205. Stereochemistry-Odor Relationships in Enantiomeric Ambergris Fragrances

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Summary

Twelve tricyclic ethers of the labdane and *ent*-labdane series, **5**–**16**, have been synthesized; compounds **6**–**15** are new. The intramolecular C_{18}-acetals **1**–**4** and the tricyclic ethers **5**–**16** were submitted to an olfactory test which was characterized by an exceptionally high percentage of 'wrong' answers (*cf. Table 1*, footnote b). For most compounds specific anosmia, rapidly ensuing fatigue and a high percentage of odor deviation were the most salient features.

Pronounced ambergris-like odors were only noted in compounds of the labdane series, and were strongest in ethers **1**, **5** and **15**, followed by the ethers **9** and **11**. In contrast, both labdane derivatives **3** and **7** were practically odorless. Their enantiomers **4** and **8**, on the other hand, have relatively strong odors which can only to a limited extent be associated with ambergris-type odors. The pairs of ethers **3**/**4** and **7**/**8** are the first recorded examples of optical antipodes in which only one isomer possesses olfactory properties.

The human olfactory organ is capable of distinguishing chiral compounds. Odor quality and potency of enantiomeric compounds may show considerable differences. Thus, a distinct differentiation in odor perception could be observed in pairs of enantiomeric monoterpenoid odorants [1–5] and the sesquiterpenoid nootkatone [6]. However, the optical antipodes of low molecular weight 2-alkanols are difficult to distinguish [5], and the enantiomers of camphor cannot be distinguished at all [7]. In 8% of the subjects specific anosmia to (−)-carvone was observed, which dropped to 5% in the case of (+)-carvone [8]. Owing to its anosmic effect carvone has been considered as the prototype for the minty primary odor [9]. The inability to distinguish olfactorily optical antipodes is termed specific chiral anosmia [2].

The intensity of the odor of enantiomeric compounds exhibits as great a variability as does the quality. For example, the odor threshold value of (−)-carvone (0.043 ppm) is about ten times lower than that of its (+)-isomer (0.60 ppm) [8], while the odor threshold value of (+)-nootkatone (0.8 ppm) differs by a factor of about 750 from that of its enantiomer (600 ppm) [6]. However, there are cases in which no quantitative differences exist between enantiomers [8]. An explanation for this irregular olfactory behavior of enantiomeric compounds has not yet been found, *i.e.* the molecular basis of the chiral odor phenomenon is still unknown.

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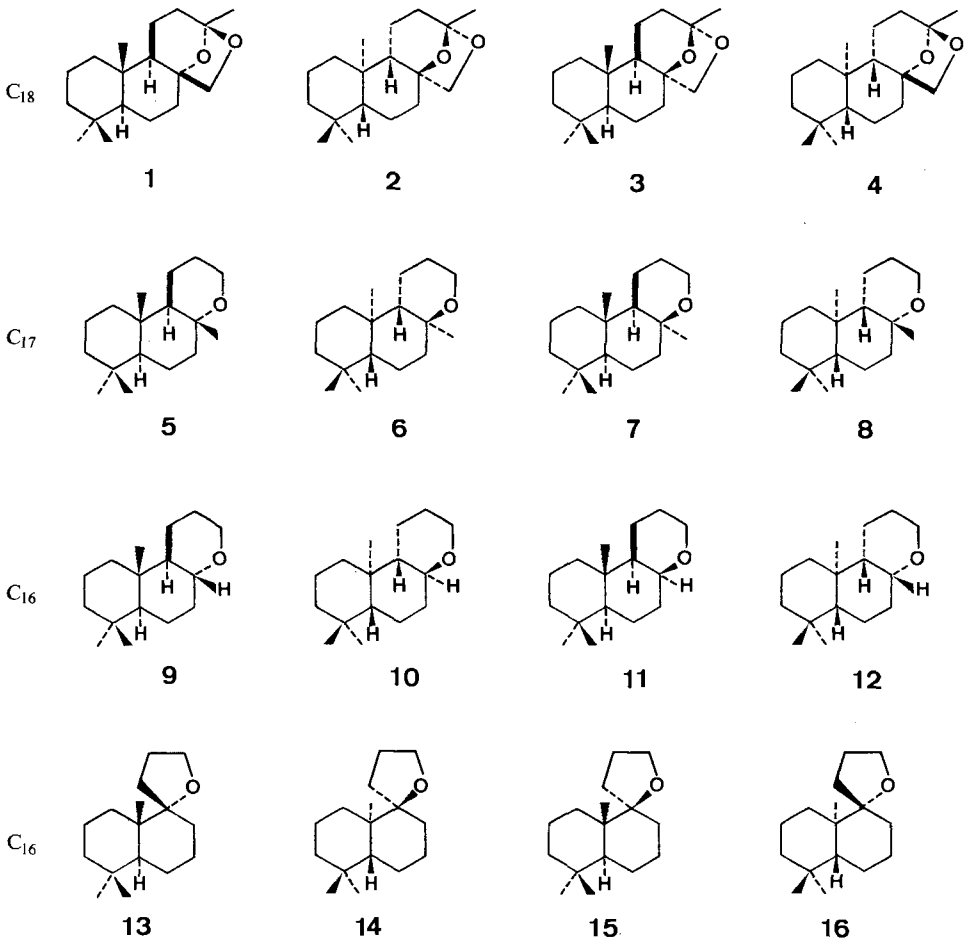
Scheme 1



The repeated observation that certain odor qualities may be lacking in one of the two enantiomers appears to be of considerable relevance to the elucidation of the mechanism of olfaction [3] [4] [6] [7]. For the purpose of investigating this phenomenon the ambergris odorants seemed particularly promising, because a definite structure-odor relationship exists [10] and their complex odor can be broken down into at least six distinct odor types [11]. Finally, it was observed that some of the ambergris odorants can provoke specific anosmia. In the case of the known C_{18}-acetals **1–4** this phenomenon manifests in varying ways [12], but in addition an enantioselectivity of odor perception was observed [13] to a hitherto unknown extent. In order to determine whether this phenomenon is generally associated with odoriferous compounds of the ambergris-type, the organoleptic properties of the tetra- and tricyclic ethers represented in *Scheme 1* were investigated.

Sensory testing of compounds 1–16. – The results of an olfactory test carried out by a panel of 30 members are summarized in *Table 1*[1]). In order to establish a connection with the previous sensory investigation of the tetracyclic C_{18}-acetals **1–4** [13], this series of diastereoisomers was included in the test. Two of the sixteen compounds *(Scheme 1)*, **3** and **7**, were considered to be odorless by nearly all subjects[2]). Compounds **2** and **6** could not be detected by more than 30% of the participants. The weakest specific anosmia was triggered by compounds **1**, **5**, **8**, **9**, **12**, **13** and **15**. All remaining compounds (**4**, **10**, **11**, **14** and **16**) were perceived with varying intensities by more than 60% of the panel. The most intense odor sensation among the twelve compounds was caused by **1**, followed by **15**, then **5** and **9**. As a rule, the odor of the ethers in the labdane series was perceived considerably more intensely than that of the ethers of the *ent*-labdane series. The *ent*-tetrahydropyran derivative **8** is an exception to this rule[3]). Although the eleven female subjects as a rule perceived the odorants more intensely in comparison with their nineteen male colleagues, odor-blindness was less related to sex. Compound **1** constitutes an exception. The greater sensitivity of females to ambergris odorants manifested itself especially on dilution; a 0.001% solution of **1** was described as still discernible by more than 60% of the female but only 30% of the male participants.

Pronounced ambergris-like notes were attributed exclusively to compounds **1**[4]), **5**[5]) and **15**[6])[7]), and to a certain extent also to **9** and **11**. These three compounds also cause extreme fatigue. Some aspects of the odor profile of the C_{17}-ether **5** were recognized in the C_{16}-ethers **9**[8]) and **11**[9]). The

[1]) We thank Dr. *W. Pickenhagen, Firmenich SA,* for the organization of these careful investigations and Miss *H. Schindler* for skilful technical assistance.

[2]) Concerning compound **3**, this result is contrary to the results of earlier investigations [12] [13] in which 50% of subjects questioned classified acetal **3** as an odorant. We can find no other explanation for this discrepancy than the fact that compound **3** used in the earlier investigations was contaminated by the very powerfully smelling diastereoisomer **1**. This assumption is supported by the fact that a 0.01% ethanolic solution of **1** was detected by 16 out of 30 subjects [13], and even a solution having one tenth this concentration was still perceived by 13 subjects. Only one subject (♀) perceived a faint urine-like note in **3**; this does not exclude the possibility of an error caused by delayed odor impulses, *cf.* footnote b) in *Table 1.*

[3]) However, none of the subjects could identify ambergris-like tonalities in **8**. Minty-camphoraceous (6 ♀, 8 ♂), fruity (2 ♀, 4 ♂) and balsamic (3 ♂) were the most frequent replies. Only four participants (2 ♀, 2 ♂) described **8** as musk-like and woody.

[4]) Five subjects gave definitely 'wrong' answers in the case of compound **1**. They described a strong odor, differing from the standard description (*cf. Table 1*, footnote a) as follows: vegetable (celery) ♀, metallic ♀, green ♂, acetone-like ♂ and 2-propanol ♂. Furthermore, when describing the odor profile of **1** almost 50% of the participants detected not only the ambergris-like tonality, but also sweaty and urine-like notes resembling those of odorous steroids.

[5]) Compound **5** was twice (♀) described as strongly fruity.

[6]) Among the eighteen subjects extremely sensitive to **15** four gave 'wrong' answers: fruity (2 ♂), menthol-like (♂), green (♂).

[7]) In contrast, the spiroethers with two more carbon atoms, (13*S*)-9,13-epoxy-15,16-dinor-9*β*-labd-8(20)-ene and (13*S*)-9,13-epoxy-15,16-dinor-9*β*-labd-7-ene, are odorless [14].

[8]) Practically 50% of the subjects being extremely odor-sensitive, including all the female participants, indicated tonalities in **9** (green, moss and ionone-like) which cannot or can only with difficulty be associated with ambergris. Less sensitive subjects, however, committed fewer errors.

[9]) The strong odor of compound **11** was described as fermented herbs by one person (♀), and as menthol-like by another (♂). Neither subject could detect ambergris-like scents in any of the compounds **9–12**.

Table 1[a])

	Strong odor perception			Perceptible			Not perceptible		
	♀	♂	%(♀/♂)	♀	♂	%(♀/♂)	♀	♂	%(♀/♂)
1	9	14	82/74	1	0	9/0	1	5	9/26
2	1	0	9/0	2	8	18/42	8	11	73/58
3	0	0	0/0	1	0	9/0	10	19	91/100
4	3	2	27/11	4	13	36/68	4	4	36/21
5	4	6	36/32	6	12	55/63	1	1	9/5
6	1	0	9/0	4	13	36/68	6	6	55/32
7	0	0	0/0	1	0	9/0	10	19	91/100
8	7	7	64/37	3	10	27/53	1	2	9/11
9	4	4	36/21	6	14	55/74	1	1	9/5
10	2	5	18/26	7	11	64/58	2	3	18/16
11	2	3	18/16	7	13	64/68	2	3	18/16
12	3	2	27/11	7	16	64/84	1	1	9/5
13	5	4	45/21	5	13	45/68	1	2	9/11
14	2	1	18/5	5	14	45/74	4	4	36/21
15	7	11	64/58	3	7	27/37	1	1	9/5
16	1	1	9/5	6	11	55/58	4	7	36/37

a) Compounds **1**–**16** applied as 1% ethanolic solutions on smelling strips, were examined by 30 subjects (11 women = ♀ and 19 men = ♂) who, in the course of their professional activities, were accustomed to handling odorants daily without having any special training as perfumers. Four diastereoisomers of each series, and two blanks (containing only 96% ethanol), after aeration for 1 h, were submitted to the subjects for quantitative and qualitative evaluations. Other combinations are mentioned in the text. The choice of the odor intensity was divided into four categories: strong, moderate, weak, and odorless. Since the most frequent mistakes (positive answers for blanks[b])) occurred in the categories of moderate and weak odor perception, all answers submitted were added up, the mistakes deducted and the result finally entered in the table under the heading of 'perceptible'. Aid in answering the questions relating to the qualitative description of odor of the compounds (including the blanks) was given by suggesting the following key words: woody, nutty, balsamic, fruity, green, musky, sour and urine-like. The subjects were free to write down any other odor impressions they had.

b) Mistakes were particularly frequent with compounds **1**–**4**, 30% of the women and 20% of the men attributing odoriferous properties to the blanks. Compound **1** was repeatedly observed to cause odor impulses of the same type, periodically and up to 1 h after sniffing. Presumably molecules of **1** are absorbed in the mucosa of the pharynx and nasal cavity, then desorbed over a certain length of time and finally migrate with the air stream to the *regio olfactoria*.

scent of these five compounds (**1**, **5**, **9**, **11** and **15**) was mostly described as woody ambergris-like in the sense of the tonality of the standard odorant *Ambrox*® [15]; the descriptions musky and balsamic followed. Owing to its additional warm animal note the ether **5** resembles ambergris most. A certain woody character was also noted in the compounds **2**[10]), **4**[10])[11]), **6**[12]) and **10**[13]) of the *ent*-series, although its intensity and ambergris tonality differed considerably from that of **1**, **5** and **15**.

10) Similarly to **1**, compounds **2** (once) and **4** (twice) were described as sweaty.

11) The proportion of failures increases in this case by two subjects since **4** was described by one of them as strongly fruity (♀) and by the other as heavy floral (♂). The remaining sensitive subjects mostly described the scent as woody, slightly musk-like as well as camphoraceous (patchouli).

12) The only subject (♀) extremely sensitive to **6** characterized it as camphoraceous, slightly sweaty and urine-like.

13) Six out of eight subjects ascribed woody ambergris-like odor qualities to the strong odor of *nor*-ether **10**. In contrast, only one (♂) recognized diastereoisomer **12** to be ambergris-like. The other four highly sensitive participants gave the following description: flowery (♀), cyclohexanone-like (♀), minty, floor polish (♂), and green-peppery (♂).

Recognition of ambergris-like tonalities in **2** dropped to 25% of the men, since in addition to the 58% anosmic subjects two indicated a fruity and one a floral odor character. Finally, the relatively strong odor sensation of *ent*-ether **8** is not so much caused by a woody-balsamic note (5 subjects) as by a musty menthol-like odor (16 subjects).

Cross-adaptation experiments with five subjects who were odor-blind to **1** showed that four were unable to detect characteristic ambergris notes in compounds **5** and **15**. The most frequent answer was woody, followed by fruity, minty and camphoraceous. The fifth anosmic person noted an ambergris-like scent only if **5** was presented in the series **1**, **10** and **15** or **9**, **10** and **15**. Together with **6–8**, **5** was described as green and slightly mentholic. The same subject described compound **15** as pungent ambergris-like whenever he tested it together with **1**, **5** and **10**. However, it appeared fruity to him when combined with compounds **5**, **9** and **10** or **13**, **14** and **16** (*cf. Table 1*, footnote b). One woman who found **1** to be strong was odor-blind to **9** and described **5** and **15** as extremely weak and vague. The reason for this confusion is not clear. Extraordinarily rapid blocking of specific ambergris receptors is, however, most likely.

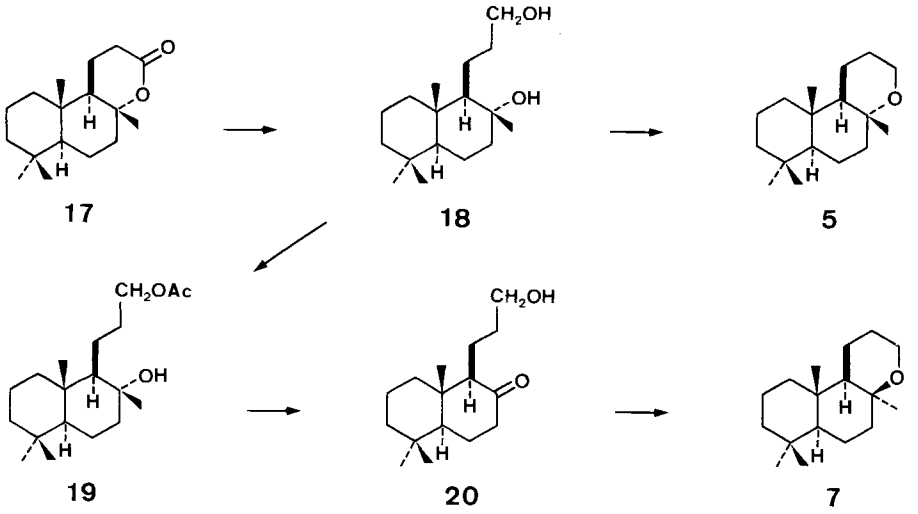
These extensive organoleptic investigations show the distinct ambergris character of the cyclic ethers to be observed exclusively in derivatives of the labdane series, of which **1**, **5**, **9**, **11** and **15** are the most typical members. 'Mistakes' occurring in the odor description of these ethers[4–9]) accumulate with compounds of the *ent*-series and the labdane series (**9**, **11** and **13**), whenever the molecular basis of the ambergris-like odor perception is not confirmed by the 'triaxial rule' without additional assumptions [10]. In the odor profiles of all compounds of the *ent*-labdane series the ambergris notes, if perceptible at all, are mostly covered by extraneous odor qualities. Their evaluation is rendered more difficult because, with the exception of ethers **8** and **10**, all the remaining compounds of the *ent*-labdane series are only faintly perceptible. As expected, ethers **3** and **7** were described as odorless, in accordance with the 'triaxial rule'. In contrast their diastereoisomers **1** and **5** belong to the strongest smelling ethers of our investigation. However, we were surprised that some subjects considered the enantiomers (**4** and particularly **8**) of the odorless ethers **3** and **7** to have a strong odor. We are thus faced with an unprecedented enantioselectivity of odor sensation. In molecules whose 'triaxial character' is not clearly pronounced, as in the case of the two series **9–12** and **13–16**, the diastereo- and enantio-selectivity decreases considerably. The strong ambergris scent of spiroether **15** remains a rare phenomenon inviting further experiments, from which we hope to gain a more general insight into the molecular processes of odor perception.

Synthesis of tricyclic ethers 5–16. – With the exception of the levorotatory tricyclic ether **5** which was prepared from (+)-ambreinolide (**17**) [16] [17][14]) *via* (−)-diol **18** [16], compounds **7**, **19** and **20** of *Scheme 2* are new. Due to the difficult accessibility of isoambreinolide [16] [19] we prepared (+)-ether **7** from hydroxyacetate **19** obtained in turn by partial acetylation of diol **18** [20]. A 3-step degradation of **19** yielded (−)-hydroxyketone **20**, and the desired ether **7** was obtained by treatment of the *p*-toluenesulfonate of **20** with methyl lithium. The introduction of an axial oxygen function at C(8) is plausible because the organometallic reagent will approach from the least hindered side of the molecule[15]).

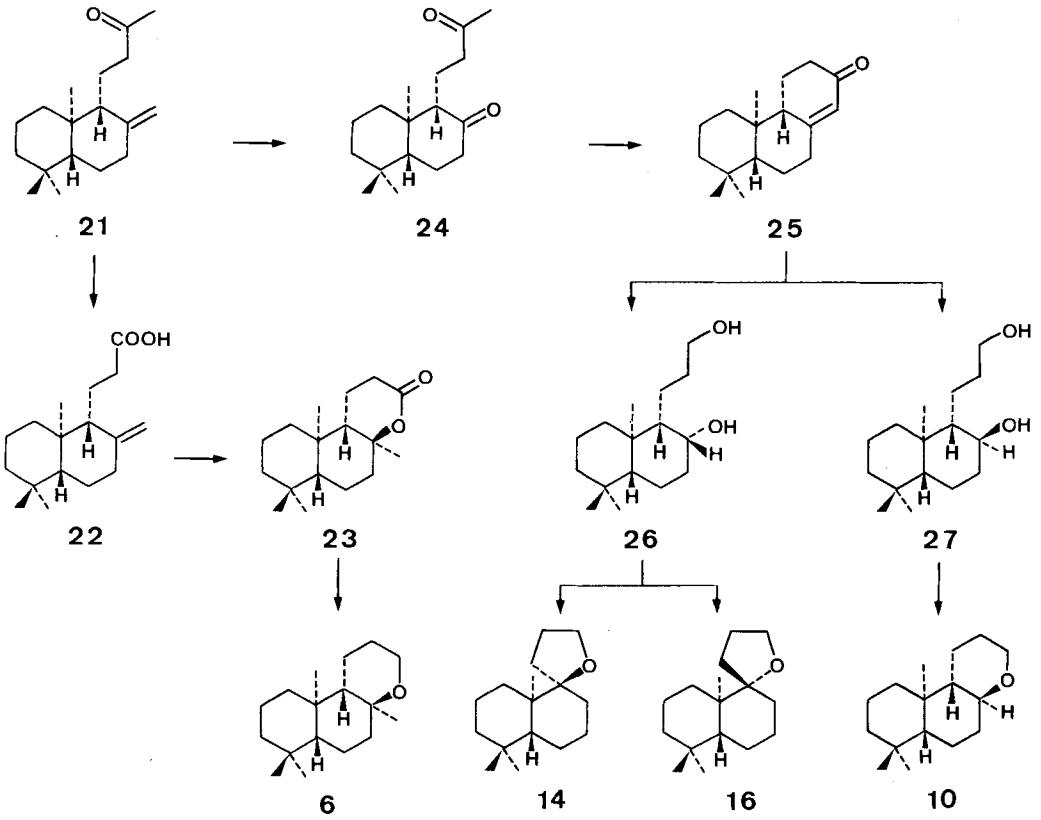
[14]) Concerning the determination of the absolute configuration of lactone **17**, *cf.* [18].

[15]) The structure of (+)-8β,13-epoxy-14,15,16-trinorlabdane (**7**) was proved by X-ray analysis of a mono-crystal. We thank Dr. *Claudine Pascard* for this work which will be published elsewhere [21].

Scheme 2



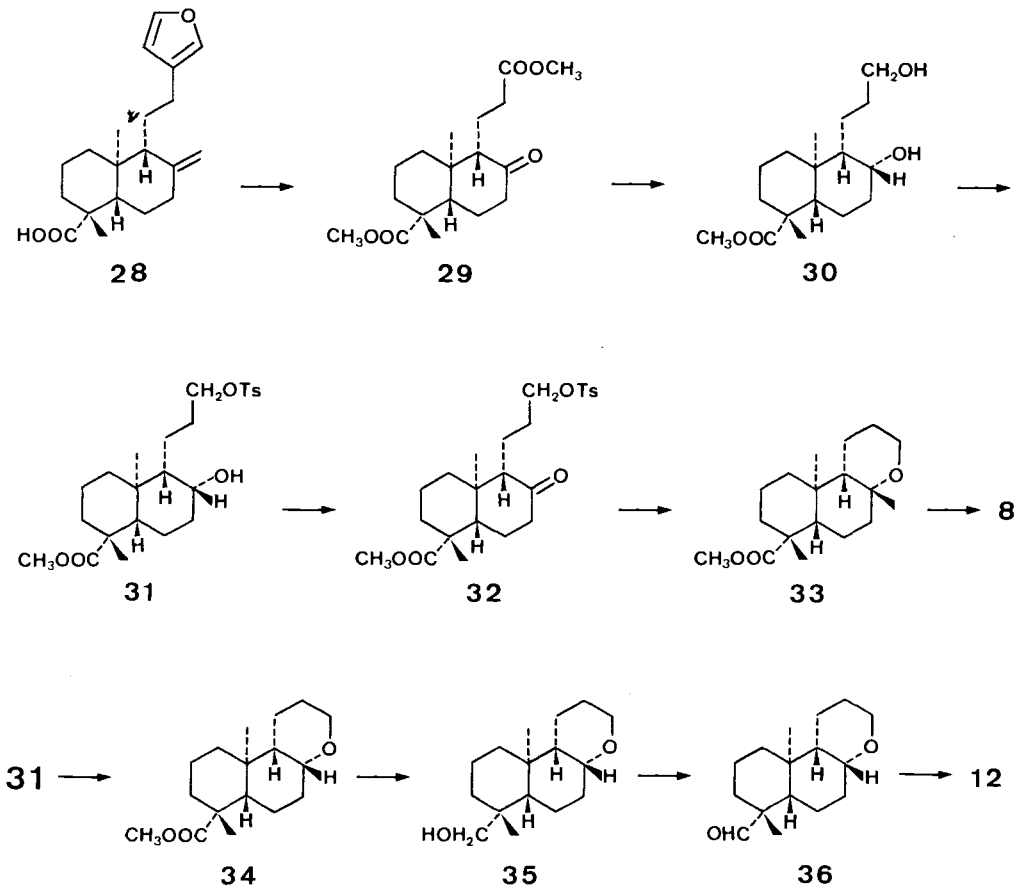
Scheme 3



The dextrorotatory tricyclic ether **6** was prepared from (−)-ambreinolide (**23**) [16] [17] *via* the corresponding diol. Lactone **23** was obtained after the hypobromite degradation of the known methyl ketone **21** [13] obtained from eperuic acid, and subsequent treatment of the unsaturated acid **22** with H_2SO_4 in glacial acetic acid.

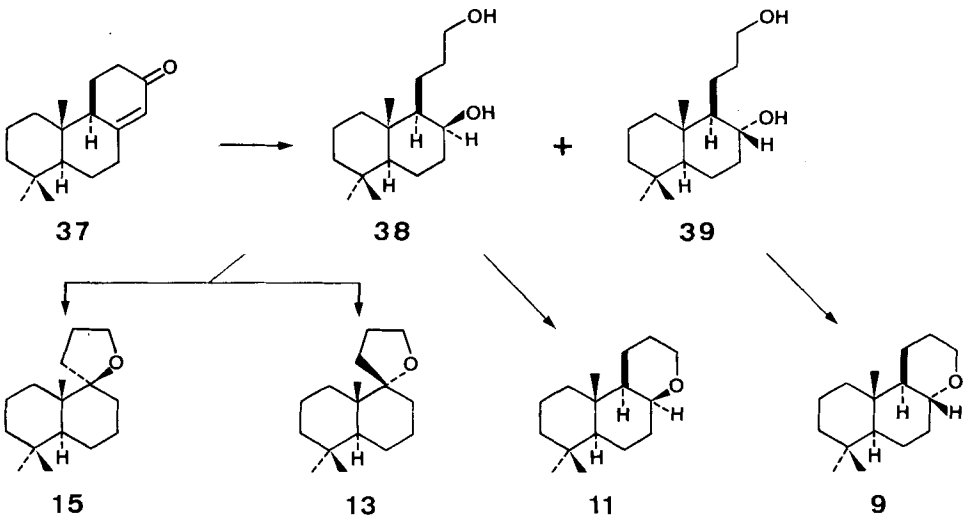
The α,β-unsaturated tricyclic ketone **25**, obtained from diketone **24** *(Scheme 3)*, served as the central intermediate for the tricyclic ethers **10**, **14** and **16**. Ozonization of **25** [23] and subsequent reduction with $LiAlH_4$ led to the diastereoisomeric diols **26** and **27**. Surprisingly, the cyclic ether formation from diastereoisomers **26** and **27** was regiospecific. Whereas the treatment of *cis*-diol **26** with *p*-toluenesulfonic acid in benzene at reflux temperature led to the formation of the spirocyclic tetrahydrofurans **14** and **16**, the *trans*-diol **27** yielded under the same conditions the *trans*-fused tetrahydropyranyl ether **10**. The assignment of the configuration of the spiro ethers **14** and **16** was made from the NMR. spectral data (see exper. part).

Scheme 4



For preparing the (−)-ether **8** we first submitted daniellic acid (**28**)[16]) to exhaustive ozonization [22] and treatment with diazomethane (→**29**, *Scheme 4*). $LiAlH_4$ reduction in ether at 0° did not attack the ester group at C(4) but yielded diol **30**, whose mono-*p*-toluenesulfonate **31** was oxidized to ketone **32** by means of *Jones*'s reagent. The reaction of **32** with methyl lithium yielded the tricyclic ether **33** whose ester group was then reduced to a methyl group in three steps to give (−)-ether **8**. The same reduction technique (s. *Scheme 4*) also led to the corresponding nor-ether **12**: treated with NaH in DMF, **31** yielded methoxycarbonylether **34** which was converted into **12** by conventional methods *via* alcohol **35** and aldehyde **36**.

Scheme 5



The four tricyclic ethers of the labdane series **9**, **11**, **13** and **15** *(Scheme 5)* were synthesized using essentially the same route as for **10**, **14** and **16** (s. *Scheme 3*). The diols **38** and **39** were prepared by degradation of (+)-podocarp-8(14)-en-13-one (**37**) [24]. (−)-Ether **11** was formed in 2% yield on treatment of diol **38** with tosyl chloride in pyridine at reflux temperature and ethers **15** and **13** by treatment of diol **38** with *p*-toluenesulfonic acid in benzene. (+)-Ether **9** was formed from diol **39** in 29% yield.

The authors are indebted to Dr. *B. Maurer* for advice in nomenclature and *W. Thommen* and *R. Brauchli (Firmenich SA)* for the measurements and interpretation of the NMR. spectra.

The ^{1}H-NMR.-250-MHz spectra were kindly performed by *C. Merrienne (Institut d'électronique d'Orsay)* and the ^{13}C-NMR.-22.36-MHz spectra by *C. Bérenger* and *M. Vuilhorgue* (C.N.R.S., Gif).

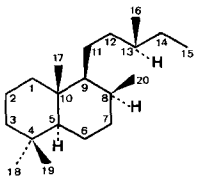
H. R. Wolf and *K. Job* thank *Ciba-Geigy*, Basle, for having supported their contribution to this paper. Some of the NMR.-spectra were kindly performed by *B. Brandenberg* and *K. Hiltbrunner* (supervision of the ETH-NMR. service: Prof. Dr. *J. F. M. Oth*) and some of the mass-spectra were measured by *L. Golgowski* (supervision of the ETH-MS. service: Prof. Dr. *J. Seibl*).

[16]) We thank Professor *D. E. U. Ekong* (University of Ibadan, Nigeria) for the generous supply of starting material.

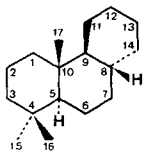
Experimental Part

General remarks. Melting points (m.p.) were determined on a stage microscope *(Reichert)* or a *Büchi* SMP-20 apparatus and are uncorrected. Optical rotations were measured on a *Quick* polarimeter *(Roussel & Jouan)* and *Perkin-Elmer* models 141 and 241 in $CHCl_3$ unless otherwise stated. ^{1}H-NMR. and ^{13}C-NMR. spectra were recorded on *Bruker* HFX-90, HX-90E, WH-360 and WP-60, *Varian* T-60, HA-100 and XL-100, and *Cameca* 250 instruments, in $CDCl_3$ unless otherwise stated. Chemical shifts (δ) are in ppm downfield from tetramethylsilane (= 0 ppm) as internal standard; abbreviations: *s* = singlet, *d* = doublet, *t* = triplet, *qa* = quadruplet, *m* = multiplet. *J* = spin-spin coupling constant (Hz), $w_{1/2}$ = half-width (Hz). Mass spectra (MS.) were recorded on *Atlas* CH 4 and MS 50-*AEI* mass spectrometers, using an inlet temperature of *ca.* 150° and electrons of *ca.* 70 eV energy; the intensity of the molecular ion (M^+) and the most intense fragment ions (*m/z*) are given in % of the most abundant peak. The chemical ionisation spectrum (CI.) was recorded on a MS-9 apparatus. Gas chromatography (GC.) was carried out on *Varian* 1800 and *Carlo Erba* 2450 instruments using *Carbowax 20 M* (5%) and *SOMB* (5%) on *Chromosorb W*, 80–100 mesh (2.5 m). Analytical thin layer chromatography (TLC.) was carried out on plasticized plates coated with silica gel F 1500 LS 254 *(Schleicher & Schüll)* or 60 F 254 *(Merck)*. Preparative TLC. was performed with silica gel 60 PF 254 *(Merck)*, and column chromatography with silica gel 60 *(Merck)*. All compounds gave correct elemental analyses. – 'Usual work-up' means that the reaction mixture was extracted 3 times with solvent, the organic phase was washed with water or saturated aq. $NaHCO_3$- and NaCl-solutions if acids were present, dried (Na_2SO_4) and concentrated under reduced pressure. – Abbreviations: DMF = dimethylformamide, THF = tetrahydrofuran, abs. = absolute, aq. = aqueous, RT. = room temperature, i.V. (i.HV.) = in vacuo (in high vacuum).

Numbering and configurations used (in accordance with Chem. Abstr. nomenclature):



labdane



podocarpane

1. Synthesis of 8α,13-epoxy-14,15,16-trinorlabdane (5). – 1.1. *Synthesis of 14,15,16-Trinorlabdane-8α,13-diol* (**18**) [16]. A solution of 1.0 g (3.79 mmol) of ambreinolide (**17**) [16] [17] (m.p. 134–136°, $[\alpha]_D^{20} = +28°$ ($c = 1.11$)) [25] in 33 ml of abs. ether/THF 10:1 was reduced with 0.4 g (10 mmol) of $LiAlH_4$. The mixture was heated under reflux for 1 h, cooled, poured onto ice, and the precipitated alumina dissolved with dil. H_2SO_4-solution. After usual work-up (ether), 1.01 g (100%) of **18** [16] was obtained, which was recrystallized from ether; m.p. 132–133°, $[\alpha]_D^{20} = -26°$ ($c = 1.20$). – ^{1}H-NMR. (100 MHz): 0.78 (*s*, 6 H, $H_3C(17)$ and $H_3C(19)$); 0.86 (*s*, 3 H, $H_3C(18)$); 1.10 (*s*, 3 H, $H_3C(20)$); 3.50 (*m*, 2 H, $H_2C(13)$). – ^{13}C-NMR.: *Table 3.* – MS.: 268 (0, M^+), 250 (15), 235 (100), 191 (20), 177 (11), 165 (5), 149 (6), 137 (44), 121 (21), 109 (40), 95 (40), 81 (35), 69 (38), 55 (39), 41 (47), 29 (15).

1.2. *Conversion of* **18** *to* **5.** To 854 mg (3.19 mmol) of **18** in 15 ml of abs. pyridine at 0° were added 730 mg (3.83 mmol) of tosyl chloride. The mixture was stirred for 12 h at RT. and poured into ice/water. After usual work-up (ether) 664 mg (83%) of **5** [16] were obtained and recrystallized from methanol, m.p. 83–84°, $[\alpha]_D^{20} = -13°$ ($c = 1.22$). – ^{1}H-NMR. and ^{13}C-NMR.: *Tables 2* and *3.* – MS.: 250 (1, M^+), 235 (100), 202 (4), 137 (19), 121 (6), 111 (24), 95 (12), 81 (17), 69 (14), 55 (16), 43 (59), 31 (40).

2. Synthesis of 8β,13-epoxy-14,15,16-trinorlabdane (7). – 2.1. *Synthesis of 8α-hydroxy-14,15,16-trinorlabd-13-yl acetate* (**19**). A solution of 1.75 g (6.53 mmol) of **18** in 12 ml of dist. pyridine/acetic anhydride 1:1 was stirred for 12 h at RT. After usual work-up (ether) 2.0 g (99%) of **19** were obtained as a yellow oil which was used without further purification. – ^{1}H-NMR. (60 MHz): 0.77

(6 H) and 0.85 (3 H) (2 *s*, $H_3C(17)$, $H_3C(18)$ and $H_3C(19)$); 1.13 (*s*, 3 H, $H_3C(20)$); 2.0 (*s*, 3 H, CH_3COO); 4.00 (*m*, 2 H, $H_2C(13)$). – MS.: 310 (67, M^+), 295 (9), 292 (12), 277 (19), 250 (8), 235 (21), 195 (27), 180 (32), 179 (42), 177 (55), 165 (50), 157 (23), 137 (53), 131 (55), 125 (95), 124 (95), 123 (94), 116 (58), 109 (94), 107 (32), 97 (94), 96 (61), 93 (45), 83 (92), 82 (55), 81 (93), 71 (92), 69 (100), 56 (51), 55 (92), 43 (95), 41 (76).

2.2. *Synthesis of 13-hydroxy-14,15,16,20-tetranorlabdan-8-one* (**20**). A solution of 2.0 g (6.45 mmol) of **19** in 6 ml of dist. pyridine, was treated with 4 ml (23.7 mmol) of mesyl chloride. After 12 h at 0° the mixture was poured onto ice and the excess of mesyl chloride destroyed with $NaHCO_3$. After usual work-up (CH_2Cl_2) the brown oil obtained was chromatographed by prep. TLC. (ethyl acetate/hexane 3:7). A mixture of products was obtained (1.64 g, 87%) in which one with a methylidene group was predominant. A solution of 3.7 g of this mixture in 110 ml of CH_2Cl_2/dist. pyridine 10:1 was ozonized for 4½ h at −40°. After decomposition of the ozonides (s. chap. 4.1) and usual work-up (CH_2Cl_2), the product was chromatographed on a column of silica gel (hexane containing increasing quantities of ethyl acetate), to give 2.3 g (60%) of a colorless oil. This was dissolved in 10 ml of anh. methanol and the solution saturated with ammonia at 0°. After 48 h at 0°, it was concentrated and chromatographed by prep. TLC. (ethyl acetate/hexane 3:7) to yield 1.0 g (50%) of **20**, m.p. 90–94° (from ether), $[\alpha]_D^{20} = -63°$ ($c = 1.09$). – ^{1}H-NMR. (60 MHz): 0.71, 0.87 and 0.98 (3 *s*, 3 H each, $H_3C(17)$, $H_3C(18)$ and $H_3C(19)$); 2.17 (*s*, 1 H, HO exchangeable with D_2O); 3.57 (*m*, 2 H, $H_2C(13)$). – MS.: 252 (75, M^+), 234 (100), 219 (94), 137 (40), 123 (33), 110 (50), 96 (60), 81 (55), 69 (53), 55 (45), 41 (50).

2.3. *Conversion of* **20** *to* **7**. To 60 mg (0.24 mmol) of **20**, in 1 ml of dist. pyridine were added at 0° 54.5 mg (0.29 mmol) of tosyl chloride in 1 ml of dist. pyridine. The mixture was stirred for 2 h and poured into ice/water. After usual work-up (ether) 79 mg (82%) of an oily tosyl derivative were obtained. – ^{1}H-NMR. (60 MHz): 0.65, 0.83 and 0.97 (3 *s*, 3 H each, $H_3C(17)$, $H_3C(18)$ and $H_3C(19)$); 2.4 (*s*, 3 H, $CH_3C_6H_4$); 4.0 (*m*, 2 H, $H_2C(13)$); 7.18 and 7.67 (2 *d*, $J = 8$, 4 H, 4 arom. H). – MS. (inlet temp. 200°): 406 (1, M^+), 251 (2), 234 (65), 220 (95), 219 (100), 191 (25), 172 (85), 163 (28), 149 (40), 123 (27), 107 (30), 91 (65), 79 (21), 77 (17), 65 (15), 60 (20), 55 (17), 41 (25).

To 429 mg of the *p*-toluenesulfonate in 20 ml of abs. ether at 0° under N_2 were added 4 ml of a 5% solution of methyllithium in ether. The mixture was heated under reflux for 6 h, cooled, hydrolyzed with precaution and acidified with ice-cold 12 N HCl. After usual work-up (ether) and chromatography on a prep. TLC. (ethyl acetate/hexane 1:9) 80 mg (30%) of **7** were obtained and recrystallized from pentane, m.p. 90–91° (sublimation at about 80°), $[\alpha]_D^{20} = +11°$ ($c = 1.05$). – ^{1}H-NMR. and ^{13}C-NMR.: *Tables 2* and *3*. – MS. (CI.) [27]: 251 (0, MH^+), 235 (100), 137 (27), 121 (7), 111 (34), 95 (15), 81 (18), 69 (20), 55 (22), 43 (31), 29 (8).

3. Synthesis of *ent*-8α,13-epoxy-14,15,16-trinorlabdane (6). – 3.1. *Synthesis of* ent-*14,15,16-trinorlabd-8(20)-en-13-oic acid* (**22**). The ketone **21** ($[\alpha]_D^{20} = -32°$ [13], 5.2 g, 19.8 mmol) was subjected to the haloform reaction [26], yielding 4.3 g (82%) of **22** which was recrystallized from pentane at −70°, m.p. 108–110°, $[\alpha]_D^{20} = -36°$ ($c = 1.00$). – ^{1}H-NMR. (CCl_4, 100 MHz): 0.68, 0.79 and 0.86 (3 *s*, 3 H each, $H_3C(17)$, $H_3C(18)$ and $H_3C(19)$); 4.47 and 4.80 (2 *s*, 2 H, $H_2C{=}C(8)$); 8.80–9.50 (br. *s*, 1 H, COOH). – ^{13}C-NMR.: *Table 3*. – MS.: 264 (18, M^+), 249 (26), 221 (3), 208 (3), 195 (4), 177 (18), 167 (10), 137 (67), 123 (18), 107 (15), 95 (22), 81 (51), 69 (34), 57 (67), 56 (43), 55 (44), 43 (100), 42 (63), 41 (96).

3.2. *Synthesis of* ent-*8α,13-epoxy-14,15,16-trinorlabdan-13-one* (**23**; isoambreinolide). The acid **22** (1.46 g, 5.53 mmol) was cyclized by conc. sulfuric acid in acetic acid [28]. After chromatography on silica gel (ether/pentane/cyclohexane 4:1:1) 740 mg (52%) of **23** were obtained, m.p. 143° (from pentane), $[\alpha]_D^{20} = -30°$ ($c = 1.00$). – ^{1}H-NMR. (CCl_4, 100 MHz): 0.80 (6 H) and 0.88 (3 H) (2 *s*, $H_3C(17)$, $H_3C(18)$ and $H_3C(19)$); 1.32 (*s*, 3 H, $H_3C(20)$); 2.3–2.6 (*m*, 2 H, $H_2C(12)$). – ^{13}C-NMR.: *Table 3*. – MS.: 264 (7, M^+), 249 (31), 192 (43), 177 (35), 149 (11), 137 (44), 123 (43), 109 (48), 95 (56), 81 (50), 69 (55), 55 (55), 43 (100), 29 (35).

3.3. *Conversion of* **23** *to* **6**. Using 1.0 g (3.79 mmol) of **23**, the sequence **17**→**18**→**5** (s. chap. 1.1 and 1.2) was followed to yield 615 mg (65%) of **6**, m.p. 83–84° (from methanol), $[\alpha]_D^{20} = +12°$ ($c = 1.00$). – ^{1}H-NMR., ^{13}C-NMR. and MS.: identical in all respects with those of **5**.

4. Synthesis of *ent*-8β,13-epoxy-14,15,16-trinorlabdane (8). – 4.1. *Synthesis of dimethyl* ent-*8-oxo-14,15,16,20-tetranorlabdane-13,19-dioate* (**29**). A solution of 2.0 g (6.33 mmol) of daniellic acid (**28**)

in 110 ml of CH_2Cl_2/pyridine 10:1 was ozonized at $-70°$ until a blue color appeared. The solution was warmed to RT. and concentrated i.V. A few ml of water, 40 ml of H_2O_2-solution (30%) and 40 ml of KOH-solution (10%) were added. After 16 h at RT. the mixture was acidified with 12N HCl and worked up in the usual way (ether). The oily product (1.8 g) was esterified with diazomethane. The products resulting from several batches (total 19.0 g (60 mmol) of **28**) were combined and chromatographed on 600 g silica gel (petroleum ether/ether 2:3): 11.7 g (60%) of **29** which was used without further purification. – ^{1}H-NMR. (60 MHz): 0.55 (*s*, 3 H, $H_3C(17)$); 1.27 (*s*, 3 H, $H_3C(18)$); 3.63 (*s*, 6 H, 2 $COOCH_3$).

4.2. *Synthesis of methyl* ent-*8β,13-dihydroxy-14,15,16,20-tetranorlabdan-19-oate* (**30**). A solution of 11.7 g (36.1 mmol) of **29** in 500 ml of abs. ether was reduced at 0° by gradual addition of 5.0 g (131.6 mmol) of $LiAlH_4$. The course of the reaction was monitored by TLC. (chloroform/methanol 9:1). The solution was stirred 30 h, hydrolyzed and acidified with 6N HCl. After the usual work-up (ether) and chromatography on 500 g silica gel (chloroform containing increasing amounts of methanol) 7.6 g (71%) of **30** and its 8-epimer were obtained and 1.5 g (15%) of a mixture of the corresponding triols. Diol **30** was recrystallized from ether, its 8-epimer remaining in the mother liquors; m.p. 152–154°, $[\alpha]_D^{20} = -67°$ ($c = 1.01$, C_2H_5OH). – ^{1}H-NMR. (250 MHz): 0.80 (*s*, 3 H, $H_3C(17)$); 1.19 (*s*, 3 H, $H_3C(18)$); 3.63 (*s*, 3 H, $COOCH_3$); 3.67 (*m*, 2 H, $H_2C(13)$); 3.98 (*m*, $w_{1/2} \approx 7$, 1 H, H–C(8)). – MS. (inlet temp. 190°): 298 (5, M^+), 280 (21), 266 (17), 248 (22), 221 (95), 220 (46), 206 (50), 205 (54), 181 (46), 180 (40), 169 (72), 161 (33), 147 (40), 121 (100), 109 (72), 81 (72), 55 (75), 41 (76).

4.3. *Synthesis of methyl* ent-*8β-hydroxy-13-tosyloxy-14,15,16,20-tetranorlabdan-19-oate* (**31**). To 2.8 g (9.4 mmol) of **30**, dissolved in 20 ml of abs. pyridine at 0°, a solution of 2.0 g (10.5 mmol) of tosyl chloride in 20 ml of abs. pyridine was added. The mixture was stirred 12 h at 0°. After usual work-up ($CHCl_3$) and prep. TLC. (chloroform/methanol 9:1), 2.3 g (59%) of **31** were obtained and used without further purification. – ^{1}H-NMR. (250 MHz): 0.73 (*s*, 3 H, $H_3C(17)$); 1.18 (*s*, 3 H, $H_3C(18)$); 2.50 (*s*, 3 H, $CH_3C_6H_4$); 3.63 (*s*, 3 H, $COOCH_3$); 3.86 (*m*, $w_{1/2} \approx 8$, 1 H, H–C(8)); 4.00 (*t*, 2 H, $H_2C(13)$); 7.34 and 7.80 (2 *d*, $J \approx 8$, 4 H, 4 arom. H).

4.4. *Synthesis of methyl* ent-*8-oxo-13-tosyloxy-14,15,16,20-tetranorlabdan-19-oate* (**32**). To a solution of 2.0 g (4.42 mmol) of **31** in 20 ml of acetone at 0° were added a few drops of *Jones*'s reagent until the yellow coloration persisted. After 2 h a few drops of methanol were added. The mixture was neutralized with $NaHCO_3$, filtered, the solid washed with ether and the filtrate concentrated under reduced pressure: 1.9 g (95%) of **32** which was used without further purification. – ^{1}H-NMR. (60 MHz): 0.47 (*s*, 3 H, $H_3C(17)$); 1.23 (*s*, 3 H, $H_3C(18)$); 2.38 (*s*, 3 H, $CH_3C_6H_4$); 3.55 (*s*, 3 H, $COOCH_3$); 3.95 (*m*, 2 H, $H_2C(13)$); 7.22 and 7.65 (2 *d*, $J = 8$, 4 H, 4 arom. H).

4.5. *Synthesis of methyl* ent-*8β,13-epoxy-14,15,16-trinorlabdan-19-oate* (**33**). To 1.9 g (4.22 mmol) of **32** in 40 ml of abs. ether at 0° were added 10 ml of 5% methyl lithium in ether. The mixture was heated under reflux for 10 h. After 48 h at 0° a few ml of water were added, and the mixture was worked up as usual. The crude oil (2.4 g) was purified by prep. TLC. (chloroform/hexane 3:2): 0.7 g (51%) of pure oily **33**. – ^{1}H-NMR. (60 MHz): 0.97, 1.17 and 1.23 (3 *s*, 3 H each, $H_3C(17)$, $H_3C(18)$ and $H_3C(20)$); 3.60 (*s*, 3 H, $COOCH_3$); 3.77 (*m*, 2 H, $H_2C(13)$). – MS.: 294 (1, M^+), 280 (20), 279 (100), 219 (6), 121 (7), 111 (12), 55 (6), 41 (5).

4.6. *Conversion of* **33** *to* **8**. Ether **33** (0.7 g, 2.38 mmol) was treated following the sequence **31**→**34**→**35**→**36**→**12** (s. chap. 5.2, 5.3 and 5.4). The resulting **8** (16.8%) was recrystallized from ethanol/water, m.p. 84–87°, $[\alpha]_D^{20} = -12°$ ($c = 1.06$). – ^{1}H-NMR., ^{13}C-NMR. and MS.: identical with those of **7**.

5. Synthesis of *ent*-8β,13-epoxy-14,15,16,20-tetranorlabdane (**12**). – 5.1. *Synthesis of methyl* ent-*8β,13-epoxy-14,15,16,20-tetranorlabdan-19-oate* (**34**). A solution of 4.6 g (10.2 mmol) of **31** in 20 ml of dist. DMF was added under N_2 to 1.5 g of NaH (washed with abs. ether). After 4 h at RT. a small quantity of methanol and a few drops of water were added. The solution was extracted with $CHCl_3$ and washed with dilute HCl-solution. After the usual work-up (ether) and recrystallization from ether 1.3 g (46%) of **34** were obtained, m.p. 95–98°, $[\alpha]_D^{20} = +96°$ ($c = 1.02$). – ^{1}H-NMR. (60 MHz): 0.96 and 1.15 (2 *s*, 6 H, $H_3C(17)$ and $H_3C(18)$); 3.42 and 3.87 (2 *m*, 3 H, H–C(8) and $H_2C(13)$); 3.57 (*s*, 3 H, $COOCH_3$).

5.2. *Synthesis of* ent-*8β,13-epoxy-14,15,16,20-tetranorlabdan-19-ol* (**35**). To 1.4 g (5 mmol) of **34**, in 50 ml of abs. THF, 1.8 g (47.4 mmol) of $LiAlH_4$ were gradually added. The mixture was heated

under reflux for 4 h, cooled and a few ml of water were added. The usual work-up ($CHCl_3$) gave 1.1 g (89%) of **35**, m.p. 112–115° (from ether/hexane), $[\alpha]_D^{20} = +9°$ ($c = 1.27$). – ^{1}H-NMR. (60 MHz): 0.95 and 1.13 (2 *s*, 3 H each, $H_3C(17)$ and $H_3C(18)$); 1.45 (*s*, 1 H, HO exchangeable with D_2O); 3.60 (*m*, 5 H, H–C(8), $H_2C(13)$ and $H_2C(19)$).

5.3. *Synthesis of* ent-*8β,13-epoxy-14,15,16,20-tetranorlabdan-19-al* (**36**). A solution of 1.0 g (3.97 mmol) of **35** in 15 ml of ether was oxidized at 0° with 4.2 ml of aq. chromic acid [29]. The course of the reaction was monitored by TLC. (ether). At the end of the reaction the upper phase was separated. The usual work-up (ether) gave 0.86 g (82%) of oily **36** which was used without further purification. – ^{1}H-NMR. (60 MHz): 1.00 (*s*, 6 H, $H_3C(17)$ and $H_3C(18)$); 3.47 and 4.03 (2 *m*, 3 H, H–C(8) and $H_2C(13)$); 9.72 (*s*, 1 H, H–C(19)).

5.4. *Conversion of* **36** *to* **12**. A solution of 860 mg (3.44 mmol) of **36** in 67 ml of diethylene glycol/hydrazine hydrate 42:25 was heated to 160° and concentrated during 3 h at the same temp. Then 3.8 g of KOH pellets were added slowly, the solution stirred 45 min at 160° and concentrated until 200° was reached. After 2 h at 200° the mixture was cooled and poured into ice-cold 1 N HCl. Usual work-up (ether) and chromatography on a prep. TLC. (ether/hexane 1:1) yielded 600 mg (80%) of pure crystallized **12**, m.p. 69–73°, $[\alpha]_D^{20} = +13°$ ($c = 1.09$). – ^{1}H-NMR. and ^{13}C-NMR.: *Tables 2* and *3*. – MS.: 236 (53, M^+), 221 (34), 202 (5), 163 (12), 149 (4), 137 (79), 123 (36), 111 (60), 98 (100), 81 (60), 69 (37), 55 (47), 41 (52), 29 (16).

6. Synthesis of *ent*-8α,13-epoxy-14,15,16,20-tetranorlabdane (10). – 6.1. *Synthesis of* ent-*15,16,20-trinorlabdan-8,13-dione* (**24**). A solution of 10.0 g (38.2 mmol) of **21** in 76 ml of CH_2Cl_2/pyridine 15:4 was ozonized at −70° until the blue coloration persisted. The solution was washed 3 times with 15 ml of 10% HCl-solution, and the organic phase stirred for 1 h with 15 ml of 10% NaI-solution. The lower phase was washed with an aq. solution of sodium thiosulfate, worked up in the usual way, and the crude product (8.5 g) was chromatographed on silica gel (ether/hexane 3:7): 6.2 g (61%) of **24**, b.p. 150°/0.01 Torr, $[\alpha]_D^{20} = +23°$ (c = 1.32). – ^{1}H-NMR. (100 MHz): 0.70, 0.85 and 0.95 (3 *s*, 3 H each, $H_3C(17)$, $H_3C(18)$ and $H_3C(19)$); 1.98 (*s*, 3 H, $H_3C(14)$). – MS.: 264 (15, M^+), 249 (100), 231 (19), 207 (9), 179 (19), 137 (36), 121 (28), 109 (25), 95 (41), 81 (41), 69 (48), 55 (53), 43 (95), 29 (15).

6.2. *Synthesis of* ent-*podocarp-8(14)-en-13-one* (**25**). A solution of 6.0 g (22.7 mmol) of **24** in 82 ml of 10% NaOH-solution/methanol 7:75 was stirred overnight at RT., saturated with NaCl, and stirred for 2 h with ether. After the usual work-up and chromatography on silica gel (ether) 4.2 g (75%) of pure **25** were obtained, m.p. 67° (hexane), $[\alpha]_D^{20} = -40°$ ($c = 1.00$). – ^{1}H-NMR. (CCl_4, 100 MHz): 0.81, 0.87 and 0.91 (3 *s*, 3 H each, $H_3C(15)$, $H_3C(16)$ and $H_3C(17)$); 5.70 (br. *s*, $w_{1/2} \approx 5$, 1 H, H–C(14)). – ^{13}C-NMR.: *Table 3*. – MS.: 246 (12, M^+), 231 (6), 177 (5), 161 (5), 149 (7), 137 (8), 123 (71), 110 (100), 95 (21), 81 (32), 69 (28), 55 (27), 41 (39), 29 (10).

6.3. *Synthesis of* ent-*14,15,16,20-tetranorlabdane-8β,13-diol* (**26**) and ent-*14,15,16,20-tetranorlabdane-8α,13-diol* (**27**). Ozonization of 8.0 g (32.5 mmol) of **25** in 132 ml of CH_2Cl_2/pyridine 10:1 as described in chap. 6.1 gave 7.0 g of crude product; this was directly reduced with 7.0 g (0.2 mol) of $LiAlH_4$ in 300 ml of abs. ether. The mixture was vigorously stirred for 1 h at reflux temp., then aq. NH_4Cl-solution was added until the evolution of H_2 ceased. The precipitate was filtered off on *Celite* and abundantly rinsed with ether. After usual work-up (ether) the 3.0 g of product were chromatographed on 300 g of silica gel (ether): 0.57 g of unidentified products, 1.3 g of **26** and 0.79 g of **27** (order of elution). Extraction of the residue in the *Celite* filter with ether in a *Soxhlet* apparatus for 14 days gave a further 1.65 g of **27**. Total yield (based on **25**): 1.3 g (16%) **26** and 2.44 g (30%) **27**. *Diol* **26**: m.p. 133–135° (ether), $[\alpha]_D^{20} = -36°$ ($c = 1.30$). – ^{1}H-NMR. (360 MHz): 0.84, 0.87 and 0.99 (3 *s*, 3 H each, $H_3C(17)$, $H_3C(18)$ and $H_3C(19)$); 3.66 (*m*, 2 H, $H_2C(13)$); 3.97 (*m*, $w_{1/2} = 7.5$, 1 H, H–C(8)). – ^{13}C-NMR.: *Table 3*. – MS.: 254 (0, M^+), 236 (60), 221 (45), 177 (37), 164 (16), 149 (42), 137 (79), 129 (21), 124 (81), 116 (47), 109 (100), 95 (74), 81 (82), 69 (82), 55 (68), 41 (84).

Diol **27**: m.p. 140–141° (ether), $[\alpha]_D^{20} = +39°$ ($c = 1.27$). – ^{1}H-NMR. (360 MHz): 0.79, 0.81 and 0.88 (3 *s*, 9 H, $H_3C(17)$, $H_3C(18)$ and $H_3C(19)$); 3.47 ($d \times d \times d$, $J_1 = 5$, $J_2 = 11$, $J_3 = 11$, $w_{1/2} \approx 16$, 1 H, H–C(8)); 3.61 ($d \times d \times d$, $J_1 = 6$, $J_2 = 6$, $J_3 = 11$) and 3.69 ($d \times d \times d$, $J_1 = 4$, $J_2 = 8$, $J_3 = 11$) (1 H each, $H_2C(13)$). – ^{13}C-NMR.: *Table 3*. – MS.: 254 (0, M^+), 236 (57), 221 (39), 177 (29), 164 (19), 149 (36), 137 (100), 135 (38), 129 (16), 124 (68), 123 (48), 121 (20), 116 (36), 112 (29), 109 (70), 95 (54), 81 (66), 69 (70), 67 (41), 55 (79), 43 (50), 41 (93).

6.4. *Conversion of* **27** *to* **10**. A solution of 0.98 g (3.9 mmol) of **27** and 150 mg of *p*-toluenesulfonic acid in 30 ml of benzene was stirred overnight at RT. After usual work-up (ether) and chromatography on silica gel (ether/hexane 5:95) 0.45 g (54%) of **10** were isolated in addition to 0.05 g of **27** and 0.2 g of unidentified products. *Ether* **10**: m.p. 33–34°, $[\alpha]_D^{20} = -10°$ ($c = 1.42$). – ^{1}H-NMR. and ^{13}C-NMR.: *Tables 2* and *3*. – MS.: 236 (100, M^+), 221 (97), 207 (6), 195 (8), 177 (2), 163 (5), 151 (10), 137 (51), 123 (51), 111 (49), 98 (65), 81 (35), 69 (34), 55 (45), 41 (53), 29 (16).

7. Synthesis of *ent*-9α,13-epoxy-14,15,16,20-tetranorlabdane (14) and *ent*-9β,13-epoxy-14,15,16,20-tetranorlabdane (16). – After treatment of 1.0 g (3.9 mmol) of **26** following chap. 6.4, the product was chromatographed on silica gel (ether/hexane 5:95), to give 0.24 g (27%) of **14**, 0.17 g (19%) of **16** and 0.21 g of an unidentified product. *Ether* **14**: $[\alpha]_D^{20} = +14°$ ($c = 1.28$). – ^{1}H-NMR.[17]) and ^{13}C-NMR.[18]): *Tables 2* and *3*. – MS.: 236 (22, M^+), 221 (5), 135 (3), 123 (11), 110 (7), 97 (100), 84 (31), 69 (9), 55 (21), 41 (17), 29 (29).

Ether **16**: $[\alpha]_D^{20} = +29°$ ($c = 1.30$). – ^{1}H-NMR.[17]) and ^{13}C-NMR.[18]): *Tables 2* and *3*. – MS.: 236 (23, M^+), 221 (7), 150 (2), 135 (5), 123 (14), 110 (8), 97 (100), 84 (36), 69 (15), 55 (25), 41 (22), 29 (5).

Table 2. *^{1}H-NMR. chemical shifts ($CDCl_3$) of compounds* **5**–**16** *relative to* TMS (= 0 ppm)

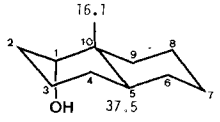
Compounds	$H_3C(17)$	$H_3C(18)$	$H_3C(19)$	$H_3C(20)$	H–C(8)	$H_2C(13)$
5 and **6**[a])	0.75[c])	0.80[c])	0.86[c])	1.25	–	3.65
7 and **8**[a])	1.20	0.88		1.23	–	3.70
9 and **10**[b])	0.82[c])	0.84[c])	0.87[c])	–	3.88	3.21
						3.33
11 and **12**[b])	1.18	0.86		–	4.02	3.48
13 and **14**[a])	0.93[c])[17])	0.82[c])	0.88[c])	–	–	3.81
15 and **16**[a])	1.09[17])	0.87		–	–	3.75

[a]) 90 MHz. [b]) 360 MHz. [c]) Uncertain contribution.

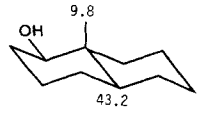
8. Synthesis of 8α,13-epoxy-14,15,16,20-tetranorlabdane (9). – 8.1. *Synthesis of 14,15,16,20-tetranorlabdane-8β,13-diol* (**38**) and *14,15,16,17-tetranorlabdane-8α,13-diol* (**39**). Under the conditions described in chap. 6.3 8.0 g (32.5 mmol) of **37** [24] ($[\alpha]_D^{20} = +41°$, $c = 1.77$) were ozonized to yield

[17]) The ^{1}H-NMR. data *(Table 2)* shows $H_3C(17)$ to be at *ca.* 0.16 ppm lower field in **16** (1.09 ppm) than in **14** (0.93 ppm), probably owing to an interaction between the equatorial O-atom and the angular methyl group in **16**. In **14** the axial orientation of the O-atom precludes such an interaction with the C(17) methyl group.

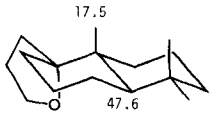
[18]) In the *trans*-methyldecalols **A** and **B**, the angular methyl C-atom appears at lower field in isomer **A** than in isomer **B** but C(5) appears at higher field in **A** than in **B** [30]. Comparison of the ^{13}C-NMR. of **14** and **16** (see *Table 3*) with that of **A** and **B** allows also assignment of the axial and equatorial ether linkages in **14** and **16** respectively.



isomer **A**



isomer **B**



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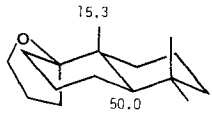

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Table 3. *^{13}C-NMR. chemical shifts ($CDCl_3$) of ethers* **5–16** *and of some intermediates*

	5/6	**7/8**	**9/10**	**11/12**	**13/14**	**15/16**	**17/23**	**18**	**22**	**25/37**	**26/38**	**27/39**	**28**	**34**
C(1)	39.0 *t*	41.5 *t*	38.6 *t*	40.8 *t*	33.4 *t*	34.1 *t*	39.2 *t*	39.8 *t*	38.9[a] *t*	39.2 *t*	39.3 *t*	38.8 *t*	38.5[a] *t*	40.9 *t*
C(2)	18.6 *t*	18.6 *t*	18.6 *t*	18.3[a] *t*	18.7 *t*	18.6 *t*	18.4 *t*	18.4 *t*	19.3[b] *t*	18.7 *t*	18.3 *t*	18.5 *t*	19.6 *t*	19.6[a] *t*
C(3)	42.0[a] *t*	41.9[a] *t*	42.2 *t*	42.2 *t*	42.1 *t*	42.5 *t*	41.3[a] *t*	42.0 *t*	42.1 *t*	41.7 *t*	42.1 *t*	42.1 *t*	37.4 *t*	38.3 *t*
C(4)	33.4 *s*	33.2 *s*	33.3 *s*	33.2 *s*	33.4 *s*	33.1 *s*	33.1 *s*	33.4 *s*	33.6 *s*	33.3 *s*	33.3 *s*	33.3 *s*	43.7 *s*	43.7 *s*
C(5)	56.5 *d*	55.3 *d*	55.1 *d*	55.5 *d*	47.6 *d*	50.0 *d*	56.0 *d*	56.1 *d*	56.2[c] *d*	53.8 *d*	54.4 *d*	54.8 *d*	55.6[b] *d*	56.4 *d*
C(6)	20.0 *t*	18.6[b] *t*	20.7 *t*	18.5[a] *t*	21.6 *t*	21.3 *t*	19.6 *t*	20.5[a] *t*	24.4 *t*	21.9 *t*	17.1 *t*	20.9 *t*	24.0[c] *t*	19.0[a] *t*
C(7)	42.2[a] *t*	42.8[a] *t*	33.9 *t*	34.0 *t*	26.1 *t*	27.4 *t*	41.8[a] *t*	44.2 *t*	38.2[a] *t*	35.6 *t*	35.2 *t*	36.7 *t*	38.2[a] *t*	34.2 *t*
C(8)	74.7 *s*	72.8 *s*	77.1 *d*	77.2 *d*	32.2[a] *t*	32.0[a] *t*	83.6 *s*	74.5 *s*	147.7 *s*	165.3 *s*	67.3 *d*	72.7 *d*	146.0 *s*	76.9 *d*
C(9)	57.9 *d*	50.3 *d*	54.3 *d*	47.5 *d*	88.3 *s*	88.9 *s*	56.0 *d*	59.4 *d*	55.5[c] *d*	51.5 *d*	56.1 *d*	57.3 *d*	54.6[b] *d*	46.4 *d*
C(10)	36.9 *s*	38.7 *s*	37.1 *s*	38.5 *s*	41.7 *s*	42.3 *s*	37.2 *s*	39.2 *s*	39.7 *s*	38.9 *s*	37.9 *s*	38.8 *s*	39.8 *s*	38.7 *s*
C(11)	18.2 *t*	17.8[b] *t*	22.4 *t*	22.8[b] *t*	31.5[a] *t*	31.3[a] *t*	15.6 *t*	20.8[a] *t*	18.9[b] *t*	20.5 *t*	20.7 *t*	22.9 *t*	23.3[c] *t*	22.9 *t*
C(12)	27.7 *t*	21.6 *t*	27.0 *t*	23.2[b] *t*	22.7 *t*	23.6 *t*	29.0 *t*	34.4 *t*	33.1 *t*	36.7 *t*	31.1 *t*	33.9 *t*	25.7 *t*	22.9 *t*
C(13)	60.9 *t*	60.3 *t*	67.8 *t*	68.9 *t*	68.2 *t*	67.2 *t*	171.4 *s*	61.8 *t*	180.8 *s*	199.3 *s*	62.9 *t*	61.9 *t*	123.9 *s*	68.9 *t*
C(14)	-	-	-	-	-	-	-	-	-	125.8 *d*	-	-	109.6 *d*	-
C(15)	-	-	-	-	-	-	-	-	-	33.6 *qa*	-	-	137.0 *d*	-
C(16)	-	-	-	-	-	-	-	-	-	22.1 *qa*	-	-	140.9 *d*	-
C(17)	15.6 *qa*	19.1 *qa*	14.5 *qa*	19.3 *qa*	17.5 *qa*	15.3 *qa*	15.0 *qa*	15.3 *qa*	14.3 *qa*	15.3 *qa*	15.9 *qa*	14.3 *qa*	12.6 *qa*	17.9 *qa*
C(18)	33.4 *qa*	34.2 *qa*	33.6 *qa*	34.2 *qa*	33.4 *qa*	33.7 *qa*	33.3 *qa*	33.4 *qa*	33.6 *qa*	-	33.7 *qa*	33.5 *qa*	28.6 *qa*	28.8 *qa*
C(19)	21.4 *qa*	22.3 *qa*	21.8 *qa*	22.2 *qa*	22.1 *qa*	21.8 *qa*	21.4 *qa*	21.5 *qa*	21.7 *qa*	-	21.8 *qa*	21.8 *qa*	182.4 *s*	178.1 *s*
C(20)	20.0 *qa*	25.9 *qa*	-	-	-	-	22.9 *qa*	24.4 *qa*	106.5 *t*	-	-	-	105.2 *t*	-
$-OCH_3$	-	-	-	-	-	-	-	-	-	-	-	-	-	51.1 *qa*

[a][b][c] Values within any vertical column may be reversed.

diols **38** and **39** (39% total). *Diol* **38**: m.p. 95–96°, $[\alpha]_D^{20} = +36°$ ($c = 1.2$). – ^{1}H-NMR., ^{13}C-NMR. and MS.: identical with those of **26**.

Diol **39**: m.p. 135–136°, $[\alpha]_D^{20} = -37°$ ($c = 1.0$). – ^{1}H-NMR., ^{13}C-NMR. and MS.: identical with those of **27**.

8.2. *Conversion of* **39** *to* **9**. Under the conditions described in chap. 1.2 800 mg (3.15 mmol) of **39** were heated under reflux for 28 h: 214 mg (28.8%) of pure **9**, m.p. 34–35°, $[\alpha]_D^{20} = +13°$ ($c = 0.87$). – ^{1}H-NMR., ^{13}C-NMR. and MS.: identical with those of **10**.

9. Synthesis of 8β,13-epoxy-14,15,16,20-tetranorlabdane (11). – Under the conditions described in chap. 8.2 1.0 g (3.94 mmol) of **38** yielded 18.6 mg (2%) of pure **11** which sublimed at 60°/0.01 Torr, m.p. 70–71°, $[\alpha]_D^{20} = +13°$ ($c = 0.37$). – ^{1}H-NMR., ^{13}C-NMR. and MS.: identical with those of **12**.

10. Synthesis of 9α,13-epoxy-14,15,16,20-tetranorlabdane (13) and 9β,13-epoxy-14,15,16,20-tetranorlabdane (15). Under the conditions described in chap. 6.4 and 7 1.0 g (3.94 mmol) of **38** yielded **13** (359 mg, 39%) and **15** (239 mg, 26%). *Ether* **13**: b.p. 120–130°/0.1 Torr (bulb dist.), $[\alpha]_D^{20} = -14°$ ($c = 1.09$). – ^{1}H-NMR., ^{13}C-NMR. and MS.: identical with those of **14**.

Ether **15**: b.p. 120–130°/0.1 Torr (bulb dist.), $[\alpha]_D^{20} = -28°$ ($c = 0.69$). – ^{1}H-NMR., ^{13}C-NMR. and MS.: identical with those of **16**.

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