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ATTEMPTED ACID-CATALYZED TRANSANNULAR REACTIONS IN THE CEMBRANOIDS

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Abstract—Several cembrane diterpenes were treated by various acids under different experimental conditions. All tested compounds were found to be acid sensitive, leading either to local chemical transformations (e.g. opening of epoxides), to transannular reactions and/or to unidentified mixtures. Sarcophine (**7**), the principal cembrane tested, was found to afford either all types of possible epoxide opening products (**11**–**22**), or, by a transannular reaction, when treated with $SnCl_4$, two tetrahydrooxepine derivatives (**23** and **24**). The structure determination of the various derivatives of sarcophine was based mainly on the ^1H and ^{13}C-NMR spectra and also on several chemical transformations.

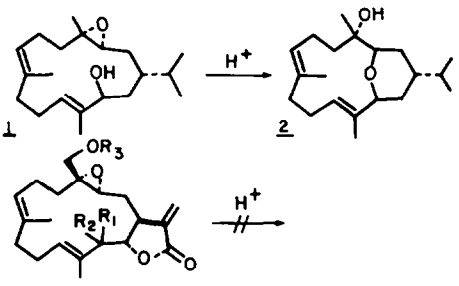
Flaccidoxide (**8**), another cembranoid examined, was found to yield, with Zn/Cu couple, the expected deoxygenation product (sarcophytol-B, **32**) together with an unexpected transannular reaction product (**33**). The structure, including the stereochemistry, of the latter THF-derivative of **8** (**33**) was elucidated by NMR and chemical reactions.

Among the most common secondary metabolites isolated so far from soft corals are the cembranoid diterpenes, characterized by a functionalized 14-membered macrocycle.[1-3] In part, these diterpenes have been shown to be toxic to fish and thus are believed to play a role in the defense mechanism of the soft corals.[1-3]

While stable in the freeze-dried animal and in the crude extracts, most likely, *inter alia*, because of the existence of natural stabilizers, many of the cembranoids undergo rapid changes after chromatographic purification.[4] The two major factors causing these changes seem to be atmospheric oxygen and acidity. Thus, for example, the acidity of $CDCl_3$ is sufficient to induce all kinds of chemical transformations in this class of compounds.

Within the frame of this work, we undertook the examination of some intentionally induced acid catalyzed transformations of several cembranoids (**3**-**9**).

The sensitivity of the cembranoids to acid can at least in part be attributed to the medium size C_{14}-macrocycle, which enables transannular reactions.[1,5] The tetrahydropyran closure in compound **1** to afford compound **2**[6] (Scheme 1) is a good example for the acid catalyzed transannular reaction.† Similar transformations are also believed to occur in nature to give by C–O bond formation compounds like eunicin and compounds like eunicellin, where a new C–C bond is formed leading to a new carbocyclic skeleton (the bicyclo[8.4.0]tetradecane).[1]



1

2

9a R_1 = H, R_2 = OH, R_3 = Ac

9b R_1 = OH, R_2 = H, R_3 = Ac

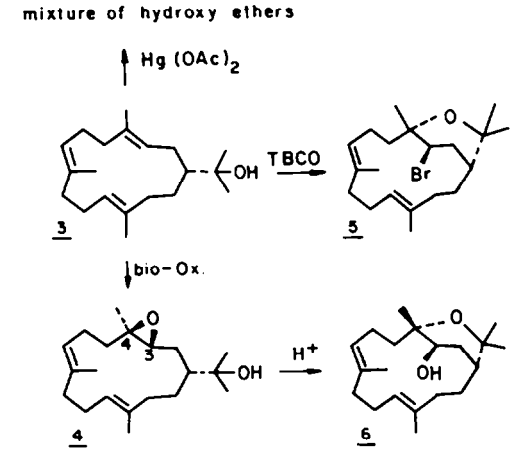
Scheme 1.

Having on hand the two epimeric 13-hydroxylobolides, isolated from *L. crasum*, (**9a** and **9b**)[7] (Scheme 1), we have treated each of them with acid, under the same conditions as were used for the transformation of compound **1** to **2**.[6] No ether formation was observed. This is best rationalized by a different conformation of the macrocycle in **9a** and **9b** as compared to **1**, which prevents the 13-alcohol from occupying the required position for ring closure. The difference between **9** and **1** stems, most likely, from the partial C_{14}-ring fixation by the butenolide in **9**. The latter results point clearly to the great importance of the cembrane conformation on the ratio between the transannular and other local reactions.

Two additional molecules which were tested by us were nephthenol (**3**) and its 3,4-epoxide (**4**)—both isolated together with decaryiol (**6**) from *S. decaryi*.[8] Compound **4** affords, under mild acidic conditions, decaryiol **6** (Scheme 2), a reaction which most likely also takes place in nature.[8] Similarly, the 3,4-bromonium intermediate obtained from nephthenol (**3**) by TBCO, affords in a smooth reaction the 3-bromo analog of decaryiol (**5**).[8] In contrast, however, to the latter regioselective reaction (where the TBCO reacts specifically with the 3,4-bond), $Hg(OAc)_2$ affords from **3** a very complex mixture of hydroxy ethers.

Our main substrate for the study of the cembrane alterations caused by acid was the fish toxin sarcophine (**7**) isolated from *S. glaucum*.[4] Treatment of **7** for 15 min with 1% *p*-TsOH in HOAc furnished four major new compounds: **11** (30%), **13** (30%), **14** (5%), **15** (7%) and *ca* 30% of unreacted **7** (Scheme 4). The new 1710 cm^{-1} band in the IR spectrum of **11**,

†For further examples see Ref. 1.



Scheme 2.

the 213.4 ppm signal in its ^{13}C-NMR and the secondary Me group in the ^{1}H-NMR (δ 1.11d, J = 7 Hz) suggested **11** to be the 7-keto rearrangement product. The ketone results from the well-known acid catalyzed epoxide–ketone rearrangement, and must therefore possess the 8-Me in the β-configuration† (**8***S*). Depending on the work-up conditions, **11** was found to be accompanied by varying amounts of the 8-epimer, the **8***R*-ketone, **12**. Basic equilibration (1% KOH/MeOH for 1 hr) of mixtures of ketones **11** and **12** afforded always a 1:1 mixture of the two.

The same ketones were also obtained, almost exclusively, when **7** was treated with *p*-TsOH in $CHCl_3$ or with $BF_3{\cdot}OEt_2$ in benzene solution.

The δ 3.61 ppm multiplet arising from a proton next to a secondary OH together with the 3-proton singlet at δ 1.45 ppm in the ^{1}H-NMR spectrum of **13** suggested it to be the 7β-OH, 8α-OAc (7*S*, 8*R*) derivative of **7**, obtained by the expected normal acid catalyzed epoxide opening. The stereochemistry at C-8 was confirmed by correlation with **14** and **15** (Scheme 4).

The ^{1}H-NMR spectrum of **14**, δ 1.07 s (3H) and δ 4.97 brd (1H), suggests a Me carbinol and a CHOAc group. Obtaining a 7-OAc, 8-OH derivative is best explained by a neighboring group migration of the acetate from C-8 to C-7.[10] The macrocycle is flexible enough to allow these two substituents to occupy the required conformation for the formation of the 5-membered intermediate. Indeed, **13** in acetic acid with catalytic amounts of *p*-TsOH affords **14**, thereby also establishing its 7β-OAc, 8α-OH (7*S*, 8*R*) configuration.

Compound **15** was assigned the 7β, 8α-dihydroxy structure. On acetylation it gave the monoacetate **14** and on treatment with $NaIO_4$ the expected keto aldehyde (δ 2.17 s(MeCO) and δ 9.70 s(CHO)). The stereochemistry of this diol was established by an X-ray diffraction analysis.[11]

In all four products the butenolide as well as the 3(4) & 11(12) double bonds remained unchanged.

When acetic acid was replaced by MeOH, **7** yielded the same ketone and diol (compounds **11** and **15** respectively) together with the 7*S*, 8*R*-7β-hydroxy-8α-methoxy derivative **16** (80%). The location of the OH (δ 3.45 br) on C-7 was confirmed by its oxidaion to the corresponding ketone **17**.

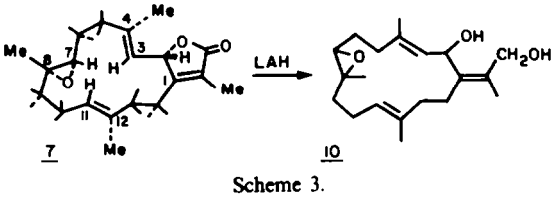
Treating sarcophine with 2% H_2SO_4 in acetone gave again **11** and **15** accompanied, however, this time with the 8(19) methylene-7β-hydroxy derivative (**18**). The latter compound was also the major product when **7** was stirred for 48 hr with activated Al_2O_3 in n-hexane.[12] The allyl alcohol of **18** (δ 4.09 d CHOH and δ 4.93 s & 5.07 s $\diagdown$C=CH$_2$) was confirmed by its oxidation to the $\alpha\beta$-unsaturated ketone **19** (the terminal vinyl protons were shifted to δ 5.83 s & 6.06 s ppm as expected). As the opening of an epoxide to allyl alcohol is known to yield the alcohol with the same configuration as the original epoxide,[12,13] the 7β-configuration (7*S*) was assigned to OH of **18**.

Of special interest was the reaction of **7** with $SnCl_4$ in ethanol-free $CHCl_3$ (distilled over CaH_2) at $-60°$ for 30 min. Work-up of the mixture gave, in order of polarity, a mixture of the two 7-ketones (**11** & **12**, *ca* 35–40%), unreacted sarcophine (**7**, 2–8%), two new compounds **24** (8–15%) & **23** (25–50%), the allyl alcohol **18** (3–5%) and traces of other products (Scheme 5). The various compounds were separated by extensive flash chromatography and HPLC.

Compound **23**, *m/z* 316, $C_{20}H_{28}O_3$, still possesses 7 unsaturations as sarcophine itself. However, as there was no more epoxide (disappearance of the δ 2.68 t of H-3 and the δ 61.4 & 59.9 lines of C-7 & 8), no other CO apart from the lactonic one, and there are still 3 double bonds in the molecule, an ether bridge is proposed. As deduced from the IR and NMR spectra (no alteration in the proton and carbon resonances of the C_1–C_4 moiety), the butenolide and the 3,4-double bond remained unchanged. The existence of the ether bridge was also obvious from the ^{13}C-NMR spectrum where in addition to the lactonic C-2 methinoxy signal two other oxygen bearing C atoms appear at δ 72.5 d, —CH— and δ 78.0 s, —C— (Table 1).

The ^{1}H-NMR spectrum exhibits signals of 4 Me-groups, two of which, at δ 1.83 and 1.87, belong to Me-17 and 18, which appear at approximately the same values in the whole series and were confirmed by double irradiations. One at δ 1.67 is a vinyl Me, located on the third double bond of the molecule and the most upfield resonance line (1.54) has therefore to belong to a Me on an oxygen bearing C-atom. This

†The α and β notation relates to the ring conformation drawn according to Weinheimer's suggestion[1] and shown in Scheme 3. This, however, is not the preferred conformation of **7** as determined by X-ray studies and also in solution by NOE measurements.[4] The absolute configuration of **7** as shown in the Schemes was determined by the CD spectrum.[9]



Scheme 3.

Table 1. ^{13}C-NMR data of sarcophine and derivatives (22.63 MHz, $CDCl_3$)

C	mult.	7	28	29	26	10	11	23	24
1	s	162.3	162.1	160.9	133.9	139.6	163.1	162.9	163.0
2	d	78.8	78.5	78.5	78.3	68.4	79.4	79.2	79.0
3	d	120.7	121.4	121.7	123.4	127.8	119.7	121.5	122.0
4	s	143.9	143.6	141.1	140.2	134.5	144.8	143.4	142.7
5[a]	t	36.3	36.4	36.6	36.5	40.5	35.7	36.3	36.1
9[a]	t	37.4	37.5	37.6	37.7	35.5	32.0	124.1d	124.0d
13[a]	t	38.9	39.1	36.8	38.9	39.6	38.3	39.1	39.8
6[b]	t	25.3	25.5	25.3	23.7	28.0	32.0	27.9	28.0
10[b]	t	23.3	23.5	25.3	23.1	24.2	25.5	26.0	25.3
14[b]	t	27.4	27.6	25.3	27.4	26.8	26.3	24.9	24.9
7	d	61.4	60.7	61.9	62.3	62.5	213.4s	72.5	72.1
8	s	59.9	59.2	59.3	60.1	59.7	46.8d	134.9	134.4
11	d	125.0	125.2	62.4	125.5	124.0	123.9	35.5t	35.6t
12	s	135.4	135.6	61.3	135.8	135.2	134.8	78.0	81.4
15	s	122.9	122.6	124.1	128.1	136.5	122.7	123.0	122.9
16	s	173.0	173.6	174.5	85.3t	62.9t	173.8	171.4	174.9
17	q	8.9	8.8	9.2	10.3	18.2	8.8	9.1	9.0
18[c]	q	16.1	15.9	16.0	16.4	16.0	16.0	16.0	16.1
19[c]	q	17.2	17.3	16.8	17.7	17.8	19.0	15.9	15.7
20[c]	q	15.5	15.3	16.8	15.4	15.2	18.2	26.5	25.8

a-c Signals differing by less than 2ppm, as a result of changes in conformation, may be interchanged. The line assignments are based, inter alia, on δ-comparisons. For example, comparison of the various compounds with 10 & 26 helped with the butenolide moiety assignment, comparison with ketone 11 supported the C-6 and C-9 determinations and compound 29, the 11,12 epoxy derivative of 7 enabled the 3,4 and 11,12-double bond C-atom assignments.

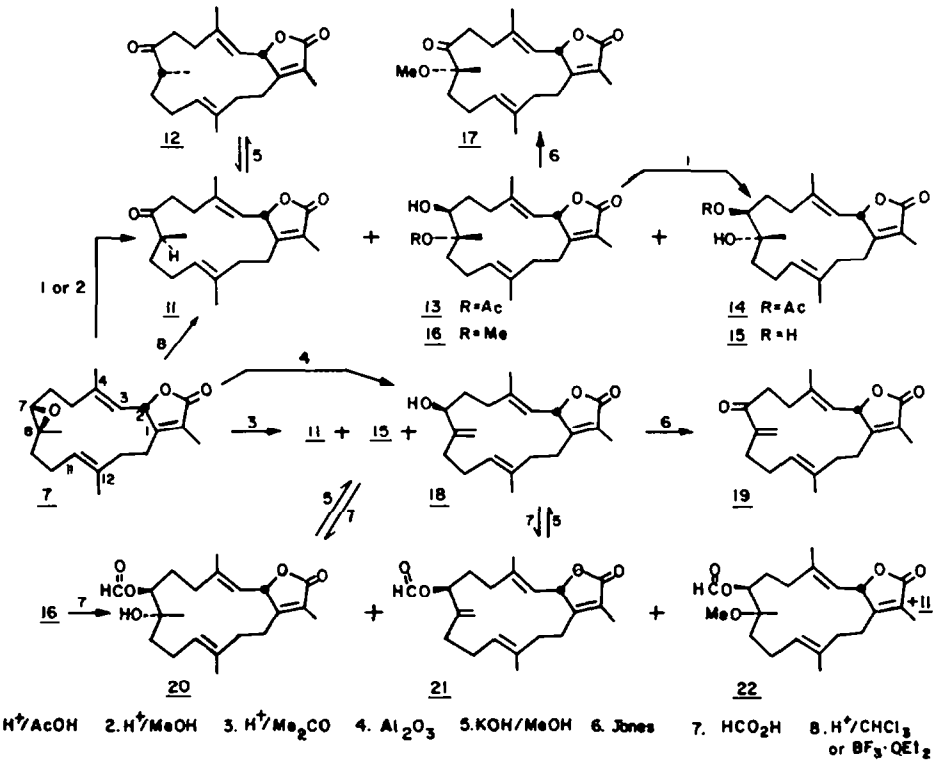
means that the oxygen links C-8 or C-12 to a transannular C-atom.

The two latter Me's together with a vinyl proton (δ 5.13 d, J = 5.6) and a methinoxy group (δ 3.68 d, J = 11) can *a priori* agree with each one of 4 structures: the Δ^7-9,12-oxa, Δ^8-7,12-oxa, Δ^{11}-8, 13-oxa or the Δ^{12}-8, 11-oxa isomer. Low temperature ozonolysis of **23** (30 sec at −78°) left the butenolide as well as the 3,4-bond unattached (as judged by the characteristic NMR absorptions of this moiety). Only the third double bond of **23** suffered cleavage. Ozonolysis at −20°, on the other hand, cleaved both ring double bonds. Although the exact structure of the product, which undergoes further transformations, is still under investigation, it was clear that all four Me's still hang together, which means that the molecule did not split in two, thus excluding two out of the 4 possible isomers (the Δ^7-9,12-oxa and Δ^{12}-8,11-oxa isomers).

A double irradiation experiment showed the methylene next to the methinoxy group to resonate at δ 1.60. This group therefore cannot be in the allylic position and hence, we suggest for **23**, the Δ^8-7, 12-oxa structure. This structure is also the only one that can be arrived at by a straightforward mechanism.

This suggested mechanism (Scheme 6) calls for the initial attack of the 11(12)-double bond rather than the epoxide. (Ring closures by C–C bond formations, induced by $SnCl_4$ attacking double bonds, are well known.[14]) Attack of the epoxide by $SnCl_4$,[12,15] on the other hand, leads as with Lewis acids (*vide supra*) to the major products of the reaction: compounds **11** & **12** and to compound **18**. The reaction of $SnCl_4$ with the 11(12)-bond becomes most likely competitive with the oxirane opening reaction because of steric hindrance of the epoxide (see Scheme 6 for the preferred conformation of **7** as found by X-ray[4c]). This crowdedness also explains the reaction of **7** with LAH (Scheme 3), a reduction that opens the butenolide to the 2, 16-diol (**10**) without reducing the epoxide.† The 11-membered ring of the proposed bicyclo[8.4.1]pentadecane can explain the unexpected high chemical shift of H-7, in the ^{1}H-NMR spectrum,

†For an additional example see Ref. 6.



Scheme 4.

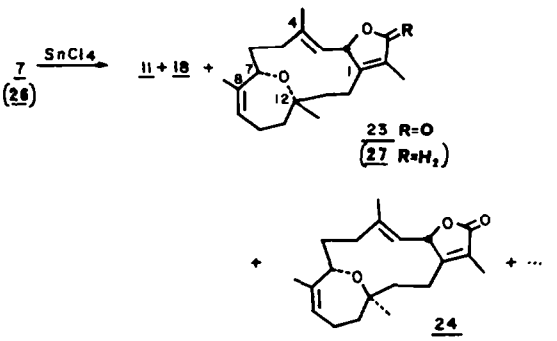
by a transannular shield effect of its 3(4)-double bond. Indeed, hydrogenation of **23**, to **25**, the tetrahydro derivative, caused a downfield rather than upfield shift of H-7 (to δ 3.88). Compound **25** is the major isomer (*ca* 70%) in a stereoisomer mixture that was not separated.

From previous studies of sarcophine[4] we knew that the 11(12)-double bond can be approached from both sides affording a *ca* 1 : 3 mixture on hydrogenation, and a *ca* 1 : 4 mixture on epoxidation. Therefore it was not surprising to find together with **23** a second possible isomer, **24** (in a ratio of *ca* 1 : 4), believed to be obtained as a result of the approach of the $SnCl_4$ molecule from the other side of the 11(12)-bond. All spectral data of **24** are in full agreement with such a 12-epimeric structure. Tentative stereochemistry (assuming C-7 to keep its original configuration) is suggested for C-12 in **23** (and **24**), on the basis of a d-NOE experiment. Irradiation of Me-20, of **23**, causes a peak enhancement of H-3 and H-7 (of 5 and 4% respectively), whereas such an effect was not observed with **24**.

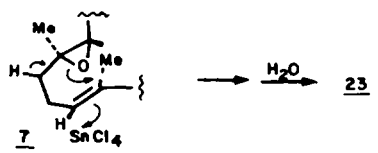
The ^{13}C-NMR spectra of **23** and **24** as well as the spectra of sarcophine itself (**7**), diol **10**, the 7-ketone **11**, episarcophine (**28**), 16-deoxysarcophine (**26**) and 11,12-epoxysarcophine (**29**)[4] are given in Table 1. The line assignments are based on chemical shift correlations and SFORD experiments.

As with sarcophine, the 16-deoxy analog of **23** (compound **27**) has also been isolated from the reaction mixture of 16-deoxysarcophine (**26**) with $SnCl_4$, confirming once more that the butenolide (as well as the dihydrofurane) does not participate in the reaction with $SnCl_4$.

Encouraged by the **7** to **23**, **24** transformation, we undertook the study of a possible transannular reaction between C-7 (or C-8) and one of the ring double bonds. We chose **16**, bearing functionalities at C-7 and C-8, as the substrate for this experiment. As known from the literature[10] and shown above, an ester or an ether can migrate under acidic conditions to a neighboring OH. Thus, **16** could have been expected to give under acidic conditions a carbonium



Scheme 5.



Scheme 6.

ion at C-7 or C-8 which could then be attacked internally by one of the ring double bonds to give a new C–C bond.

Actually, treatment of **16** with HCO_2H[16] for 2 hr at 50° afforded **11** and three secondary formates **20–22** (Scheme 4). The most polar among the three, **20**, was assigned the 7β-formyl-8α-hydroxyl structure based on its proton NMR spectrum (Experimental) and hydrolysis (KOH/MeOH) to diol **15**. Back formylation of **15** afforded as expected **20**. The structure of **21** was readily assigned by correlation with the allyl alcohol **18** (Scheme 4). Obtaining of compounds **11** and **21** (due to elimination, followed in the case of **11** by tautomerization) is in full agreement with the looked for carbonium ion at C–8. Furthermore, even **20** can serve as a good precursor for the C-8 carbonium ion. That no cyclization product could, however, be isolated can be best explained, on the one hand as a result of a possible rigid structure of the product, or on the other hand, from easy elimination under the reaction conditions. Compound **22**, the third product of the reaction with HCO_2H, was determined to be the 7-formyl derivative of **16** (Experimental).

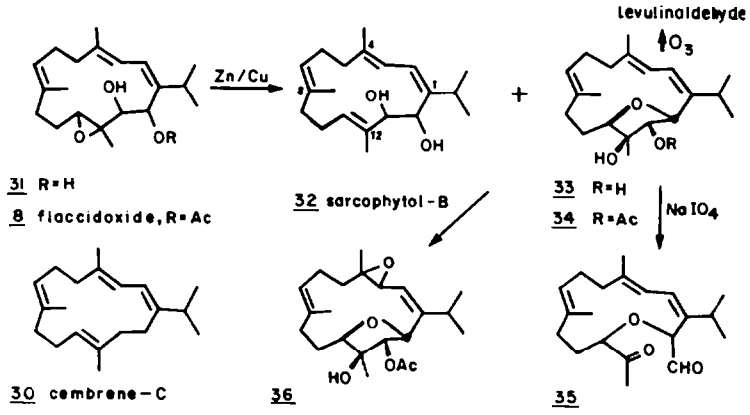
Table 2 summarizes the ^{13}C-NMR data of the 7,8-derivatives of deepoxysarcophine. The line assignment is based on SFORD experiments and chemical shift comparisons.

Another transannular reaction was revealed in the case of the Zn/Cu couple deoxygenation of flaccidoxide (**8**). The latter was recently isolated together with cembrene-C (**30**), and sarcophytol-B (**32**, the 13,14-dihydroxy derivative of **30**), from the Red Sea soft coral *Alcyonium flaccidum*.[7b] The structure of **8** (11,12-epoxy-13-hydroxy-14-acetoxy cembrene-C) suggested on the basis of its spectral data, was confirmed unequivocally by the Zn/Cu deoxygenation[17] of the diol derivative **31** to sarcophytol-B **32** (Scheme 7). The latter reaction afforded as the major product, in addition to the expected tetraene (**32**), **33**. This compound still possesses all three O atoms, but no longer an epoxide as there are no signals around δ 60 ppm in the ^{13}C-NMR spectrum. As the unsaturation of the molecule (MS) did not change, the oxiran must have been replaced by an ether bridge. Compound **33** could also be obtained from flaccidoxide by itself; moreover, it could have been shown that **33** is obtained from **8** via diol **31**. Even if the Zn/Cu couple was washed thoroughly, hydrolysis of the acetate was first noticed by TLC. The UV and NMR spectra together with a micro-ozonolysis experiment,[18] affording leuvlinaldehyde, proved that the 1,3-diene and the 7(8)-double bond of **8** remained intact. It was also obvious from the NMR spectra, that beside the ether the molecule contains two OH-groups. A positive

Table 2. ^{13}C-NMR data of deepoxysarcophine derivatives (22.63 MHz, $CDCl_3$)

C	mult.	13	14	15	16	18	21	22
1	s	162.8	163.6	163.4	163.0	162.8	163.5	163.7
2	d	78.6	78.9	79.7	79.1	78.8	78.9	78.9
3	d	121.9	122.4	121.4	120.9	121.5	122.4	122.4
4	s	143.2	142.4	144.6	144.9	143.7	142.7	141.1
5[a]	t	35.6	36.6	36.0	35.5	36.0	36.0	35.5
9[a]	t	35.4	35.5	37.0	31.0	33.8	34.6	33.5
13[a]	t	36.6	37.4	37.5	36.4	36.8	36.6	36.5
6[b]	t	26.9	25.0	27.3	26.4	26.3	25.5	25.0
10[b]	t	23.3	23.6	24.7	23.3	32.2	30.1	23.7
14[b]	t	26.6	26.8	27.4	26.8	27.0	25.7	25.6
7	d	70.9	76.3	73.3	72.6	70.5	72.6	76.4
8	s	89.9	75.2	77.5	79.4	154.5	149.4	77.1
11	d	124.9	124.4	125.8	125.5	125.9	125.0	124.5
12	s	135.2	136.0	135.2	134.3	135.0	136.1	135.1
15	s	122.7	122.4	123.3	122.8	123.0	122.7	122.4
16	s	174.9	174.4	175.5	173.7	174.9	175.0	174.8
17	q	8.8	9.0	9.4	9.0	8.9	9.1	9.0
18[c]	q	15.8	16.3	16.9	16.2	16.0	16.1	16.2
19	q	22.1	25.0	25.2	18.4	110.0	111.7	18.6
20[c]	q	15.5	15.3	15.8	15.7	15.4	15.7	15.5
CO_2	s	171.9	170.7				160.4	160.8
OAc/OMe	q	19.3	20.9		49.2			50.0

a-c See note Table 1



Scheme 7.

$NaIO_4$ reaction indicated that the two OH-groups are vicinal; furthermore, obtaining monomethyl ketone monoaldehyde (compound **35**, Experimental) proved that one of the alcohols is tertiary and must therefore be located at C-12. *A priori*, the sec alcohol, which gives an acetate, **34**, could be on C-11 or C-13, but as the ^{13}C-NMR excluded an epoxide in the molecule, the OH-group had to be at C-13 and the ether bridge between C-11 and C-14. The ^{1}H-NMR spectrum of the C-11 to C-14 moiety (Table 3) is in full agreement with the suggested structure. Moreover, from the vicinal J(H-13/H-14) coupling constant, the relative configuration of H-13 and H-14 could be concluded.[19] The THF ring in **33** is expected to be quite rigid because of its fusion to the macrocycle. Observation of a Dreiding model of **33** shows that only a dihedral angle of *ca* 120° in accordance with a 4 Hz coupling is possible between H-13 and H-14.[19] Therefore the latter two protons have to be in the *trans*-configuration. Furthermore, the cleavage of the diol by $NaIO_4$-oxidation (*vide supra*) points to a *cis*-configuration of the two OH-groups.[20] At last, a *cis*-configuration could have also been suggested between Me-20 and H-11 on the basis of a d-NOE experiment. Irradiation of the latter methyl causes simultaneous enhancement of H-11 and H-13. Unfortunately, the elucidation of the stereochemistry of the THF-substituents in **33** has not solved the stereochemistry of the epoxide in flaccidoxide (**8**), as the epoxide-opening and THF-closure can go in two ways. Worth mentioning in this context is the NOE-effect between H-11 and H-13 in flaccidoxide itself, pointing to the preferred conformation of compound **8** in solution.

Essentially, the **8** to **33** transformation is a Lewis acid catalyst transannular reaction between an epoxide and an alcohol (as, e.g. the **1** to **2** transformation). The initiation of this reaction by the Zn/Cu couple, however, was unexpected. It is most likely that such a reaction will be preferred over the deoxygenation only in cases where the OH-group occupies the suitable geometry relative to the epoxide.

Of special interest was an oxidation product (**36**), obtained by prolonged stirring of **33** in Pyr/Ac_2O solu-

Table 3. ^{1}H-NMR data of flaccidoxide and derivatives (300 MHz, $CDCl_3$)

	30			33			34			36			35		
Hat C	δ	mult.	J,Hz	δ	mult.	J,Hz	δ	mult.	J,Hz	δ	mult.	J,Hz	δ	mult.	J,Hz
2	5.92	d	11.0	6.40	d	11.0	6.13	d	11.3	5.07	d	9.4	6.49	d	10.5
3	5.83	d	11.0	6.25	d	11.0	6.06	d	11.3	3.45	d	9.4	6.02	d	10.5
7	4.99	brt*		5.19	brm		5.23	brm		5.37	d	7.5	5.12	brs	
11	4.78	brt*		3.57	dd	10.6, 1.5	3.68	dd	10.3, 2.6	3.62	dd	11.7, 2.7	3.83	dd	5, 3.5
13				3.65	d	3.9	5.01	d	4.1	5.01	d	3.5	9.72	s	
14				4.66	d	3.9	4.56	d	4.1	4.55	d	3.5	4.81	s	
Me(16)	0.96	d	5.9	1.08*	d	6.9	1.05	d	6.2	1.04	d	6.7	1.02	d	6.5
Me(17)	0.96	d	5.9	1.07*	d	6.9	0.98	d	6.5	0.98	d	6.7	1.02	d	6.5
Me(18)	1.64	brs		1.74	s		1.72	s		1.34*	s		1.74	d	1.2
Me(19)	1.49	brs*		1.60	s		1.61	d	0.9	1.61	s		1.61	s	
Me(20)	1.42	brs*		1.20	s		1.31	s		1.35*	s		2.18	s	
OAc							2.00	s		2.16	s				

* Asterisked values may be interchanged. Vicinal relationships were confirmed by double irradiations.

tion under air atmosphere while attempting a double acetylation of the molecule. The spectral data of **36** (UV and ^{1}H-NMR spectra; Experimental and Table 3) are in full agreement with a 3,4-epoxy derivative of **34**. As mentioned by us previously, it was found that in special cases which are presently under investigation, double bonds undergo easy air-epoxidation, as for example, the 4,5-double bond of caryophyllene and of xeniaphyllenes.[13]

From the above reactions and the failure to induce transannular reactions in other cembranoids, it can be concluded that such reactions take place only (a) when the molecule possesses the correct conformation of the macrocycle; (b) the substituents involved in the reaction are in proper configuration; and (c) suitable experimental conditions (catalyst, solvent, temperature, etc.) are employed. Concerning the first requirement, it seems to be that the macrocycle of the cembranoids is not as flexible as might have been expected. Therefore, it is not easy to foresee, or if desirable, to influence the ratio of transannular to competing elimination, hydrolysis and other side reactions which can take place under acidic conditions.

EXPERIMENTAL

For general part see Ref. 7*b*. For ^{13}C-NMR see Tables 1 and 2. Mass spectra were taken with an EI of 12–15 eV.

p-TsOH/CH_3CO_2H *Treatment of sarcophine.* Sarcophine (**7**, 210 mg) was stirred for 15 min in a cooled soln (10°) of AcOH (10 mL) in the presence of a few mg of *p*-TsOH. $CHCl_3$ (50 mL) was then added and the soln neutralized with 10% $NaHCO_3$, washed with water, dried (Na_2SO_4) and evaporated to give 190 mg of the products. The mixture was separated by flash chromatography, using Silica-H (Merck). The various compounds **7**, **11**, (**12**), **13**, **14** and **15** (30, 30, 30, 5 and 7%, respectively) were eluted with petroleum ether with rising percentage of ether.

7-Oxo-deepoxysarcophines **11** *and* **12**. Compound **11**, m.p. 70° (hexane–acetone), $[\alpha]_D^{24}$ + 58° (*c* 0.03, $CHCl_3$); ν_{max}^{neat} 2920, 1740, 1710, 1675, 1440, 1390, 1090, 990, 760 cm^{-1}; *m/z*(%): 316 (M^+, 4), 222(3), 180(6), 120(10); δ 5.49d (*J* = 13.5, H-2), 4.96d (*J* = 13.5, H-3), 4.88t (*J* = 9, H-11), 1.83s (Me-17), 1.94s (Me-18), 1.11d (*J* = 7.3, Me-19), 1.59s (Me-20). Compound **12**, an oil, same IR and mass spectrum as that of **11**; δ 5.65d (*J* = 13, H-2), 5.17d (*J* = 13, H-3), 5.12t (*J* = 9, H-11), 1.83s (Me-17), 1.94s (Me-18), 1.05d (*J* = 6.9, Me-19), 1.61s (Me-20); ^{13}C-NMR 214.4 (C-7), 162.1 (C-1), 142 (C-4).

7β-Hydroxy-8α-acetoxy-deepoxysarcophine (**13**); m.p. 149°, $[\alpha]_D$ + 123° (*c* 0.04, $CHCl_3$); ν_{max} 3300br, 2930, 1730, 1725, 1670, 1445, 1370, 1260, 1085, 765 cm^{-1}; *m/z*(%) 376 (M^+, 1.6), 358 (M^+–H_2O, 4.2), 316 (M^+–HOAc, 48), 298 (M^+–HOAc–H_2O, 24); δ 5.69d (*J* = 12, H-2), 5.01d (*J* = 12, H-3), 3.61brd (*J* = 10.5, H-7), 5.01brd (H-11), 1.83s (Me-17), 1.92s (Me-18), 1.45s (Me-19), 1.68s (Me-20), 2.06s (OAc).

7β-Acetoxy-8α-hydroxy-deepoxysarcophine (**14**), an oil, $[\alpha]_{D_1}$ + 87° (*c* 0.01, $CHCl_3$); ν_{max}^{neat} 3300br, 2940, 1743, 1725, 1675, 1445, 1375, 1300 cm^{-1}; *m/z*(%) 376 (M^+, 4), 358 (M^+–H_2O, 7), 316 (M^+–HOAc, 90), 298 (M^+–HOAc–H_2O, 43); δ 5.56dd (*J* = 10, 1.2, H-2), 4.81d (*J* = 10, H-3), 4.97brd (*J* = 6, H-7), 4.93t (*J* = 6, H-11), 1.82t (*J* = 1.2, Me-17), 1.92s (Me-18), 1.07s (Me-19), 1.65s (Me-20), 2.08s (OAc).

7β,8α-Dihydroxy-deepoxysarcophine (**15**), m.p. 145°, $[\alpha]_D$ + 100° (*c* 0.01, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 3300br, 2860, 1710, 1670, 1430, 1370, 1320, 1090, 980, 940 cm^{-1}; *m/z*(%) 334 (M^+, 14), 316 (M^+–H_2O, 55), 298 (M^+–$2H_2O$, 12); δ 5.60dd (*J* = 11.2, 1.9, H-2), 4.95d (*J* = 11.2, H-3), 3.60dd (*J* = 10.5, 2.2, H-7), 4.99t (*J* = 6.2, H-11), 1.82s (Me-17), 1.92s (Me-18), 1.20s (Me-19), 1.66s (Me-20).

Transformation of compound **13** *to* **14**. Treatment of **13** with *p*-TsOH/HOAc as described above for **7**, for 18 hr furnished **14**.

Transformation of sarcophine (**7**) *to ketones* **11** *and* **12**

(a) To a soln of **7** (50 mg) in dry benzene (5 mL) at 7° was added BF_3·OEt_2 (0.05 mL freshly distilled under reduced pressure from CaH_2). After 2 min ice was added and the mixture worked up in the usual manner to furnish a mixture of **11** and **12** (in a *ca* 3:1 ratio, 45 mg).

(b) To a soln of **7** (50 mg) in $CHCl_3$ (5 mL) at r.t. was added a trace of *p*-TsOH. After 18 hr ice was added and the mixture was worked up in the usual manner to give the same ketone mixture as in (a) (over 90% pure).

p-TsOH/MeOH *Treatment of sarcophine to afford compounds* **11**, **15** *and* **16**. Sarcophine **7** (400 mg) was stirred for 1 hr in a solution of MeOH (10 mL) in the presence of *p*-TsOH (15 mg). After neutralization with $NaHCO_3$ most of the MeOH was evaporated, $CHCl_3$ added and the soln washed with water, dried (Na_2SO_4) and evaporated to give a mixture of **11**, **15** and **16**. The latter three were separated by flash chromatography on a silica gel column eluted with benzene and rising amounts of ether to afford **11**, **16** and **15** (11, 81 and 5%, respectively).

8-Methoxy-7-hydroxy-deepoxysarcophine (**16**), m.p. 106°, $\nu_{max}^{CHCl_3}$ 3420br, 2920, 1730, 1670, 1440, 1370, 1205, 1095, 990, 915 cm^{-1}; *m/z*(%) 348 (M^+, 13), 330 (M^+–H_2O, 2), 314 (M^+–MeOH, 59), 296 (M^+ – MeOH–H_2O, 15); δ 5.56dd (*J* = 10.0, 1.3, H-2), 4.93d (*J* = 10, H-3), 3.45brd (*J* = 10.7, H-7), 5.07t (*J* = 6.7, H-11), 1.83s (Me-17), 1.87s (Me-18), 1.12s (Me-19), 1.65s (Me-20), 3.18s (OCH_3).

Jones oxidation of compound **16**. To a soln of **16** (18 mg) in acetone (10 mL) at 0° were added two drops of Jones reagent. After 15 min the mixture was worked up in the usual way to give **17** (12 mg); an oil, ν_{max}^{neat} 3400br, 2920, 1730, 1710, 1670 cm^{-1}; *m/z* 346 (M^+); δ 5.49brd (*J* = 10.6, H-3), 5.16brd (*J* = 10.6, H-3), 4.74m (H-11), 3.24s (OMe), 3.07ddd (*J* = 16, 11, 2.3, H-6), 2.68m (3H), 1.83br (Me-17), 1.68br (Me-18), 1.54br (Me-20), 1.18s (Me-19).

2%-H_2SO_4/Acetone treatment of sarcophine to afford compounds **11**, **15** *and* **18**. Sarcophine **7** (100 mg) was stirred for 30 min in a soln of acetone (5 mL) and aq 2% H_2SO_4 (1 mL) at 60°. Work-up, as described above for **16**, afforded a mixture of **11**, **18** and **15** (10, 17 and 70%, respectively).

7β-Hydroxy-Δ$^{8(19)}$-deepoxysarcophine (**18**), an oil, $\nu_{max}^{CHCl_3}$ 3320br, 2920, 1745, 1675, 1450, 1380, 1100, 1000 cm^{-1}; *m/z*(%) 316 (M^+, 20), 298 (M^+–H_2O, 29); δ 5.61d (*J* = 9.5, H-2), 5.07d (*J* = 9.5, H-3), 4.09d (*J* = 10.9, H-7), 5.15t (*J* = 6.3, H-11), 1.88s (Me-17), 1.84d (*J* = 1.3, Me-18), 4.93s and 5.07s (H-19 & 19'), 1.62s (Me-20).

Jones oxidation of compound **18** *to* **19**. Jones oxidation of **18** (15 mg) as described for **16** afforded 7-keto-Δ$^{8(19)}$-deepoxysarcophine (**19**), an oil, $\nu_{max}^{CHCl_3}$ 2940, 2840, 1730, 1710, 1675, 1445, 1370, 1225, 1040 cm^{-1}; *m/z*(%) 314 (M^+, 1.5), 286 (M^+–CO, 1.5); λ_{max}^{MeOH} 274 nm (ε = 11,690); δ 5.46d (*J* = 10.5, H-2), 5.01d (*J* = 10.5, H-3), 4.97t (*J* = 6, H-11), 1.81s (Me-17), 1.86s (Me-18), 5.83s and 6.06s (H-19 & 19'), 1.56s (Me-20).

Al_2O_3-Treatment of sarcophine. Sarcophine **7** (100 mg) was stirred for 2 d at r.t. in a n-hexane (10 mL) soln over activated acidic alumina (2.5 g).[12] Filtration of the alumina followed by washing with ether, and evaporation furnished 70 mg of the crude product which was separated on a silica gel column using hexane–ether mixtures for elution. The major compound, which was eluted second, was **18** (45%).

$SnCl_4$-Treatment of sarcophine to afford compounds **11**, **18**, **23** *and* **24**. To a cooled soln of **7** (800 mg) in dry $CHCl_3$ (10 mL, freshly distilled from CaH_2) at −60° was added $SnCl_4$ (0.1 mL, distilled from P_2O_5). After 30 min 10% $NaHCO_3$ aq was added and then more $CHCl_3$ (50 mL). The organic phase was washed with water, dried (Na_2SO_4) and evaporated. Flash chromatography, and also eventually HPLC, afforded compounds: **11** & **12**, **7**, **24** & **23** in 35–40%, 2–8%, 8–15% and 25–50%, respectively.

7,12-Oxa-Δ$^{8(9)}$-deepoxysarcophines **23**, **24**. Compound **23**, m.p. 145°, $\nu_{max}^{CHCl_3}$ 2900, 1725, 1665, 1435, 1375, 1095, 990 cm^{-1}; *m/z*(%) 316 (M^+, 100), 298 (M^+–H_2O, 50), 283 (M^+–H_2O–CH_3, 25); δ 85.55d (*J* = 10, H-2), 4.96d (*J* = 10, H-3), 3.68d (*J* = 11, H-7), 5.13d (*J* = 5.6, H-9), 1.83t (*J* = 1, Me-17), 1.87s (Me-18), 1.67s (Me-19), 1.54s (Me-20). Compound **24**,

m.p. 135°; $\nu_{max}^{CHCl_3}$ 2930, 1745, 1675, 1450, 1390, 1100, 1000 cm^{-1}; *m/z*(%) 316 (M^+, 7), 298 (M^+-H_2O, 2); δ 5.54d (*J* = 10.5, H-2), 5.01d (*J* = 10.5, H-3), 3.62dd (*J* = 11.5, 2.0, H-7), 5.15t (*J* = 7.3, H-9), 1.80s (Me-17), 1.84t (*J* = 1.5, Me-18), 1.65s (Me-19), 1.51s (Me-20).

$LiAlH_4$ *Reduction of sarcophine* (**7**) *to compound* **10**. Sarcophine **7** (100 mg) in ether (20 mL) was refluxed for 1 hr with LAH (30 mg). Saturated soln of Na_2SO_4 (*ca* 0.5 mL), was then added, the mixture filtered and then evaporated to afford **10**, an oil; $\nu_{max}^{CHCl_3}$ 3400br, 2900, 1650, 1380, 1430, 1065, 995, 860 cm^{-1}; *m/z*(%) 302 (M^+-H_2O), 287, 256 (M^+-H_2O–Me–CH_2OH); δ 5.36d (*J* = 6.2, H-2), 5.46dd (*J* = 6.2, 1.5, H-3), 3.01t (*J* = 6.0, H-7), 5.08brt (*J* = 7.5, H-11), 4.03d and 4.43d (*J* = 12, H-16, 16'), 1.59s (Me-17), 1.86s (Me-18), 1.29s (Me-19), 1.66s (Me-20). The compound is unstable on silica gel.

7,12-Oxa-$\Delta^{8(9)}$*-deepoxy-16-deoxysarcophine* (**27**). 16-Deoxysarcophine **26** (400 mg) afforded, under the same conditions by which **23** was produced, the 16-deoxy analog, compound **27**; an oil; $\nu_{max}^{CCl_4}$ 2910, 2820, 1440, 1370, 1260, 1035, 935 cm^{-1}; *m/z*(%) 302 (M^+, 52), 287 (M^+-CH_3, 11); δ 5.48m (H-2), 4.9m (H-3 and H-9), 4.49 (H-16, 16'), 3.71dd (*J* = 11.3, 1.5, H-7), 1.62s (Me-17), 1.79d (*J* = 1, Me-18), 1.62s (Me-19), 1.53s (Me-20).

HCO_2H-*Treatment of compound* **16**. Compound **16** (115 mg) in HCO_2H (6 mL) was stirred for 2 hr at 50°. The acid was then removed under reduced pressure and the residue separated on a silica-60 HPLC column to afford in order of polarity **21**, **11**, **22**, starting **16** and **20** (12, 25, 20, 25 and 6%, respectively). Compound **21**; an oil, $\nu_{max}^{CHCl_3}$ 2920, 1740, 1720, 1675, 1440, 1170, 1090, 900 cm^{-1}; *m/z*(%) 344 (M^+, 2), 316 (M^+–CO, 74), 298 (M^+-HCO_2H, 64), 283 (M^+-HCO_2H–Me, 23), 205 (100); δ 5.60dd (*J* = 10, 1.5, H-2), 4.87d (*J* = 10, H-3), 5.39d (*J* = 10.6, H-7), 5.17t (*J* = 6.5, H-11), 1.84t (*J* = 1.5, Me-17), 1.92d (*J* = 1, Me-18), 4.94s, 4.97s(H-19, 19'), 1.67s (Me-20), 8.10s ($\underline{H}CO_2$). Compound **22**, an oil; $\nu_{max}^{CHCl_3}$ 3370br, 2920, 1745, 1725, 1675, 1450, 1375, 1185, 1165, 1100 cm^{-1}; *m/z*(%) 331 (M^+-HCO_2, 10), 317 (M^+-HCO_2–Me, 60), 299 (M^+-HCO_2–MeOH, 20); δ 5.59d (*J* = 10.3, H-2), 4.81d (*J* = 10.3, H-3), 5.16d (*J* = 11.4, H-7), 4.98t (*J* = 8, H-11), 1.83t (*J* = 1.6, Me-17), 1.92s (Me-18), 1.11s (Me-19), 1.67s (Me-20), 8.15s ($\underline{H}CO_2$), 3.25s (OMe). Compound **20**; an oil; $\nu_{max}^{CHCl_3}$ 2900, 1745, 1715, 1675, 1445, 1330, 1185, 1170, 1105, 1015, 990 cm^{-1}; *m/z*(%) 362 (M^+, 0.1), 317 (M^+-HCO_2, 2), 2.99 ($M^+-HCO_2-H_2O$, 0.5), 83 (100); δ 5.5d (*J* = 10.3, H-2), 4.83d (*J* = 10.3, H-3), 5.15d (*J* = 9.5, H-7), 4.99dd (*J* = 6.5, 1.5, H-11), 1.84t (*J* = 1.7, Me-17), 1.94d (*J* = 0.5, Me-18), 1.12s (Me-19), 1.67s (Me-20), 8.16s ($\underline{H}CO_2$).

Treatment of flaccidoxide (**8**) *with* Zn/Cu *couple*. Flaccidoxide **8** (60 mg) was refluxed in abs MeOH (12 mL) over freshly prepared Zn/Cu couple[17] (10 g) for 24 hr. The solution was then filtered, the Zn/Cu couple thoroughly washed with MeOH to give after evaporation a bluish oil. Chromatography over a silica-gel column eluted with petrol ether–ether 1:3 gave first sarcophytol-B (**32**, 5 mg) and then **33** (25 mg). Compound **33**, an oil; $\nu_{max}^{CHCl_3}$ 3370br, 2900, 1620, 1450, 1380, 1355, 1175, 1060, 960 cm^{-1}; $\lambda_{max}^{CH_3CN}$ 250 nm (ε = 10,300); *m/z*(%) 320 (M^+, 19), 302 (M^+-H_2O, 3), 286 (4), 278 (19), 277 (M^+–iPr, 100); for ^{1}H-NMR see Table 3; δ_c ($CDCl_3$) 139.3s, 138.0s, 132.7s, 127.7d, 124.5d, 82.9d, 80.2d, 77.5d, 38.4t, 37.2t, 34.2d, 25.2t, 25.0t, 22.8q, 22.3q, 18.7q, 17.2q, 14.6q in C_6D_6 an additional singlet is observed at δ 78.3 (compare with Table II, Ref. 7*b*).

Acetylation of **33** *to* **34**. Acetylation of **33** (30 mg) with Ac_2O/Pyr at r.t. overnight furnished after the usual work-up the monoacetate **34**; an oil: $\nu_{max}^{CHCl_3}$ 3425, 2950, 1745, 1675, 1460, 1380, 1365, 1220, 1110, 1060, 1015, 960 cm^{-1}; λ_{max} 249 nm (ε = 8000); *m/z*(%) 362 (M^+, 12), 319 (M^+–iPr, 100), 302 (M^+–HOAc, 8), 259 (10), 137 (44); for ^{1}H-NMR see Table 3; δ_c 169.8s, 141.4s, 134.6s, 132.1s, 127.8d, 124.4d, 122.1d, 81.3d, 80.1d, 79.7d, 77.4s, 39.5t, 36.5t, 34.0d, 25.2t, 24.8t, 22.9q, 21.7q, 21.1q, 19.7q, 16.4q, 14.3q.

$NaIO_4$ *Oxidation of* **33** *to ketoaldehyde* **35**. Compound **33** (30 mg) in a mixture of MeOH–H_2O (1:1, 10 mL) was stirred with $NaIO_4$ (18 mg) for 5 hr at r.t. Most of the MeOH was removed under vacuum, CH_2Cl_2 (20 mL) was added and the organic phase washed with water, dried (Na_2SO_4) and evaporated to yield **35**; an oil, ν_{max}^{neat} 2960, 2940, 2870, 1735, 1715, 1690, 1450, 1385, 1360, 1100 cm^{-1}; *m/z*(%) 318 (M^+, 3), 303 (M^+–Me, 5), 289 (M^+–CHO, 6), 137 (100); for ^{1}H-NMR see Table 3.

Oxidation of **34** *to* **36**. Compound **33** or **34** (30 mg) was stirred for 7 d in a 1:1 Ac_2O/Pyr soln (1 mL). The excess of solvents was then removed under reduced pressure to give after flash chromatography the 3,4-epoxy-13-acetoxy derivative (20 mg). An oil; $\nu_{max}^{CHCl_3}$ 3630br, 2950, 2920, 1745, 1665, 1370, 1225, 1100, 1060, 1045, 1015 cm^{-1}; *m/z*(%) 378 (M^+, 12), 335 (1), 318 (M^+–HOAc, 3), 205 (14), 138 (32); for ^{1}H-NMR see Table 3.

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