# 31. Determination of the Relative Configurations in the Side Chains of the Antibiotics Hedamycin and Pluramycin A; Synthesis and NMR. Data of Suitable Model Compounds[1])

by **Mario Ceroni** and **Urs Séquin**

Institut für Organische Chemie der Universität Basel, St. Johanns-Ring 19, CH-4056 Basel

(17. XI. 81)

*Summary*

Several diepoxyhexanoates and epoxyhexenoates were prepared by epoxidation of methyl 2-methyl-2,4-hexadienoate or by *Darzens* condensation. Their $^1$H- and $^{13}$C-NMR. spectra were measured and assigned. Comparison of these data with the spectra of the antibiotics hedamycin (**1**) and pluramycin A (**2**) allowed the determination of the relative configurations in the side chains of these antibiotics. They were found to be (14*R**,16*S**,17*R**,18*S**) for hedamycin (**1**) and (14*R**,16*S**,17*Z*) for pluramycin A (**2**).

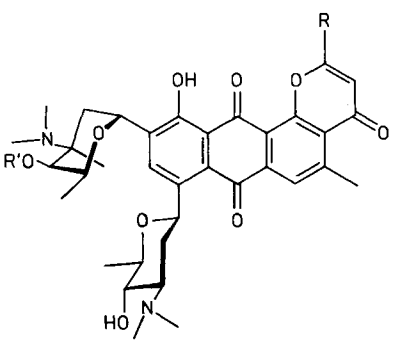
**Introduction.** – Epoxides and particularly diepoxides are known to have interesting biological activities; many of them are cytotoxic [4]. In recent years several natural products were isolated having a 1,2:3,4-diepoxy moiety. Among them are the honey-dew toxins of the tutin type [5], prepacifenol epoxide isolated from red algae [6], the antibiotic LL-Z 1220 [7] as well as the cytotoxic plant metabolite crotepoxide [8] and the antileukemic substances of the triptolide family [9]. In all these compounds one or both epoxy groups are part of a cyclic C-skeleton. So far, only two natural products with an open chain 1,2:3,4-diepoxy function have been described: the marine diterpenoid spatol [10] and the antitumor antibiotic hedamycin (**1**) [11]. The structure of hedamycin (**1**)[2]) [12] and of the closely related pluramycin A (**2**) [13] has recently been determined. The relative configurations in the diepoxy moiety of hedamycin could not yet be established, however. And in pluramycin A there seemed to be a discrepancy between the proposed configurations in the side chain and the NMR. data.

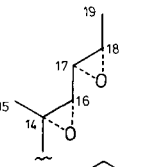
---

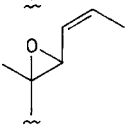
[1]) From the dissertation of *M.C.* [1]; preliminary accounts of this work: [2] [3].

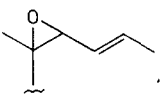
[2]) All compound in the *Schemes* are racemic, except **1** and **2**. The numbering of **1** and **2** is that used in earlier papers from this and other laboratories. The systematic name for hedamycin (**1**) is: 2-(1,2:3,4-diepoxy-1-methylpentyl)-11-hydroxy-5-methyl-8-[3-(dimethylamino)-2,3,6-trideoxy-$\beta$-D-*arabino*-hexopyranosyl]-10-[3-dimethylamino)-3-*C*-methyl-2,3,6-trideoxy-$\alpha$-L-*lyxo*-hexopyranosyl]-4*H*-anthra[1,2-*b*]-pyran-4,7,12-trione.

0018-019X/82/1/0302-15$01.00/0 



**1** (hedamycin) R =  , R' = H

**2** (pluramycin A) R =  , R' = Ac

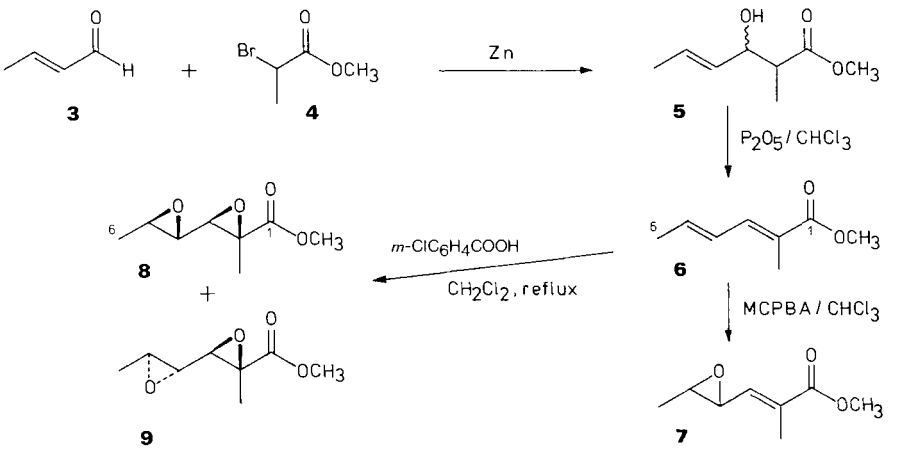
**2a** R =  , R' = Ac

Therefore, we have undertaken the synthesis of suitable model compounds, the NMR. data of which should be of help in the determination of the relative configurations in the side chains of pluramycin-like antibiotics. Ring A and the substituent at C(2) of the pluramycin antibiotics form a vinylogous ester function. The simplest model compounds thus would be the corresponding methyl esters; 2-substituted chromones would represent preciser models but need a greater synthetic effort.

Eight diastereoisomeric racemates are possible for methyl 2,3:4,5-diepoxy-2-methylhexanoate and four are possible for methyl 2,3-epoxy-2-methyl-4-hexenoate. It would be desirable to have all these isomers at hand. However, some of them are rather tedious to prepare. Therefore, those more readily prepared were synthesized first, and finally proved sufficent for the configurational assignments in hedamycin and pluramycin A. None of these compounds have been described before. Yet, methyl 2,3:4,5-diepoxyhexanoate, a compound closely related to the above-mentioned models, had been synthesized by epoxidation of methyl sorbate with perbenzoic acid [14] and by *Darzens* condensation [15]. The stereoisomers formed during the reactions were, however, either not detected or could not be properly separated.

**Syntheses and spectoscopic data.** – The *Reformatsky* condensation of crotonaldehyde (**3**) and methyl 2-bromopropionate (**4**) gave a mixture of the diastereoisomeric hydroxyesters **5**. Gas chromatography (GC.) demonstrated that the ratio of the two isomers was *ca.* 1:1. A complete preparative separation could not be achieved, since the two compounds had relative retention times of 0.97:1 under the conditions used. Elimination to the hexadienoate was not spontaneous even when the *Reformatsky* reaction was carried out at elevated temperature or when the product was distilled *in vacuo* at 98°. Thus, the mixture of hydroxyesters **5** was refluxed with $P_2O_5$ in chloroform. The reaction was monitored by GC. and proved to be complete after 30 min. Three products were formed with relative retention times of 0.58, 0.79 and 1, and in a ratio of 11.5:7:81.5. The main component was thought to be methyl (2*E*,4*E*)-2-methyl-2,4-hexadienoate (**6**). A similar GC. investigation of the geometric isomers of trimethylsilyl 2,4-hexadienoate [16] also had shown a longer retention time for the (2*E*,4*E*)-isomer than for the (2*Z*,4*E*)-isomer. The two minor products obtained in the dehydration were not investigated further; one of them is most probably the corresponding (2*Z*,4*E*)-isomer. Vacuum distillation of the mixture gave the desired

(2*E*,4*E*)-ester **6** in 97% purity. The *(E,E)*-configuration was confirmed by the 16 Hz coupling constant for the protons at the 4,5-double bond (see *Table 1*), and by the $^{13}$C-NMR. chemical shift (12.5 ppm) of the methyl group at C(2) (see *Table 2*), which is typical for the (2*E*)-configuration (*cf.* methyl 2-methylcrotonate [17]). Treatment of the dienoate **6** with *m*-chloroperbenzoic acid in $CHCl_3$ gave only the monoepoxy derivative **7**; the 2,3-double bond was not attacked, even after prolonged treatment at elevated temperature. The same was true for the reaction with alkaline 30% $H_2O_2$-Solution [18], even when benzonitrile and $KHCO_3$ were added [19]. Peracetic acid (13 or 40%) in acetic anhydride led to the same product. However, when the hexadienoate **6** was refluxed in $CH_2Cl_2$ with *m*-chloroperbenzoic acid for 4–5 days [20], a 1:1 mixture of the desired diepoxy esters **8** and **9** was formed in 89% yield. A separation of these isomers was not possible on silica gel; its acidic character seemed to cause decomposition of the diepoxy derivatives to rather polar substances. Analytical separation could, however, be achieved by GC., and preparative separation was possible with a *Florisil* column. The $^1$H-NMR. spectra of these two diepoxy esters were easily assigned (see *Table 1*). All the signals showed the expected chemical shifts and very characteristic coupling patterns. In the $^{13}$C-NMR. spectra of **8** and **9**, the resonances of the three methyl groups were readily assigned from a comparison with related glycidic esters [17] and were confirmed for C(6) and $H_3C$–C(2) by specific proton-decoupling experiments. Off-resonance decoupling revealed the C(2)-resonance as a singlet. The distinction between the resonances of the remaining epoxide C-atoms (C(3), C(4) and C(5)) was possible from several low power single frequency proton decoupling experiments over the rather narrow range 2.6 to 3.3 ppm. The residual splittings were plotted against the decoupler frequency to yield the $^1$H-NMR. frequencies associated with each $^{13}$C-NMR. signal [21]. At this point, it was not yet possible to assign the relative configurations *(ido vs. galacto)* of the two esters **8** and **9** (see below).




**3** **4** **5** **6** **7** **8** **9**

The diepoxy esters **8** and **9** are derived from the (2*E*,4*E*)-hexadienoate **6**. In order to obtain also diepoxy esters related to methyl (2*Z*,4*E*)-2-methyl-2,4-hexadienoate, a different synthetic route was chosen. *Darzens* condensation of (2*R**,3*S**)-2,3-epoxybutyraldehyde (**10**) and methyl 2-chloropropionate (**11**) gave

in poor yield a 3:3:1:1 mixture of four diepoxy esters, the GC. *(Carbowax)* of which is shown in the ***Figure***. The compounds with the longest retention times were readily identified as the *ido*- and *galacto*-isomers **8** and **9**, so that the two less retained products had to be the *gulo*- and *talo*-isomers **12** and **13**. The four diastereoisomers could not be separated by distillation. Furthermore, preparative GC. seemed hardly feasible since the difference in retention times between **12** and **13** was even smaller than between **8** and **9**. Column chromatography on *Florisil* gave the partly successful but surprising result that **12** was indeed separated from **13** but eluted together with **8**. The isomer **9** was found in the same fractions as **13**. Apparently *Florisil* differentiates the relative configuration at C(3) and C(4) (3,4-*threo vs.* 3,4-*erythro*), whereas *Carbowax* (GC.) is more sensitive to the substitution pattern of the 2,3-epoxy function. Preparative GC. the two mixtures obtained from the *Florisil* chromatography (**12** and **8**; **13** and **9**) led easily to the isolation of the pure *gulo*- and *talo*-esters **12** and **13**, respectively. They were characterized by their $^1$H- and $^{13}$C-NMR. spectra (see *Tables 1* and *2*). The $^1$H-NMR. spectra were assigned on the basis of the observed coupling patterns, and the $^{13}$C-NMR. spectra by comparison with the spectra of **8** and **9**. Again, the relative configurations of **12** and **13** *(gulo vs. talo)* could not yet be determined at this point.

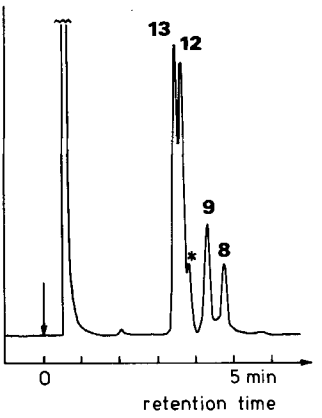



Figure. *Gas chromatogram (160°, 3%* Carbowax 20M) of the *diepoxy-ester mixture obtained from* Darzens *condensation of (2*R*,3S*)-2,3-epoxybutyraldehyde* (**10**) *and methyl 2-chloropropionate* (**11**) (* = unidentified by-product)

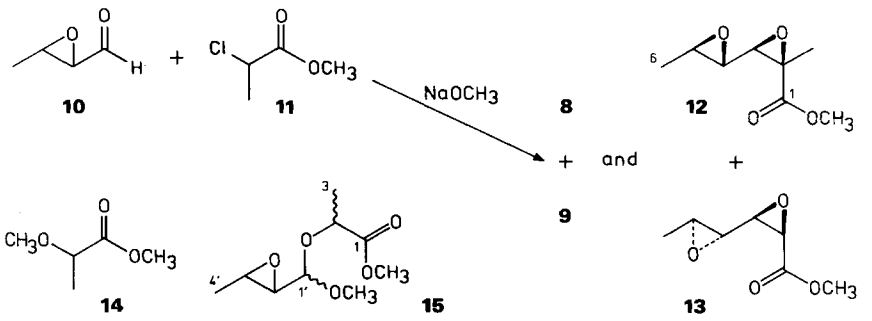


Table 1. *$^1$H-NMR. data of* **6–9, 12, 13, 16** *and* **17**[a])

| | H–C(3) | H–C(4) | H–C(5) | 3H–C(6) | $H_3C$–C(2) | $CH_3O$ |
|---|---|---|---|---|---|---|
| **6** | 7.11 *d*×*qa* (*J*=10.9 and 1.5) | 6.37 *d*×*d* (*J*=10.9 and 16.0) | 6.03 *d*×*qa* (*J*=16.0 and 6.2) | 1.86 *d* (*J*=6.2) | 1.89 br/*s* | 3.69 *s* |
| **7** | 6.29 *d*×*qa* (*J*=8.8 and 1.5) | 3.32 *d*×*d* (*J*=8.8 and 1.9) | 3.03 *d*×*qa* (*J*=1.9 and 5.3) | 1.40 *d* (*J*=5.3) | 2.01 *d* (*J*=1.5) | 3.75 *s* |
| **8** | 3.10 *d* (*J*=5.3) | 2.69 *d*×*d* (*J*=5.3 and 2.3) | 3.01 *d*×*qa* (*J*=2.3 and 5.3) | 1.37 *d* (*J*=5.3) | 1.65 *s* | 3.75 *s* |
| **9** | 3.05 *d* (*J*=6.5) | 2.64 *d*×*d* (*J*=6.5 and 2.0) | 3.10 *d*×*qa* (*J*=2.0 and 5.3) | 1.36 *d* (*J*=5.3) | 1.65 *s* | 3.75 *s* |
| **12** | 2.79[b]) | 2.79[b]) | 2.99 br. *qa* (*J*=5.0) | 1.30 *d* (*J*=5.0) | 1.58 *s* | 3.80 *s* |
| **13** | 2.77[b]) | 2.77[b]) | 3.07 br. *qa* (*J*=5.0) | 1.33 *d* (*J*=5.0) | 1.60 *s* | 3.81 *s* |
| **16** | 3.63 br. *d* (*J*=7.8) | 5.31 *d*×*d*×*qa* (*J*=7.8, 15.4 and 1.8) | 6.03 *d*×*qa*×*d* (*J*=15.4, 6.4 and 0.6) | 1.79 *d*×*d* (*J*=6.4 and 1.8) | 1.53 *s* | 3.76 *s* |
| **17** | 3.36 br. *d* (*J*=8.5) | 5.31 *d*×*d*×*qa* (*J*=8.5, 15.2 and 1.5) | 6.05 *d*×*qa*×*d* (*J*=15.2, 6.4 and 0.6) | 1.75 *d*×*d* (*J*=6.4 and 1.5) | 1.59 *s* | 3.78 *s* |

a) Chemical shifts in ppm downfield from internal TMS; coupling constants *J* in Hz. The spectral width used was 1200 Hz with 8k/4k data points; this corresponds to 0.29 Hz per data point in the real spectrum.

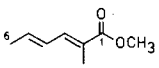
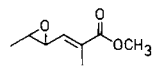
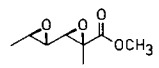
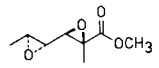
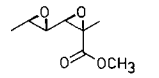
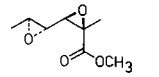
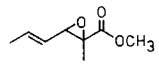
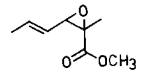
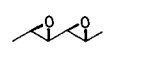
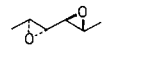
b) Multiplicity and coupling constant could not be determined due to overlap.

Already *Yanowskaya et al.* [15] had annotated the low yield of the *Darzens* condensation with similar compounds. Probably the strongly alkaline medium favors side-reactions like aldol condensation, ester condensation and nucleophilic opening of the epoxy rings. When the more reactive methyl 2-bromopropionate (**4**) was used instead of the chloro ester **11**, the main products were methyl 2-methoxypropionate (**14**) and a mixture of four diastereoisomers of methyl 2-(2,3-epoxy-1-methoxybutoxy)propionate (**15**). Its structure was derived from the elemental analysis (pointing to $C_9H_{16}O_5$) and from spectral data.

The $^1$H-NMR. spectrum of **15** indicated two methoxy groups belonging to an ether (3.4 ppm) and an ester (3.7 ppm) function, two epoxide protons (3.0 ppm), two *C*-methyl groups (1.4 ppm) and two protons at oxygenated C-atoms (4.4 ppm). In the $^{13}$C-NMR. spectrum a cluster of four signals around 102 ppm pointed to a mixture of four acetals. The presence of an additional oxygenated C-atom, two epoxide C-atoms, as well as the methoxy and *C*-methyl groups was corroborated.

The acetal mixture **15** is probably formed by addition of methoxide to the aldehyde carbonyl group. The resulting hemiacetal anion then substitutes the bromide of the bromopropionate. No attempt was made to isolate the different isomers from the mixture **15**.

Table 2. *$^{13}$C-NMR. data of* **6–9, 12, 13, 16, 17, 23** *and* **24**[a])

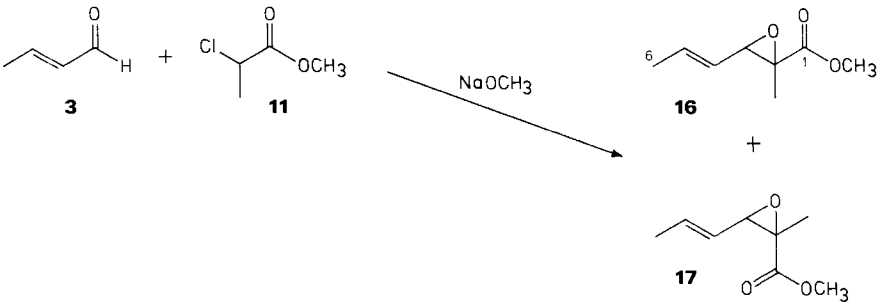
| | | C(1) | C(2) | C(3) | C(4) | C(5) | C(6) | $CH_3$–C(2) | $CH_3O$ |
|---|---|---|---|---|---|---|---|---|---|
|  | **6** | 168.8 *s* | 124.9 *s* | 138.8 *d*[b]) | 127.7 *d*[b]) | 137.5 *d*[b]) | 18.8 *qa* | 12.5 *qa* | 51.6 *qa* |
|  | **7** | 167.4 *s* | 132.1 *s* | 138.5 *d* | 55.3 *d*[b]) | 56.1 *d*[b]) | 17.5 *qa* | 12.8 *qa* | 51.8 *qa* |
|  | **8** | 170.6 *s* | 57.2 *s* | 60.8 *d*[b]) | 55.4 *d*[b]) | 51.5 *d*[b]) | 17.1 *qa* | 14.0 *qa* | 52.6 *qa* |
|  | **9** | 170.6 *s* | 57.4 *s* | 60.5 *d*[b]) | 55.0 *d*[b]) | 53.6 *d*[b]) | 17.1 *qa*[b]) | 13.7 *qa*[b]) | 52.8 *qa* |
|  | **12** | 169.8 | 58.6 | 63.0 | 55.5 | 51.9 | 17.1 | 19.1 | 52.5 |
|  | **13** | 169.5 | 58.9 | 62.5 | 54.8 | 53.6 | 17.0 | 18.9 | 52.6 |
|  | **16** | 171.5 *s* | 59.1 *s* | 62.1 *d* | 124.0 *d*[b]) | 134.7 *d*[b]) | 18.1 *qa* | 13.6 *qa* | 52.5 *qa* |
|  | **17** | 170.2 *s* | 61.0 *s* | 64.3 *d* | 124.4 *d*[b]) | 134.9 *d*[b]) | 18.0 *qa* | 19.2 *qa* | 52.3 *qa* |
|  | **23** | 17.2 | 51.8 | 57.6 | 57.6 | 51.8 | 17.2 | | |
|  | **24** | 17.2 | 53.1 | 57.9 | 57.9 | 53.1 | 17.2 | | |

| | | C(14) | C(16) | C(17) | C(18) | C(19) | C(15) |
|---|---|---|---|---|---|---|---|
| Hedamycin[c]) | **1** | 57.7 *s* | 63.9 *d* | 55.4 *d* | 51.8 *d* | 17.2 *qa* | 14.5 *qa* |
| Pluramycin A[d]) | **2** | 60.3 *s* | 61.7 *d* | 123.3 *d* | 134.1 *d* | 14.4 *qa* | 14.9 *qa* |

a) Chemical shifts in ppm downfield from internal TMS. The multiplicities given were determined by off-resonance decoupling.
b) Assigned from specific proton-decoupling experiments.
c) Data from [32].
d) Data from [13].

*Darzens* condensation of crotonaldehyde (**3**) and methyl 2-chloropropionate (**11**) gave in low yield a 1:1 mixture of the diastereoisomeric methyl 2,3-epoxy-2-methyl-4-hexenoates (**16** and **17**), serving in the configurational assignments of pluramycin A (**2**). *Florisil* column chromatography removed the more polar side-products, but did not separate **16** from **17**. However, this could be achieved by preparative GC. The $^1$H-NMR. spectra of **16** and **17** were readily assigned (see *Table 1*) and confirmed the *(E)*-configuration of the double bond. The configuration at C(2) and C(3) was derived from the $^{13}$C-NMR. data (see *Table 2*). The compound with the $H_3C$–C(2) resonance at higher field was assigned structure **16**, where this methyl C-atom is in a *γ-cis*-relationsship to C(4). Confirmation came from the carbonyl *chemi-*

cal shifts: the $C{=}O$ of **17** appears at higher field than the one of **16**, as expected. Reinvestigation of the assignments of the olefinic C-resonances in these compounds by selective H-decoupling experiments revealed, that the assignments given in our preliminary communications on hedamycin [3], pluramycin A [2] and rubiflavin [22] should be interchanged.




**3** **11** **16** **17**

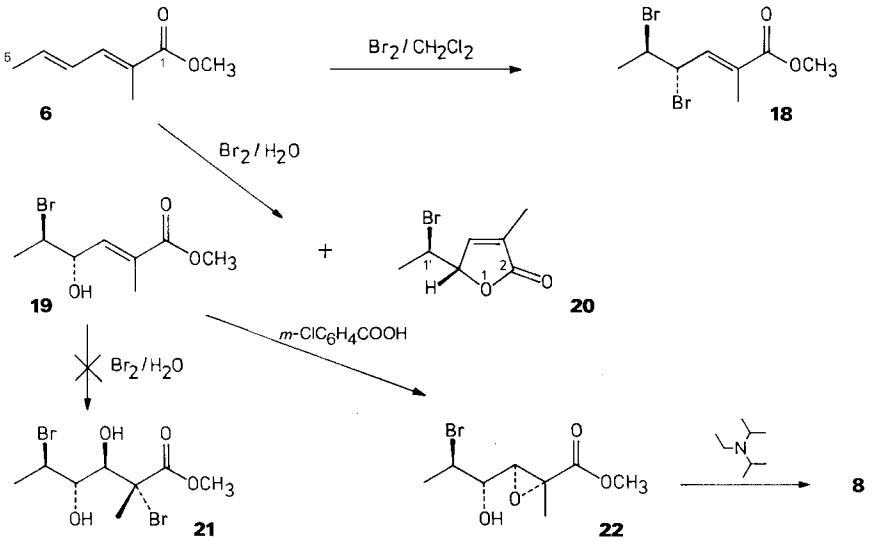
**Configurational analysis of the diepoxy esters.** – Whereas the configurations of the monoepoxy esters **7**, **16** and **17** were quite easily assigned with the aid of the NMR. data, this could not be done in the case of the diepoxy esters. The distinction of *threo vs. erythro* was considerably more difficult.

Three ways may be envisaged to solve this problem: transformation of the diepoxy esters to derivatives whose configurations can be more readily determined, stereoselective synthesis instead of the rather general and unselective routes described above, and comparison with related substances of known configuration.

Several accounts of configurational assignments of diepoxides can be found in the literature. *Marshall et al.* [23] used sequences of stereoselective reactions, which ultimately led to cyclic products. Their configurations were determined by $^1$H-NMR. spectroscopy. On the other hand, *Vogel et al.* synthesized the two diastereoisomeric benzenediepoxides using selective reactions [24]. In both these examples there is no free rotation about the bond between the two epoxy groups, which facilitates both, selective reaction sequences and configurational assignments from NMR. data. Only two papers have appeared, where the configurational analysis of open-chain 1,2:3,4-diepoxides was described. *Bernhardt & Korte* were able to transform 2,3:4,5-diepoxy-2,5-dimethylhexanes with dilute $H_2SO_4$-solution into 2,3-dihydroxytetrahydrofurans [25]. The $^1$H-NMR. spectra then allowed assignment of the configurations. Each epoxide contained one di- and one monosubstituted C-atom. This made the ring opening by the dilute acid, known to proceed *via* the most stable carbenium ion, selective. *Heasley,* who reported the synthesis of 2,3:4,5-diepoxyhexanes from the corresponding dienes [26], relied on stereoselective synthesis of some of the isomers for configurational analysis. The key reactions there were the 1,4-addition of bromine to the diene [27] and the oxidation of the resulting central double bond with permanganate to the *cis*-diol.

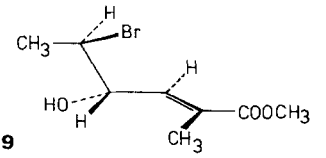
In the case of the four diepoxy esters **8**, **9**, **12** and **13**, a stereoselective transformation seemed not very promising. An opening of the trisubstituted 2,3-epoxy moiety might be selective, whereas the 4,5-epoxy group would probably be attacked randomly at C(4) or C(5). A selective synthesis was therefore envisaged in analogy to *Heasley*'s experiments. However, bromination of the hexadienoate **6** gave only the

4,5-dibromo derivative **18**; no 1,4-addition to the diene system was observed. Bromination of **6** in aqueous solution gave selectively the bromohydrin **19**, together with small amounts of the dibromo derivative **18** and of a bromolactone **20**. The formation of **20** must involve an isomerization of the 2,3-double bond prior to ring closure. We tried to convert **19** into the bis-bromohydrin **21**, which then could hopefully be cyclized with base to **9** and also be transformed into a cyclic acetal for configurational analysis by NMR. However, treatment of the bromohydrin **19** with aqueous $Br_2$-solution was very unselective; a mixture of six products in about equal amounts was obtained. *Ueno*'s procedure for the selective transformation of $\alpha,\beta$-unsaturated esters into $\alpha$-bromo-$\beta$-hydroxyesters by reaction with formic acid and *N,N*-dibromobenzenesulfonamide and subsequent hydrolysis with 1% hydrochloric acid [28] also yielded a mixture. GC./MS. analysis showed it to consist of bromolactone **20** (21%), dienoate **6** (27%), starting material **19** (16%), two isomeric monobromo compounds of unknown structure (20 and 11%), and two dibromo derivatives of the expected molecular weight (4 and 1%). This route was therefore abandoned.




The allylic hydroxy group of **19** suggested that this compound might be epoxidized in a selective way. Cyclohexenols are known to be epoxidized *cis* to the hydroxy group [29] due to H-bonding between the hydroxyl and the peracid. In open-chain allyl alcohols selectivity is only expected when a certain conformation is preferred over others in the transition state. It was shown that *cis*-methyl substitution of the double bond with respect to the allyl C-atom bearing the HO-group leads to predominant formation of the *threo*-epoxide [30]. An investigation of the conformations of the bromohydrin **19** with space-filling molecular models suggests that the arrangement shown below, where OH and Br on the one hand and H–C(3) and H–C(4) on the other hand are antiperiplanar, would be the most stable. In this conformation the Br-atom effectively blocks one side of the olefin so that selective attack by the peracid from the opposite side would be expected. This is also the side where H-bonding of the reagent to the allylic HO-group is possible. Indeed, treat-

ment of **19** with *m*-chloroperbenzoic acid in refluxing $CH_2Cl_2$ gave a mixture of two epoxy-bromohydrins in the ratio of 9:1. It seems reasonable to assign structure **22** to the product formed to a greater extent. This mixture of epoxy-bromohydrins was treated with base. The main product formed was shown by $^1$H-NMR. spectroscopy and GC. to be identical with one of the diepoxyhexanoates previously obtained from the direct epoxidation of methyl 2-methyl-2,4-hexadienoate (**6**); this product was then assigned the *ido*-configuration **8**.




**19**

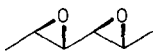
Since *Heasley* had carefully assigned the configurations of the various 2,3:4,5-diepoxyhexanes [26], comparison of our diepoxyhexanoates **8** and **9** with the corresponding compounds **23** and **24** seemed appropriate for a corroboration of the configurational assignments made above. Compounds **23** and **24** were prepared by epoxidation of (2*E*,4*E*)-2,4-hexadiene with *m*-chloroperbenzoic acid. Separation of the diastereoisomers was achieved by *Florisil* column chromatography, the *erythro*-isomer **24** being eluted before the *threo*-isomer **23**; the same was true for the separation of **8** and **9**. Since **8** and **9** differ from **23** and **24** only by an additional methoxycarbonyl group both pairs may be expected to behave similarly upon GC. with the same stationary phase. The compounds were characterized by their *Kováts* indices [31] (see *Table 3*). Due to the differences in molecular weight and in adsorptivity

Table 3. *GC. behaviour of the methyl 2,3:4,5-diepoxy-2-methylhexanoates* **8** *and* **9**, *and the 2,3:4,5-diepoxyhexanes* **23** *and* **24** (3% *Carbowax 20M*)

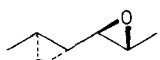
| Temp. | Retention times (min) | | | | | | | | *Kováts* indices [31] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $C_{12}$[a]) | **24** | **23** | $C_{14}$ | $C_{18}$ | **9** | **8** | $C_{20}$ | **24** | **23** | $\Delta$[b]) | **9** | **8** | $\Delta$ |
| 80° | 3.68 | 6.40 | 7.90 | 11.74 | | | | | 1295 | 1332 | 37 | | | |
| 90° | 2.65 | 4.24 | 5.36 | 7.58 | | | | | 1297 | 1334 | 37 | | | |
| 100° | 1.96 | 3.15 | 3.73 | 4.96 | | | | | 1302 | 1339 | 37 | | | |
| 110° | 1.56 | 2.39 | 2.76 | 3.51 | | | | | 1305 | 1341 | 36 | | | |
| 120° | 1.30 | 1.89 | 2.16 | 2.61 | | | | | 1307 | 1345 | 38 | | | |
| 130° | | | | | 10.50 | 12.90 | 14.55 | 26.55 | | | | 1844 | 1870 | 26 |
| 150° | | | | | 4.85 | 5.90 | 6.50 | 10.67 | | | | 1850 | 1874 | 24 |
| 160° | | | | | 3.50 | 4.25 | 4.67 | 7.30 | | | | 1853 | 1878 | 25 |
| 170° | | | | | 2.70 | 3.23 | 3.53 | 5.20 | | | | 1855 | 1882 | 27 |
| 180° | | | | | 2.06 | 2.48 | 2.68 | 3.76 | | | | 1862 | 1887 | 25 |

[a]) Unbranched alkane with 12 C-atoms. [b]) Difference of the *Kováts* indices.

stemming from the methoxycarbonyl group, the hexadienoates **8** and **9** had to be measured in a different temperature interval than the diepoxyhexanes **23** and **24**. However, the *Kováts* indices and, more specifically, their differences are only slightly dependent on the temperature. In each pair of isomers, the differences of the *Kováts* indices, which are representative for the differences in configuration (3,4-*threo vs.* 3,4-*erythro*), are of comparable size and thus confirm the configurations as-



23



24

signed to **8** and **9**. A comparison of the $^{13}$C-NMR. of **8** and **23**, and of **9** and **24** (see *Table 2*) further corroborates the configurational assignments. There is a significant difference in the chemical shifts of the C(5)-resonances. This signal appears at higher field ($\Delta\delta$= 1.5–2 ppm) in the 3,4-*threo*-compounds **8** and **23**.

The configurations of the other two diastereoisomeric esters **12** and **13** obtained from the *Darzens* condensation were assigned in an analogous way. The compound eluted later from the GC. column and having its C(5)-resonance at higher field must be the 3,4-*threo*-isomer and thus was assigned the *gulo*-configuration **12**.

**The configuration of hedamycin (1).** – Comparison of the $^{13}$C-NMR. data of hedamycin [32] with those of the model diepoxy esters **8**, **9**, **12** and **13** (see *Table 2*) shows that compounds **8** and **12** come closest to the antibiotic. In **8** the line for C(3) does not well agree with the corresponding signal of hedamycin, whereas in **12** this is the case for $H_3C$–C(2). The substitution pattern of trisubstituted epoxides can be deduced from vicinal C,H-coupling constants [17]. A fully proton coupled $^{13}$C-NMR. spectrum of hedamycin (**1**) showed a sharp quadruplet for C(15) (= $H_3C$–C(14)). The absence of any C,H long-range coupling proves that C(15) and H–C(16) have a *trans*-relationship. Then, the side chain of hedamycin must have the same relative configurations as the *ido*-diepoxyhexanoate **8**, *viz.* (14*R**,16*S**,17*R**, 18*S**). The large (3 ppm) difference between the resonances of C(3) of **8** and C(16) of hedamycin has lately been shown to be typical for the $^{13}$C-NMR. spectra of glycidic esters and corresponding 2-substituted chromones [33].

Recently, an X-ray structure determination of hedamycin was achieved [34]. The relative configurations derived above for the diepoxy side-chain were fully confirmed.

**The configuration of pluramycin A (2).** – Some years ago, *Kondo et al.* suggested the structure **2a** for pluramycin A, an antibiotic closely related to hedamycin (**1**) [13]. There were, however, inconsistencies between the spectral data reported and the structure suggested. In a nucleare *Overhauser* effect (NOE) experiment an increase in signal intensity was noticed for the H–C(16) resonance when C(15) was irradiated. It was concluded that C(15) and H–C(16) must be *cis*-oriented with respect to each other. In this configuration a chemical shift of *ca.* 19 ppm is expected for C(15) as can be seen from the spectra of the corresponding model compounds **12**, **13** and **17**. However, the value reported by *Kondo et al.* is 14.9 ppm and rather points to a *trans*-arrangement (compare compounds **1**, **16**, **8** and **9**). We believe that the chemical shift of C(15) is more reliable for the assignment of the configuration at C(14) and C(16) than the NOE experiment.

The configuration of the double bond in the pluramycin A side-chain was suggested to be *trans* by *Kondo et al.* The arguments were an 11 Hz coupling-constant measured for the olefinic protons and the 2 Hz allylic coupling-constant observed for $H_3C$(19) and H–C(17) [13]. However, a $J$ of 11 Hz between olefinic protons is well known to be indicative for the *cis*-configuration; whereas *ca.* 16 Hz are usually measured in *trans*-disubstituted olefins; furthermore, according to *Barfield et al.*

[35] the size of the allylic coupling should not be used for the assignment of the double-bond geometry in acyclic systems. Support for the *cis*-configuration of the double bond in pluramycin A is obtained from the $^{13}$C-NMR. data. In all model compounds with a terminal *trans*-double bond (*viz.* **5, 6, 16** and **17**) the resonance of the terminal methyl group is around 18 ppm. The chemical shift measured by *Kondo et al.* for this methyl group in pluramycin A is 14.4 ppm, which clearly corroborates the *cis*-geometry deduced above from the coupling data.

Thus, from the spectroscopic data of pluramycin A and our model compounds the conclusion must be drawn that the side-chain configurations in this antibiotic are not represented by formula **2a** as suggested by *Kondo et al.*, but rather by structure **2** with a *cis*-double bond, and with the pyrone substituent and C(17) arranged *trans* at the 14,16-epoxy moiety.

Financial support by the *Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung*, the *Ciba-Stiftung*, Basel, and the *Van't Hoff Fonds* is gratefully acknowledged.

## Experimental Part

*General remarks.* The samples used for microanalyses and for spectroscopic measurements were – volatility permitting – dried for at least 1 h at room temp. under high vacuum, or they were obtained directly from GC. Elemental analyses were carried out in the analytical laboratory of the *Institut für Organische Chemie (E. Thommen)*, Basel. UV., IR., and NMR. spectra were measured in the spectral laboratory of the *Institut für Organische Chemie (K. Aegerter)*, Basel, on the following instruments: *Perkin-Elmer 125* or *177*, *Beckman* DK 2, *Bruker WH 90* (90 MHz for $^1$H, 22.63 MHz for $^{13}$C; spectra were measured at these frequencies, if not stated otherwise) or *Varian EM 360* (60 MHz). Mass spectra and GC./MS. analyses were measured by *A. Raas* with a *Hitachi-Perkin-Elmer RMU 7* in the *Physikalisch-chemisches Institut*, Basel.

Silica gel (63–200 μm, *Merck*) and *Florisil* (150–250 μm, *Fluka*) were used for column chromatography. Analytical GC. were run on a *Perkin-Elmer Sigma 3* or on a *Perkin-Elmer 3920*; this latter was also used for preparative runs. Packed columns were used with *Chromosorb W* as support (80/100 mesh for analytical and 60/80 mesh for preparative purposes) and various stationary phases (detailed below).

*Synthesis of methyl (4E)-3-hydroxy-2-methyl-4-hexenoate* (**5**). Zinc (50 g, 0.76 mol) was activated for 5 min with 2N HCl and then washed with two portions each of water, acetone and benzene. It was then suspended in 250 ml of dry benzene, and a mixture of crotonaldehyde (**3**; 60 ml, 0.73 mol) and methyl 2-bromopropionate (**4**; 74 ml, 0,66 mol) was added dropwise. The reaction started spontaneously when *ca.* 1/3 of the reagents had been added. Boiling was maintained by regulating the addition rate and/or cooling. When addition was complete, the mixture was refluxed for additional 30 min. After cooling, 200 ml of 2N $H_2SO_4$ were added, the phases were separated, and the organic layer was washed successively with 2N $H_2SO_4$, $NaHCO_3$-solution and water and then dried over $Na_2SO_4$. Removal of the benzene *in vacuo* yielded 65 g (63%) of crude **5**. A sample was distilled: b.p. 98–100°/24 mbar ([36]: 98°/20 mbar). GC. (3% *Carbowax 20M*) showed the distillate to be a 1:1 mixture of the diastereoisomers **5a** and **5b** (configurations not assigned) with relative retention times of 0.97:1.

$C_8H_{14}O_3$ (158.20) Cal. C 60.74 H 8.92% Found C 60.52 H 9.06%

Prep. GC. gave a 2:1 mixture of **5a** and **5b**, which permitted assignment of the NMR. signals.

*NMR. data of* **5a**. – $^1$H-NMR. ($CDCl_3$): 6.0–5.3 (*m*, 2 H, H–C(4) and H–C(5)); 4.3 (br. *s*, 1 H, H–C(3)); 3.70 (*s*, 3 H, $CH_3O$); 2.8–2.3 (*m*, 2 H, H–C(2) and HO); 1.71 (br. *d*, $J$=5, 3 H, 3 H–C(6)); 1.17 (*d*, $J$=7.3, 3 H, $H_3C$–C(2)). – $^{13}$C-NMR. ($CDCl_3$): 175.7 (C=O); 130.6 and 128.3 (C(4), C(5)); 73.4 (*C*(3)); 51.7 ($CH_3O$); 45.3 (C(2)); 17.7 (C(6)); 11.6 ($CH_3$–C(2)).

NMR. *data of* **5b**. – $^1$H-NMR. ($CDCl_3$): 6.0–5.3 (*m*, 2 H, H–C(4) and H–C(5)); 4.3 (br. *s*, 1 H, H–C(3)); 3.72 (*s*, 3 H, $CH_3O$); 2.8–2.3 (*m*, 2 H, H–C(2) and HO); 1.71 (br. *d*, $J$=5, 3 H, 3 H–C(6)); 1.14 (*d*,

$J$=7.3, 3 H, $H_3C$–C(2)). – $^{13}$C-NMR. ($CDCl_3$): 175.7 (C=O); 131.3 and 129.0 (C(4), C(5)); 74.8 (C(3)); 51.7 ($CH_3O$), 45.8 (C(2)); 17.7 (C(6)); 11.6 ($CH_3$–C(2)).

*Synthesis of methyl (2*E*,4*E*)-2-methyl-2,4-hexadienoate* (**6**) [37]. Crude **5** (65 g) was refluxed in $CHCl_3$ for 30 min with 75 g of *Sicapent* drying agent ($P_2O_5$ on an inert support, *Merck*). The mixture was filtered and the filtrate washed with water, dried over $Na_2SO_4$ and evaporated *in vacuo*. Vacuum distillation gave 39 g (67%) of **6**, b.p. 52–53°/5 mbar ([37]: 86°/16 mbar), $n_D^{25}$ = 1.502 ([37]: $n_D^{20}$ = 1.5044). The product was contaminated with *ca.* 5% of an unidentified isomer. Partial polymerization during distillation could not be avoided even when a radical scavenger (*Santonox R*) was added. – UV. (ethanol): 263 (24'000). – IR. ($CCl_4$): 2950, 1700, 1640, 1610, 1432, 1290, 1235, 1110, 1100, 965. – $^1$H-NMR. ($CDCl_3$): see *Table 1.* – $^{13}$C-NMR. ($CDCl_3$): see *Table 2.*

$C_8H_{12}O_2$ (140.18) Calc. C 68.54 H 8.63% Found C 68.37 H. 8.67%

*Synthesis of methyl (4*R**,5*R**,2*E*)-4,5-epoxy-2-methyl-2-hexenoate* (**7**). To a solution of 5.17 g of *m*-chloroperbenzoic acid (*Fluka, ca.* 90%, 27 mmol) in 70 ml of $CHCl_3$ was added **6** (3.3 g, 25.5 mmol). The solution was stirred at 25° for 7 h and then washed with 30 ml each of 10% $Na_2SO_3$-solution, 0.5N NaOH and water, dried over $Na_2SO_4$ and evaporated *in vacuo*: 2.9 g (79%) of crude **7** containing, according to GC. (170°, 10% *Carbowax 20M*), 10% of an impurity. Purification by column chromatography (450 g $SiO_2$, $CH_2Cl_2$ with 0–4% acetone) yielded 1.9 g of pure **7**, b.p. 192°/*ca.* 1 bar, $n_D^{20}$ = 1.471. – UV. (ethanol): 224 (14'700). – IR. ($CCl_4$): 2990, 2950, 1715, 1650, 1430, 1310, 1250, 1235, 1190, 1160, 1095, 840. – $^1$H-NMR. ($CDCl_3$): see *Table 1.* – $^{13}$C-NMR. ($CDCl_3$): see *Table 2.*

$C_8H_{12}O_3$ (156.18) Calc. C 61.52 H 7.75% Found C 61.53 H 7.75%

*Synthesis of methyl (2*R**,3*S**,4*R**,5*S**)-2,3:4,5-diepoxy-2-methylhexanoate* (**8**) *and methyl (2*R**,3*S**,4*S**,5*R**)-2,3:4,5-diepoxy-2-methylhexanoate* (**9**). To a solution of 27 g of *m*-chloroperbenzoic acid (*ca.* 90%, 141 mmol) in 200 ml of $CH_2Cl_2$ was added **6** (6 g, 42.8 mmol). The mixture was refluxed for 5 days. After cooling, the white precipitate of *m*-chlorobenzoic acid, which had formed after *ca.* 3 days, was removed by filtration, the filtrate was washed with 100 ml each of 10% $Na_2SO_3$-solution, 2N NaOH and water, dried over $Na_2SO_4$ and evaporated *in vacuo*. A 1:1 mixture (6.55 g, 89%) of **8** and **9** (contaminated with a small amount of **6**) resulted. The crude product (500 mg) was purified and separated on a *Florisil* column (75 g, cyclohexane/acetone 96:4): Fr. 1 (650 ml, 0 mg); Fr. 2 (40 ml, 13.5 mg): 100% **8**; Fr. 3 (40 ml, 54.0 mg): 100% **8**; Fr. 4 (40 ml, 66.4 mg): **8/9** 99.5: 0.5; Fr. 5 (40 ml, 61.9 mg): **8/9** 86.8: 13.2; Fr. 6 (40 ml, 52.5 mg): **8/9** 48.5: 51.5; Fr. 7 (40 ml, 46.2 mg): **8/9** 14.4: 85.6; Fr. 8 (40 ml, 42.8 mg): **8/9** 5:95; Fr. 9 (40 ml, 36.7): **8/9** 1:99; Fr. 10 (400 ml, 61.6 mg) 100% **9**; total: 435.6 mg.

*Data of* **8**. – $n_D^{23}$ = 1.447. – IR. ($CHCl_3$): 3000, 1735, 1430, 1375, 1305, 1290, 1185, 1160, 860. – $^1$H-NMR. ($CDCl_3$): see *Table 1.* – $^{13}$C-NMR. ($CDCl_3$): see *Table 2.*

$C_8H_{12}O_4$ (172.17) Calc. C 55.80 H 7.03% Found C 55.56 H 7.26%

*Data of* **9**. – $n_D^{23}$ = 1.447. – IR. ($CCl_4$): 3000, 2950, 1740, 1435, 1305, 1290, 1190, 1160, 1090, 860. – $^1$H-NMR. ($CDCl_3$): see *Table 1.* – $^{13}$C-NMR. ($CDCl_3$): see *Table 2.*

$C_8H_{12}O_4$ (172.17) Calc. C 55.80 H 7.03% Found C 55.57 H 7.28%

*Synthesis of (2*R**,3*S**)-2,3-epoxybutyraldehyde* (**10**). The procedure of *Yanovskaya et al.* [15] was slightly modified: to a solution of crotonaldehyde (**3**; 90 ml, 1.1 mol) in 700 ml of water, in which 100 g of $KHCO_3$ was suspended, was added dropwise 120 ml of 30% $H_2O_2$ over 1 h. Cooling was necessary to maintain the temp. below 40°. Stirring was continued for 4 h. The pH of the solution remained constant at pH 8. The solution was then saturated with NaCl and extracted exhaustively with $CH_2Cl_2$. The extract was dried over $Na_2SO_4$ and evaporated. The resulting crude product (82 g, 87%) was vacuum distilled to give 22 g of **10** containing *ca.* 10% of **3** and a second fraction of almost pure **10**, (25 g), b.p. 55–57°/80 mbar, $n_D^{25}$ = 1.417 ([15]: 53–55°/80 mbar, $n_D^{20}$ = 1.4210; [38]: 66–68°/133 mbar, $n_D^{20}$ = 1.4185). – $^1$H-NMR. (60 MHz, $CDCl_3$): 9.06 (*d*, $J$=6, 1 H, H–C(1)); 3.37 (*qa*×*d*, $J$=5 and 2, 1 H, H–C(3)); 3.12 (*d*×*d*, $J$=6 and 2, 1 H, H–C(2)); 1.44 (*d*, $J$=5, 3 H, 3 H–C(4)). – $^{13}$C-NMR. ($CDCl_3$): 198.5 (*d*, C(1)); 60.1 (*d*×*d*, C(2)); 53.0 (*d*, C(3)); 16.8 (*qa*, C(4)).

*Synthesis of methyl (2*R**,3*R**,4*S**,5*R**)-2,3:4,5-diepoxy-2-methylhexanoate* (**12**) *and methyl (2*R**,3*R**,4*R**,5*S**)-2,3:4,5-diepoxy-2-methylhexanoate* (**13**). A solution of Na (3 g, 130 mmol) in 26 ml of abs. methanol was added dropwise to a mixture of **10** (10.5 g, 122 mmol) and methyl 2-chloropropionate (**11**; 17.9 g, 145 mmol) at 0–10°. The mixture was stirred for 2 h at 20° and then poured into 200 ml of ether. This ether extract was washed with sat. $Na_2SO_4$-solution, dried over $Na_2SO_4$ and evaporated *in*

*vacuo*. Vacuum distillation yielded 3.7 g (18%) of a mixture of **8, 9, 12,** and **13** (b.p. 73–91°/1.3 mbar). Of that 1 g was subjected to *Florisil* column chromatography (100 g, cyclohexane/acetone 10:0→9:1) yielding 285 mg of a 7:3 mixture of **13** and **9**, and 190 mg of a 3:1 mixture of **12** and **8**. Samples of **12** and **13** for spectral analyses were obtained by prep. GC. of each of the above mixtures (170°, 10% *Carbowax 20M*).

*NMR. data of* **12**. – $^1$H-NMR. ($CDCl_3$): see *Table 1*. – $^{13}$C-NMR. ($CDCl_3$): see *Table 2*.

*NMR. data of* **13**. – $^1$H-NMR. ($CDCl_3$): see *Table 1*. – $^{13}$C-NMR. ($CDCl_3$): see *Table 2*.

*Attempted* Darzens *condensation with methyl 2-bromopropionate (***4***).* A solution of Na (5.13 g, 223 mmol) in 41 ml of abs. methanol was added dropwise at 0–10° to a mixture of **10** (17.6 g, 204 mmol) and **4** (42.5 g, 254 mmol). The solution was stirred at room temp. for 2.5 h and then worked up as described above for **12** and **13** yielding 54 g of crude product, which was vacuum distilled. The fraction collected at 30°/13 mbar yielded 9.8 g of nearly colorless oil, consisting according to GC./MS. of **10** (10%) and **4** (20%) and *methyl 2-methoxypropionate* (**14**; 70%). The fraction boiling at 68°/0.013 mbar (7 g) was a colorless oil consisting of a mixture **15**.

*Data of* **14** [39]: MS.: 119 (0.5, $M^+ + 1$), 118 (0.9, $M^+$), 117 (0.9), 103 (3.4), 88 (54), 75 (12), 59 (100), 43 (62), 31 (24).

*Data of methyl 2-(2,3-epoxy-1-methoxybutoxy)propionate* (**15**; mixture of diastereoisomers). – $^1$H-NMR. ($CDCl_3$): 4.5–4.2 (*m*, 2 H, H–C(2) and H–C(1′)); 3.75, 3.73 (2 *s*, 3 H, $COOCH_3$); 3.45, 3.44, 3.43, 3.41 (4 *s*, 3 H, $CH_3O$); 3.1–2.8 (*m*, 2 H, H–C(2′) and H–C(3′)); 1.5–1.3 (*m*, 6 H, 3 H–C(3) and 3 H–C(4′)). – MS: 189 (1.0, $M^+ - CH_3$), 173 (16, $M^+ - CH_3O$), 147 (89), 145 (4.0, $M^+ - COOCH_3$), 101 (100, $C_5H_9O_2$), 87 (96, $CH_3$–CH(O)–$COOCH_3$), 73 (21), 69 (19), 61 (29), 59 (32), 55 (37), 45 (23), 43 (26), 41 (28), 33 (34), 31 (11).

*Synthesis of methyl (2*R**,3*S**,4*E*)-2,3-epoxy-2-methyl-4-hexenoate (***16***) and methyl (2*R**,3*R**,4*E*)-2,3-epoxy-2-methyl-4-hexenoate* (**17**). A solution of Na (35 g, 1.52 mol) in 300 ml of abs. methanol was added dropwise to a mixture of **3** (100 g, 1.43 mol) and **11** (212 g, 1.73 mol) at 0–10°. The mixture was stirred for 2 h at 20° and worked up as described above for the preparation of **12** and **13**. The 170 g of crude product obtained were distilled. The fractions collected at 65–70°/0.13 mbar contained 12.7 g of a 1:1 mixture of **16** and **17** contaminated with unidentified by-products. Column chromatography of 0.5 g of this distillate (75 g of *Florisil*, cyclohexane with increasing amounts of acetone) yielded 350 mg of a pure **16/17**, which was separated by prep. GC. (180°, 10% *Carbowax 20M*).

*Data of* **16**. – $n_D^{23} = 1.455$. – IR. (film): 2960, 1735, 1670, 1450, 1435, 1380, 1285, 1195, 1160, 1095, 965, 855, 735. – $^1$H-NMR. ($CDCl_3$): see *Table 1*. – $^{13}$C-NMR. ($CDCl_3$): see *Table 2*.

$C_8H_{12}O_3$ (156.18) Calc. C 61.52 H 7.75% Found C 61.55 H. 7.93%

*Data* of **17**. – $n_D^{23} = 1.455$. – IR. (film): 2960, 1745, 1735, 1665, 1450, 1435, 1380, 1270, 1250, 1190, 1145, 1080, 965, 865, 745. – $^1$H-NMR. ($CDCl_3$): see *Table 1*. – $^{13}$C-NMR. ($CDCl_3$): see *Table 2*.

$C_8H_{12}O_3$ (156.18) Calc. C 61.52 H 7.75% Found C 61.79 H 7.89%

*Synthesis of methyl (2*E*)-4,5-dibromo-2-methyl-2-hexenoate* (**18**). A solution of bromine (1.84 g, 11 mmol) in 10 ml of $CH_2Cl_2$ was added dropwise to a solution of **6** (2 g, 14.3 mmol) in 25 ml of $CH_2Cl_2$ at –15°. Discoloration occurred at once. The solvent was removed *in vacuo*, and 4,1 g (95%) of crude **18** resulted, containing some starting material **6** according to GC. (130°, 2.5% *SE 30*). – IR. (film): 2960, 1770, 1720, 1640, 1440, 1290, 1250, 1200, 755. – $^1$H-NMR. (60 MHz, $CDCl_3$): 6.74 (*d*×*qa*, *J*=10 and 1.5, 1 H, H–C(3)); 4.82 (*d*×*d*, *J*=10 and 9, 1 H, H–C(4)); 4.20 (*d*×*qa*, *J*=9 and 6, 1 H, H–C(5)); 3.74 (*s*, 3 H, $CH_3O$); 1.90 (*m*, 6 H, 3 H–C(6) and $H_3C$–C(2)).

*Synthesis of methyl (2*E*,4*R**,5*S**)-5-bromo-4-hydroxy-2-methyl-2-hexenoate* (**19**) *and 5-(1-bromoethyl)-3-methyl-2(5*H*)-furanone* (**20**). Dienoate **6** (7.1 g, 50.7 mmol) was suspended in 950 ml of water to which 200 mg of *Santonox R* (radical scavenger) was added. At 75–85° a solution of bromine (10.4 g, 65 mmol) in 500 ml of water was added dropwise. After cooling, the solution was saturated with NaCl and extracted with 4 300-ml portions of $CH_2Cl_2$. These extracts were dried over $Na_2SO_4$ and evaporated *in vacuo*. The crude product obtained (10.5 g) had the following composition: **6** (7%), **18** (7%), **19** (81%; yield from **6**: 71%), and **20** (5%). Vacuum distillation (0.26 mbar) of this mixture gave 4 fractions. In fr. 1 (<104°, 1 g), **20** was enriched to about 30%. Fr. 2 (104–108°, 3.5 g) contained *ca.* 90% pure **19**; fr. 3 (108°, 3.5 g) was almost pure **19**, and fr. 4 (>108°, 1.2 g) was mainly **19**.

*Data* of **19**. – IR. ($CCl_4$): 3610, 3560, 1775, 1720, 1430, 1250, 1220, 1130, 1065, 1020, 930. – $^1$H-NMR. ($CDCl_3$): 6.70 (*d*×*d*, *J*=8.5 und 1.5, 1 H, H–C(3)); 4.51 (*d*×*d*, *J*=8.5 and 5, 1 H, H–C(4)); 4.22 (*d*×*qa*, *J*=5 and 6.8, 1 H, H–C(5)); 3.85 (br. *s*, 1 H, HO); 3.76 (*s*, 3 H, $CH_3O$); 1.92 (*d*, *J*=1.5, 3 H, $H_3C$–C(2));

1.68 (*d*, $J$=6.8, 3 H, 3 H–C(6)). – $^{13}$C-NMR. ($CDCl_3$): 168.2 (*s*, C(1)); 139.3 (*d*, C(3)); 131.1 (*s*, C(2)); 72.0 (*d*, C(4)); 54.0 (*d*, C(5)); 52.2 (*qa*, $CH_3O$); 21.0 (*qa*, C(6)); 13.4 (*qa*, $CH_3$–C(2)).

$C_8H_{13}BrO_3$ (237.09) Calc. C 40.52 H 5.52% Found C 39.91 H 5.70%

*Data of* **20**. – IR. ($CCl_4$): 2980, 2920, 1775, 1660, 1440, 1380, 1310, 1290, 1200, 1180, 1075, 1050, 1005, 955, 895, 850. – $^1$H-NMR. ($CDCl_3$): 7.25 (*qi*, $J$=1.6, 1 H, H–C(4)); 4.93 (*d*×*qi*, $J$=7.0 and 1.8, 1 H, H–C(5)); 4.08 (*qi*, $J$=6.6, 1 H, H–C(1')); 1.94 (*t*, $J$=1.8, 3 H, $H_3C$–C(3)); 1,81 (*d*, $J$=6.6, 3 H, 3 H–C(2')). – $^{13}$C-NMR. ($CDCl_3$): 173.0 (*s*, C(2)); 146.2 (*d*, C(4)); 132.1 (*s*, C(3)); 83.2 (*d*, C(5)); 47.3 (*d*, C(1')); 22.3 (*qa*, C(2')); 10.6 (*qa*, $H_3C$–C(3)).

*Synthesis of methyl (2R*,3S*,4S*,5R*)-5-bromo-2,3-epoxy-4-hydroxy-2-methylhexanoate* (**22**). A solution of **19** (2.5 g, 10.5 mmol) and *m*-chloroperbenzoic acid (1.82 g, 90%; 9.5 mmol) in 50 ml of $CH_2Cl_2$ was refluxed for 14 days. Work-up as described above for the synthesis of **8** and **9** gave 2.2 g of crude product, which was distilled to yield 1.6 g (60%) of **22**, b.p. 116°/0.4 mbar. This product was uniform according to GC. (130°, 2.5% *SE 30*), but contained *ca.* 10% of a contamination according to $^{13}$C-NMR., most probably the corresponding (2*R**,3*S**,4*R**,5*S**)-isomer. – IR. (film): 3460, 2980, 2950, 1735, 1440, 1380, 1290, 1200, 1170, 1085, 1035, 1000, 870, 765. – $^1$H-NMR. (60 MHz, $CDCl_3$): 4.12 (*qi*, $J$=6, 1 H, H–C(5)); 3.77 (*s*, 3 H, $CH_3O$); 3.54 (*t*, $J$=6, 1 H, H–C(4)); 3.34 (*d*, $J$=6, 1 H, H–C(3)); 2.64 (br. *s*, 1 H, HO); 1.78 (*d*, $J$=6, 3 H, 3 H–C(6)); 1.65 (*s*, 3 H, $H_3C$–C(2)). – $^{13}$C-NMR. ($CDCl_3$): 170.6 (C(1)); 72.5 (C(4)); 63.5 (C(3)); 59.2 (C(2)); 52.8 ($CH_3O$); 49.9 (C(5)); 21.7 (C(6)); 14.5 ($CH_3$–C(2)). Contamination: 171.0, 61.2, 56.9, 53.7, 20.2, 13.7.

*Transformation of* **22** *into* **8**. At room temp. **22** (*ca.* 90% pure, 50 mg) was stirred in 5 ml of $CH_2Cl_2$ with 0.5 ml of ethyldiisopropylamine for 12 h. The solution was carefully washed with dil. HCl-solution, dried over $Na_2SO_4$ and evaporated. The GC. (190°, 3% *Carbowax 20M*) revealed three compounds. The main product (90%) was identified as **8** by its retention time and $^1$H-NMR. One of the minor products (7%) had the same retention time as **9**; the third product was not identified.

*Synthesis of (2R*,3S*,4S*,5R*)-2,3:4,5-diepoxyhexane* (**23**) *and (2R*,3S*,4R*,5S*)-2,3:4,5-diepoxyhexane* (**24**) [26]. (2*E*,4*E*)-2,4-Hexadiene (1.7 g, 20.7 mmol; *Fluka*) was added to a solution of *m*-chloroperbenzoic acid (11.2 g, *ca.* 90%, 58 mmol) in 120 ml of $CH_2Cl_2$. The mixture was stirred for 3 h and then worked up as described for **7**. Samples for spectral analyses were obtained by prep. GC. (90°, 3% *Carbowax 20M*). – $^{13}$C-NMR. of **23** and **24** ($CDCl_3$): see *Table 2*.

## REFERENCES


[1] *M. Ceroni*, Dissertation, Basel 1980.
[2] *U. Séquin & M. Ceroni*, Helv. Chim. Acta *61*, 2241 (1978).
[3] *M. Ceroni & U. Séquin*, Tetrahedron Lett. *1979*, 3703.
[4] *J. L. Everett & G. A. R. Kon*, J. Chem. Soc. *1950*, 3131;
*S. M. Kupchan*, Federation Proc. *33*, 2288 (1974);
*W. Adam & M. Balci*, Tetrahedron *36*, 833 (1980).
[5] *J. W. Blunt, M. H. G. Munro & W. H. Swallow*, Aust. J. Chem. *32*, 1339 (1979).
[6] *D. J. Faulkner, M. O. Stallard & C. Ireland*, Tetrahedron Lett. *1974*, 3571.
[7] *D. B. Borders & J. E. Lancaster*, J. Org. Chem. *39*, 435 (1974).
[8] *S. M. Kupchan & W. L. Sunshine*, J. Org. Chem. *43*, 171 (1978).
[9] *S. M. Kupchan, W. A. Court, R. G. Dailey, jr., C. G. Gilmore & R. F. Bryan*, J. Am. Chem. Soc. *94*, 7194 (1972).
[10] *W. H. Gerwick, W. Fenical, D. Van Engen & J. Clardy*, J. Am. Chem. Soc. *102*, 7991 (1980).
[11] *H. Schmitz, K. E. Crook, jr. & J. A. Bush*, Antimicrob. Agents Chemother. *1966*, 606 (1967).
[12] *U. Séquin*, Tetrahedron *34*, 761 (1978).
[13] *S. Kondo, M. Miyamoto, H. Naganawa, T. Takeuchi & H. Umezawa*, J. Antibiot. *30*, 1143 (1977).
[14] *B. Phillips, P. S. Starcher & D. L. MacPeek (Union Carbide)*, British patent 863 446 (1961).
[15] *L. A. Yanovskaya, B. I. Kozyrkin & V. F. Kucherov*, Izv. Akad. Nauk. SSSR, Ser. Khim. *1966*, 1595.
[16] *J. H. Vermeer & J. R. Dean*, J. Chromatogr. *60*, 253 (1971).
[17] *U. Séquin*, Tetrahedron Lett. *1979*, 1833.
[18] *G. B. Payne*, J. Org. Chem. *24*, 2048 (1959).

[19] *G. B. Payne,* Tetrahedron *18*, 763 (1962).
[20] *V. R. Valente & J. L. Wolfhagen,* J. Org. Chem. *31*, 2509 (1966).
[21] *B. Birdsall, N. J. M. Birdsall & J. Feeney,* J. Chem. Soc., Chem. Commun. *1972,* 316.
[22] *H. Nadig & U. Séquin,* Helv. Chim. Acta *63*, 2446 (1980).
[23] *J. A. Marshall & M. E. Lewellyn,* J. Org. Chem. *42*, 1311 (1977).
[24] *H. J. Altenbach, H. Stegelmeier & E. Vogel,* Tetrahedron Lett. *1978,* 3333.
[25] *G. Bernhardt & F. Korte,* Angew. Chem. *77*, 133 (1965).
[26] *G. E. Heasley, R. V. Hodges & V. L. Heasley,* J. Org. Chem. *39*, 1769 (1974).
[27] *G. E. Heasley, V. L. Heasley, S. L. Manatt, H. A. Day, R. V. Hodges, P. A. Kroon, D. A. Redfield, T. L. Rold & D. E. Williamson,* J. Org. Chem. *38*, 4109 (1973).
[28] *Y. Ueno, A. Yamasaki, H. Terauchi & S. Takemura,* Chem. Pharm. Bull. *22*, 1646 (1974).
[29] *H. B. Henbest & R. A. L. Wilson,* J. Chem. Soc. *1957*, 1958.
*P. Chamberlain, M. L. Roberts & G. H. Whitham,* J. Chem. Soc. (B) *1970*, 1374.
[30] *J.-L. Pierre, P. Chautemps & P. Arnaud,* Bull. Soc. Chim. Fr. *1969*, 1317.
[31] *A. Wehrli & E. Kováts,* Helv. Chim. Acta *42*, 2709 (1959).
[32] *U. Séquin & M. Furukawa,* Tetrahedron *34*, 3623 (1978).
[33] *U. Séquin,* Helv. Chim. Acta *64,* 2654 (1981).
[34] *M. Zehnder, U. Séquin & H. Nadig,* Helv. Chim. Acta *62*, 2525 (1979).
[35] *M. Barfield, R. J. Spear & S. Sternhell,* Chem. Rev. *76*, 593 (1976).
[36] *R. W. Aben & J. W. Scheeren,* Synthesis *1978*, 400.
[37] *S. H. Harper & H. W. B. Reed,* J. Chem. Soc. *1955*, 779.
[38] *C. Schaer,* Helv. Chim. Acta *41*, 614 (1958).
[39] *M. H. Palomaa,* Ann. Acad. Scient. Fennia *A4*, 1 (1913) (see Chem. Zbl. *1913 II,* 1956); *C. Niemann, A. A. Benson & J. F. Mead,* J. Org. Chem. *8*, 397 (1943).