19.4 (*c* = 2.0). – IR ($CHCl_3$): 1720 (C=O). – ^{1}H NMR (300 MHz): δ = 0.58 [q, *J* = 7.7 Hz, 6H, $Si(CH_2Me)_3$], 0.89 (t, *J* = 7.4 Hz, 3H, CCH_2CH_3), 0.94 [t, *J* = 7.7 Hz, 9H, $Si(CH_2CH_3)_3$], 1.15 (d, *J* = 6.2 Hz, 3H, CH_3CH), 1.26 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.50–1.58 (m, 2H, CCH_2Me), 2.30 (ddd, *J* = 9.4, 7.6, and 5.3 Hz, 1H, $CHCO_2$), 4.01 (dq, *J* = 7.5 and 6.2 Hz, 1H, CH–OSi), 4.13 (q, *J* = 7.2 Hz, 2H, OCH_2). – MS: *m/z* = 246 (12%, M^+ – C_2H_4), 245 (64%, M^+ – Et), 159 (21%, $MeCHOSiEt_3$), 131 (76%, $OSiEt_3$), 115 (51%, $SiEt_3$ or $MeCH_2CHCO_2Et$), 103 (100%, $HOSiEt_2$), 75 (40%, $HOSiEt_2$ – C_2H_4).

$C_{14}H_{30}O_3Si$ (274.5) Calcd. C 61.26 H 11.02 Found C 61.17 H 10.81

(2S,3R)-2-Ethyl-3-triethylsilyloxy-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%). − B. p. 79.5−81.5°C/0.08 Torr; $[\alpha]_D = -10.8$ ($c = 1.02$). − IR ($CHCl_3$): 3600−3150 (O−H). − ^{1}H NMR (300 MHz): δ = 0.62 [q, J = 8.0 Hz, 6H, $Si(CH_2Me)_3$], 0.95 (t, J = 7.4 Hz, 3H, CCH_2CH_3), 0.97 [t, J = 8.1 Hz, 9H, $Si(CH_2CH_3)_3$], 1.26 (d, J = 6.3 Hz, 3H, CH_3CH), 1.16−1.28 (m, 1H, $CHCH_2O$), 1.36−1.58 (m, 2H, CCH_2Me), 3.13−3.16* (br., 1H, OH), 3.56−3.64 (m, 1H, CH_AH_BO), 3.90−4.00 (m, 2H, CH−OSi and CH_AH_BO). − MS: m/z = 217 (10%, M^+ − Me), 203 (14%, M^+ − Et), 159 (23%, $MeCHOSiEt_3$), 131 (7%, $OSiEt_3$), 115 (21%, $SiEt_3$), 103 (100%, $HOSiEt_2$), 75 (70%, $HOSiEt_2 - C_2H_4$).

$C_{12}H_{28}O_2Si$ (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** (2.51 g, 84%). − B. p. 68.5−70°C/0.09 Torr; $[\alpha]_D = -21.2$ ($c = 1.12$). − IR (film): 2720 (H−CO), 1723 (C=O). − ^{1}H NMR (300 MHz): δ = 0.59 [q, J = 7.6 Hz, 6H, $Si(CH_2Me)_3$], 0.91 (t, J = 7.5 Hz, 3H, CCH_2CH_3), 0.95 [t, J = 7.7 Hz, 9H, $Si(CH_2CH_3)_3$], 1.22 (d, J = 6.3 Hz, 3H, CH_3CH), 1.48−1.62 (m, 1H, CH_AH_BMe), 1.65−1.80 (m, 1H, CH_AH_BMe), 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−OSi), 9.69 (d, J = 3.7 Hz, 1H, CH=O). − MS: m/z = 229 (1%, M^+ − H), 202 (9%, $M^+ - C_2H_4$ or M^+ − CO), 201 (53%, M^+ − CHO or M^+ − Et), 159 (9%, $MeCHOSiEt_3$), 115 (14%, $SiEt_3$ or $M^+ - SiEt_3$), 103 (100%, $HOSiEt_2$), 98 (16%, $M^+ - SiEt_3OH$), 75 (94%, $HOSiEt_2 - C_2H_4$).

$C_{12}H_{26}O_2Si$ (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 chlorotrimethylsilane (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 × 100 ml). The combined organic extracts were wahed with cold saturated ammonium chloride solution (3 × 100 ml) and with saturated sodium hydrogen carbonate solution (100 ml), dried, filtered, and fractionally distilled through a *Vigreux* column (20 cm) to remove the solvents,

the residue was then fractionally distilled through a spaltrohrkolonne (supplier: *Fischer*) to give **33** (13.7 g, 45%) as an oil[88], b. p. 115–119°C. – IR ($CHCl_3$): 1630 (C=CH_2), 1250 ($SiMe_3$). – ^{1}H NMR (90 MHz): δ = 0.20 (s, 9H, $SiMe_3$), 1.00 (t, *J* = 7 Hz, 3H, CH_3), 2.00 (t, *J* = 7 Hz, 2H, CH_2C=C), 4.03 (br., 2H, C=CH_2). – MS: *m/z* = 144 (17%, M^+), 129 (33%, M^+ – Me), 73 (24%, $SiMe_3$), 28 (100%).

$C_7H_{16}OSi$ (144.3) Calcd. C 58.27 H 11.18 Found C 58.19 H 11.13

(5R,6R,7R)-5-(tert-Butyldimethylsilyloxy)-6-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-trimethylsilyloxy-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 × 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): δ = 0.61 [q, *J* = 8 Hz, 6H, $Si(CH_2Me)_3$], 0.96 [t, *J* = 8 Hz, 9H, $Si(CH_2CH_3)_3$], 0.80–1.18 (m, 8H, $CHCH_2CH_3$ and $COCH_2CH_3$), 1.28 (d, *J* = 7 Hz, 3H, CH_3CH-O), 1.25–1.60 (m, 1H, $CHCH_2Me$), 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 × 50 ml). The combined extracts were washed with water (50 ml), dried, filtered, and evaporated. The residue was chromatographed 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. p. 130–140°C/0.003 Torr; $[\alpha]_D$ = +27.8 (*c* = 1.89). – IR (film): 1720 (C=O). – ^{1}H NMR (300 MHz): δ = 0.00 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.60 [q, *J* = 8.1 Hz, 6H, $Si(CH_2Me)_3$], 0.86 [s, 9H, $SiC(CH_3)_3$], 0.94 (t, *J* = 8.0 Hz, 3H, $HCCH_2CH_3$), 0.97 [t, *J* = 8.0 Hz, 9H, $Si(CH_2CH_3)_3$], 1.05 (t, *J* = 7.3 Hz, 3H, $O=CCH_2CH_3$), 1.23 (d, *J* = 6.4 Hz, 3H, CH_3CH-O), 1.30–1.44 (m, 3H, $MeCH_2CH$), 2.44 (q, *J* = 7.3 Hz, 2H, $O=CCH_2Me$), 2.53 (dd, *J* = 15.7 and 4.3 Hz, 1H, $CH-CH_AH_BC=O$), 2.74 (dd, *J* = 15.7 and 7.8 Hz, 1H, $CH-CH_AH_BC=O$), 3.99 (dq, *J* = 6.4 and 3.6 Hz, 1H, $CHOSiEt_3$), 4.37–4.44 (m, 1H, $CH-OSiMe_2tBu$). – MS: *m/z* = 387 (1%, M^+ – Et), 255 (13%, M^+ – Et – $HOSiC_6H_{15}$), 159 (68%, $MeCHOSiEt_3$), 131 (19%, $OSiEt_3$), 115 (56%, $SiEt_3$), 87 (27%, $SiEt_3$ – C_2H_4), 75 (100%).

$C_{22}H_{48}O_3Si_2$ (416.8) Calcd. C 63.40 H 11.61 Found C 63.28 H 11.49

(2S,4R,5R,6R)-4-(tert-Butyldimethylsilyloxy)-2,5-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): δ = 0.05 (s, 6H, $SiMe_2$), 0.90 [s, 9H, $SiC(CH_3)_3$], 1.12 (d, *J* = 6 Hz, 3H, CH_3CH-O), 0.80–2.10 (m, 13H), 2.72–3.10* (br., 1H, OH), 3.58–4.08 (m, 2H, CH_3CH-O and CH_2CH-O).

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 etheral solvents were washed with phosphate buffer (pH = 7; 10 ml), dried, filtered, and evaporated to give the methoxy acetal **37** (85 mg, 77% based on **36**) as an oil; $[\alpha]_D = +42.4$ ($c = 0.79$). – ^{1}H NMR (300 MHz): $\delta = 0.07$ [s, 6H, $Si(CH_3)_2$], 0.85 (t, $J = 7.5$ Hz, 3H, CH_2CH_3), 0.86 (t, $J = 7.6$ Hz, 3H, CH_2CH), 0.88 [s, 9H, $SiC(CH_3)_3$], 1.13 (tt, $J = 10.4$ and 4.1 Hz, 1H, $CHCH_2Me$), 1.19 (d, $J = 6.3$ Hz, 3H, CH_3CH-O), 1.30 (dd, $J = 12.6$ and 10.6 Hz, 1H, $CH_{ax}H_{eq}CO-Si$), 1.46 [dq, $J = 14.3$ and 7.5 Hz, 1H, $(MeO)CCH_AH_BMe$], 1.48–1.66 (m, 2H, $CHCH_2Me$), 1.73 (dq, $J = 14.3$ and 7.6 Hz, 1H, $(MeO)CCH_AH_BMe$], 2.00 (dd, $J = 12.6$ and 5.0 Hz, 1H, $CH_{ax}H_{eq}CO-Si$), 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%, $M^+ - t$Bu – MeOH), 152 (36%, $M^+ -$ HOSi-tBuMe$_2$ – MeOH), 137 (10%, $M^+ -$ HOSitBuMe$_2$ – MeOH – Me), 123 (25%, $M^+ -$ HOSitBuMe$_2$ – MeOH – Et), 75 (100%), 57 (8%, tBu).

(2S,4R,5S,6R)-2,5-Diethyl-3,4,5,6-tetrahydro-4-hydroxy-2-methoxy-6-methyl-2H-pyran (**38**): Tetrabutylammonium 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 chromatographed on silica gel eluting with ether/hexane (1 : 1) to give **38** (41 mg, 94%; $R_F = 0.22$) as an oil; $[\alpha]_D = +64.4$ ($c = 1.04$). – IR (CCl_4): 3560–3300 (O–H). – ^{1}H NMR (300 MHz): $\delta = 0.87$ (t, $J = 7.6$ Hz, 3H, CH_2CH_3), 0.92 (t, $J = 7.6$ Hz, 3H, CH_2CH_3), 1.11 (tt, $J = 10.2$ and 3.9 Hz, 1H, $CHCH_2Me$), 1.21 (d, $J = 6.3$ Hz, 3H, CH_3CH-O), 1.31 (dd, $J = 12.5$ and 11.0 Hz, 1H, $CH_{ax}H_{eq}CH-O$), 1.34–1.41* (br., 1H, OH), 1.47 [dq, $J = 14.4$ and 7.5 Hz, 1H, $(MeO)CCH_AH_BMe$], 1.50–1.70 (m, 2H, $CHCH_2Me$), 1.77 [dq, $J = 14.3$ and 7.6 Hz, 1H, $(MeO)CCH_AH_BMe$], 2.14 (dd, $J = 12.4$ and 4.9 Hz, 1H, $CH_{ax}H_{eq}CH-O$), 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 – H_2O), 137 (6%, $M^+ -$ MeOH – Me – H_2O), 123 (21%, $M^+ -$ MeOH – Et – H_2O), 117 (100%).

[3E,5E,7S,8S,8(1S,2R,3S,6R,7R,8R),11E,13E,15S,16S,16(1S,2R,3S,6R,7R,8R)]- (**40a**), *[3E,5E,7S,8S,8(1S,2R,3S,6R,7R,8R),11E,13E,15S,16S,16(1S,2S,3R,6R,7R,8R)]-* (**40b**), *and [3E,5E,7S,8S,8(1S,2S,3R,6R,7R,8R),11E,13E,15S,16S,16(1S,2S,3R,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-3,5,11,13-tetraene-2,10-dione* (**40c**): Ethyldiisopropylamine (148 µl, 0.87 mmol) was added dropwise to a stirred solution of di-*n*-butylboron triflate (0.75 ml, 1.0 N 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 (CCl_4) (**40a**): 3700–3100 (O–H), 1710 (C=O), 1640 (C=C), 1613 (C=C). – ^{1}H NMR (300 MHz); **40a** (for numbering see formula at the beginning of the Experimental Part): δ = 0.03 (s, 6H, 2 SiMe), 0.05 (s, 6H, 2 SiMe), 0.50–0.64 [m, 12H, 2 Si(CH_2Me)$_3$], 0.83 [s, 18H, 2 SiC(CH_3)$_3$], 0.84–1.48 [m, 36H, 2 Si(CH_2CH_3)$_3$, 2 $CHCH_2CH_3$ and 2 CH_3], 1.04 (d, J = 6.7 Hz, 6H, 2 CH_3), 1.10 (d, J = 7.0 Hz, 6H, 2 CH_3), 1.22 (d, J = 6.5 Hz, 6H, 2 CH_3), 1.82–1.96 [m, 2H, 2 CH(1′)], 2.44–2.65 [m, 6H, 2 $H_AH_BC(5')$, 2 HC(3′), HC(7) and HC(15)], 2.91 [dd, J = 17 and 9 Hz, 2H, 2 $H_AH_BC(5')$], 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)].

^{1}H NMR (300 MHz); **40b** (for numbering see formula at the beginning of the Experimental Part): δ = –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(CH_2Me)$_3$], 0.80 [s, 9H, SiC(CH_3)$_3$], 0.83 [s, 9H, SiC(CH_3)$_3$], 0.84–1.46 [m, 35H, 2 $CHCH_2CH_3$, CH_3, 2 OH and 2 Si(CH_2CH_3)$_3$], 1.04 (d, J = 6.4 Hz, 3H, CH_3), 1.04 (d, J = 6.5 Hz, 3H, CH_3), 1.11 (d, J = 7.1 Hz, 3H, CH_3), 1.12 (d, J = 6 Hz, 3H, CH_3), 1.13 (d, J = 7.1 Hz, 3H, CH_3), 1.18 (d, J = 6.4 Hz, 3H, CH_3), 1.23 (d, J = 6.5 Hz, 3H, CH_3), 1.86–2.02 [m, 2H, HC(1′$_8$) and HC(1′$_{16}$)], 2.44–2.65 [m, 4H, HC(7), HC(15), HC(3′$_8$) and $H_AH_BC(5'_8)$], 2.66–2.82 [m, 2H, $H_AH_BC(5'_{16})$], 2.92 [dd, J = 17.0 and 8.2 Hz, 1H, $H_AH_BC(5'_8)$], 3.01 [dq, J = 2 and 7 Hz, 1H, HC(3′$_{16}$)], 3.70–3.80 [m, 2H, HC(2′$_8$) and HC(2′$_{16}$)], 3.90–4.04 [m, 2H, HC(8′$_8$) and HC(8′$_{16}$)], 4.34–4.44 [m, 2H,. HC(6′$_8$) and HC(6′$_{16}$)], 4.71 [dd, J = 9.7 and 1.1 Hz, 1H, HC(16)], 5.09 [dd, J = 10.5 and 1.2 Hz, 1H, CH(8)], 5.58 [d, J = 15.4 Hz, 1H, HC(11)], 5.60 [dd, J = 15.0 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 [dd, 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)].

^{1}H NMR (300 MHz); **40c** (for numbering see formula at the beginning of the Experimental Part): δ = –0.06 (s, 6H, 2 SiMe), 0.03 (s, 6H, 2 SiMe), 0.50–0.66 [m, 12H, 2 Si(CH_2Me)$_3$], 0.80 [s, 18H, 2 SiC(CH_3)$_2$], 0.80–1.50 [m, 30H, 2 $CHCH_2CH_3$ and 2 Si(CH_2CH_3)$_3$], 1.04 (d, J = 6.5 Hz, 6H, 2 CH_3), 1.12 (d, J = 6.6 Hz, 6H, 2 CH_3), 1.13 (d, J = 7.1 Hz, 6H, 2 CH_3), 1.18 (d, J = 6.4 Hz, 6H, 2 CH_3), 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 $H_AH_BC(5')$], 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)].

Methanolysis 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 ethereal 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 ($60F_{254}$) developing with ether/hexane (3 : 1) to give a homogenous fraction **8a** (0.7 mg, 16%; R_F =

0.28); $[\alpha]_D = +86 \pm 17$ ($c = 0.07$, CCl_4). 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 **8b** (1.1 mg, 48%; $R_F = 0.19$, ether/hexane = 3 : 1) as an oil. – ^{1}H NMR (300 MHz, C_6D_6); (for numbering see formula at the beginning of the Experimental Part): δ = 0.42* (br., 6H, 4 OH and 2 MeO*H*), 0.63 (d, $J = 6.8$ Hz, 3H, CH_3), 0.72 (d, $J = 6.6$ Hz, 3H, CH_3), 0.87 (d, $J = 6.6$ Hz, 3H, CH_3), 0.87 (d, $J = 6.6$ Hz, 3H, CH_3), 0.87 (t, $J = 7.4$ Hz, 3H, $CHCH_2CH_3$), 0.94 (t, $J = 7.5$ Hz, 3H, $CHCH_2CH_3$), 1.17 (d, $J = 5.7$ Hz, 3H, CH_3), 1.20–1.75 (m, 6H, 2 $CHCH_2$Me), 1.23 (d, $J = 6.0$ Hz, 3H, CH_3), 1.25 (d, $J = 5.9$ Hz, 3H, CH_3), 1.30 (d, $J = 7.0$ Hz, 3H, CH_3), 1.70–1.85 [m, 2H, H_{ax}(C3″$_8$) and H_{ax}C(3″$_{16}$)], 1.90–2.06 [m, 2H, HC(1′$_8$) and HC(1′$_{16}$)], 2.20–2.36 [m, 4H, HC(7), HC(15), HC(3′$_8$) and H_{eq}C(3″$_{16}$)], 2.50 [dq, $J = 1.5$ and 7 Hz, 1H, HC(3′$_{16}$)], 2.80 [dd, $J = 13.0$ and 4.5 Hz, 1H, H_{eq}C(3″$_8$)], 3.07 (s, 3H, OMe), 3.13 (s, 6H, 2 *Me*OH), 3.20 (s, 3H, OMe), 3.44 [dt, $J = 4.4$ and 10 Hz, 1H, HC(4″$_{16}$)], 3.52–3.65 [m, 2H, HC(4″$_8$) and HC(6″$_8$)], 3.69 [dq, $J = 10$ and 6.4 Hz, 1H, HC(6″$_{16}$)], 3.89–3.95 [m, 1H, HC(2′$_{16}$)], 4.11–4.17 [m, 1H, HC(2′$_8$)], 4.93 [dd, $J = 8.8$ and 1 Hz, 1H, HC(16)], 5.12 [dd, $J = 10$ and 1 Hz, 1H, HC(8)], 5.23 [dd, $J = 15.2$ and 9.3 Hz, 1H, HC(6)], 5.36 [dd, $J = 15.1$ and 9.7 Hz, 1H, HC(14)], 5.41 [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%; $R_F = 0.15$, ether/hexane = 3 : 1). – ^{1}H NMR (300 MHz, C_6D_6); (for numbering see formula at the beginning of the Experimental Part): δ = 0.42* (br., 6H, 4 OH and 2 MeO*H*), 0.73 (d, $J = 6.6$ Hz, 6H, 2 CH_3), 0.87 (d, $J = 6.5$ Hz, 6H, 2 CH_3), 0.87 (t, $J = 7.5$ Hz, 6H, 2 $CHCH_2CH_3$), 1.17 (d, $J = 5.5$ Hz, 6H, 2 CH_3), 1.20–1.68 (m, 6H, 2 $CHCH_2$Me), 1.26 (d, $J = 6.7$ Hz, 6H, 2 CH_3), 1.74 [dd, $J = 13.0$ and 10.6 Hz, 2H, 2 H_{ax}C(3″)], 1.95–2.06 [m, 2H, 2 HC(1′)], 2.30–2.40 [m, 4H, 2 H_{eq}(C3″), HC(7) and HC(15)], 2.49 [dq, $J = 1.6$ and 6.9 Hz, 2H, 2 HC(3′)], 3.13 (s, 6H, 2 *Me*OH), 3.20 (s, 6H, 2 MeO), 3.44 [dt, $J = 4.5$ and 11.0 Hz, 2H, 2 HC(4″)], 3.69 [dq, $J = 10.1$ 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 [d, $J = 15.4$ 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)].

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