

Synthesis and Conformational Analysis of Macrocyclic Dilactones Mimicking the Pharmacophore of Aplysiatoxin

by Henner Knust and Reinhard W. Hoffmann*

Fachbereich Chemie der Philipps Universität Marburg, D-35032 Marburg
(e-mail: rwho@chemie.uni-marburg.de; fax: +49 6421 2825677)

A small number of macrocyclic dilactones of type **3**, i.e., **9**, **10**, **11**, and epi-**11**, comprising a 3,4-dihydroxypentanoic acid unit, the pharmacophore of aplysiatoxin, and a conformationally preorganized ω -hydroxynonanoic acid unit were synthesized. Conformational analysis – based on 2J and 3J NMR coupling constants – of the dihydroxypentanoyl part of these macro-dilactones indicates the extent to which a conformation induction across the macro-dilactone ring occurs from the stereogenic centres implemented in the ω -hydroxynonanoic acid part.

Introduction. – Aplysiatoxin [1][2] (**1**) is a highly potent protein kinase C (PKC) activator, in which the (3*R*,4*R*)-3,4-dihydroxypentanoyl unit constitutes [3] the pharmacophore [1][2] (Fig. 1). This pharmacophore, the so-called recognition domain, mimics a 1,2-di-*O*-acylglycerol unit **2**, the physiological activator of PKC.

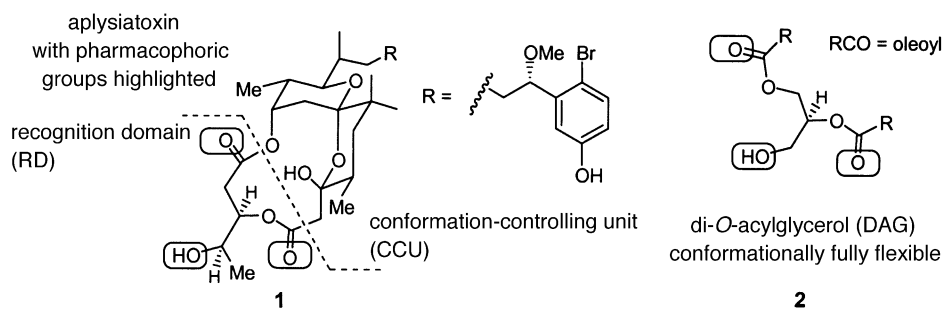


Fig. 1. Structure of Aplysiatoxin (**1**) and 1,2-Di-*O*-acylglycerol (**2**)

Aplysiatoxin (**1**) is *ca.* 50 times more active than di-*O*-oleoylglycerol **2** [4]. This has been ascribed to a disposition of the flexible recognition domain in a specific conformation of **1** optimal for binding to PKC. This disposition is realized by a conformation-controlling unit (CCU) of **1** (cf. Fig. 1) which serves as a template to hold the flexible recognition domain (RD) properly in space. Kishi and co-workers showed [2] that the same conformation prevails in solution as well as in the solid state. Therefore, the conformation found in the crystal structure of debromoaplysiatoxin [5] (Fig. 2) might represent the biologically active conformation.¹⁾

¹⁾ Arbitrary numbering; for systematic names, see *Exper. Part*.

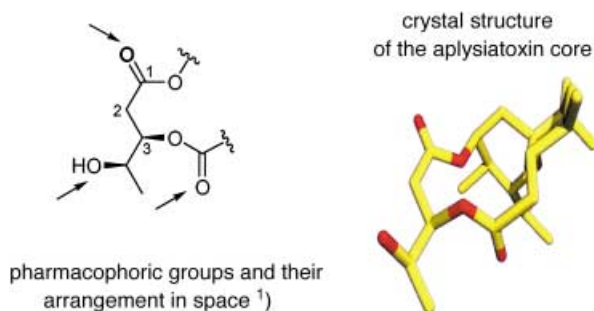


Fig. 2. Pharmacophoric groups and their arrangement in space as seen from the crystal structure of the debromo-aplysiatoxin core

From a chemical point of view, aplysiatoxin (**1**) is a macro-dilactone with a 12-membered ring, in which the conformation of a flexible section (the RD) is being controlled by the remaining, more rigid part of the ring. Transmission of conformational information across macrocyclic rings such as 14-membered macro-lactones has been demonstrated by *Still* and co-workers [6] and *Weiler* and co-workers [7]. The conformational transmission is aided by the fact that 14-membered rings have only few low-energy conformations [8]. This suggested to us that the recognition domain, the dihydroxypentanoyl unit of aplysiatoxin, could probably be conformationally controlled as well by incorporation into a much simpler 14-membered macro-dilactone such as **3**, derived from 3,4-dihydroxypentanoic acid and an ω -hydroxynonanoic acid [4] (Fig. 3). The nature of such an ω -hydroxynonanoic acid forms the object of this study. In the context of our interest in the conformation control of flexible structures [9], we wanted to find out which and how many rigidifying elements have to be incorporated into an ω -hydroxynonanoic acid to serve as a conformation-controlling unit in aplysiatoxin analogues of type **3**. The ability of the ω -hydroxynonanoic acid in macro-dilactones of type **3** to induce the dihydroxypentanoyl unit to adopt a conformation similar to that found in aplysiatoxin could be monitored by determining conformation-dependent 2J or 3J coupling constants in the NMR spectra.

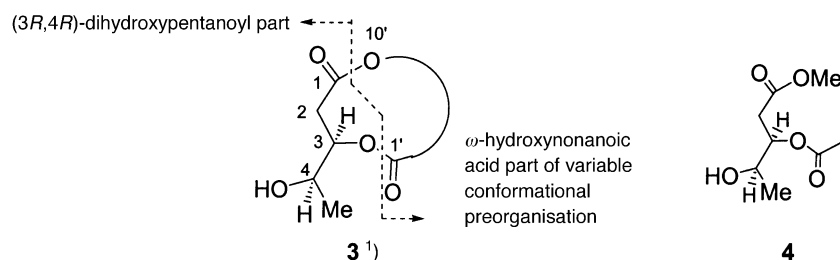
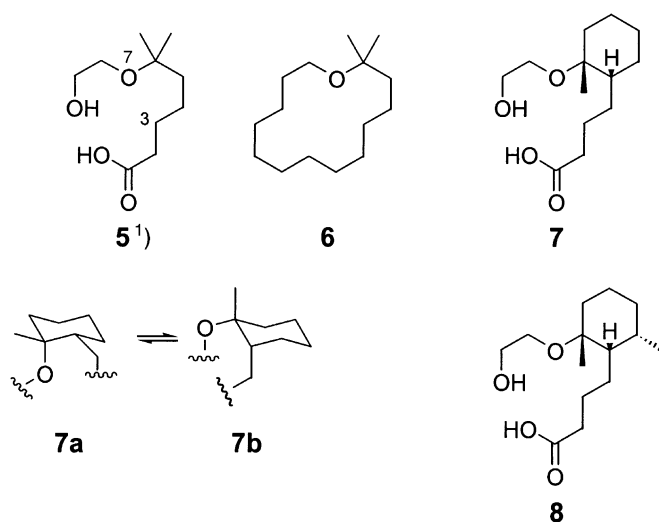


Fig. 3. Macro-dilactone **3** and conformationally unconstrained dihydroxypentanoyl model **4**

Aplysiatoxin itself shows a strong conformational preorganization at the C(2)–C(3) bond¹⁾ of the dihydroxypentanoyl unit. In contrast, the conformational preorganization at the C(3)–C(4) bond is moderate only [5]. The conformational

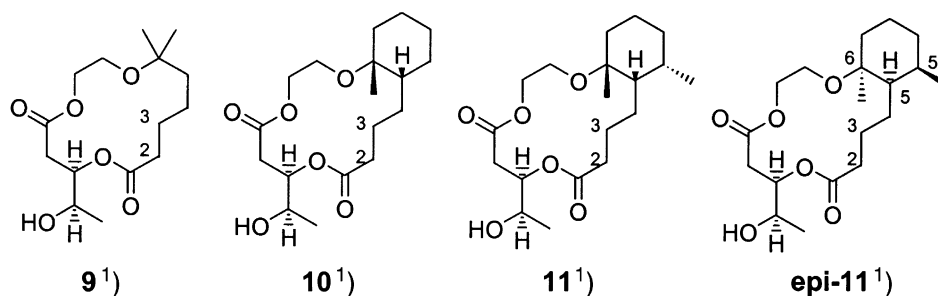
preferences of the dihydroxypentanoyl unit in the macro-dilactones **3** are then expected to be in-between that of aplysiatoxin itself and that of **4**, a model for a conformationally unconstrained dihydroxypentanoyl unit.

The choice of the ω -hydroxynonanoic acid **5** as a starting point for our study was inspired by the macrocyclic ether **6**, which populates a single low-energy conformation to *ca.* 90% [10]. In the preferred conformation of **6**, the *gem*-dimethyl moiety takes up a corner position in the ring. Hence, the *gem*-dimethyl moiety of **5** would mark one corner position of the macro-dilactone ring of **3** and should coincide with the *gem*-dimethyl moiety present in aplysiatoxin itself. Furthermore, the placement of an O-atom in position 7 of **5** would lessen any transannular interactions with CH₂(3), after incorporation into a macro-dilactone. As a further refinement of **5**, we considered the 'ring-fused' ω -hydroxynonanoic acid derivative **7**. Incorporation of one of the backbone bonds into a six-membered ring should introduce a certain sense of folding into the macro-dilactone derived from **7**. As will be seen later, the 'fused' cyclohexane ring in **7** takes up conformation **7a**. With the intent to study the effect of the other chair conformation **7b** as well, *i.e.*, of another folding pattern, a further Me group was placed at the ring, such as in compound **8**, which was also included in this study.



A different aspect comes into play as the components **7** and **8** are chiral. The sense of folding induced by these components on the derived macro-dilactones **3** could be reinforcing or counteracting the conformational preference resulting from the chiral dihydroxypentanoyl unit. To learn about such effects, we included also *ent*-**8** in this study.

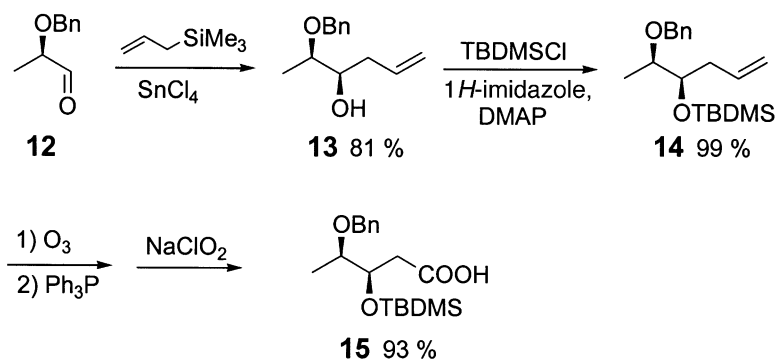
The set of compounds chosen for this study, therefore, comprises the macro-dilactones **9**, **10**, **11**, and 5,5',6-triepi-isomer¹⁾ epi-**11**. Admittedly, this set is rather limited. But the efforts involved in the synthesis of these macro-dilactones did not in the end permit the inclusion of further dilactones [11] into this study. What could be included, though, were the corresponding $\Delta^{2,3}$ -unsaturated systems¹⁾, which were part of the synthesis sequence.



Synthesis. – A convergent synthesis of the target molecules outlined above was initiated. It turned out that the synthesis of the individual building blocks was not a major problem. However, their assembly to the macro-dilactones met with considerable difficulties: The Achilles heel was the β -(acyloxy)pentanoyl unit with its high tendency towards base-induced elimination. This prevented macro-ring closure *via* a *Wadsworth–Horner–Emmons* reaction [11] at bonds C(2)–C(3) or interfered with deprotection schemes to generate macrolactonization precursors. In the long run, it was olefin metathesis to form a C=C bond between position 2 and 3 which turned out to be successful in closing the macro-dilactone rings.

Our standard building block for the dihydroxypentanoyl unit was the differentially protected acid **15** (*Scheme 1*). It was derived from the protected (*R*)-lactaldehyde **12** [12] by tin(IV) chloride catalyzed reaction with an allylsilane [13] to give **13**. Protection as (*tert*-butyl)dimethylsilyl ether ($\rightarrow$ **14**) was followed by oxidative cleavage of the C=C bond to furnish the acid **15**.

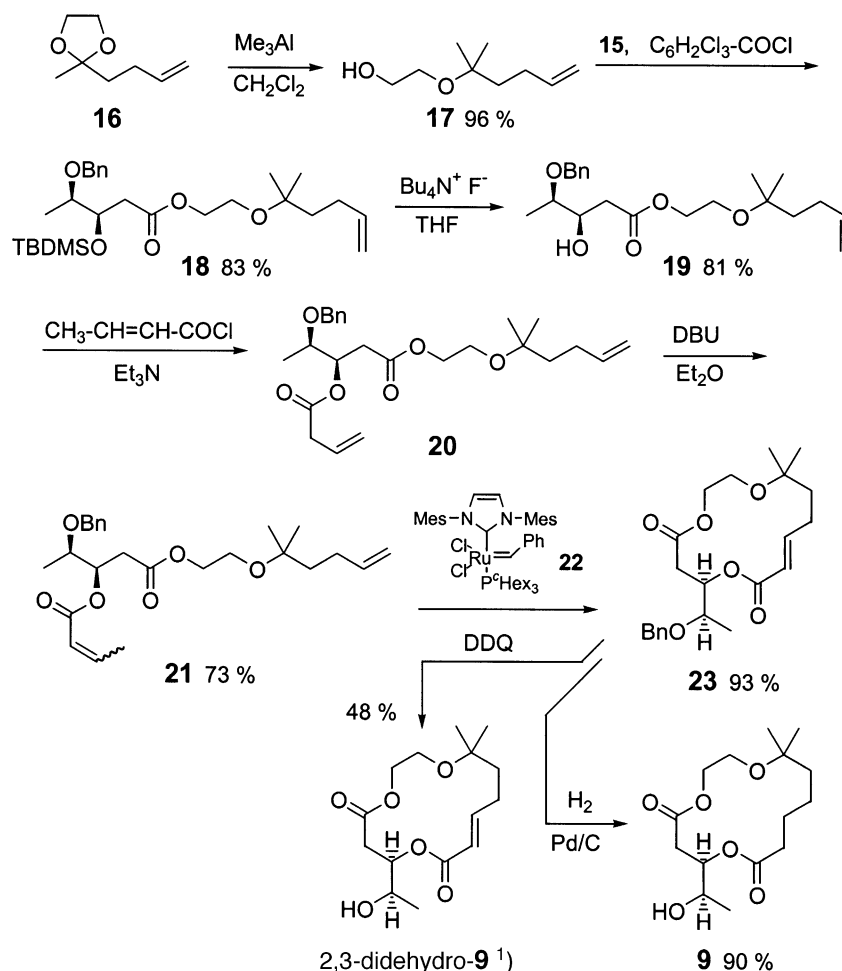
Scheme 1



TBDMS = ^tBuMe₂Si

The next intermediate in the synthesis of the macro-dilactone **9** was the building block **19** (*Scheme 2*). Its elaboration started from the dioxolane **16** [14]. Alkylative ring opening [15] with Me₃Al furnished the alkoxy alcohol **17** which was then esterified with the dihydroxypentanoic acid **15** under *Yamaguchi* activation [16] of the acid function. This resulted in 83% of the ester **18**. The silyl protecting group was then removed from **18** with (Bu₄N)F to give 81% of the β -hydroxy ester **19**.

Scheme 2

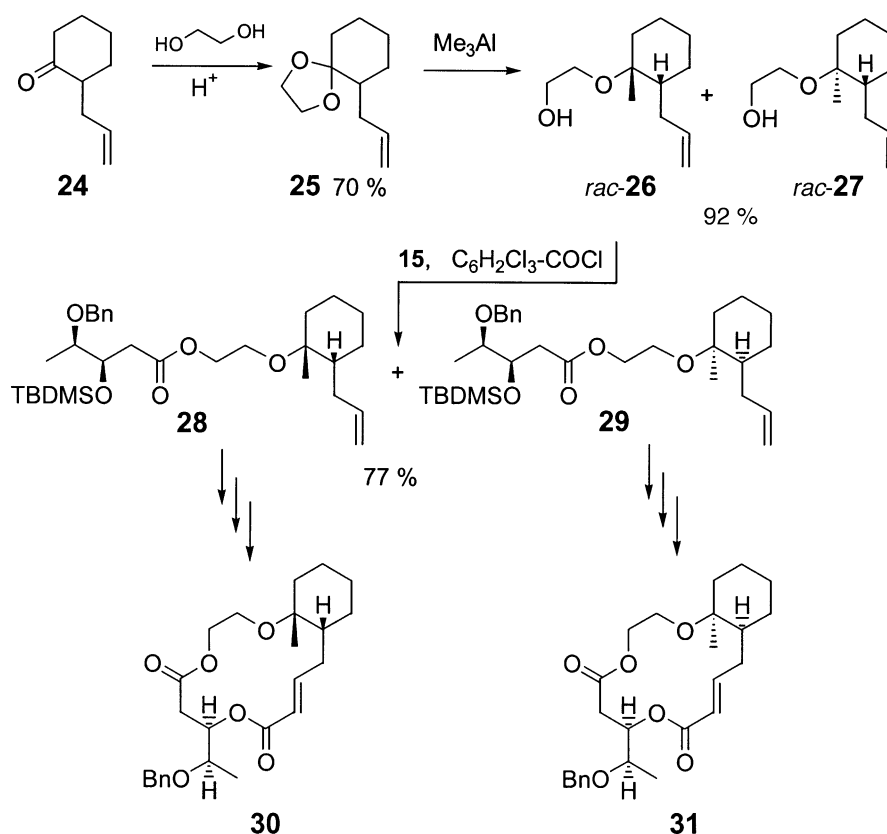


TBDMS = $\text{t-BuMe}_2\text{Si}$, Bn = PhCH_2 , DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Mes = MeSO_2 , DDQ = 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile

To prepare for ring-closing metathesis, we tried to esterify the hydroxy function of **19** with acryloyl chloride. This succeeded, if at all, in only low yield. Fortunately at that time, the second generation of *Grubbs* catalysts [17][18] became available, which are able to metathesize (*2E*)-but-2-enoates as well. With the intent to generate the (*2E*)-but-2-enoate **21**, we esterified **19** with (*2E*)-but-2-enoyl chloride and Et_3N . This reaction furnished, however, the but-3-enoate **20**, which fortunately could readily be isomerized to an (*E*)/(*Z*) mixture of the desired but-2-enoates **21** in 73% overall yield. Ring-closing metathesis of **21** with 0.02 equiv. of **22** as catalyst furnished 93% of the protected macro-dilactone **23**. The latter could be readily deprotected as indicated to give either **9** (90%) or 2,3-didehydro-**9** (48%).

A similar approach to **10** then relied on the building block *rac*-**26**: The latter was obtained from allylcyclohexanone **24** [19] via alkylative ring opening of the acetal **25** (Scheme 3). This led to 92% of a 2.2 : 1 mixture of diastereoisomers *rac*-**26** and *rac*-**27**. Assignment of the relative configuration rests on the chemical shift of the Me group, the one of the major product *rac*-**26** being equatorial ($\delta(\text{C})$ 23.7) and the one of the other diastereoisomer *rac*-**27** being axial ($\delta(\text{C})$ 18.3). The products were separated by chromatography. Coupling of *rac*-**26** with the enantiomerically pure building block **15** led in 77% (> 50%) yield by necessity to a mixture of diastereoisomeric coupling products **28** and **29**, although the spectra did not reveal that. After carrying the diastereoisomer mixture **28/29** on through the subsequent steps (the same as in the preparation of **9**), it was only after ring-closing metathesis that the diastereoisomers, a 1.65 : 1 mixture **30/31**, could be differentiated and separated.

Scheme 3



The major diastereoisomer **30** was carried forward as before to give **10** and 2,3-didehydro-**10** (Scheme 4). As **10** turned out to be crystalline, an X-ray crystal-structure secured its relative configuration as shown in Fig. 4. Moreover, the crystal structure shows the cyclohexane ring in a conformation related to **7a**. This conformation

Scheme 4

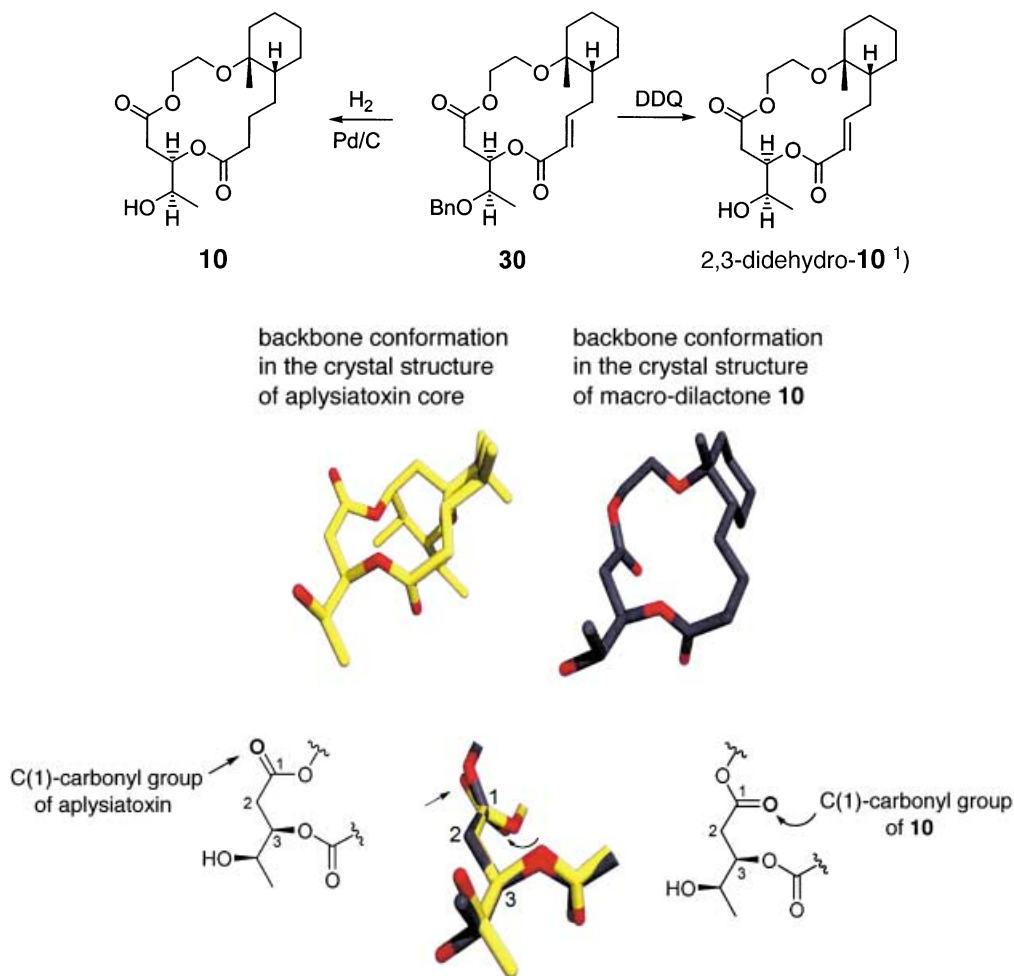
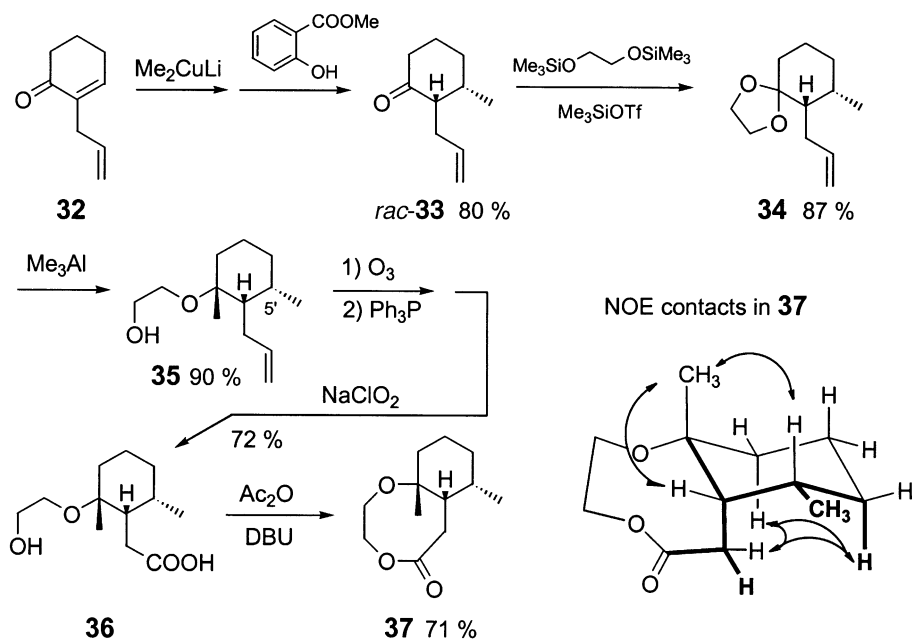


Fig. 4. Comparison of the backbone conformation of the dihydroxypentanoyl part of the aplysiatoxin core and of the macro-dilactone **10** as taken from the X-ray crystal structures¹⁾

apparently prevails also in solution, as the ^{13}C -NMR spectrum of **10** (and of the precursor molecules) shows a signal of an equatorial Me group ($\delta(\text{C})$ ca. 23).

The synthesis of the macro-dilactone **11** required compound **35** as a key building block. Its synthesis started by addition of $\text{Me}_2\text{CuLi} \cdot \text{LiI}$ to 2-allylcyclohexenone **32** [20] followed by diastereoselective protonation [21] of the resulting enolate by methyl salicylate to give 80% of *rac*-**33** as a 96:4 *cis/trans* mixture (Scheme 5). To avoid epimerization to the *trans* compound during acetalization, we applied the *Noyori* method [22] which furnished **34** as a 93:7 *cis/trans* mixture. Reductive alkylation of **34** as before gave alkoxy alcohol **35** as a >10:1 epimer mixture, from which pure **35** was obtained by chromatography. To secure the relative configuration at the stereogenic

Scheme 5

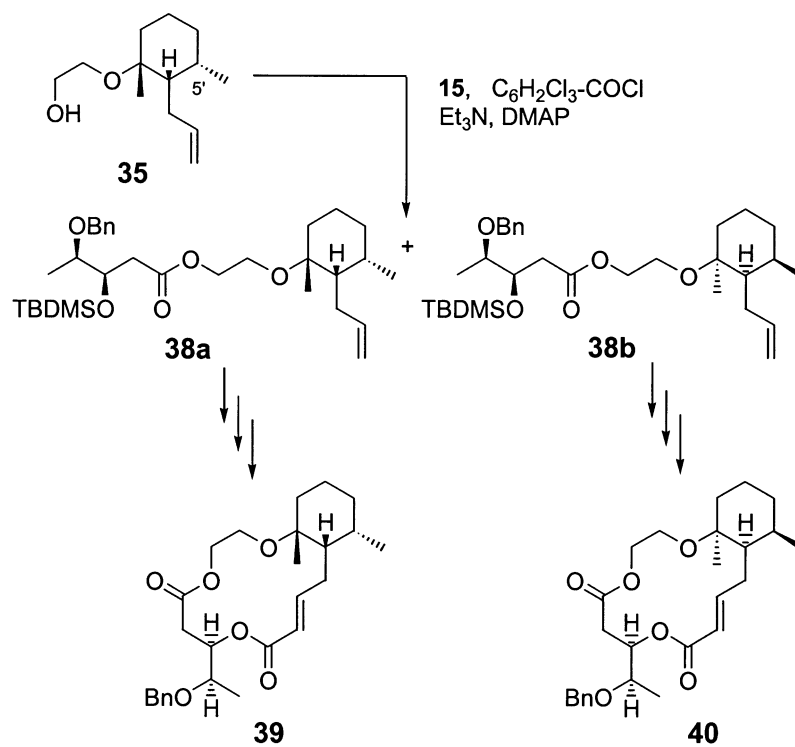


center formed in the reductive alkylation, the double bond of **35** was cleaved to furnish carboxylic acid **36** in a two-step process. Treatment of **36** with Ac_2O led to the formation of lactone **37**, which displayed characteristic NOE contacts that established the relative configuration of **35** as shown.

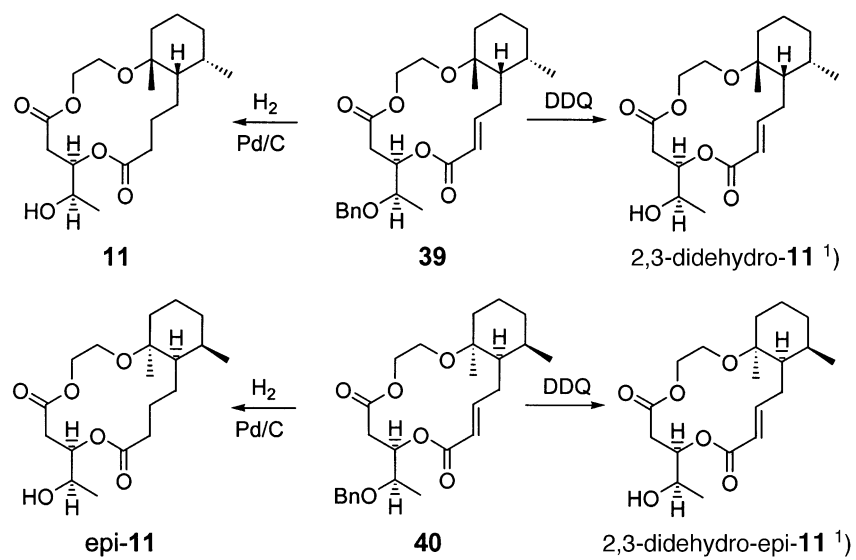
With the racemic building-block **35** in hand, the synthesis of **11** was attained in the usual fashion: Coupling with the enantiomerically pure dihydroxypentanoyl unit **15** proceeded in 79% yield (Scheme 6). The resulting product **38** must be a diastereoisomer mixture, without that being noticeable in the spectra. This mixture was then subjected to a reaction sequence of desilylation (66%), butenoylation (90%), and ring-closing metathesis (69%): This led to a 1.46:1 diastereoisomer mixture **39/40** (relative configuration not assigned) that could be separated by chromatography. Each isomer was carried forward to give **11** and 2,3-didehydro-**11** or epi-**11** and 2,3-didehydro-epi-**11** (Scheme 7).

The idea of having a Me group at C(5') in **35** was to favor the chair conformation **35b**, rather than conformation **35a** corresponding to **7a**, the conformation prevailing in **10** and its precursors (Scheme 8). However, the ^{13}C -NMR-signal positions of the Me groups of **35** (tertiary Me at δ 23.2 (*i.e.*, an equatorial position), secondary Me at δ 17.9 (*i.e.*, an axial position)) indicate that conformer **35a** prevails as – contrary to our expectations – Me–C(5') is not in a position to shift the conformer equilibrium from **35a** to **35b**. This holds also for all the compounds in this series up to the macro-lactonization step and results in a downfield shift of the signal of the secondary Me group (to δ *ca.* 20), whereas the signal of the tertiary Me group remains essentially constant. This indicates that the initially aspired chair conformation corresponding to

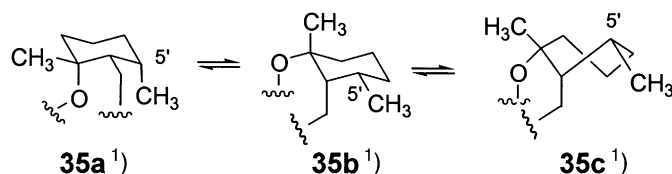
Scheme 6



Scheme 7



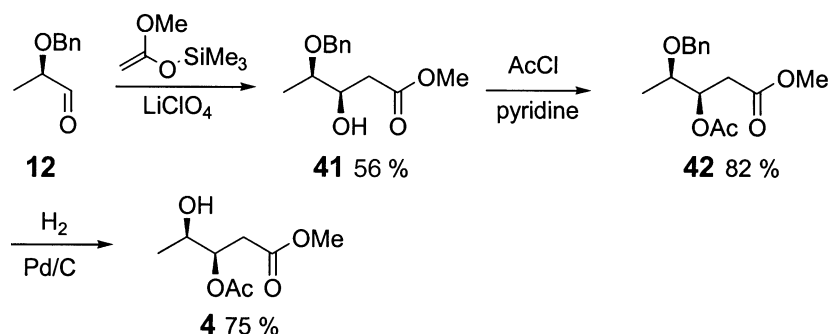
Scheme 8



35b is neither populated in the macro-dilactones **39** and **40**, *etc.*; rather the twist-boat conformation corresponding to **35c** may come into play.

Finally, we wanted to study compound **4** as a model for a conformationally non-preorganized dihydroxypentanoyl unit. The synthesis of **4** started also from the benzyl-protected lactaldehyde **12** (Scheme 9). LiClO_4 -Induced *Mukaiyama* aldol reaction furnished β -hydroxy ester **41** [23] in diastereoisomerically pure form (56%). The hydroxy group of **41** was acetylated to give **42**. Subsequent hydrogenolytic benzyl deprotection furnished the desired model compound **3**.

Scheme 9



Conformational Analysis of the Dihydroxypentanoyl Unit. – The (3*R*,4*R*)-3,4-dihydroxypentanoyl unit comprises the pharmacophore of aplysiatoxin and of the analogues discussed here (Fig. 5). The folding of the dihydroxypentanoyl unit may be characterized by the dihedral angles of rotation about the three backbone bonds C(1)–C(2), C(2)–C(3), and C(3)–C(4). When incorporated into aplysiatoxin or into the macro-dilactones described here, bonds C(1)–C(2) and C(2)–C(3) are endocyclic, bond C(3)–C(4) is exocyclic.

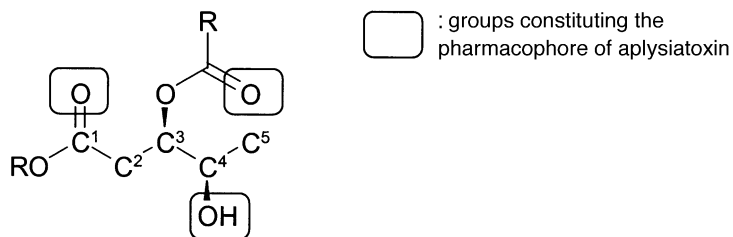


Fig. 5. (3*R*,4*R*)-Dihydroxypentanoyl unit comprising the pharmacophores of aplysiatoxin

A detailed conformational analysis about individual conformationally flexible bonds can be based on the determination of 2J or 3J NMR coupling constants. *Murata* and co-workers have recently shown how powerful this method is for oxygenated alkane chains [24] (*cf.* also [25]). Conformational analysis by this method of the dihydroxypentanoyl part of the molecules of interest here is limited to an analysis of the situation at bonds C(2)–C(3) and C(3)–C(4). Regarding these two bonds, a total of nine diamond-lattice-type conformations are possible which are depicted in *Fig. 6*.

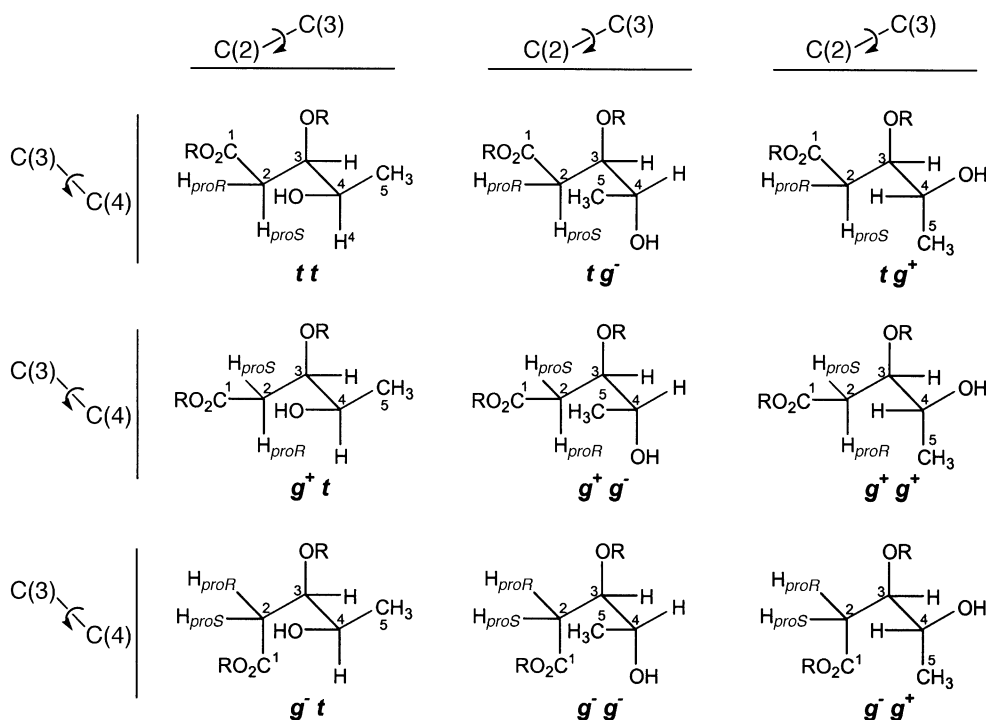


Fig. 6. Diamond-lattice-type conformations of the dihydroxypentanoyl unit

Conformational analysis of the situation at bond C(2)–C(3) looks simple at first, as any coupling-constant pair of either $^3J(\text{H}, \text{H}')$ and $^2J(\text{C}, \text{H})$ or $^3J(\text{C}, \text{H}')$ across this bond would suffice to identify a preferred conformation, provided that the individual signals of the diastereotopic protons $\text{H}_{\text{proR}}-\text{C}(2)$ and $\text{H}_{\text{proS}}-\text{C}(2)$ can be assigned. Their assignment is, however, not given *a priori*. We therefore resorted to an expanded set of 6 coupling constants characteristic for the situation at bond C(2)–C(3). These comprise also $^2J(\text{C}, \text{H})$ coupling constants to C(3) which are diagnostic as C(3) bears an electronegative atom [24] [26]. As the compilation of the characteristic magnitudes of these coupling constants in *Table 1* shows, this leads to a self-consistent picture which implies an assignment of the chemical shifts to $\text{H}_{\text{proR}}-\text{C}(2)$ and $\text{H}_{\text{proS}}-\text{C}(2)$.

Table 1. Predicted [24][27] Magnitude of the Various Conformation-Characteristic Coupling Constants of the Dihydroxypentanoyl Unit

Bond ^{a)}	Coupling constant	Conformation		
		<i>t</i>	<i>g</i> ⁺	<i>g</i> [−]
C(2)–C(3)	³ <i>J</i> (H _{proR} –C(2),H–C(3))	large ^{b)}	small ^{c)}	small ^{c)}
	³ <i>J</i> (H _{proS} –C(2),H–C(3))	small ^{c)}	small ^{c)}	large ^{b)}
	² <i>J</i> (C(3),H _{proR} –C(2))	large ^{d)}	small ^{c)}	large ^{d)}
	² <i>J</i> (C(3),H _{proS} –C(2))	small ^{c)}	large ^{d)}	large ^{d)}
	³ <i>J</i> (C(4),H _{proR} –C(2))	small ^{f)}	small ^{f)}	large ^{g)}
	³ <i>J</i> (C(4),H _{proS} –C(2))	small ^{f)}	large ^{g)}	small ^{f)}
C(3)–C(4)	³ <i>J</i> (H–C(3),H–C(4))	small ^{c)}	large ^{b)}	small ^{c)}
	² <i>J</i> (C(4),H–C(3))	small ^{d)}	large ^{c)}	large ^{c)}
	² <i>J</i> (C(3),H–C(4))	small ^{d)}	large ^{c)}	large ^{c)}
	³ <i>J</i> (C(5),H–C(3))	small ^{f)}	small ^{f)}	large ^{g)}
	³ <i>J</i> (C(2),H–C(4))	small ^{f)}	small ^{f)}	large ^{g)}

^{a)} Numbering of the dihydroxypentanoyl unit. ^{b)} Large: 9–12 Hz. ^{c)} Small: 2–4 Hz). ^{d)} Large: 5–7 Hz. ^{e)} Small: 0–2 Hz. ^{f)} Small: 1–3 Hz. ^{g)} Large: 6–8 Hz.

Regarding the conformational analysis of bond C(3)–C(4), the situation is straightforward. Each backbone conformation leads to a different pattern (small/large) of ³*J*(H,H) and ³*J*(C,H). Actually, any combination of ³*J*(H,H) and one of the ³*J*(C,H) would suffice to identify a given conformation, provided it is populated to a large extent. When the ²*J*(C,H) to C(4) are considered as well, we have an overdetermined system as the compilation in Table 1 shows.

Experimentally, the ³*J*(H,H) coupling constants for the macrocyclic dilactones were directly taken from the ¹H-NMR spectra, and the ²*J*(C,H) and ³*J*(C,H) coupling constants were determined by HETLOC experiments [28]. The data are summarized in Table 2. A good criterion [29] for the extent of conformational preorganization at the C(2)–C(3) bond is the difference (alternation) between the ³*J*(H,H) coupling constants to the two diastereotopic protons at C(2). This difference is also listed in Table 2.

As outlined above, the assignment of the chemical shifts to the diastereotopic protons H_{proR}–C(2) and H_{proS}–C(2) was not given *a priori*. It could be derived from the total set of 6 coupling constants characteristic for the situation at bond C(2)–C(3). When this assignment was done for each of the compounds studied, a common picture emerged, in that H_{proR}–C(2) generally resonated downfield from H_{proS}–C(2) (Fig. 7).

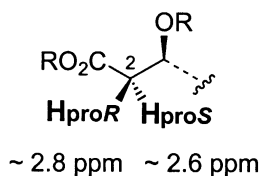


Fig. 7. Chemical shifts of the diastereotopic protons at C(2) of the dihydroxypentanoyl unit

The experimental coupling constants listed in Table 2 may then be compared with the predicted ones in Table 1. Two extremes can be noted: Aplysiatoxin (**1**) itself shows

Table 2. Coupling Constants [Hz] for the Dihydroxypentanoyl Part in **4**, the Macrocyclic Dilactones **9**, **10**, **11**, and epi-**11**, and Aplysiatoxin (**1**) [2][5]^a

Bond ¹⁾	Coupling constant	1	4	9	10	11	epi- 11
C(2)–C(3)	³ J(H _{proR} –C(2),H–C(3))	12.0 (l)	5.5 (m)	3.2 (s)	7.8 (l)	9.2 (l)	3.4 (s)
	³ J(H _{proS} –C(2),H–C(3))	2.0 (s)	7.5 (m)	7.5 (m)	3.8 (s)	2.3 (s)	8.1 (l)
	⁴ J(H–C(2),H–C(3))	10.0	2.0	4.9	4.0	6.9	4.7
	² J(C(3),H _{proR} –C(2))		3.4 (m)	1.9 (s)	4.6 (l)	6.1 (l)	2.2 (s)
	² J(C(3),H _{proS} –C(2))		4.4 (l)	5.1 (l)	1.7 (s)	2.1 (s)	4.9 (l)
	³ J(C(4),H _{proR} –C(2))		3.2 (m)	2.9 (s)	3.4 (s)	2.7 (s)	1.0 (s)
	³ J(C(4),H _{proS} –C(2))		3.2 (m)	7.1 (l)	n.d.	3.1 (s)	2.9 (s)
	³ J(H–C(3),H–C(4))	4.2 (m)	4.0 (m)	5.0 (m)	5.0 (m)	4.5 (m)	5.0 (m)
C(3)–C(4)	² J(C(4),H–C(3))		1.4 (s)	2.9 (s)	1.8 (s)	2.2 (s)	0.5 (s)
	² J(C(3),H–C(4))		0.4 (s)	1.9 (s)	0.3 (s)	2.2 (s)	2.1 (s)
	³ J(C(5),H–C(3))		2.2 (s)	1.9 (s)	2.2 (s)	2.0 (s)	2.6 (s)
	³ J(C(2),H–C(4))		0.9 (s)	1.2 (s)	2.2 (s)	n.d.	0.5 (s)
	Preferred conformation	<i>tt</i>	<i>g⁺t</i>	<i>g⁺t</i>	<i>tt</i>	<i>tt</i>	<i>g⁺t</i>

^a) m = medium, s = small, l = large, n.d. = not determined.

a very strong conformational preorganization at the C(2)–C(3) bond, whereas the conformational preorganization at the C(3)–C(4) bond is moderate only. The preferred conformation of the dihydroxypentanoyl unit was established as *tt*. On the other extreme is the open-chain dihydroxypentanoyl model compound **4** which shows a conformational mix (*vic.* the ‘middle’ values of the coupling constants) with a slight preference for the *g⁺t* conformer.

The values for the simple macro-dilactone **9** indicate a preference for the *g⁺t* conformation which is only marginally more marked than that for the model compound **4**. The fused macro-dilactone **10** shows a preference for the *tt* conformation of the dihydroxypentanoyl unit, albeit much smaller than that seen in **1** itself. In compound **11**, the preference for the *tt* conformation is substantial. Any interpretation, though, is hampered by the fact that we do not know the relative configuration of **11** and epi-**11**. The similarity of the coupling constants between **10** and **11** suggests that **11** may have the same relative configuration at the stereogenic centres as the structurally established **10**. But this remains an ill-founded speculation.

If it is the chirality of the ω -hydroxynonanoic unit in **11** that induces a strong preference for the *tt* conformation in the dihydroxypentanoyl part, it is not astonishing that the opposite chirality in the ω -hydroxynonanoic tether of epi-**11** should induce another conformational preference in the dihydroxypentanoyl unit. The latter prefers in epi-**11** a *g⁺t* conformation and, as the difference of the ³J(H,H) coupling constants to the diastereotopic protons at C(2) shows, even to a larger extent than in **11**.

In summary it becomes clear, that conformational induction across the macro-dilactone ring from the ω -hydroxynonanoic part to the dihydroxypentanoyl pharmacophore is substantial, especially in compounds **11**, despite the fact that the inducing stereogenic centers are few and remote. However, none of the compounds studied reached a level of conformational preorganization in the dihydroxypentanoyl unit as that displayed by aplysiatoxin (**1**) itself.

Increasing rigidity in the macro-dilactone ring should lead to enhanced conformational induction across the ring from the conformation-controlling ω -hydroxynonanoic

part to the dihydroxypentanoyl unit. For this reason, the data of the 2,3-didehydro derivatives are of interest, which are compiled in Table 3. Introduction of a C=C bond into compound **11**, which already has a significant conformational preorganization of the dihydroxypentanoyl part, to give 2,3-didehydro-**11** turned out to be without consequence. In the macro-dilactone **10**, however, introduction of the C=C bond (*i.e.*, going to 2,3-didehydro-**10**) brings a substantial increase in the population of the *tt* conformer as evidenced by the Δ^3J value of 7.5 Hz, approaching that of aplysiatoxin (**1**) itself. Apparently rigidification of the ring by the C=C bond favors the *tt* arrangement of the dihydroxypentanoyl unit. Thus, 2,3-didehydro-**9** and 2,3-didehydro-*epi*-**11** now also adopt the *tt* conformation, rather than the *g⁺t* one recorded for **9** and *epi*-**11**. It is, therefore, evident that remote conformational control of the dihydroxypentanoyl pharmacophore unit in simple aplysiatoxin analogues of the type **3** is principally possible.

Table 3. Coupling Constants [Hz] for the Dihydroxypentanoyl Part in **3**, the Macrocyclic Unsaturated Dilactones 2,3-Didehydro-**9**, 2,3-Didehydro-**10**, 2,3-Didehydro-**11**, 2,3-Didehydro-*epi*-**11**, and Aplysiatoxin (**1**)^a

Bond ^b)	Coupling constant	1	3	2,3-didehydro- 9 ¹)	2,3-didehydro- 10 ¹)	2,3-didehydro- 11 ¹)	2,3-didehydro- <i>epi</i> - 11 ¹)
C(2)–C(3)	$^3J(\text{H}_{\text{proR}}-\text{C}(2), \text{H}-\text{C}(3))$	12.0 (l)	5.5 (m)	8.8 (l)	10.5 (l)	8.9 (l)	9.3 (s)
	$^3J(\text{H}_{\text{proS}}-\text{C}(2), \text{H}-\text{C}(3))$	12.0 (s)	7.5 (m)	3.9 (s)	3.0 (s)	3.7 (s)	3.5 (s)
	$\Delta^3J(\text{H}-\text{C}(2), \text{H}-\text{C}(3))$	10.0	2.0	4.9	7.5	5.2	5.8
	$^2J(\text{C}(3), \text{H}_{\text{proR}}-\text{C}(2))$		3.4 (m)	5.4 (l)	n.d.	6.8 (l)	6.1 (l)
	$^2J(\text{C}(3), \text{H}_{\text{proS}}-\text{C}(2))$		4.4 (l)	2.1 (s)	n.d.	1.8 (s)	2.3 (l)
	$^3J(\text{C}(4), \text{H}_{\text{proR}}-\text{C}(2))$		3.2 (m)	1.9 (s)	n.d.	n.d.	2.1 (s)
	$^3J(\text{C}(4), \text{H}_{\text{proS}}-\text{C}(2))$		3.2 (m)	2.0 (s)	n.d.	n.d.	n.d.
	$^3J(\text{H}-\text{C}(3), \text{H}-\text{C}(4))$		4.0 (m)	5.2 (m)	5.0 (m)	5.2 (m)	5.3 (m)
	$^2J(\text{C}(4), \text{H}-\text{C}(3))$		1.4 (s)	1.7 (s)	n.d.	2.1 (s)	0.5 (s)
C(3)–C(4)	$^2J(\text{C}(3), \text{H}-\text{C}(4))$		0.4 (s)	1.4 (s)	n.d.	n.d.	1.2 (s)
	$^3J(\text{C}(5), \text{H}-\text{C}(3))$		2.2 (s)	1.7 (s)	n.d.	1.4 (s)	1.2 (s)
	$^3J(\text{C}(2), \text{H}-\text{C}(4))$		0.9 (s)	1.2 (s)	n.d.	n.d.	n.d.
	Preferred conformation		<i>tt</i>	<i>tt</i>	<i>tt</i>	<i>tt</i>	<i>tt</i>

^a) m = medium, s = small, l = large, n.d. = not determined. ^b) Numbering of the dihydroxypentanoyl unit¹).

But a shadow fell on this picture when the crystal structure of compound **10** became available: In line with the NMR studies, the dihydroxypentanoyl unit has the desired conformation at bonds C(2)–C(3) and C(3)–C(4) in the solid state, but another conformation at bond C(1)–C(2) than that in aplysiatoxin (**1**). An overlay of these structures in Fig. 4 (see above) illustrates this point.

Regarding the conformation at the C(1)–C(2) bond in solution, we have no experimental information other than the crystal structure for the solid state. Force-field (Macromodel) calculations [11] for **11** suggest that the desired conformation at the C(1)–C(2) bond is not likely to be populated in excess of 10%. Hence, further improvement of the conformation induction in macro-dilactones of type **3** could be guided by force-field calculations. This approach indicated [30] distinct modifications of the macro-dilactones studied here, which should permit to master the problems of conformation control of the pharmacophore moiety in aplysiatoxin analogues of type **3**.

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Experimental Part

General. Boiling range of petroleum ether: 40–60°. pH 7 Buffer: $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$ (56.2 g) and $\text{Na}_2\text{HPO}_4 \cdot 4\text{H}_2\text{O}$ (213.6 g) filled up to 1 l with H_2O . All temperatures quoted are uncorrected. Flash chromatography (FC): Silica gel *SI 60* (*E. Merck KGaA*, Darmstadt), 40–63 μm . NMR Spectra: *Bruker ARX-200*, *AC-300*, *WH-400*, and *AMX-500*; δ in ppm rel. to Me_4Si , *J* in Hz.

1. **(2*R*,3*R*)-2-(Benzyloxy)hex-5-en-3-ol (13).** To a soln. of (2*R*)-2-(benzyloxy)propanal (**12**; 3.458 g, 21.06 mmol) in CH_2Cl_2 (100 ml) at -78° , SnCl_4 (2.46 ml, 21.1 mmol) was added dropwise, and stirring was continued for 15 min. Allyltrimethylsilane (3.67 ml, 23.1 mmol) was added. After stirring for 2 h at -78° , the reaction was quenched by addition of H_2O (50 ml). After reaching r.t., the aq. layer was extracted with CH_2Cl_2 (5 $\times$ 30 ml). The combined extract was dried (Na_2SO_4) and evaporated and the residue submitted to FC (BuOMe/pentane 1:9): **13** (3.497 g, 81%). Colorless liquid. $[\alpha]_{\text{D}}^{20} = -54.1$ ($c = 2.2$, CHCl_3). $^1\text{H-NMR}$ (200 MHz, CDCl_3): 1.17 (*d*, $J = 6.0$, 3 H); 2.09–2.24 (*m*, 1 H); 2.24–2.42 (*m*, 1 H); 2.52 (*br. s*, 1 H); 3.35–3.58 (*m*, 2 H); 4.41 (*d*, $J = 11.5$, 1 H); 4.65 (*d*, $J = 11.5$, 1 H); 5.00–5.14 (*m*, 2 H); 5.74–5.98 (*m*, 1 H); 7.19–7.38 (*m*, 5 H). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): 15.3; 37.4; 70.9; 74.1; 77.4; 117.1; 127.6; 127.7 (2 C); 128.4 (2 C); 134.7; 138.2. The spectral data correspond to those given in [13].

2. **(4*R*,5*R*)-5-(Benzyloxy)-4-[[*tert*-butyl]dimethylsilyl]oxy]pent-1-ene (14).** At r.t., 1*H*-imidazole (4.09 g, 60.0 mmol) and *N,N*-dimethylpyridin-4-amine (DMAP; 611 mg, 5.00 mmol) were added to a soln. of **13** (2.06 g, 10.0 mmol) in DMF (120 ml). Then a soln. of (*tert*-butyl)chlorodimethylsilane (50% (*w/w*) in toluene; 9.04 g, 30.0 mmol) was added within 20 min. After heating 4.5 h to 40° , the mixture was poured into H_2O (1 l). The resulting soln. was extracted with BuOMe (4 $\times$ 150 ml), the combined extract washed with H_2O (150 ml) and brine (150 ml), dried (MgSO_4), and evaporated, and the residue submitted to FC (BuOMe/pentane 1:49): **14** (3.16 g, 99%). Colorless liquid. $[\alpha]_{\text{D}}^{20} = +0.04$ ($c = 16.4$, CHCl_3). $^1\text{H-NMR}$ (200 MHz, CDCl_3): -0.04 (*s*, 3 H); 0.00 (*s*, 3 H); 0.85 (*s*, 9 H); 1.12 (*d*, $J = 6.3$, 3 H); 2.01–2.20 (*m*, 1 H); 2.29–2.46 (*m*, 1 H); 3.50 (*dq*, $J = 4.8$, 6.4, 1 H); 3.66–3.77 (*m*, 1 H); 4.48 (*d*, $J = 12.0$, 1 H); 4.58 (*d*, $J = 12.0$, 1 H); 4.94–5.10 (*m*, 2 H); 5.68–5.94 (*m*, 1 H); 7.23–7.35 (*m*, 5 H). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): -4.54 ; -4.50 ; 14.0; 18.1; 25.8 (3 C); 36.3; 71.0; 73.8; 77.3; 116.5; 127.4; 127.5 (2 C); 128.3 (2 C); 136.1; 139.0. Anal. calc. for $\text{C}_{19}\text{H}_{32}\text{O}_2\text{Si}$ (320.5): C 71.19, H 10.06; found: C 71.23, H 10.04.

3. **(3*R*,4*R*)-4-(Benzyloxy)-3-[[*tert*-butyl]dimethylsilyl]oxy]pentanoic Acid (15).** A stream of ozone was introduced at -78° into a soln. of **14** (5.12 g, 16.0 mmol) in CH_2Cl_2 (100 ml) until the blue color persisted. Triphenylphosphine (6.28 g, 24.0 mmol) was added, and stirring was continued for 1.5 h at -78° . After warming to r.t., the mixture was adsorbed on silica gel (*ca.* 5 g) which was placed on top of a chromatography column. Elution with BuOMe/pentane 1:19 furnished the aldehyde (4.78 g, 93%). Colorless oil. $[\alpha]_{\text{D}}^{20} = -5.97$ ($c = 12.4$, CHCl_3). $^1\text{H-NMR}$ (200 MHz, CDCl_3): -0.02 (*s*, 3 H); 0.03 (*s*, 3 H); 0.85 (*s*, 9 H); 1.14 (*d*, $J = 6.4$, 3 H); 2.49 (*ddd*, $J = 15.9$, 7.6, 3.0, 1 H); 2.69 (*ddd*, $J = 15.9$, 4.4, 1.8, 1 H); 3.56 (*dq*, $J = 4.5$, 6.4, 1 H); 4.33 (*dt*, $J = 7.6$, 4.4, 1 H); 4.47 (*d*, $J = 12.0$, 1 H); 4.57 (*d*, $J = 12.0$, 1 H); 7.24–7.37 (*m*, 5 H); 9.78 (*dd*, $J = 3.0$, 1.8, 1 H). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): -4.9 ; -4.7 ; 13.4; 17.9; 25.7 (3 C); 45.9; 68.9; 70.9; 76.5; 127.6 (3 C); 128.3 (2 C); 138.4; 201.7.

The aldehyde obtained was taken up in BuOH (175 ml), and 2-methylbut-2-ene (92.0 ml, 868 mmol) was added. After stirring for 15 min at r.t., a soln. of NaClO_2 (14.3 g, 158 mmol) and $\text{NaH}_2\text{PO}_4 \cdot \text{H}_2\text{O}$ (13.5 g, 86.3 mmol) in H_2O (140 ml) was added dropwise. Upon stirring for 30 min, the initial yellow color disappeared. Sat. aq. NH_4Cl soln. (200 ml) was added, and the mixture was extracted with BuOMe (4 $\times$ 150 ml). The combined extract was washed with brine (200 ml), dried (MgSO_4), and evaporated, the residue taken up in pentane (5 ml), the soln. evaporated again, and the co-evaporation repeated (5 $\times$): **15** (5.00 g, 99%). Colorless oil. $[\alpha]_{\text{D}}^{20} = +17.6$ ($c = 12.3$, CHCl_3). $^1\text{H-NMR}$ (200 MHz, CDCl_3): 0.01 (*s*, 3 H); 0.03 (*s*, 3 H); 0.85 (*s*, 9 H); 1.15 (*d*, $J = 6.4$, 3 H); 2.42 (*dd*, $J = 15.3$, 8.3, 1 H); 2.71 (*dd*, $J = 15.3$, 3.8, 1 H); 3.58 (*dq*, $J = 4.6$, 6.4, 1 H); 4.22–4.33 (*m*, 1 H); 4.54 (*d*, $J = 11.8$, 1 H); 4.58 (*d*, $J = 11.8$, 1 H); 7.27–7.37 (*m*, 5 H). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): -5.0 ; -4.8 ; 13.3; 17.9; 25.7 (3 C); 36.8; 70.1; 71.0; 76.3; 127.6 (3 C); 128.3 (2 C); 138.4; 178.5. Anal. calc. for $\text{C}_{18}\text{H}_{30}\text{O}_4\text{Si}$ (338.5): C 63.87, H 8.93; found: C 63.74, H 8.80.

4. **2-[(1*i*,1-Dimethylpent-4-enyl)oxy]ethanol (17).** At 0° , 2*M* Me_3Al in heptane (10.0 ml, 20.0 mmol) was added to a precooled soln. of acetal **16** [14] (1.42 g, 10.0 mmol) in CH_2Cl_2 (30 ml). After stirring for 4 h at 0° , the mixture was heated to reflux for 6 h. The clear and colorless soln. was added in small portions to sat. aq.

potassium sodium tartrate soln. (150 ml). The aq. layer was extracted with Et₂O (3 × 100 ml) and the combined org. phase washed with brine (150 ml), dried (MgSO₄), and evaporated: **17** (1.51 g, 96%). Colorless liquid. ¹H-NMR (200 MHz, CDCl₃): 1.17 (s, 6 H); 1.51–1.63 (m, 2 H); 1.99–2.16 (m, 2 H); 2.01 (br. s, 1 H); 3.43 (br. t, *J* = 4.6, 2 H); 3.68 (br. t, *J* = 4.5, 2 H); 4.95 (br. d, *J* = 10.0, 1 H); 5.04 (br. d, *J* = 17.1, 1 H); 5.73–5.91 (m, 1 H). ¹³C-NMR (50 MHz, CDCl₃): 25.4 (2 C); 28.1; 39.3; 62.1; 62.2; 74.5; 113.9; 138.9. Anal. calc. for C₉H₁₈O₂ (158.2): C 68.31, H 11.47; found: C 68.09, H 11.59.

5. 2-[(1,1-Dimethylpent-4-enyl)oxy]ethyl (3*R*,4*R*)-4-(Benzyloxy)-3-[[tert-butyl(dimethylsilyl)oxy]pentanoate (**18**). DMAP (488 mg, 4.00 mmol) and Et₃N (558 μl, 4.00 mmol) were added at 0° to a soln. of **15** (676 mg, 2.00 mmol) and **17** (316 mg, 2.00 mmol) in toluene (50 ml). After stirring for 15 min at 0°, 2,4,6-trichlorobenzoyl chloride (625 μl, 4.00 mmol) was added dropwise within 20 s resulting in the formation of a white precipitate. After stirring vigorously for 10 min, sat. aq. NaHCO₃ soln. (80 ml) was added. The aq. layer was extracted with t-BuOMe (4 × 100 ml) and the combined org. phase washed with brine (200 ml), dried (MgSO₄), and evaporated. FC (t-BuOMe/pentane 1:9) furnished **18** (796 mg, 83%). Colorless liquid. $[\alpha]_D^{20} = +13.7$ (*c* = 11.8, CHCl₃). ¹H-NMR (200 MHz, CDCl₃): 0.00 (s, 3 H); 0.01 (s, 3 H); 0.84 (s, 9 H); 1.12 (d, *J* = 6.4, 3 H); 1.16 (s, 6 H); 1.50–1.59 (m, 2 H); 2.03–2.15 (m, 2 H); 2.40 (dd, *J* = 15.1, 8.8, 1 H); 2.66 (dd, *J* = 15.1, 3.5, 1 H); 3.46–3.58 (m, 1 H); 3.50 (br. t, *J* = 5.3, 2 H); 4.14 (dt, *J* = 5.3, 2.0, 2 H); 4.30–4.40 (m, 1 H); 4.52 (d, *J* = 12.0, 1 H); 4.57 (d, *J* = 12.0, 1 H); 4.93 (br. d, *J* = 10.3, 1 H); 5.01 (br. d, *J* = 17.1, 1 H); 5.83 (ddd, *J* = 17.1, 10.3, 6.7, 1 H); 7.27–7.36 (m, 5 H). ¹³C-NMR (50 MHz, CDCl₃): –5.0; –4.8; 13.3; 17.9; 25.5 (2 C); 25.7 (3 C); 28.1; 36.8; 39.1; 59.4; 64.2; 70.1; 70.9; 74.6; 76.4; 114.0; 127.4; 127.5 (2 C); 128.3 (2 C); 138.6; 139.0; 172.3. Anal. calc. for C₂₇H₄₆O₅Si (478.7): C 67.74, H 9.68; found: C 67.44, H 9.92.

6. 2-[(1,1-Dimethylpent-4-enyl)oxy]ethyl (3*R*,4*R*)-4-(Benzyloxy)-3-hydroxypentanoate (**19**). At 0°, 1*M* Bu₄NF in THF (1.20 ml, 1.21 mmol) was added over 15 min to a soln. of **18** (482 mg, 1.01 mmol) in THF (40 ml). After stirring for 1 h at 0° and 6.5 h at r.t., the mixture was evaporated and the residue submitted to FC (t-BuOMe/pentane 1:4): **19** (297 mg, 81%). Colorless liquid. $[\alpha]_D^{20} = +7.50$ (*c* = 8.36, CHCl₃). ¹H-NMR (200 MHz, CDCl₃): 1.16 (s, 6 H); 1.22 (d, *J* = 6.3, 3 H); 1.47–1.61 (m, 2 H); 2.00–2.16 (m, 2 H); 2.54 (d, *J* = 6.2, 1 H); 2.57–2.62 (m, 1 H); 2.95 (br. d, *J* = 5.0, 1 H); 3.51 (br. t, *J* = 5.1, 2 H); 3.54 (dq, *J* = 4.8, 6.3, 1 H); 4.01 (ddd, *J* = 11.1, 6.3, 4.9, 1 H); 4.19 (br. t, *J* = 5.0, 2 H); 4.48 (d, *J* = 11.8, 1 H); 4.68 (d, *J* = 11.8, 1 H); 4.87–5.07 (m, 2 H); 5.82 (ddd, *J* = 17.0, 10.3, 6.6, 1 H); 7.22–7.37 (m, 5 H). ¹³C-NMR (50 MHz, CDCl₃): 15.1; 25.4 (2 C); 28.1; 37.9; 39.1; 59.3; 64.4; 71.0 (2 C); 74.8; 76.5; 114.1; 127.66; 127.73 (2 C); 128.4 (2 C); 138.3; 139.0; 172.3. Anal. calc. for C₂₁H₃₂O₅ (364.5): C 69.20, H 8.85; found: C 68.84, H 9.14.

7. 2-[(1,1-Dimethylpent-4-enyl)oxy]ethyl (3*R*,4*R*)-4-(Benzyloxy)-3-(but-2-enoyloxy)pentanoate (**21**). Et₃N (486 μl, 3.48 mmol) and directly afterwards (2*E*)-but-2-enoyl chloride (technical grade, 90%; 204 μl, 1.92 mmol) were added at 0° to a soln. of **19** (635 mg, 1.74 mmol) in Et₂O (50 ml). After stirring for 1 h at 0° and 1 h at r.t.; Et₃N (486 μl, 3.48 mmol) and directly afterwards (2*E*)-but-2-enoyl chloride (technical grade, 90%; 204 μl, 1.92 mmol) were added again. Stirring was continued for 1.5 h, then H₂O (100 ml) was added. The aq. layer was extracted with Et₂O (3 × 100 ml) and the combined org. layer washed with brine (200 ml), dried (Na₂SO₄), and evaporated. FC (t-BuOMe/pentane 3:17) furnished **20**/(*E*)-**21**/(*Z*)-**21** (672 mg, 1.55 mmol, 89%). The mixture was taken up in Et₂O (30 ml). DBU (255 μl, 1.71 mmol) was added, and the suspension was stirred for 13.5 h. H₂O (50 ml) was added, the aq. layer extracted with Et₂O (3 × 50 ml), and the combined org. phase dried (Na₂SO₄) and evaporated. FC (t-BuOMe/pentane 1:4) furnished (*E*)-**21** (415 mg, 62%) and (*Z*)-**21** (137 mg, 20%).

Data of (*E*)-**21**: $[\alpha]_D^{20} = +2.39$ (*c* = 4.59, CHCl₃). ¹H-NMR (300 MHz, CDCl₃): 1.12 (s, 6 H); 1.13 (d, *J* = 6.5, 3 H); 1.46–1.55 (m, 2 H); 1.83 (dd, *J* = 7.0, 1.6, 3 H); 1.99–2.08 (m, 2 H); 2.63 (dd, *J* = 16.1, 8.3, 1 H); 2.74 (dd, *J* = 16.1, 5.0, 1 H); 3.44 (br. t, *J* = 5.0, 2 H); 3.75 (dq, *J* = 3.7, 6.5, 1 H); 4.10 (br. t, *J* = 5.3, 2 H); 4.49 (d, *J* = 11.7, 1 H); 4.59 (d, *J* = 11.7, 1 H); 4.90 (br. d, *J* = 10.3, 1 H); 5.01 (br. d, *J* = 16.9, 1 H); 5.42 (ddd, *J* = 4.6, 8.3, 3.9, 1 H); 5.73–5.87 (m, 2 H); 6.95 (dq, *J* = 15.1, 7.0, 1 H); 7.24–7.34 (m, 5 H). ¹³C-NMR (75 MHz, CDCl₃): 14.8; 17.9; 25.4 (2 C); 28.1; 34.6; 39.1; 59.3; 64.4; 71.0; 71.1; 73.7; 74.6; 114.0; 122.4; 127.6; 127.7 (2 C); 128.3 (2 C); 138.2; 139.0; 145.2; 165.5; 170.7. HR-MS (ESI): 455.2459 ([C₂₅H₃₆O₆ + Na]⁺; calc. 455.2410).

Data of (*Z*)-**21**: $[\alpha]_D^{20} = +2.08$ (*c* = 2.41, CHCl₃). ¹H-NMR (300 MHz, CDCl₃): 1.15 (s, 6 H); 1.17 (d, *J* = 6.5, 3 H); 1.50–1.58 (m, 2 H); 2.02–2.11 (m, 2 H); 2.14 (dd, *J* = 7.3, 2.0, 3 H); 2.66 (dd, *J* = 16.1, 8.3, 1 H); 2.78 (dd, *J* = 16.1, 5.0, 1 H); 3.48 (br. t, *J* = 5.1, 2 H); 3.79 (dq, *J* = 4.0, 6.5, 1 H); 4.14 (br. t, *J* = 5.3, 2 H); 4.53 (d, *J* = 11.7, 1 H); 4.63 (d, *J* = 11.7, 1 H); 4.93 (br. d, *J* = 10.3, 1 H); 5.00 (br. d, *J* = 17.1, 1 H); 5.46 (ddd, *J* = 5.0, 8.3, 4.0, 1 H); 5.80 (dq, *J* = 11.6, 2.0, 1 H); 5.76–5.90 (m, 1 H); 6.35 (dq, *J* = 11.6, 7.3, 1 H); 7.30–7.37 (m, 5 H). ¹³C-NMR (75 MHz, CDCl₃): 14.8; 14.9; 25.4 (2 C); 28.1; 34.6; 39.1; 59.3; 64.5; 70.7; 71.2; 73.8; 74.7; 114.1; 120.3; 127.6; 127.7 (2 C); 128.3 (2 C); 138.2; 139.0; 145.9; 165.4; 170.7. HR-MS (ESI): 455.2377 ([C₂₅H₃₆O₆ + Na]⁺; calc. 455.2410).

8. (7*R*,10*E*)-7-[(1*R*)-1-(Benzyloxy)ethyl]-14,14-dimethyl-1,4,8-trioxacyclotetradec-10-ene-5,9-dione (**23**). Ruthenium complex **22** [18] (22 mg, 26 μ mol) was added to a soln. of (*E*)- and (*Z*)-**21** (552 mg, 1.28 mmol) in CH_2Cl_2 (320 ml). After heating to reflux for 1 d, the mixture was evaporated and the residue submitted to FC ('BuOMe/pentane 3:17 $\rightarrow$ 3:7): **23** (348 mg, 93%). Colorless oil. $[\alpha]_D^{20} = +17.5$ ($c = 2.03$, CHCl_3). $^1\text{H-NMR}$ (300 MHz, CDCl_3): 1.13 (s, 3 H); 1.19 (*d*, $J = 6.4$, 3 H); 1.21 (s, 3 H); 1.66 (*ddd*, $J = 14.4$, 8.4, 4.6, 1 H); 1.74 (*ddd*, $J = 14.4$, 7.6, 4.7, 1 H); 2.19–2.43 (*m*, 2 H); 2.58 (*dd*, $J = 13.7$, 2.9, 1 H); 2.79 (*dd*, $J = 13.7$, 10.4, 1 H); 3.38–3.46 (*m*, 2 H); 3.81 (*dq*, $J = 4.8$, 6.4, 1 H); 4.00 (*ddd*, $J = 11.8$, 3.8, 5.6, 1 H); 4.32 (*ddd*, $J = 11.8$, 4.2, 3.0, 1 H); 4.55 (*d*, $J = 11.9$, 1 H); 4.64 (*d*, $J = 11.9$, 1 H); 5.31 (*ddd*, $J = 10.3$, 4.5, 3.0, 1 H); 5.67 (*dd*, $J = 15.6$, 0.7, 1 H); 7.20–7.30 (*m*, 1 H); 7.31–7.35 (*m*, 5 H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 14.8; 24.2; 25.5; 28.5; 35.3; 39.3; 59.1; 65.2; 71.2; 72.0; 74.1; 75.2; 119.5; 127.5; 127.7 (2 C); 128.3 (2 C); 138.2; 152.2; 165.7; 171.6. HR-MS (EI): 390.2034 ($\text{C}_{22}\text{H}_{30}\text{O}_6^+$; calc. 390.2042).

9. (7*R*)-7-[(1*R*)-1-Hydroxyethyl]-14,14-dimethyl-1,4,8-trioxacyclotetradecane-5,9-dione (**9**). Pd/C (10%; ca. 5 mg) was added to a soln. of **23** (30 mg, 77 μ mol) in THF (3 ml). The suspension was stirred for 1.5 h under 1 bar of H_2 . The mixture was filtered through a pad of silica gel and evaporated. FC ('BuOMe/pentane 1:1 $\rightarrow$ 1:0) furnished **9** (21 mg, 90%). Colorless oil. $[\alpha]_D^{20} = -29.5$ ($c = 2.15$, CHCl_3). $^1\text{H-NMR}$ (200 MHz, CDCl_3): 1.14 (s, 3 H); 1.16 (s, 3 H); 1.19 (*d*, $J = 6.8$, 3 H); 1.27–1.49 (*m*, 4 H); 1.54–1.71 (*m*, 2 H); 2.30–2.47 (*m*, 2 H); 2.35 (br. s, 1 H); 2.69 (*dd*, $J = 16.0$, 7.0, 1 H); 2.79 (*dd*, $J = 16.0$, 4.0, 1 H); 3.39–3.53 (*m*, 2 H); 3.92–4.08 (*m*, 1 H); 4.16 (*ddd*, $J = 11.8$, 3.3, 5.5, 1 H); 4.38 (*ddd*, $J = 11.8$, 5.1, 3.1, 1 H); 5.14 (*ddd*, $J = 6.8$, 5.0, 4.0, 1 H). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 19.0; 21.6; 25.2; 26.0; 26.5; 34.3; 36.0; 37.5; 59.7; 64.8; 68.4; 74.1; 74.2; 171.1; 171.3. HR-MS (EI): 302.1709 ($\text{C}_{15}\text{H}_{26}\text{O}_6^+$; calc. 302.1729).

10. (7*R*,10*E*)-7-[(1*R*)-1-Hydroxyethyl]-14,14-dimethyl-1,4,8-trioxacyclotetradec-10-ene-5,9-dione (2,3-didehydro-**9**). Molecular sieves (freshly powdered, 153 mg) and 2,3-dichloro-5,6-dicyanobenzoquinone (= 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile; DDQ; 173 mg, 768 μ mol) were added to a soln. of **23** (30 mg, 77 μ mol) in CH_2Cl_2 (12 ml). After refluxing the suspension for 1 d, sat. aq. NaHCO_3 soln. (20 ml) was added. The aq. layer was extracted with CH_2Cl_2 (4×10 ml), the combined extract washed with brine (25 ml), dried (Na_2SO_4), and evaporated, and the residue submitted to FC ('BuOMe/pentane 1:1): 2,3-didehydro-**9** (11 mg, 48%). Colorless oil. $[\alpha]_D^{20} = +10.7$ ($c = 1.68$, CHCl_3). $^1\text{H-NMR}$ (200 MHz, CDCl_3): 1.14 (s, 3 H); 1.21 (s, 3 H); 1.24 (*d*, $J = 6.5$, 3 H); 1.59–1.82 (*m*, 2 H); 2.24–2.42 (*m*, 3 H); 2.68 (*dd*, $J = 13.8$, 4.0, 1 H); 2.77 (*dd*, $J = 13.8$, 8.8, 1 H); 3.45 (br. *dd*, $J = 5.1$, 3.4, 2 H); 3.95 (br. *q*, $J = 6.0$, 1 H); 4.07 (*ddd*, $J = 11.9$, 5.3, 4.2, 1 H); 4.28 (*ddd*, $J = 11.9$, 4.1, 3.1, 1 H); 5.07 (*ddd*, $J = 8.8$, 5.2, 3.8, 1 H); 5.70 (*dt*, $J = 15.5$, 1.1, 1 H); 7.27 (*ddd*, $J = 15.5$, 9.8, 5.8, 1 H). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): 19.3; 24.1; 25.5; 28.6; 36.5; 39.5; 59.2; 65.5; 69.0; 74.8; 75.3; 119.3; 152.9; 166.3; 171.2. HR-MS (ESI): 323.1481 ($[\text{C}_{15}\text{H}_{24}\text{O}_6 + \text{Na}]^+$; calc. 323.1471).

11. (6*RS*)-6-Allyl-1,4-dioxaspiro[4.5]decane (**25**). Ethylene glycol (5.01 g, 80.7 mmol) and TsOH (ca. 100 mg) were added to a soln. of *rac*-2-allylcyclohexanone [19] (**24**, 9.32 g, 67.4 mmol) in toluene (80 ml). The soln. was heated to reflux for 20 h with azeotropic removal of the H_2O formed. The soln. was washed with sat. aq. NaHCO_3 soln. (50 ml) and H_2O (50 ml), dried (MgSO_4), and evaporated. Distillation (91°/106 mbar) [31] afforded **25** (9.69 g, 70%). Colorless liquid. $^1\text{H-NMR}$ (200 MHz, CDCl_3): 1.08–1.45 (*m*, 3 H); 1.48–1.90 (*m*, 7 H); 2.30–2.46 (*m*, 1 H); 3.85–3.99 (*m*, 4 H); 4.88–5.04 (*m*, 2 H); 5.62–5.86 (*m*, 1 H). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): 23.9; 24.6; 28.8; 32.9; 34.8; 44.3; 64.6; 64.8; 110.5; 115.3; 137.9. HR-MS (EI): 182.1306 ($\text{C}_{11}\text{H}_{18}\text{O}_2^+$; calc. 182.1307).

12. 2-[(1*RS*,2*RS*)- and (1*RS*,2*SR*)-2-Allyl-1-methylcyclohexyl]oxy]ethanol (*rac*-**26** and *rac*-**27**, resp.). At -78° , 2*M* Me_3Al in toluene (31.5 ml, 63.0 mmol) was added dropwise over 1.5 h to a precooled soln. of **25** (5.75 g, 31.6 mmol) in CH_2Cl_2 (50 ml). The mixture was allowed to reach r.t. over 12 h and was carefully stirred into sat. aq. potassium sodium tartrate soln. (400 ml). The aq. layer was extracted with CH_2Cl_2 (4×100 ml), the combined extract dried (Na_2SO_4) and evaporated, and the residue submitted to FC ('BuOMe/pentane 1:4): *rac*-**26** (3.93 g, 63%) and *rac*-**27** (1.84 g, 29%) as colorless liquids.

Data of *rac*-**26**: $^1\text{H-NMR}$ (200 MHz, CDCl_3): 1.16 (s, 3 H); 1.21–1.64 (*m*, 8 H); 1.81–2.02 (*m*, 2 H); 2.12 (br. s, 1 H); 2.29–2.41 (*m*, 1 H); 3.33–3.38 (*m*, 2 H); 3.64–3.69 (*m*, 2 H); 4.90–5.01 (*m*, 2 H); 5.76 (*dddd*, $J = 16.9$, 10.2, 8.3, 5.9, 1 H). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): 21.8; 23.7; 25.5; 26.6; 33.9; 34.6; 46.6; 61.0; 62.4; 74.8; 115.0; 138.8. Anal. calc. for $\text{C}_{12}\text{H}_{22}\text{O}_2$ (198.3): C 72.68, H 11.18; found: C 72.53, H 11.16.

Data of *rac*-**27**: $^1\text{H-NMR}$ (200 MHz, CDCl_3): 1.06 (s, 3 H); 1.15–1.75 (*m*, 9 H); 2.32–2.48 (*m*, 2 H); 3.38–3.46 (*m*, 2 H); 3.62–3.69 (*m*, 2 H); 4.89–5.01 (*m*, 2 H); 5.74 (*dddd*, $J = 16.6$, 10.5, 7.8, 6.0, 1 H). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): 18.3; 23.5; 25.0; 28.1; 34.1; 36.3; 44.1; 60.9; 62.3; 76.9; 115.1; 138.5. HR-MS (EI): 198.1576 ($\text{C}_{12}\text{H}_{22}\text{O}_2^+$; calc. 198.1619).

13. 2-[(1*R*,2*R*)- and (1*S*,2*S*)-2-Allyl-1-methylcyclohexyl]oxy]ethyl (3*R*,4*R*)-4-(Benzyloxy)-3-[(tert-butyl)dimethylsilyl]oxy]pentanoate (**28** and **29**, resp.). As described in *Exper.* 5, with **15** (338 mg, 1.00 mmol)

and *rac*-**26** (198 mg, 1.00 mmol). FC (BuOMe/pentane 1:19) furnished **28/29** (400 mg, 77%). Colorless oil. ¹H-NMR (200 MHz, CDCl₃): 0.01 (s, 3 H); 0.02 (s, 3 H); 0.84 (s, 9 H); 1.14 (d, *J* = 6.3, 3 H); 1.15 (s, 3 H); 1.23–1.52 (m, 7 H); 1.58–1.68 (m, 1 H); 1.79–1.99 (m, 2 H); 2.30–2.37 (m, 1 H); 2.39 (dd, *J* = 14.9, 8.8, 1 H); 2.66 (dd, *J* = 14.9, 3.7, 1 H); 3.40–3.49 (m, 2 H); 3.55 (qd, *J* = 6.3, 4.8, 1 H); 4.15 (br. t, *J* = 5.3, 2 H); 4.34 (ddd, *J* = 8.6, 4.2, 4.2, 1 H); 4.52 (d, *J* = 11.9, 1 H); 4.57 (d, *J* = 11.9, 1 H); 4.91–5.00 (m, 2 H); 5.76 (dddd, *J* = 17.0, 10.1, 8.0, 6.6, 1 H); 7.29–7.35 (m, 5 H). ¹³C-NMR (50 MHz, CDCl₃): –5.0; –4.8; 13.4; 17.9; 21.7; 23.5; 25.5; 25.7 (3 C); 26.4; 33.6; 34.5; 36.9; 46.6; 58.4; 64.2; 70.1; 70.9; 74.7; 76.4; 115.0; 127.4; 127.5 (2 C); 128.2 (2 C); 138.6; 138.9; 172.3. HR-MS (ESI): 541.3315 ([C₃₀H₅₀O₅Si + Na]⁺; calc. 541.3325).

14. [(1*R*,2*R*)- and (1*S*,2*S*)-2-Allyl-1-methylcyclohexyl]oxyethyl (3*R*,4*R*)-4-(Benzyloxy)-3-hydroxypentanoate. The mixture **28/29** (170 mg, 328 μmol) was treated as described in *Exper.* 6. FC (BuOMe/pentane 1:4 → 1:0) furnished the product (80 mg, 60%). Colorless oil. ¹H-NMR (200 MHz, CDCl₃): 1.15 (s, 3 H); 1.09–1.32 (m, 3 H); 1.23 (d, *J* = 6.4, 3 H); 1.33–1.51 (m, 3 H); 1.54–1.72 (m, 2 H); 1.75–2.03 (m, 2 H); 2.28–2.43 (m, 1 H); 2.53 (br. d, *J* = 6.3, 1 H); 2.55 (br. d, *J* = 6.3, 1 H); 3.89 (br. s, 1 H); 3.46 (br. t, *J* = 5.0, 2 H); 3.55 (dq, *J* = 4.8, 6.4, 1 H); 3.95–4.08 (m, 1 H); 4.21 (br. t, *J* = 5.1, 2 H); 4.46 (d, *J* = 11.8, 1 H); 4.66 (d, *J* = 11.8, 1 H); 4.90–5.04 (m, 2 H); 5.65–5.87 (m, 1 H); 7.22–7.41 (m, 5 H). ¹³C-NMR (50 MHz, CDCl₃): 15.0; 21.7; 23.4; 25.4; 26.4; 33.6; 34.5; 37.8; 46.5; 58.4; 64.4; 70.9 (2 C); 74.8; 76.5; 115.0; 127.6; 127.7 (2 C); 128.3 (2 C); 138.2; 138.8; 172.2. HR-MS (ESI): 427.2419 ([C₂₄H₃₆O₅ + Na]⁺; calc. 427.2460).

15. 2-[(1*R*,2*R*)- and (1*S*,2*S*)-2-Allyl-1-methylcyclohexyl]oxyethyl (3*R*,4*R*)-4-(Benzyloxy)-3-(but-2-enoyloxy)pentanoate. The alcohol obtained in *Exper.* 14 (400 mg, 988 μmol) was esterified with (2*E*)-but-2-enoyl chloride and isomerized as described in *Exper.* 7. FC (BuOMe/pentane 1:19 → 1:9) furnished the (2*E*)- (285 mg, 68%) and (2*Z*)-but-2-enoyl derivatives (100 mg, 22%) as colorless oils.

Data of (2E)-But-2-enoyl Derivative: ¹H-NMR (200 MHz, CDCl₃): 1.13 (s, 3 H); 1.16 (d, *J* = 6.5, 3 H); 1.08–1.30 (m, 3 H); 1.31–1.49 (m, 4 H); 1.52–1.70 (m, 1 H); 1.75–1.99 (m, 2 H); 1.86 (dd, *J* = 6.9, 1.6, 3 H); 2.26–2.42 (m, 1 H); 2.65 (dd, *J* = 16.2, 8.0, 1 H); 2.78 (dd, *J* = 16.2, 5.0, 1 H); 3.42 (br. t, *J* = 5.1, 2 H); 3.78 (dq, *J* = 4.0, 6.5, 1 H); 4.14 (br. t, *J* = 5.1, 2 H); 4.52 (d, *J* = 12.0, 1 H); 4.63 (d, *J* = 12.0, 1 H); 4.88–5.04 (m, 2 H); 5.40–5.51 (m, 1 H); 5.65–5.86 (m, 1 H); 5.90 (dq, *J* = 15.4, 1.5, 1 H); 6.99 (dq, *J* = 15.5, 6.9, 1 H); 7.24–7.37 (m, 5 H). ¹³C-NMR (50 MHz, CDCl₃): 15.1; 18.2; 22.0; 23.7; 25.7; 26.6; 33.9; 34.7; 34.8; 46.8; 58.6; 64.7; 71.4 (2 C); 73.9; 75.0; 115.2; 122.6; 127.8; 127.9 (2 C); 128.5 (2 C); 138.4; 139.1; 145.5; 165.8; 170.9. Anal. calc. for C₂₈H₄₀O₆ (472.6): C 71.16, H 8.53; found: C 70.97, H 8.62.

Data of (2Z)-But-2-enoyl Derivative: ¹H-NMR (200 MHz, CDCl₃): 1.14 (s, 3 H); 1.18 (d, *J* = 6.3, 3 H); 1.07–1.31 (m, 3 H); 1.32–1.51 (m, 4 H); 1.53–1.70 (m, 1 H); 1.75–2.00 (m, 2 H); 2.14 (dd, *J* = 7.3, 1.8, 3 H); 2.27–2.42 (m, 1 H); 2.65 (dd, *J* = 16.0, 8.0, 1 H); 2.79 (dd, *J* = 16.0, 5.1, 1 H); 3.43 (br. t, *J* = 5.3, 2 H); 3.79 (dq, *J* = 3.9, 6.3, 1 H); 4.15 (br. t, *J* = 5.1, 2 H); 4.53 (d, *J* = 11.8, 1 H); 4.64 (d, *J* = 11.8, 1 H); 4.89–5.03 (m, 2 H); 5.46 (ddd, *J* = 8.0, 5.1, 3.9, 1 H); 5.64–5.86 (m, 1 H); 5.84 (dq, *J* = 11.5, 1.8, 1 H); 6.35 (dq, *J* = 11.5, 7.3, 1 H); 7.23–7.39 (m, 5 H). ¹³C-NMR (50 MHz, CDCl₃): 14.9; 15.4; 21.7; 23.5; 25.5; 26.4; 33.6; 34.5; 34.6; 46.5; 58.3; 64.4; 70.7; 71.1; 73.7; 74.8; 115.0; 120.3; 127.6; 127.7 (2 C); 128.3 (2 C); 138.2; 138.9; 145.9; 165.4; 170.7. Anal. calc. for C₂₈H₄₀O₆ (472.6): C 71.16, H 8.53; found: C 70.83, H 8.36.

16. (7*R*,10*E*,12*aR*,16*aR*)-7-[(1*R*)-1-(Benzyloxy)ethyl]-2,3,6,7,12*a*,13,14,15,16,16*a*-decahydro-16*a*-methyl-5*H*-1,4,8-benzotrioxacyclotetradecine-5,9(12*H*)-dione (**30**) and (7*R*,10*E*,12*aS*,16*aS*)-7-[(1*R*)-1-(Benzyloxy)ethyl]-2,3,6,7,12*a*,13,14,15,16,16*a*-decahydro-16*a*-methyl-5*H*-1,4,8-benzotrioxacyclotetradecine-5,9(12*H*)-dione (**31**). The mixture of the butenoyl derivatives (285 mg, 638 μmol) obtained in *Exper.* 15 was cyclized as described in *Exper.* 8 in the presence of 5 mol-% of the catalyst. FC (BuOMe/pentane 1:9 → 1:4 → 3:7) furnished **30** (120 mg, 33%) and **31** (72 mg, 20%) as colorless oils.

Data of 30: [α]_D²⁰ = +27.5 (*c* = 9.93, CHCl₃). ¹H-NMR (200 MHz, CDCl₃): 1.13–1.17 (m, 3 H); 1.18 (d, *J* = 6.4, 3 H); 1.25 (s, 3 H); 1.35–1.46 (m, 2 H); 1.49–1.57 (m, 1 H); 1.65–1.79 (m, 2 H); 1.85–2.00 (m, 2 H); 2.54 (dd, *J* = 13.2, 2.2, 1 H); 2.64–2.74 (m, 1 H); 2.77 (dd, *J* = 13.3, 11.4, 1 H); 3.34 (br. d, *J* = 10.5, 1 H); 3.57 (br. t, *J* = 10.4, 1 H); 3.87 (qd, *J* = 6.3, 4.5, 1 H); 3.94 (br. d, *J* = 11.7, 1 H); 4.39 (br. t, *J* = 11.0, 1 H); 4.57 (d, *J* = 12.0, 1 H); 4.65 (d, *J* = 12.0, 1 H); 5.30 (ddd, *J* = 11.4, 3.2, 3.2, 1 H); 5.36 (d, *J* = 15.6, 1 H); 7.23–7.37 (m, 6 H). ¹³C-NMR (50 MHz, CDCl₃): 14.6; 21.4; 23.4; 26.3; 26.9; 34.0; 34.7; 35.2; 47.0; 57.9; 65.2; 71.2; 72.0; 73.8; 75.1; 119.4; 127.6; 127.8 (2 C); 128.3 (2 C); 138.2; 150.6; 165.9; 172.1. HR-MS (EI): 430.2384 (C₂₅H₃₄O₆⁺; calc. 430.2355).

Data of 31: [α]_D²⁰ = +1.26 (*c* = 3.96, CHCl₃). ¹H-NMR (200 MHz, CDCl₃): 1.09 (s, 3 H); 1.23 (d, *J* = 6.4, 3 H); 1.07–1.31 (m, 3 H); 1.32–1.48 (m, 3 H); 1.49–1.63 (m, 1 H); 1.74–1.94 (m, 1 H); 1.95–2.19 (m, 2 H); 2.58–2.82 (m, 3 H); 3.29 (br. dt, *J* = 11.1, 2.9, 1 H); 3.41 (ddd, *J* = 11.0, 7.3, 3.6, 1 H); 3.82 (dq, *J* = 5.3, 6.4, 1 H); 4.06–4.20 (m, 2 H); 4.55 (d, *J* = 11.9, 1 H); 4.66 (d, *J* = 11.9, 1 H); 5.26 (br. ddd, *J* = 8.4, 4.4, 4.4, 1 H); 5.59 (br. dd, *J* = 15.5, 2.0, 1 H); 7.22–7.39 (m, 6 H). ¹³C-NMR (50 MHz, CDCl₃): 15.2; 21.6; 22.7; 26.5; 27.2; 34.5;

35.2; 35.5; 46.4; 57.8; 65.4; 71.2; 72.0; 74.4; 75.4; 118.3; 127.5; 127.7 (2 C); 128.3 (2 C); 138.4; 151.4; 166.0; 171.5. HR-MS (EI): 430.2391 ($C_{25}H_{34}O_6^+$; calc. 430.2355).

17. (7R,12aR,16aR)-2,3,6,7,11,12,12a,13,14,15,16,16a-Dodecahydro-7-[(1R)-1-hydroxyethyl]-16a-methyl-5H-1,4,8-benzotrioxacyclotetradecine-5,9(10H)-dione (**10**). As described in *Exper. 9*, with **30** (30 mg, 70 μ mol): **10** (15 mg, 63%). Colorless oil. $[\alpha]_D^{20} = +11.1$ ($c = 2.07$, $CHCl_3$). 1H -NMR (200 MHz, $CDCl_3$): 1.14 (s, 3 H); 1.18 (d, $J = 6.4$, 3 H); 1.22–1.29 (m, 4 H); 1.31–1.42 (m, 3 H); 1.43–1.50 (m, 1 H); 1.50–1.59 (m, 3 H); 1.62–1.72 (m, 2 H); 2.23–2.29 (m, 1 H); 2.31–2.39 (m, 1 H); 2.65–2.74 (m, 3 H); 3.41 (dt, $J = 10.6$, 2.1, 1 H); 3.48 (td, $J = 10.3$, 1.8, 1 H); 3.89 (br. d, $J = 11.8$, 1 H); 3.95 (qd, $J = 6.3$, 5.0, 1 H); 4.69 (br. t, $J = 10.4$, 1 H); 5.25 (ddd, $J = 7.8$, 4.9, 3.8, 1 H). ^{13}C -NMR (50 MHz, $CDCl_3$): 19.1; 22.0; 23.4; 24.1; 24.3; 27.0; 28.2; 34.4; 35.77; 35.81; 45.2; 58.8; 64.0; 68.5; 73.7; 75.2; 170.6; 173.5. HR-MS (EI): 342.2046 ($C_{18}H_{30}O_6^+$; calc. 342.2042).

Crystallographic data (excluding structure factors) of **10** have been deposited with the Cambridge Crystallographic Data Centre as private communication no. CCDC-196858 (Klaus Harms, University of Marburg, 2002). Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1233 336-033; e-mail: deposit@ccdc.cam.ac.uk).

18. (7R,10E,12aR,16aR)-6,7,12a,13,14,15,16,16a-Decahydro-7-[(1R)-1-hydroxyethyl]-16a-methyl-2,3,5H-1,4,8-trioxabenzocyclotetradecine-5,9(12H)-dione (2,3-didehydro-**10**¹). As described in *Exper. 10*, with **30** (30 mg, 70 μ mol): didehydro-**10**¹ (14 mg, 56%). Colorless oil. $[\alpha]_D^{20} = +33.2$ ($c = 1.34$, $CHCl_3$). 1H -NMR (200 MHz, $CDCl_3$): 1.22 (d, $J = 6.5$, 3 H); 1.25 (s, 3 H); 1.27–1.45 (m, 3 H); 1.47–1.61 (m, 2 H); 1.64–1.79 (m, 3 H); 1.86 (br. s, 1 H); 1.90–2.03 (m, 2 H); 2.56 (dd, $J = 13.3$, 3.0, 1 H); 2.62–2.76 (m, 1 H); 2.78 (dd, $J = 13.4$, 10.5, 1 H); 3.36 (ddd, $J = 10.6$, 2.9, 1.6, 1 H); 3.57 (ddd, $J = 10.6$, 9.9, 1.0, 1 H); 3.90–4.10 (m, 2 H); 4.43 (ddd, $J = 11.8$, 10.0, 1.8, 1 H); 5.08 (ddd, $J = 10.5$, 5.0, 3.0, 1 H); 5.59 (d, $J = 15.5$, 1 H); 7.29 (ddd, $J = 15.6$, 9.8, 6.9, 1 H). ^{13}C -NMR (50 MHz, $CDCl_3$): 14.1; 19.2; 21.5; 23.5; 26.3; 34.0; 34.8; 36.7; 47.0; 58.0; 65.4; 69.1; 75.1; 79.2; 119.2; 151.3; 166.7; 171.6. HR-MS (EI): 340.1908 ($C_{18}H_{28}O_6^+$; calc. 340.1886).

19. (2RS,3RS)-2-Allyl-3-methylcyclohexanone (rac-**33**). To a suspension of CuI (286 mg, 1.5 mmol) in Et_2O (10 ml), 1.6M MeLi in hexane (1.88 ml, 3.0 mmol) was added. After cooling the clear soln. to -78° , 2-allylcyclohex-2-en-1-one [**20**] (**32**; 136 mg, 1.0 mmol) was added. After stirring for 1 h at this temp., the suspension was added dropwise into a precooled (-78°) soln. of methyl 2-hydroxybenzoate (0.52 ml, 4.0 mmol) in Et_2O (40 ml). After the formation of a white precipitate, the mixture was allowed to reach r.t. AcOH (229 μ l, 4 mmol) was added, and stirring was continued for 2 h. The mixture was filtered through a pad of 'Kieselgur', and the filtrate was washed with sat. aq. $NaHCO_3$ soln. (50 ml) and H_2O (3 $\times$ 50 ml). The org. layer was dried ($MgSO_4$) and evaporated. FC ('BuOMe/pentane 1:19) furnished rac-**33** (96:4 diastereoisomer mixture; 122 mg, 80%) as a colorless liquid.

cis-Isomer: 1H -NMR (200 MHz, $CDCl_3$): 0.80 (d, $J = 7.0$, 3 H); 1.62–1.68 (m, 1 H); 1.79–1.91 (m, 3 H); 1.91–2.03 (m, 1 H); 2.21–2.36 (m, 3 H); 2.40–2.47 (m, 1 H); 2.48–2.56 (m, 1 H); 4.95–5.05 (m, 2 H); 5.64–5.80 (m, 1 H). ^{13}C -NMR (75 MHz, $CDCl_3$): 14.0; 23.3; 30.7; 31.8; 35.5; 41.5; 54.6; 115.9; 136.4; 212.6. Anal. calc. for $C_{10}H_{16}O$ (152.2): C 78.89, H 10.59; found: C 78.67, H 10.80.

trans-Isomer: 1H -NMR (200 MHz, $CDCl_3$): 1.04 (d, $J = 6.1$, 3 H).

20. (6RS,7RS)-6-Allyl-7-methyl-1,4-dioxaspiro[4.5]decane (**34**). At -78° , 1,2-bis-[(trimethylsilyl)oxy]ethane (2.54 ml, 10 mmol) was added to a soln. of trimethylsilyl triflate (5 drops) in CH_2Cl_2 (5 ml). Ketone rac-**33** (93:7 diastereoisomer mixture; 761 mg, 5.0 mmol) was added dropwise within 10 min. The mixture was allowed to reach r.t. over 12 h. Sat. aq. $NaHCO_3$ soln. (15 ml) was added, the aq. phase extracted with 'BuOMe' (3 $\times$ 10 ml), the combined extract dried ($MgSO_4$) and evaporated, and the crude product submitted to FC ('BuOMe/pentane 1:19): **34** (93:7 diastereoisomer mixture (GC); 856 mg, 87%). Colorless liquid. 1H -NMR (200 MHz, $CDCl_3$): 0.90 (d, $^3J = 7.2$, 3 H); 1.24–1.48 (m, 4 H); 1.59–1.73 (m, 4 H); 1.96–2.04 (m, 1 H); 2.13–2.24 (m, 1 H); 3.80–3.95 (m, 4 H); 4.90 (br. d, $^3J = 10.1$, 1 H); 4.94 (br. d, $^3J = 17.1$, 1 H); 5.73–5.93 (m, 1 H). ^{13}C -NMR (75 MHz, $CDCl_3$): 16.6; 21.0; 29.7; 30.2; 31.9; 32.7; 47.3; 64.0; 64.6; 111.3; 114.3; 139.4. Anal. calc. for $C_{12}H_{20}O_2$ (196.3): C 73.43, H 10.27; found: C 73.50, H 10.31.

21. 2-[(1RS,2SR,3SR)-2-Allyl-1,3-dimethylcyclohexyl]oxy]ethanol (**35**). At -78° , 2M Me_3Al in hexane (16 ml, 32 mmol) was added to a precooled soln. of **34** (93:7 diastereoisomer mixture; 760 mg, 3.87 mmol) in CH_2Cl_2 (100 ml). After reaching 0° over 12 h, the mixture was hydrolyzed by careful addition of sat. aq. NH_4Cl soln. (50 ml). The mixture was filtered and acidified to pH < 1 with aq. HCl soln. The aq. layer was extracted with 'BuOMe' (3 $\times$ 40 ml) and the combined extract washed with brine (150 ml), dried ($MgSO_4$), and evaporated: **35** (92:8 diastereoisomer mixture (GC); 740 mg, 90%). Colorless oil. 1H -NMR (300 MHz, $CDCl_3$): 0.94 (d, $^3J = 7.0$, 3 H); 1.22 (s, 3 H); 1.24–1.42 (m, 3 H); 1.52–1.63 (m, 4 H and OH); 1.78–1.82 (m, 1 H); 2.02–2.17 (m, 2 H); 2.23–2.35 (m, 1 H); 3.41 (m, 2 H); 3.67 (m, 2 H); 4.90–4.97 (m, 2 H); 5.74–5.92 (m, 1 H).

^{13}C -NMR (75 MHz, CDCl_3): 17.9; 20.4; 23.2; 29.1; 30.6; 31.4; 33.3; 48.8; 61.2; 62.5; 77.1; 114.1; 140.6. Anal. calc. for $\text{C}_{13}\text{H}_{24}\text{O}_2$ (212.3): C 73.54, H 11.39; found: C 73.49, H 11.64.

22. (1*RS*,2*SR*,6*RS*)-2-(2-Hydroxyethoxy)-2,6-dimethylcyclohexanecarboxylic Acid (**36**). As described in *Exper. 3*, with **35** (396 mg, 1.87 mmol): crude aldehyde (314 mg, 78%). ^1H -NMR (300 MHz, CDCl_3): 0.90 (*d*, $^3J = 6.9$, 3 H); 0.94–1.08 (*m*, 1 H); 1.27 (*s*, 3 H); 1.33–1.47 (*m*, 3 H); 1.56–1.70 (*m*, 2 H); 1.80–1.95 (*m*, 1 H); 2.19 (*dd*, $^3J = 3.7$, $^2J = 15.4$, 1 H); 2.27 (*br. dd*, $^3J = 8.8$, $^2J = 4.0$, 2 H and OH); 2.48 (*ddd*, $^3J = 8.8$, $^2J = 4.8$, $^2J = 15.4$, 1 H); 3.33–3.47 (*m*, 2 H); 3.53–3.60 (*m*, 2 H); 9.64 (*d*, $^3J = 4.7$, 1 H). ^{13}C -NMR (75 MHz, CDCl_3): 19.8; 21.9; 22.4; 28.7; 30.6; 31.5; 39.0; 45.4; 61.8; 62.1; 77.2; 204.0.

The aldehyde (29 mg, 135 μmol) was oxidized as described in *Exper. 3*: **36** (29 mg, 93%). Colorless solid. M.p. 132°. ^1H -NMR (300 MHz, $(\text{D}_6)\text{DMSO}$): 0.80 (*d*, $^3J = 6.9$, 3 H); 0.97–1.07 (*m*, 1 H); 1.00 (*s*, 3 H); 1.27–1.41 (*m*, 3 H); 1.50–1.54 (*m*, 1 H); 1.71–1.78 (*m*, 1 H); 2.00–2.07 (*m*, 2 H); 2.14–2.18 (*m*, 1 H); 2.44–2.49 (*m*, 1 H); 3.22–3.33 (*m*, 2 H); 3.38–3.46 (*m*, 2 H). ^{13}C -NMR (75 MHz, $(\text{D}_6)\text{DMSO}$): 18.9; 21.4; 22.1; 28.7; 29.1; 31.4; 32.7; 43.9; 61.3; 61.7; 75.8; 175.7. Anal. calc. for $\text{C}_{12}\text{H}_{22}\text{O}_4$ (230.3): C 62.58, H 9.63; found: C 62.41, H 9.60.

23. (6*aRS*,7*RS*,10*aSR*)-2,3,6*a*,7,8,9,10,10*a*-Octahydro-7,10*a*-dimethyl-1,4-benzodioxocin-5(6*H*)-one (**37**). A soln. of **36** (29 mg, 126 μmol) in pyridine (2 ml) was heated to 80°. Ac_2O (18 μl , 190 μmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 30 μl , 201 μmol) were added, and the mixture was stirred for 2 h at 80°. Toluene (2 ml) was added and the mixture evaporated, a process that was repeated (3 $\times$). The residue was adsorbed on silica gel followed by FC (BuOMe/pentane 3:7): **37** (19 mg, 71%). Colorless oil. ^1H -NMR (500 MHz, CDCl_3): 0.93 (*d*, $^3J = 6.8$, Me–C(7)); 1.04–1.15 (*m*, 1 H–C(8)); 1.30 (*s*, Me–C(10*a*)); 1.36–1.47 (*m*, 2 H–C(9), 1 H–C(10)); 1.56–1.64 (*m*, 1 H–C(10)); 1.65–1.71 (*m*, 1 H–C(8)); 1.72–1.80 (*m*, H–C(7)); 2.25–2.29 (*m*, H–C(6*a*)); 2.33 (*dd*, $^2J = 14.0$, $^3J = 4.9$, 1 H–C(6)); 2.48 (*dd*, $^2J = 14.0$, $^3J = 10.2$, 1 H–C(6)); 3.63 (*dt*, $^2J = 12.0$, $^3J = 2.4$, 1 H–C(2)); 3.79 (*ddd*, $^3J = 10.2$, $^3J = 3.1$, $^2J = 12.6$, 1 H–C(2)); 4.09 (*ddd*, $^2J = 12.0$, $^3J = 3.1$, $^3J = 2.2$, 1 H–C(3)); 4.61 (*ddd*, $^3J = 10.2$, $^3J = 2.6$, $^2J = 12.0$, 1 H–C(3)). ^{13}C -NMR (100 MHz, CDCl_3): 20.0 (Me–C(10*a*)); 21.9 (Me–C(7)); 22.7 (C(9)); 27.8 (C(6)); 30.6 (C(8)); 31.7 (C(7)); 32.3 (C(10)); 47.3 (C(6*a*)); 62.2 (C(3)); 70.2 (C(2)); 78.4 (C(10*a*)); 177.4 (C(5)). HR-MS (EI): 212.1417 ($\text{C}_{12}\text{H}_{20}\text{O}_3^+$; calc.: 212.1413), 213.1444 ($^{13}\text{C}_1^{12}\text{C}_{11}\text{H}_{20}\text{O}_3^+$; calc.: 213.1446).

24. 2-[[[(1*RS*,2*SR*,3*SR*)-2-Allyl-1,3-dimethylcyclohexyl]oxy]ethyl (3*R*,4*R*)-4-(Benzyloxy)-3-[[[(tert-butyl)-dimethylsilyl]oxy]pentanoate (**38**). As described in *Exper. 5*, with **35** (122 mg, 575 μmol) and **15** (194 mg, 575 μmol): **38** (243 mg, 79%). Colorless liquid. ^1H -NMR (200 MHz, CDCl_3): 0.01 (*s*, 3 H); 0.02 (*s*, 3 H); 0.84 (*s*, 9 H); 0.95 (*d*, $J = 7.0$, 3 H); 1.14 (*d*, $J = 6.5$, 3 H); 1.20 (*s*, 3 H); 1.23–1.44 (*m*, 4 H); 1.46–1.70 (*m*, 3 H); 1.72–1.89 (*m*, 1 H); 1.97–2.17 (*m*, 1 H); 2.27–2.44 (*m*, 1 H); 2.40 (*dd*, $J = 15.1$, 8.8, 1 H); 2.67 (*dd*, $J = 15.1$, 3.6, 1 H); 3.39–3.64 (*m*, 3 H); 4.08–4.20 (*m*, 2 H); 4.29–4.41 (*m*, 1 H); 4.52 (*d*, $J = 12.0$, 1 H); 4.59 (*d*, $J = 12.0$, 1 H); 4.91 (*br. d*, $J = 10.0$, 1 H); 5.00 (*br. d*, $J = 17.0$, 1 H); 5.81 (*dddd*, $J = 17.0$, 10.0, 7.2, 6.8, 1 H); 7.27–7.38 (*m*, 5 H). ^{13}C -NMR (50 MHz, CDCl_3): –5.0; –4.8; 13.4; 17.9 (2 C); 20.1; 23.0; 25.7 (3 C); 28.3 (spurious); 29.0; 30.8; 31.4; 33.5; 36.9; 48.4; 58.5; 64.2; 70.1; 70.9; 77.2 (2 C); 114.3; 127.46; 127.51 (2 C); 128.3 (2 C); 138.6; 140.4; 172.3. Anal. calc. for $\text{C}_{31}\text{H}_{52}\text{O}_5\text{Si}$ (532.8): C 69.88, H 9.84; found: C 69.63, H 9.72.

25. 2-[[[(1*RS*,2*SR*,3*SR*)-2-Allyl-1,3-dimethylcyclohexyl]oxy]ethyl (3*R*,4*R*)-4-(Benzyloxy)-3-hydroxypentanoate. As described in *Exper. 6*, with **38** (218 mg, 409 μmol). FC (BuOMe/pentane 3:7) furnished the product (113 mg, 66%). Colorless liquid. ^1H -NMR (200 MHz, CDCl_3): 0.93 (*d*, $J = 7.0$, 3 H); 1.20 (*s*, 3 H); 1.25 (*d*, $J = 6.3$, 3 H); 1.27–1.43 (*m*, 4 H); 1.46–1.68 (*m*, 3 H); 1.70–1.89 (*m*, 1 H); 1.96–2.17 (*m*, 1 H); 2.25–2.43 (*m*, 1 H); 2.55 (*br. d*, $J = 6.5$, 2 H); 2.91 (*br. d*, $J = 4.8$, 1 H); 3.40–3.60 (*m*, 3 H); 4.01 (*ddd*, $J = 11.2$, 6.3, 4.8, 1 H); 4.20 (*br. t*, $J = 5.0$, 2 H); 4.46 (*d*, $J = 11.6$, 1 H); 4.66 (*d*, $J = 11.6$, 1 H); 4.91 (*br. d*, $J = 10.1$, 1 H); 5.00 (*br. d*, $J = 17.2$, 1 H); 5.81 (*dddd*, $J = 17.2$, 10.1, 7.0, 6.9, 1 H); 7.22–7.43 (*m*, 5 H). ^{13}C -NMR (50 MHz, CDCl_3): 15.1; 17.9; 20.3; 23.0; 28.9; 30.6; 31.4; 33.4; 37.8; 48.3; 58.3; 64.5; 71.0 (2 C); 76.5; 77.2; 114.3; 127.65; 127.71 (2 C); 128.4 (2 C); 138.2; 140.4; 172.3. HR-MS (ESI): 441.2600 ($[\text{C}_{25}\text{H}_{38}\text{O}_5 + \text{Na}]^+$; calc.: 441.2617).

26. 2-[[[(1*RS*,2*SR*,3*SR*)-2-Allyl-1,3-dimethylcyclohexyl]oxy]ethyl (3*R*,4*R*)-4-(Benzyloxy)-3-(but-2-enyloxy)pentanoate. The alcohol obtained in *Exper. 25* (67 mg, 0.16 mmol) was esterified with (2*E*)-but-2-enoyl chloride and isomerized as described in *Exper. 7*. FC (BuOMe/pentane 1:9) furnished the (2*Z*)- (21 mg, 28%) and (2*E*)-but-2-enoyl derivatives (50 mg, 68%) as colorless oils.

Data of (2*E*)-But-2-enoyl Derivative: ^1H -NMR (200 MHz, CDCl_3): 0.87 (*d*, $J = 7.0$, 3 H); 1.10 (*d*, $J = 6.4$, 3 H); 1.12 (*s*, 3 H); 1.14–1.35 (*m*, 4 H); 1.39–1.63 (*m*, 3 H); 1.64–1.78 (*m*, 1 H); 1.80 (*dd*, $J = 6.9$, 1.7, 3 H); 1.91–2.12 (*m*, 1 H); 2.21–2.34 (*m*, 1 H); 2.60 (*dd*, $J = 16.0$, 8.2, 1 H); 2.71 (*dd*, $J = 16.0$, 5.0, 1 H); 3.32–3.48 (*m*, 2 H); 3.72 (*qd*, $J = 6.4$, 3.9, 1 H); 4.04–4.11 (*m*, 2 H); 4.46 (*d*, $J = 11.8$, 1 H); 4.56 (*d*, $J = 11.8$, 1 H); 4.84 (*br. d*, $J = 10.0$, 1 H); 4.93 (*br. d*, $J = 16.9$, 1 H); 5.35–5.43 (*m*, 1 H); 5.66–5.79 (*m*, 1 H); 5.79 (*br. d*, $J = 15.2$, 1 H); 6.93 (*dq*, $J = 15.2$, 6.9, 1 H); 7.17–7.29 (*m*, 5 H). ^{13}C -NMR (50 MHz, CDCl_3): 14.8; 17.7; 17.9; 20.1; 22.9;

28.9; 30.7; 31.3; 33.4; 34.5; 48.3; 58.3; 64.4; 71.05; 71.09; 73.6; 77.0; 114.2; 122.4; 127.5; 127.7 (2 C); 128.3 (2 C); 138.2; 140.4; 145.2; 165.5; 170.7. HR-MS (ESI): 509.2909 ($[\text{C}_{29}\text{H}_{42}\text{O}_6 + \text{Na}]^+$; calc. 509.2879).

Data of (2Z)-But-2-enoyl Derivative: $^1\text{H-NMR}$ (200 MHz, CDCl_3): 0.86 (*d*, $J = 7.1$, 3 H); 1.11 (*d*, $J = 6.4$, 3 H); 1.12 (*s*, 3 H); 1.15–1.36 (*m*, 4 H); 1.40–1.60 (*m*, 3 H); 1.66–1.78 (*m*, 1 H); 1.92–2.05 (*m*, 1 H); 2.08 (*dd*, $J = 7.3$, 1.7, 3 H); 2.21–2.33 (*m*, 1 H); 2.59 (*dd*, $J = 15.8$, 8.7, 1 H); 2.74 (*dd*, $J = 15.8$, 4.2, 1 H); 3.32–3.48 (*m*, 2 H); 3.73 (*dq*, $J = 3.9$, 6.3, 1 H); 4.08 (*br. t*, $J = 5.3$, 2 H); 4.47 (*d*, $J = 12.0$, 1 H); 4.56 (*d*, $J = 12.0$, 1 H); 4.84 (*br. d*, $J = 10.0$, 1 H); 4.94 (*br. d*, $J = 17.1$, 1 H); 5.37–5.43 (*m*, 1 H); 5.67–5.79 (*m*, 1 H); 5.74 (*dq*, $J = 11.5$, 1.5, 1 H); 6.23 (*dq*, $J = 11.5$, 7.3, 1 H); 7.17–7.30 (*m*, 5 H). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): 14.9; 15.4; 17.8; 20.2; 23.0; 29.0; 30.7; 31.4; 33.4; 34.6; 48.4; 58.3; 64.5; 70.7; 71.2; 73.7; 77.0; 114.2; 120.3; 127.6; 127.7 (2 C); 128.3 (2 C); 138.2; 140.4; 145.9; 165.4; 170.7. HR-MS (ESI): 509.2870 ($[\text{C}_{29}\text{H}_{42}\text{O}_6 + \text{Na}]^+$; calc. 509.2879).

27. (7R,10E,12aS,13S,16aR)-7-[(1R)-1-(Benzoyloxy)ethyl]-2,3,6,7,12a,13,14,15,16,16a-decahydro-13,16a-dimethyl-5H-1,4,8-benzotrioxacyclotetradecine-5,9(12H)-dione (**39**) and (7R,10E,12aR,13R,16aS)-7-[(1R)-1-(Benzoyloxy)ethyl]-2,3,6,7,12a,13,14,15,16,16a-decahydro-13,16a-dimethyl-5H-1,4,8-benzotrioxacyclotetradecine-5,9(12H)-dione (**40**). A mixture of the (2Z)- (16 mg, 32 μmol) and (2E)-but-2-enoyl derivative (38 mg, 78 μmol) obtained in *Exper. 26* was cyclized as described in *Exper. 8* in the presence of 6.4 mol-% of the catalyst. FC (BuOMe/pentane 1:3) furnished **39** (or **40**?; 20 mg, 41%) and **40** (or **39**?; 14 mg, 28%) as colorless oils.

Data of 39: $[\alpha]_D^{20} = +16.5$ ($c = 2.01$, CHCl_3). $^1\text{H-NMR}$ (300 MHz, CDCl_3): 1.00 (*d*, $J = 6.8$, 3 H); 1.20 (*d*, $J = 6.6$, 3 H); 1.22 (*s*, 3 H); 1.28–1.50 (*m*, 4 H); 1.61–1.76 (*m*, 3 H); 1.78–1.90 (*m*, 1 H); 2.17–2.31 (*m*, 2 H); 2.55 (*dd*, $J = 13.4$, 2.7, 1 H); 2.77 (*dd*, $J = 13.4$, 10.3, 1 H); 3.46 (*ddd*, $J = 10.6$, 6.9, 1.2, 1 H); 3.53 (*ddd*, $J = 11.0$, 5.0, 1.5, 1 H); 3.82 (*qd*, $J = 6.2$, 4.8, 1 H); 3.99 (*ddd*, $J = 12.0$, 6.7, 1.5, 1 H); 4.31 (*ddd*, $J = 12.0$, 5.6, 1.5, 1 H); 4.55 (*d*, $J = 11.8$, 1 H); 4.64 (*d*, $J = 11.8$, 1 H); 5.28 (*ddd*, $J = 10.3$, 4.4, 2.9, 1 H); 5.64 (*d*, $J = 15.6$, 1 H); 7.27–7.35 (*m*, 5 H); 7.47 (*ddd*, $J = 15.6$, 7.9, 7.9, 1 H). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): 14.9; 19.8; 21.8; 22.3; 28.4; 29.1; 31.1; 33.1; 35.6; 51.4; 58.5; 65.9; 71.2; 71.9; 74.2; 78.7; 119.0; 127.6; 127.7 (2 C); 128.3 (2 C); 138.2; 154.4; 166.4; 171.8. HR-MS (EI): 444.2537 ($\text{C}_{26}\text{H}_{36}\text{O}_6^+$; calc. 444.2512).

Data of 40: $[\alpha]_D^{20} = -6.02$ ($c = 0.83$, CHCl_3). $^1\text{H-NMR}$ (500 MHz, CDCl_3): 0.93 (*d*, $J = 6.7$, 3 H); 1.22 (*d*, $J = 6.4$, 3 H); 1.27 (*s*, 3 H); 1.26–1.32 (*m*, 2 H); 1.34–1.40 (*m*, 2 H); 1.42–1.49 (*m*, 1 H); 1.53–1.58 (*m*, 1 H); 1.63–1.69 (*m*, 1 H); 1.82–1.93 (*m*, 1 H); 2.28 (*ddd*, $J = 16.4$, 9.9, 9.7, 1 H); 2.36 (*br. d*, $J = 16.3$, 1 H); 2.55 (*dd*, $J = 13.5$, 3.0, 1 H); 2.80 (*dd*, $J = 13.4$, 10.5, 1 H); 3.43 (*ddd*, $J = 10.8$, 5.5, 2.0, 1 H); 3.54 (*ddd*, $J = 10.7$, 7.6, 2.0, 1 H); 3.79 (*qd*, $J = 6.2$, 4.6, 1 H); 4.03 (*ddd*, $J = 11.6$, 5.4, 1.9, 1 H); 4.10 (*ddd*, $J = 11.6$, 7.5, 1.8, 1 H); 4.56 (*d*, $J = 11.9$, 1 H); 4.65 (*d*, $J = 11.9$, 1 H); 5.33 (*ddd*, $J = 10.5$, 4.3, 3.1, 1 H); 5.56 (*d*, $J = 15.7$, 1 H); 7.26–7.30 (*m*, 1 H); 7.31–7.35 (*m*, 5 H). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): 15.0; 19.8; 22.3; 25.6; 28.3; 28.9; 29.5; 32.6; 35.5; 49.7; 57.8; 65.6; 71.2; 72.1; 74.4; 78.5; 116.4; 127.6; 127.7 (2 C); 128.3 (2 C); 138.3; 155.4; 166.3; 171.9. HR-MS (ESI): 467.2440 ($[\text{C}_{26}\text{H}_{36}\text{O}_6 + \text{Na}]^+$; calc. 467.2410).

28. (7R,12aS,13S,16aR)-7-[(1R)-1-Hydroxyethyl]-2,3,6,7,11,12,12a,13,14,15,16,16a-dodecahydro-13,16a-dimethyl-5H-1,4,8-benzotrioxacyclotetradecine-5,9(10H)-dione (**11**). As described in *Exper. 9*, with **39** (22 mg, 50 μmol). FC (BuOMe) furnished **11** (or *epi-11*?; 160 mg, 91%). Colorless oil. $[\alpha]_D^{20} = -16.7$ ($c = 1.28$, CHCl_3). $^1\text{H-NMR}$ (500 MHz, CDCl_3): 0.91 (*d*, $J = 6.9$, 3 H); 1.21 (*d*, $J = 6.4$, 3 H); 1.09–1.19 (*m*, 2 H); 1.23 (*s*, 3 H); 1.30–1.37 (*m*, 2 H); 1.38–1.42 (*m*, 1 H); 1.45–1.49 (*m*, 1 H); 1.56–1.62 (*m*, 2 H); 1.66–1.79 (*m*, 4 H); 2.12 (*br. d*, $J = 6.6$, 1 H); 2.20–2.26 (*m*, 1 H); 2.47 (*ddd*, $J = 14.4$, 6.5, 3.4, 1 H); 2.63 (*dd*, $J = 15.2$, 2.4, 1 H); 2.76 (*dd*, $J = 15.2$, 9.2, 1 H); 3.49 (*ddd*, $J = 10.2$, 7.3, 2.2, 1 H); 3.56 (*ddd*, $J = 10.5$, 5.8, 2.1, 1 H); 3.85–3.94 (*m*, 1 H); 4.11 (*ddd*, $J = 11.7$, 7.2, 2.3, 1 H); 4.37 (*ddd*, $J = 11.7$, 5.8, 2.1, 1 H); 5.10 (*ddd*, $J = 9.2$, 4.5, 2.3, 1 H). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): 19.4; 20.2; 22.1; 22.6; 23.5; 27.5; 28.9; 32.0; 32.5; 35.0; 37.1; 49.3; 58.0; 64.7; 69.2; 74.6; 77.6; 171.1, 173.9. HR-MS (EI): 356.2220 ($\text{C}_{19}\text{H}_{32}\text{O}_6^+$; calc. 356.2199).

29. (7R,10E,12aS,13S,16aR)-7-[(1R)-1-Hydroxyethyl]-2,3,6,7,12a,13,14,15,16,16a-decahydro-13,16a-dimethyl-5H-1,4,8-benzotrioxacyclotetradecine-5,9(12H)-dione (2,3-didehydro-**11**¹). As described in *Exper. 10*, with **39** (22 mg, 50 μmol): 2,3-didehydro-**11**¹ (or 2,3-didehydro-*epi-11*?; 13 mg, 74%). Colorless oil. $[\alpha]_D^{20} = +60.8$ ($c = 0.51$, CHCl_3). $^1\text{H-NMR}$ (500 MHz, CDCl_3): 0.99 (*d*, $J = 6.9$, 3 H); 1.23 (*s*, 3 H); 1.24 (*d*, $J = 6.4$, 3 H); 1.29–1.43 (*m*, 2 H); 1.45–1.54 (*m*, 1 H); 1.59–1.71 (*m*, 3 H); 1.73 (*br. dt*, $J = 9.0$, 4.2, 1 H); 1.81–1.89 (*m*, 1 H); 2.20–2.31 (*m*, 2 H); 2.39 (*br. s*, 1 H); 2.62 (*dd*, $J = 13.4$, 3.7, 1 H); 2.73 (*dd*, $J = 13.4$, 8.9, 1 H); 3.49 (*ddd*, $J = 11.1$, 6.9, 1.9, 1 H); 3.53 (*ddd*, $J = 11.1$, 5.4, 1.9, 1 H); 3.96 (*br. dq*, $J = 5.8$, 5.9, 1 H); 4.04 (*ddd*, $J = 12.0$, 7.0, 1.9, 1 H); 4.28 (*ddd*, $J = 11.9$, 5.4, 1.8, 1 H); 5.04 (*ddd*, $J = 8.8$, 5.2, 3.6, 1 H); 5.65 (*dt*, $J = 15.7$, 1.0, 1 H); 7.46 (*ddd*, $J = 15.7$, 7.8, 7.8, 1 H). $^{13}\text{C-NMR}$ (50 MHz, CDCl_3): 14.2; 19.3; 19.8; 22.3; 27.0; 30.9; 33.1; 36.7; 51.6; 58.4; 66.1; 69.0; 74.6; 77.2; 78.7; 118.5; 155.2; 166.9; 171.5. HR-MS (ESI): 355.2107 ($[\text{C}_{19}\text{H}_{30}\text{O}_6 + \text{H}]^+$; calc. 355.2121).

30. (7R,12aR,13R,16aS)-7-[(1R)-1-Hydroxyethyl]-2,3,6,7,11,12,12a,13,14,15,16,16a-dodecahydro-13,16a-dimethyl-5H-1,4,8-benzotrioxacyclotetradecine-5,9(10H)-dione (*epi-11*). As described in *Exper. 9*, with **40** (13 mg, 29 μmol). FC (BuOMe) furnished *epi-11* (or **11**?; 9.0 mg, 97%). Colorless oil. $[\alpha]_D^{20} = -10.7$ ($c = 1.03$,

CHCl₃). ¹H-NMR (500 MHz, CDCl₃): 0.89 (*d*, *J* = 6.9, 3 H); 1.10–1.16 (*m*, 2 H); 1.19 (*d*, *J* = 6.6, 3 H); 1.21 (*s*, 3 H); 1.26–1.34 (*m*, 3 H); 1.35–1.42 (*m*, 1 H); 1.43–1.48 (*m*, 1 H); 1.55–1.69 (*m*, 4 H); 1.72–1.80 (*m*, 1 H); 2.15–2.22 (*m*, 1 H); 2.26 (*d*, *J* = 5.3, 1 H); 2.55–2.60 (*m*, 1 H); 2.67 (*dd*, *J* = 15.6, 8.1, 1 H); 2.82 (*dd*, *J* = 15.4, 3.4, 1 H); 3.51–3.59 (*m*, 2 H); 4.00 (*qdd*, *J* = 6.2, 5.5, 5.1, 1 H); 4.13–4.19 (*m*, 1 H); 4.25 (*ddd*, *J* = 11.6, 5.0, 1.9, 1 H); 5.06 (*ddd*, *J* = 8.0, 5.0, 3.3, 1 H). ¹³C-NMR (50 MHz, CDCl₃): 18.9; 19.4; 22.0; 22.4 (2 C); 26.9; 28.9; 31.2; 32.6; 34.5; 35.9; 49.4; 58.3; 65.5; 68.5; 73.7; 77.6; 170.9; 173.4. HR-MS (EI): 356.2196 (C₁₉H₃₂O₆⁺; calc. 356.2199).

31. (7R,10E,12aR,13R,16aS)-7-[(1R)-1-Hydroxyethyl]-2,3,6,7,12a,13,14,15,16,16a-decahydro-13,16a-dimethyl-5H-1,4,8-trioxabenzocyclotetradecine-5,9(12H)-dione (2,3-didehydro-epi-**11**¹). As described in *Exper.* 10 with **40** (22 mg, 50 μmol): 2,3-didehydro-epi-**11**¹ (or epi-**11**²; 12 mg, 68%). Colorless oil. [*α*]_D²⁰ = +12.3 (*c* = 1.38, CHCl₃). ¹H-NMR (500 MHz, CDCl₃): 0.93 (*d*, *J* = 6.9, 3 H); 1.10–1.18 (*m*, 1 H); 1.25 (*d*, *J* = 6.6, 3 H); 1.27 (*s*, 3 H); 1.29–1.33 (*m*, 2 H); 1.34–1.41 (*m*, 1 H); 1.42–1.48 (*m*, 1 H); 1.56 (*br. s*, 1 H); 1.63–1.69 (*m*, 1 H); 1.81–1.93 (*m*, 1 H); 2.25–2.32 (*m*, 2 H); 2.33–2.39 (*m*, 1 H); 2.62 (*dd*, *J* = 13.3, 3.5, 1 H); 2.77 (*dd*, *J* = 13.3, 9.3, 1 H); 3.46 (*ddd*, *J* = 10.8, 3.9, 3.9, 1 H); 3.56 (*ddd*, *J* = 10.8, 4.6, 4.6, 1 H); 3.93 (*br. q*, *J* = 6.0, 1 H); 4.09 (*br. t*, *J* = 3.9, 2 H); 5.07 (*ddd*, *J* = 9.2, 5.3, 3.8, 1 H); 5.59 (*br. d*, *J* = 15.7, 1 H); 7.35 (*ddd*, *J* = 15.6, 9.0, 4.5, 1 H). ¹³C-NMR (50 MHz, CDCl₃): 19.2; 19.7; 22.2; 26.8; 28.0; 28.6; 29.3; 32.4; 36.5; 49.6; 57.7; 65.6; 68.8; 74.7; 78.4; 116.1; 155.8; 166.5; 171.1. HR-MS (EI): 354.2042 (C₁₉H₃₀O₆⁺; calc. 354.2048).

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