The Ozonolysis of Longifolene: A Tool for the Preparation of Useful Chiral Compounds. Configuration Determination of New Stereogenic Centers by NMR Spectroscopy and X-Ray Crystallography

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The ozonolysis of (+)-longifolene (**1**) in different solvents (Et_2O, CH_2Cl_2, $CHCl_3$, acetone) at $-80°$ provided quantitatively longifolene epoxide (**3**) as a single diastereoisomer in which the O-atom is *endo*-positioned (*Scheme 2*). Upon warming to room temperature, the epoxide remained stable only in acetone and was isolated as a low-melting crystalline compound. In CH_2Cl_2, Et_2O, or $CHCl_3$ solution, epoxide **3** rapidly rearranged to the isomeric enols **4** and **5**, which underwent further rearrangement to give the *exo*-aldehyde **6**. On standing for several weeks in CH_2Cl_2 solution, or in $CHCl_3$ and Et_2O as well, at room temperature, aldehyde **6** slowly rearranged into its epimer **7**. The aldehydes **6** and **7** were isolated on the preparative scale for further synthetic use. The addition of methylmagnesium iodide to **6** and **7** provided the corresponding alcohols **13**/**14** and **15**/**16**, respectively, which were isolated as pure diastereoisomers (*Scheme 4*). The configurations of the new chiral centers in **13**–**16** were determined by NMR methods and X-ray crystallography.

Introduction. – Longifolene (**1**) is a naturally occurring sesquiterpene widely distributed in the plant family of Pinaceae (*e.g.*, *Pinus roxburghii* SARG. syn. *P. longifolia Roxb. ex Lamb. non Salisb.* [1], *Pinus caribaea* MORELET [2], *Halocarpus bidwillii* [3]). The (+)-enantiomer occurs in higher plants, whereas the (−)-enantiomer has been found in liverworts [4][5] (*e.g.*, *Scapania undulata* (L.) DUM.) and in fungi (*e.g.*, *Helmintosporium sativum* [6]). The Indian turpentine oil, which is produced commercially from the oleoresin of Himalayan pine (*P. longifolia*), contains 5–10% of (+)-longifolene.

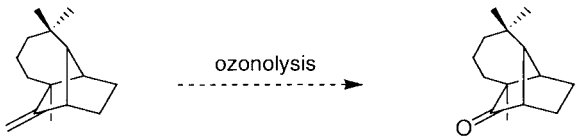
Apparently, the synthesis of the tricyclic skeleton of longifolene (**1**) has been an interesting challenge, because the total synthesis has been realized several times [7][8][1]) [9–12]. The chemistry of **1** has been investigated intensively and has provided interesting and sometimes difficult-to-interpret results due to the tendency of the tricyclic framework to undergo rearrangement [1]. The current interest in this compound centers around its significance for the fragrance industry [13].

We are interested in the synthesis of longicamphenylone (**2**) on the preparative scale for further synthetic use (*Scheme 1*). Several earlier publications describe the formation of **2**, together with several oxidation products, as a result of the ozonolysis of longifolene (**1**) [14][15]. However, depending on the reaction conditions, the ozonolysis of **1** may yield longifolene epoxide (**3**) exclusively [16]. Reviews by *Dev* [1] indicate that the reactions of **1** with different oxidizing agents (ozone, peracids, metal oxides, *etc.*) actually lead to a diverse array of products that arise from ring

[1]) In [8], the preparation of (+)-longifolene from (+)-longicamphenylone has been described, which is not possible. (+)-Longifolene can be formed from (−)-longicamphenylone, according to [7].

enlargements and/or rearrangements within the tricyclic framework. The tendency of **1** to undergo rearrangements in some reactions and thereby produce mixtures of derivatives seems to discourage synthetic chemists. This is probably the reason for the very limited use of **1** as a chiral auxiliary in asymmetric syntheses. To our knowledge, the preparation of bis(longifolyl)borane and its use as a chiral reducing agent [17] is the only example of the application of (+)-longifolene in asymmetric synthesis.

Scheme 1



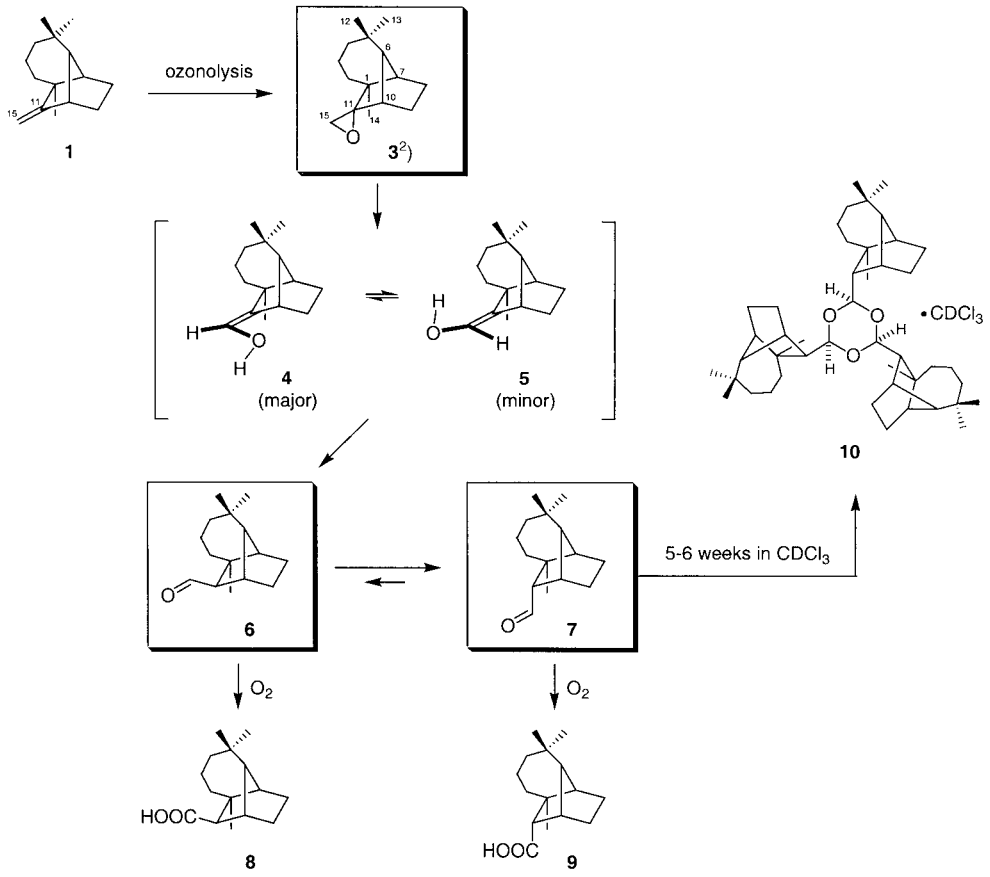
1 **2**

We recently reported results concerning the preparation of chiral ferrocene derivatives bearing the longifolyl skeleton [18]. In this paper, we describe the practical synthesis of useful chiral compounds by means of the ozonolysis of (+)-longifolene (**1**) as a tool.

Results and Discussion. – The procedure described in our previous work for ozonolytic cleavage of a C=C bond to prepare carbonyl compounds [19] was applied to (+)-longifolene (**1**). After the ozonolysis of **1** in Et_2O or CH_2Cl_2 at $-80°$, the reaction mixture was treated with Et_3N. However, only epoxide **3** was isolated (*Scheme 2*), and no longicamphenylone (**2**) could be observed. Epoxide **3** was rather unstable when left to stand in Et_2O, CH_2Cl_2, $CHCl_3$, or hexane solution, a mixture of several products being formed. It was not possible to separate well-defined products because the composition of this mixture changed rapidly with time. Only after the time dependence of product formation during ozonolysis of **1** was understood, it was possible to define suitable conditions for the preparation and isolation of the compounds described below.

The ozonolysis of **1** in different solvents (Et_2O, CH_2Cl_2, $CHCl_3$, and acetone) between -80 and $-50°$ furnished epoxide **3** (*Scheme 2*). No other product, in particular a secondary ozonide, could be observed by NMR investigations at low temperature. On warming the acetone solution to room temperature, the epoxide **3** remained stable for several days and could be obtained as a resonably pure crude product after evaporation of the solvent. Subsequent chromatography on silica gel (hexane/Et_2O 10:1) gave very pure **3**. It was also found that compound **3** could be distilled (see *Exper. Part*). In contrast, it has previously been described [20] that epoxide **3**, prepared by peracid oxidation of **1**, rearranges during chromatography over Al_2O_3 or silica gel with hexane to give an aldehyde. It must be pointed out that only after being prepared in acetone, compound **3** could be chromatographed and remain stable on silica gel for several hours. When prepared in Et_2O, $CHCl_3$, or CH_2Cl_2, epoxide **3** rearranged on warming to room temperature to the enols **4** and **5** and, then,

Scheme 2



further to aldehyde **6** (*Scheme 2*). The pure epoxide **3** can be stored for several days, but, even then, the rearrangement reaction occurs slowly with formation of **6**.

The best results for the preparation of aldehyde **6** in high yield were obtained by carrying out the ozonolysis in CH_2Cl_2. Initially, the enols **4** and **5** were characterized by NMR. After ozonolysis of **1** at $-80°$, the CH_2Cl_2 solution was warmed to room temperature and held at this temperature for *ca.* 10 min. To carry out the NMR investigations, the CH_2Cl_2 was evaporated, and the remaining oil (mixture **4**/**5**) was dissolved in $CDCl_3$ and cooled to $-50°$ to avoid further rearrangement to aldehyde **6**. The unambiguous assignment of the ^1H- and ^{13}C-NMR spectra of the enols was achieved by gs-HSQC, gs-HMBC, NOESY, and DQF-COSY experiments (see *Tables 1* and *2* and *Exper. Part*). Interestingly, it was possible to purify the enols or even to separate them by column chromatography, as shown by TLC. However, the NMR spectra obtained from $CDCl_3$ solutions of individually isolated **4** or **5** always showed the

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[2]) Arbitrary numbering. The systematic name of longifolene (**1**) is (1*S*,3a*R*,4*S*,8a*S*)-decahydro-4,8,8-trimethyl-9-methylene-1,4-methanoazulene; for other systematic names, see *Exper. Part*.

Table 1. *^{13}C-NMR Chemical Shifts* ($CDCl_3$, δ in ppm rel. to Me_4Si) *of Compounds* **1**–**9** *and* **13**–**16**. Tentative assignments are marked with asterisks; for the numbering of the C-atoms, see *Schemes 2* and *4*[2]).

	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	C(10)	C(11)	C(12)	C(13)	C(14)	C(15)	C(16)
1	43.96	43.38	21.14	36.38	33.58	62.11	45.02	25.51	29.73	47.98	167.90	30.61*	30.49*	30.13	99.04	–
2	48.22	40.15	20.16	36.70	33.55	60.60	42.91	25.20	25.23	51.05	225.26	29.11*	30.94*	25.32	–	–
3	39.72	39.76	20.60	38.41	33.41	60.57	45.35	25.89	23.90	44.66	71.83	31.00	30.30	24.25	54.33	–
4	41.90	43.44	20.96	36.00	33.49	62.04	45.02	25.51	28.55	39.02	132.90	30.99	30.07	30.75	130.02	–
5	42.80	37.73	21.03	36.53	33.45	61.52	46.00	25.57	30.78	43.54	132.22	30.22	30.45	26.95	128.50	–
6	45.88	35.76	20.92	36.70	33.31	64.04	45.79	25.10	31.65	38.34	67.76	30.52	31.82	32.63	204.94	–
7	42.56	44.41	21.40	39.15	33.28	61.79	45.82	25.67	23.11	40.40	60.80	29.62	32.40	26.19	206.38	–
8	46.72	37.08	20.48	36.86	33.13	60.81	45.56	24.80	32.31	39.60	63.97	30.05	31.68	32.25	180.26	–
9	41.55	42.73	21.39	39.47	33.17	61.77*	45.42	25.53	22.62	41.11	52.93*	29.39	32.62	25.71	179.71	–
13	45.68	36.37	21.29	38.80	32.88	64.14	45.49	24.90	34.74	41.11	65.67	31.39	31.82	33.19	68.81	24.30
14	44.84	36.37	21.37	39.11	32.99	63.89	46.28	24.97	34.51	40.07	65.04	31.26	32.10	32.51	68.18	25.20
15	41.09	45.38	21.67	39.89	33.30	61.55	46.23	21.67	25.99	42.14	55.66	29.41	32.86	23.99	67.93	23.85
16	40.39	44.79	21.58	40.10	33.48	61.07	46.77	21.83	26.27	41.39	55.18	29.57	33.07	24.13	66.45	24.19

presence of a mixture of compounds, containing mainly **4** and **5**, and aldehyde **6**. This observation indicates the high instability of the enols, which undergo an interconversion as well as rearrangement to aldehyde **6**.

The direct synthesis of aldehyde **6** on a preparative scale was conducted by ozonolysis of **1** in CH_2Cl_2 at $-80°$ followed by warming to room temperature and keeping the solution at this temperature until the formation of **6** was complete (usually within 30–40 min). Surprisingly, when the ozonolysis of **1** was carried out in acetone to give epoxide **3**, then the acetone was evaporated at room temperature, and the residue dissolved in CH_2Cl_2, the rearrangement of **3** to enols **4** and **5** and then to aldehyde **6** was very slow (more than 10 days). Solutions of aldehyde **6** always contain up to 10% of its isomer **7**, which can be removed, if necessary, by column chromatography. The crude **6** obtained after evaporation of the solvent could be used in subsequent syntheses without any purification. For the preparation of **7**, the CH_2Cl_2 solution of **6** was kept at room temperature for *ca.* 5 weeks and monitored occasionally by TLC. During this time, **6** rearranged almost quantitatively to **7**, plus a small amount of other products that were not identified. After column chromatography, aldehyde **7** was obtained in pure form. The aldehydes **6** and **7** were sensitive towards O_2 oxidation and formed the corresponding acids **8** and **9**, respectively, when stored in air. The acids **8** and **9** were identified by mass and NMR spectroscopy.

The formation of aldehyde **6** can be enhanced by introducing 10% $BF_3 \cdot OEt_2$ to the CH_2Cl_2 reaction solution after the appearance of enols **4** and **5**. The addition of $BF_3 \cdot OEt_2$ to the CH_2Cl_2 solution of epoxide **3** led to the formation of both aldehydes **6** and **7** in approximately equal quantities. The aldehydes **6** and **7** could be separated by column chromatography (silica gel, hexane/Et_2O 40:1).

The following important observation is noteworthy. In one protocol, freshly purified (by column chromatography) aldehyde **6** was kept overnight in $CDCl_3$ after recording the NMR spectra. Remarkably, a reinvestigation of the $CDCl_3$ solution by NMR showed the presence of compounds **3**–**6** in the ratio 1.9:1.3:0.8:1, respectively. Consequently, it should be assumed that these compounds exist in equilibrium with a back formation of epoxide **3**. Although, this protocol could not be reproduced, this observation indicates the presence of a process like tautomerism. Furthermore, when a $CDCl_3$ solution of **6** was left to stand for a long period of time (*ca.* 5–6 weeks),

Table 2. *^{1}H-NMR Chemical Shifts*[a]) (δ in ppm relative to Me_4Si, J in Hz) *of Compounds* **3**–**7** *and* **13**–**16**. Arbitrary numbering[2]).

	3[b])	**4**[c])	**5**[c])	**6**[b])	**7**[b])	**13**[b])	**14**[b])	**15**[b])	**16**[b])
H_a–C(2)			2.16 (*dt*, *J* = 13.2, 6.9)	2.22–2.12 (*m*)		2.11–2.04 (*m*)	1.71–1.61 (*m*)		
	1.45–1.34 (*m*)	1.58–1.43 (*m*)	and		1.71–1.52 (*m*)			1.61–1.44 (*m*)	1.48–1.35 (*m*)
H_b–C(2)			1.31 (*dd*, *J* = 14.6, 6.2)	1.46–1.39 (*m*)		1.40–1.33 (*m*)	1.35–1.27 (*m*)		
H_a–C(3)	1.54–1.46 (*m*)	1.49–1.45 (*m*)	1.54–1.47 (*m*)	1.45–1.34 (*m*)	1.77–1.65 (*m*)	1.65–1.56 (*m*)	1.68–1.57 (*m*)	1.72–1.65 (*m*)	1.74–1.62 (*m*)
		and	and		and		and		and
H_b–C(3)	1.69–1.59 (*m*)	1.38–1.34 (*m*)	1.41–1.35 (*m*)	1.65–1.54 (*m*)	1.59–1.50 (*m*)	1.49–1.43 (*m*)	1.47–1.39 (*m*)	1.60–1.50 (*m*)	1.57–1.50 (*m*)
H_a–C(4)	1.31–1.25	1.60 (*dd*, *J* = 13.2, 12.5)	1.64 (*t*, *J* = 13.2)		1.59–1.50 (*m*)	1.44–1.37 (*m*)	1.51–1.43 (*m*)	1.74–1.64 (*m*)	1.35–1.28 (*m*)
	(*dd*, *J* = 14.3, 7.8)	and	and	1.20–1.10 (*m*)	and				
H_b–C(4)	1.49–1.41 (*m*)	0.97 (*dd*, *J* = 13.9, 8.3)	1.00 (*dd*, *J* = 13.9, 8.3)		1.37–1.29 (*m*)	1.29–1.23 (*m*)	1.34–1.27 (*m*)	1.38–1.28 (*m*)	1.69–1.61 (*m*)
H–C(6)	1.52–1.49 (*m*)	1.36 (*s*)	1.29 (*s*)	1.48 (*s*)	1.45 (*s*)	1.30 (*s*)	1.38 (br. *s*)	1.32 (*s*)	1.37 (*s*)
H–C(7)	2.14–2.10 (*m*)	1.99 (*s*)	1.94 (*d*, *J* = 3.4)	2.07–2.01 (*m*)	2.06–2.03 (*m*)	1.95 (*d*, *J* = 4.4)	2.00–1.97 (*m*)	1.95–1.91 (*m*)	1.94–1.91 (*m*)
H_{exo}–C(8)	1.52–1.42 (*m*)	1.59 (*t*, *J* = 10.4)	1.63–1.57 (*m*)	1.47–1.38 (*m*)	1.68–1.57 (*m*)	1.41–1.33 (*m*)	1.45–1.36 (*m*)	1.36–1.25 (*m*)	1.34–1.28 (*m*)
		and	and		and				
H_{endo}–C(8)	1.85–1.79 (*m*)	1.39–1.29 (*m*)	1.34–1.26 (*m*)	1.74–1.66 (*m*)	1.41–1.33 (*m*)	1.70–1.63 (*m*)	1.71–1.64 (*m*)	1.69–1.59 (*m*)	1.65–1.58 (*m*)
H_{exo}–C(9)	1.56–1.47 (*m*)	1.67–1.59 (*m*)	1.68–1.58 (*m*)	1.12–1.05 (*m*)		1.60–1.52 (*m*)	1.63–1.55 (*m*)		
		and	and		1.59–1.41 (*m*)			1.31–1.13 (*m*)	1.46–1.29 (*m*)
H_{endo}–C(9)	1.74–1.66 (*m*)	1.08–1.01 (*m*)	1.10–1.01 (*m*)	1.73–1.65 (*m*)		1.16–1.10 (*m*)	1.15–1.08 (*m*)		
H–C(10)	1.81–1.77 (*m*)	2.85 (*d*, *J* = 4.4)	2.33 (*d*, *J* = 4.6)	2.70–2.65 (*m*)	2.49–2.45 (*m*)	1.88 (*d*, *J* = 4.4)	2.36–2.32 (*m*)	2.09–2.05 (*m*)	2.32–2.29 (*m*)
H–C(11)	–	–	–	1.78 (*s*)	2.65–2.61 (*m*)	1.01 (*d*, *J* = 10.4)	1.05 (*d*, *J* = 10.6)	1.80 (*ddd*, *J* = 9.6,	1.84 (*ddd*, *J* = 10.1,
								3.5, 1.0)	3.7, 1.0)
Me(12)	0.96 (*s*)	0.84 (*s*)	0.82 (*s*)	0.95 (*s*)	0.93 (*s*)	0.86 (*s*)	0.96 (*s*)	0.96 (*s*)	0.97 (*s*)
Me(13)	1.03 (*s*)	0.881 (*s*)	0.879 (*s*)	0.97 (*s*)	1.00 (*s*)	0.95 (*s*)	0.99 (*s*)	1.00 (*s*)	0.99 (*s*)
Me(14)	0.81 (*s*)	0.93 (*s*)	1.08 (*s*)	1.21 (*s*)	1.07 (*s*)	1.06 (*s*)	1.03 (*s*)	1.06 (*s*)	0.86 (*s*)
H_a–C(15)	2.83 (*d*, *J* = 4.8)	5.92 (*s*)	6.11 (*d*, *J* = 4.2)	9.94 (*s*)	9.85 (*s*)	4.16	4.01	3.98 (*dq*, *J* = 9.6, 6.1)	3.88
						(*dq*, *J* = 10.4, 6.2)	(*dq*, *J* = 10.6, 5.7)		(*dq*, *J* = 10.1, 5.8)
H_b–C(15)	3.00 (*d*, *J* = 4.8)								
Me(16)	–	4.67 (*s*)	4.54 (*s*)	–	–	1.22 (*d*, *J* = 6.2)	1.22 (*d*, *J* = 5.7)	1.16 (*d*, *J* = 6.1)	1.23 (*d*, *J* = 10.1)

[a]) Most of the ^{1}H-NMR chemical shifts of the methylene protons were extracted from the HSQC spectra because of overlapping of signals in the 1D ^{1}H-NMR spectra. [b]) $CDCl_3$. [c]) CD_2Cl_2, 223 K.

colorless crystals formed in the NMR tube. The crystalline substance was insoluble in any organic solvent and for this reason an NMR investigation could not be undertaken. The compound was identified by means of X-ray crystallography as the 2,4,6-(*endo*-longifolyl)-substituted 1,3,5-trioxane **10**, which must have formed after the initial generation of aldehyde **7** (*Scheme 2* and *Fig. 1*). The molecule is a cyclic trimer of the principle cyclic moiety **7** and sits about a crystallographic three-fold axis. There are an equivalent number of $CDCl_3$ molecules in the structure, which also sit about three-fold axes. The absolute configuration was determined independently by the diffraction experiment and is in agreement with that expected from the known configuration of the polycyclic skeleton.

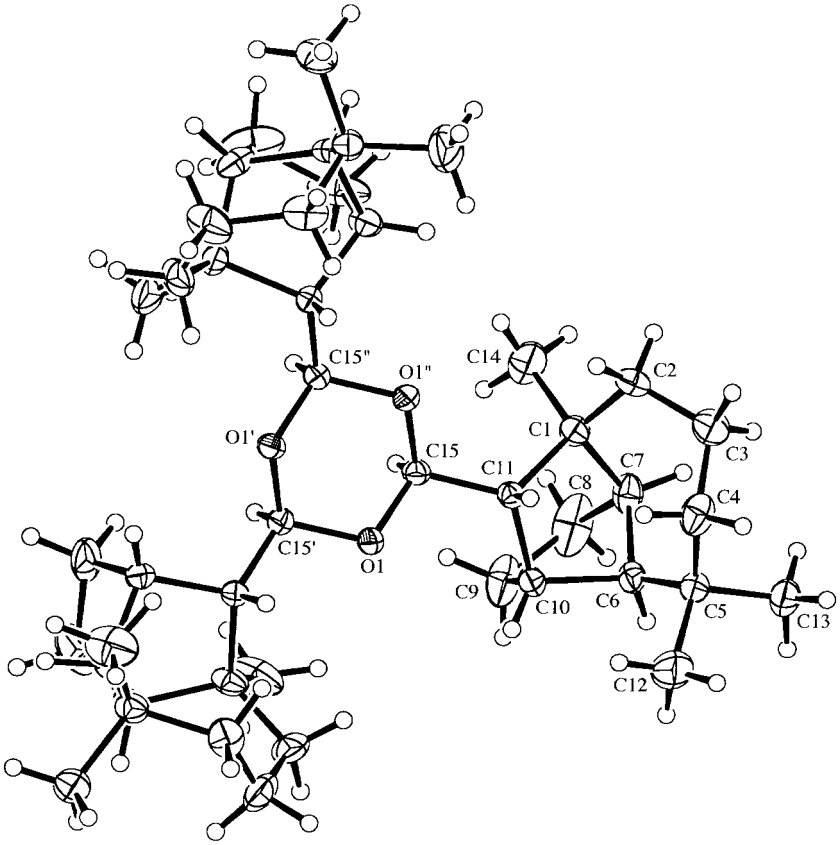
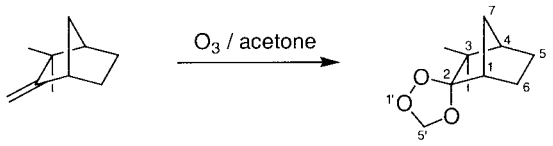


Fig. 1. *ORTEP Plot* [30] *of the molecular structure of* **10**. Ellipsoids with 30% probability; the $CDCl_3$ molecule is omitted for clarity. Arbitrary numbering.

The formation of epoxide **3** as a result of ozonolysis [16] or epoxidation with perbenzoic acid [20] and the rearrangement leading to aldehydes **6** and **7** has been described previously [1][21]. However, there are no previous reports of experimental evidence for the formation of enols **4** and **5**, and the time and solvent dependency of the rearrangement reaction had not been recognized. Thus, there is no previously published experimental procedure for the preparation of aldehydes **6** and **7**.

The formation of an epoxide as a result of the so-called 'abnormal ozonolysis' has been observed with several sterically hindered olefins [22–24]. Epoxides were also obtained during attempts to prepare ketones from two bridgehead-substituted camphene derivatives [25]. In the case of camphene itself, it seems that the ozonolysis proceeds in the usual way, however the isolated products usually result from bond cleavage within the bicyclic framework [26]. On the other hand, the chromic acid oxidation of camphene has been reported to produce camphene epoxide, which rearranges to the aldehyde [27]. For these reasons and to make a comparison with the behavior of longifolene, we carried out the ozonolysis of (+)-camphene (**11**) in acetone and could observe by NMR the 1,2,4-trioxolane **12** (so-called normal ozonide, *Scheme 3*). Interestingly, only one diastereoisomer was formed, for which we propose the configuration depicted in *Scheme 3*. On warming to room temperature, **12** converted completely to two compounds within 2 h. These seem to be the diastereoisomeric lactones formed after incorporation of an O-atom within the bicyclic moiety (determined from NMR and MS data); however, this reaction will be discussed elsewhere. Consequently, the ozonolysis of camphene proceeds as a 'normal ozonolysis'.

Scheme 3



11 **12**

^{13}C-NMR (δ(C)) of **12**

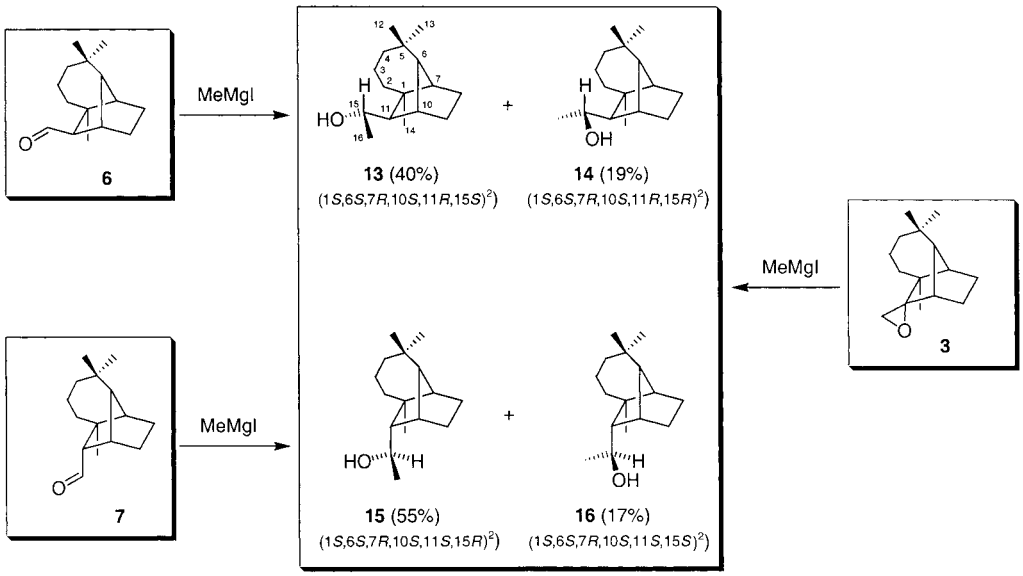
C(1)	C(2)	C(3)	C(4)	C(5)	C(6)	C(7)	Me_{exo}-C(3)	Me_{endo}-C(3)	C(5')
46.19	115.92	44.04	48.42	24.08	34.76	21.67	21.07	25.89	94.21

Finally, we could prepare longicamphenylone (**2**) in 22% yield by oxidation of **1** with $KMnO_4$ in CH_2Cl_2 in the presence of (tricapryl)methylammonium chloride as a phase-transfer catalyst, according to the published procedure [28]. Contrary to the published data [28], we also observed the formation of epoxide **3**, enols **4** and **5**, and significant amounts of the acid **8** in the oxidation reaction. These observations indicate that the oxidation of longifolene leads in the first step to the formation of epoxide **3**, which undergoes further transformations as shown in *Scheme 2*.

The aldehydes **6** and **7** were used as starting materials for the addition of MeMgI to investigate the diastereoselectivity of the reaction (*Scheme 4*). After acidic workup, the diastereoisomers **13** and **14**, and **15** and **16**, respectively, were isolated in pure form in the given yields by column chromatography. The crude aldehyde **6** that we used usually contained up to 10% **7**, and consequently, the addition of MeMgI to **6** yielded small amounts of the alcohols **15** and **16**, which were isolated as mixed fractions. The diastereoselectivity of the addition reactions could not be determined exactly by NMR

spectroscopy of the crude reaction mixtures, due to overlapping of the signals of the diastereoisomers. However, from the yields of the isolated pure compounds **13**–**16** (*Scheme 4*), we can conclude that the diastereoselectivity of the addition reactions to aldehydes **6** and **7** is low. The slightly preferential formation of alcohols **13** and **15**, which corresponds with the results obtained from the addition of monolithium ferrocene to **6** and **7**, suggests that steric hindrance at the aldehyde C-atom in **6** and **7**, caused by the chain between C(1) and C(6) and by the Me(14) group, respectively, might be influencing the yields.

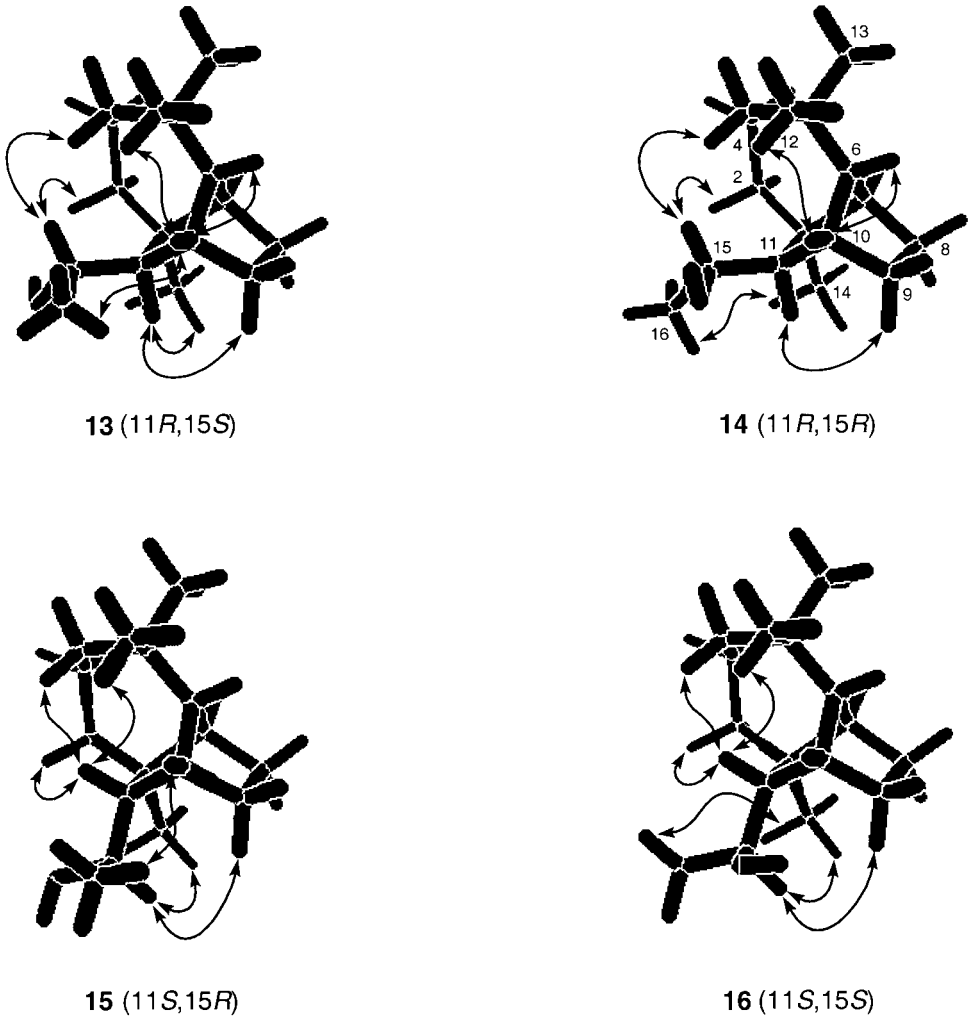
Scheme 4



It is interesting to note that the reaction of **3** with MeMgI also produced the alcohols **13**–**16** and not products of epoxide-ring opening. Therefore, the rearrangement of epoxide **3** to aldehydes **6** and **7**, which is probably caused by the *Grignard* compound or the magnesium halide contained therein, must proceed very rapidly, and the methylation occurs only subsequently.

The unambiguous assignment of the ^{1}H- and ^{13}C-NMR spectra of **13**–**16** was achieved by gs-HSQC, gs-HSQC-TOCSY, gs-HMBC, NOESY, and DQF-COSY experiments (*Tables 1* and *2*, and *Exper. Part*). The rigidity of the longifolane skeleton allowed the relative configuration to be established by NOESY experiments. Therefore, the absolute configurations of the newly formed stereogenic centers could be derived from the known configuration of the longifolane moiety. The most significant NOEs observed are illustrated with arrows in *Fig. 2*.

The *exo*-position of the hydroxyethyl moiety in **13** and **14** could be deduced from the close proximity of H–C(15) to H_a–C(2) and H_a–C(4), as well as from the corresponding NOEs of H–C(11) with the H_{endo}–C(9) and Me(14). For the *endo*-substituted compounds **15** and **16**, H–C(15) is situated, as the smallest substituent,



13 (11*R*,15*S*) **14** (11*R*,15*R*)

15 (11*S*,15*R*) **16** (11*S*,15*S*)

Fig. 2. *Most significant distance constraint obtained by the NOESY experiments of compounds* **13**–**16**. Arbitrary numbering.

near H_{endo}–C(9) and Me(14). The observed high vicinal constants $J_{H-C(11),H-C(15)}$ of *ca.* 9–11 Hz for **13**–**16** and the distance constraint obtained by the NOESY experiments allowed us to verify the corresponding preferred conformation along the C(11)–C(15) bond, as depicted in *Fig. 2*.

The most significant arguments for the configuration determined at C(15) are summarized as follows: *a*) For (15*S*) in **13**: A close proximity of H–C(15) to H_a–C(2) and H_a–C(4), and Me(16) to H–C(10) was observed. *b*) For (15*R*) in **14**: Me(16) is situated near Me(14). *c*) For (15*R*) in **15**: Me(16) is near H–C(10). *d*) For (15*S*) in **16**: Me(16) is in close proximity to Me(14).

The absolute configurations of compounds **13**–**15** were confirmed by X-ray crystal-structure analyses (*Figs. 3–5*), where the enantiomers used in the refinement were chosen by means of the known configuration of the polycyclic skeleton. The crystallographic results showed unambiguously that the assignments based on the NMR spectroscopic results were correct. For compound **13**, there are two symmetry-independent molecules in the asymmetric unit differing only in the orientation of the OH H-atom. The OH group in each molecule forms an intermolecular H-bond with the OH O-atom of an adjacent molecule of the same type. These interactions link the molecules into infinite one-dimensional chains, each composed of only one type of symmetry-independent molecule. The chains run along a four-fold screw axis parallel to the *z*-axis. In the case of alcohol **14**, there are four symmetry-independent molecules in the asymmetric unit, but there are no significant differences in their conformations. The quality of the data did not permit the reliable determination of the positions of the OH H-atoms, so the orientations of these groups is unknown. However, the O···O distances indicate that each of the four independent molecules is involved in a H-bond *via* its OH group to the OH O-atom of the next molecule in an ···A···B···C···D··· sequence to form a closed tetrameric loop involving just one of each of the four independent molecules. The OH group in **15** also forms an intermolecular H-bond with the OH O-atom of an adjacent molecule. This interaction links the molecules about a four-fold axis into tetrameric units.

In conclusion, it has been demonstrated that the ozonolysis of (+)-longifolene (**1**) can provide relatively easily the two epimeric aldehydes **6** and **7**, which are very useful as chiral starting compounds for further transformations. The aldehydes are formed from longifolene epoxide (**3**) by a rearrangement reaction, whose mechanism was

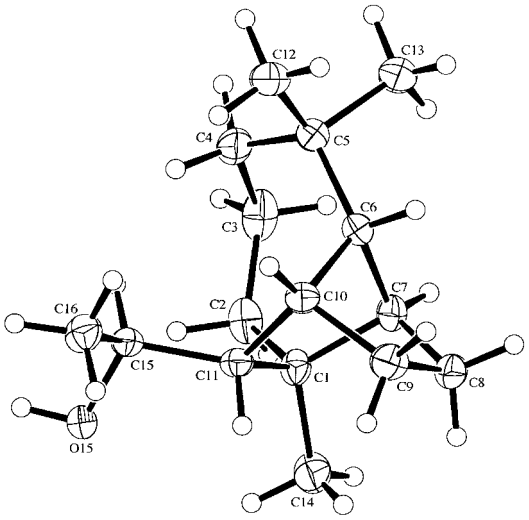


Fig. 3. *ORTEP Plot* [30] *of the molecular structure of one of the two symmetry-independent molecules of* **13**. Ellipsoids with 30% probability. Arbitrary numbering.

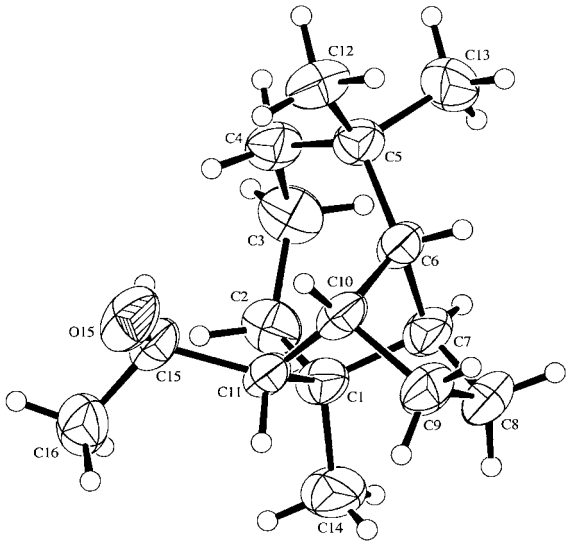


Fig. 4. *ORTEP Plot* [30] *of the molecular structure of one of the four symmetry*-independent molecules of **14**. Ellipsoids with 30% probability. Arbitrary numbering.

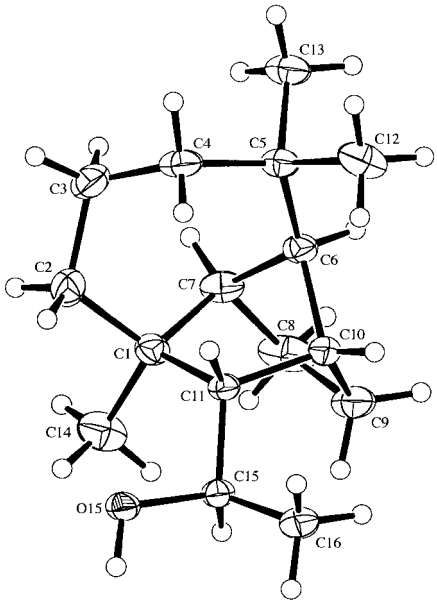


Fig. 5. *ORTEP Plot* [30] *of the molecular structure of* **15**. Ellipsoids with 30% probability. Arbitrary numbering.

deduced from the experimental data. The configurations of the new stereogenic centers were determined by NMR methods and X-ray crystallography.

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Experimental Part

General. The (+)-longifolene (**1**) used in this work is a gift of the firm '*Pharmachim Bulgaria*' and is originally from Nicaragua. The product had a slightly yellow color and a purity of 97% (NMR). The specific rotation of the unpurified material was $[\alpha]_D^{21} = +44.3$ ($c = 1.0$, EtOH). After purification by column chromatography (hexane/Et_2O 15:1), the specific rotation was $[\alpha]_D^{21} = +52.0$ ($c = 1.0$, EtOH) ([28]: $[\alpha]_D^{21} = +54.0$ ($c = 1.0$, EtOH)), $[\alpha]_D^{21} = +57.1$ ($c = 0.91$, $CHCl_3$), and +48.3 (neat) ([29]: $[\alpha]_D^{25} = +48.0$ for 100% ee). The org. solvents were distilled prior to use. Ozonolysis: ozone generator *502 Fischer* (3–5 g O_3/h). TLC: precoated silica-gel *60* F_{254} plates (*Merck*); visualization by $Ce(SO_4)_2$/phosphomolybdic acid soln. Flash chromatography (FC): silica gel *Merck 60* (0.040–0.063 mm). M.p.: *Mettler FP-5/FP-52*. Optical rotation: *Perkin-Elmer 241* polarimeter. ^1H- and ^{13}C-NMR Spectra: *Bruker DRX-250*, *Bruker ARX-300*, *Bruker DRX-500*, or *Bruker DRX-600* spectrometer; δ in ppm rel. to Me_4Si (= 0 ppm), J in Hz; unless stated otherwise, $CDCl_3$ soln. EI-MS (70 eV) and CI-MS (NH_3 as reactant gas): *Finnigan MAT 90* or *Finnigan SSQ 700*; fragment ions in m/z (rel. %).

(1′S,6′R,7′R,10′S,11′S)-1′,5′,5′-Trimethylspiro[oxiran-2,11′-tricyclo[5.4.0.0^{6,10}]undecane][2] (= *(1S,3aR,4S,8aR,9S)-1,2,3,3a,4,5,6,7,8,8a-Decahydro-4,8,8-trimethylspiro[1,4-methanoazulene-9,2′-oxirane];* **3**). A flow of ozonized O_2 was bubbled (*G1* frit) through a soln. of **1** (5.00 g, 24.47 mmol) in acetone (170 ml) at −80° until the appearance of a blue color indicated an excess of O_3. After bubbling out the excess O_3 with dry N_2, the mixture was allowed to warm to r.t. and evaporated leaving the crude **3** as a colorless oil. Bulb-to-bulb distillation at $3 \cdot 10^{-2}$ Torr/110° gave 4.90 g (91%) of **3**. Colorless crystals. M.p. 50–51°. $[\alpha]_D^{21} = +14.6$ ($c = 1.31$, $CHCl_3$). CI-MS: 238 (5, $[M + NH_4]^+$), 221 (21, $[M + H]^+$), 203 (100, $[M - OH]^+$). Anal. calc. for $C_{15}H_{24}O$ (220.35): C 81.76, H 10.98; found: C 81.87, H 11.02.

(Z)- and (E)-[(1S,6R,7R,10S)-1,5,5-Trimethyltricyclo[5.4.0.0^{6,10}]undec-11-ylidene]methanol[2] (= *(Z)- and (E)-[(1S,3aR,4S,8aR)-Decahydro-4,8,8-trimethyl-1,4-methanoazulen-9-ylidene]methanol,* resp.; **4** and **5**) *for NMR Investigations.* A flow of ozonized O_2 was bubbled (*G1* frit) through a soln. of **1** (0.33 g, 1.61 mmol) in CH_2Cl_2 (20 ml) at −80° until the appearance of a blue color indicated an excess of O_3. After bubbling out the excess O_3 with dry N_2, the mixture was allowed to warm to r.t. and kept for up to 10 min at this temp. until the formation of **4** and **5** was complete (TLC monitoring (silica gel, hexane/Et_2O 7:1): R_f 0.14 (**4**), 0.22 (**5**)). The solvent was then evaporated, and 20 mg of the remaining oil was dissolved in CD_2Cl_2, and the soln. placed in a NMR tube and cooled to −50°.

(1S,6S,7R,10S,11R)-1,5,5-Trimethyltricyclo[5.4.0.0^{6,10}]undecane-11-carbaldehyde[2] (= *(1S,3aR,4S,8aS,9R)-Decahydro-4,8,8-trimethyl-1,4-methanoazulene-9-carboxaldehyde*; **6**). As described for **4**/**5** with **1** (1.27 g, 6.21 mmol) in CH_2Cl_2 (50 ml) and O_3 until, at r.t., the formation of **6** was complete (TLC monitoring (silica gel, hexane/Et_2O 7:1): R_f 0.42). After evaporation, the crude product was chromatographed (2 × 50-cm column, silica gel (50 g), hexane/Et_2O 20:1): 1.03 g (75%) of **6**, usually containing 6–10% of aldehyde **7**. Colorless oil. $[\alpha]_D^{21} = -43.6$ ($c = 1.20$, $CHCl_3$). CI-MS: 238 (5, $[M + NH_4]^+$), 221 (30, $[M + H]^+$), 203 (100, $[M - OH]^+$). Anal. calc. for $C_{15}H_{24}O$ (220.35): C 81.76, H 10.98; found: C 81.50, H 10.83.

2,4,6-Tris[(1S,6S,7R,10S,11S)-1,5,5-trimethyltricyclo[5.4.0.0^{6,10}]undec-11-yl]-1,3,5-trioxane[2] (= *2,4,6-Tris[(1S,3aR,4S,8aS,9S)-decahydro-4,8,8-trimethyl-1,4-methanoazulen-9-yl]-1,3,5-trioxane*; **10**). A $CDCl_3$ soln. of **6** was allowed to stand in an NMR tube for 5–6 weeks, after which colorless crystals of **10** had formed. These were filtered and washed with Et_2O. Compound **10** was insoluble in Et_2O, THF, $CHCl_3$, and hydrocarbons.

(1S,6S,7R,10S,11S)-1,5,5-Trimethyltricyclo[5.4.0.0^{6,10}]undecane-11-carbaldehyde[2] (= *(1S,3aR,4S,8aS,9S)-Decahydro-4,8,8-trimethyl-1,4-methanoazulene-9-carboxaldehyde*; **7**). As described for **4**/**5**, with **1** (3.80 g, 18.59 mmol) in CH_2Cl_2 (150 ml) and O_3 until, at r.t., the formation of **7** was complete (5 weeks; TLC monitoring (silica gel, hexane/Et_2O 7:1): R_f 0.38). After evaporation, the crude product was chromatographed (5 × 40-cm column, silica gel (210 g), hexane/Et_2O 20:1): 2.10 g (51%) of **7**. Colorless oil. $[\alpha]_D^{21} = +22.8$ ($c = 1.20$, $CHCl_3$). CI-MS: 238 (10, $[M + NH_4]^+$), 221 (35, $[M + H]^+$), 203 (100, $[M - OH]^+$). Anal. calc. for $C_{15}H_{24}O$ (220.35): C 81.76, H 10.98; found: C 81.51, H 11.05.

(1S,6S,7R,10S,11R)-1,5,5-Trimethyltricyclo[5.4.0.0^{6,10}]undecane-11-carboxylic Acid[2]) (=*(1S,3aR,4S,8aS,9R)-Decahydro-4,8,8-trimethyl-1,4-methanoazulene-9-carboxylic Acid*; **8**). ^{1}H-NMR (*ARX-300*): 2.58–2.53 (*m*, H–C(10)); 2.25–2.10 (*m*, H_a–C(2)); 2.10 (*s*, H–C(11)); 2.02–1.96 (*m*, H–C(7)); 1.73–1.42 (*m*, H_b–C(3); H_{endo}–C(8), H_{endo}–C(9)); 1.39 (*s*, H–C(6)); 1.38–1.22 (*m*, H_b–C(2), H_a–C(3), H_{exo}–C(8)); 1.14 (*s*, Me(14)); 1.13–1.03 (*m*, 2 H–C(4), H_{exo}–C(9)); 1.00 (*s*, Me(13)); 0.94 (*s*, Me(12)). CI-MS: 254 (70, $[M+NH_4]^+$), 219 (100, $[M-OH]^+$).

(1S,6S,7R,10S,11S)-1,5,5-Trimethyltricyclo[5.4.0.0^{6,10}]undecane-11-carboxylic Acid[2]) (=*(1S,3aR,4S,8aS,9S)-Decahydro-4,8,8-trimethyl-1,4-methanoazulene-9-carboxylic Acid*; **9**). ^{1}H-NMR (*ARX-300*): 2.96–2.90 (*m*, H–C(11)); 2.35–2.29 (*m*, H–C(10)); 2.01–1.97 (*m*, H–C(7)); 1.76–1.47 (*m*, 2 H–C(2), 2 H–C(3), H_a–C(4), H_{endo}–C(8), 2 H–C(9)); 1.42 (*s*, H–C(6)); 1.40–1.21 (H_b–C(4), H_{exo}–C(8)); 0.99 (*s*, Me(14)); 0.98 (*s*, Me(13)); 0.92 (*s*, Me(12)). CI-MS: 254 (50, $[M+NH_4]^+$), 219 (100, $[M-OH]^+$).

(1S)- and (1R)-1-[(1S,6S,7R,10S,11R)-1,5,5-Trimethyltricyclo[5.4.0.0^{6,10}]undec-11-yl]ethanol[2]) (=*(αS,1S,3aR,4S,8aS,9R)- and (αR,1S,3aR,4S,8aS,9R)-Decahydro-α,4,8,8-tetramethyl-1,4-methanoazulene-9-methanol* resp.; **13** and **14**). A 1.5 M soln. of MeMgI in Et_2O (1.7 ml, 2.55 mmol) was added at 0° to a soln. of crude **6** (containing up to 10% of **7**) in Et_2O (30 ml), prepared from 0.50 g (2.45 mmol) of **1**. After warming to r.t., and stirring for 0.5 h, the mixture was hydrolyzed (2N aq. HCl), washed with 5% aq. $NaHCO_3$ soln. and H_2O, dried (Na_2SO_4), and evaporated. The crude product was chromatographed (2.5 × 47-cm column, silica gel (82 g), hexane/Et_2O 10:1): 0.23 g (40%) of **13**, 0.05 g (9%) of mixed fractions (containing **13**, **14**, and **15**), 0.11 g (19%) of **14**, and 0.02 g (3%) of **16**.

Data of **13**: TLC (silica gel, hexane/Et_2O 3:1): R_f 0.21. Colorless crystals from hexane/Et_2O. M.p. 123–125°. $[\alpha]_D^{21} = -12.7$ ($c = 1.00$, $CHCl_3$). CI-MS: 254 (33, $[M+NH_4]^+$), 236 (28, $[M-H_2O+NH_4]^+$), 219 (100, $[M-OH]^+$). Anal. calc. for $C_{16}H_{28}O$ (236.39): C 81.29, H 11.94; found: C 81.23, H 11.85.

Data of **14**: TLC (silica gel, hexane/Et_2O 3:1): R_f 0.18. Colorless crystals from hexane/Et_2O. M.p. 94–95°. $[\alpha]_D^{21} = -15.8$ ($c = 1.00$, $CHCl_3$).

(1R)- and (1S)-1-[(1S,6S,7R,10S,11S)-1,5,5-Trimethyltricyclo[5.4.0.0^{6,10}]undec-11-yl]ethanol[2]) (=*(αR,1S,3aR,4S,8aS,9S)- and (αS,1S,3aR,4S,8aS,9S)-Decahydro-α,4,8,8-tetramethyl-1,4-methanoazulene-9-methanol*, resp.; **15** and **16**). As described for **13**/**14** with 1.5M MeMgI in Et_2O (2 ml, 3.00 mmol) and **7** in Et_2O (30 ml). The crude product was chromatographed (2.3 × 35-cm column, silica gel (60 g), hexane/Et_2O 10:1): 0.35 g (55%) of **15** and 0.11 g (17%) of **16**.

Data of **15**: TLC (silica gel, hexane/Et_2O 3:1): R_f 0.16. Colorless crystals from hexane/Et_2O. M.p. 87–88°. $[\alpha]_D^{21} = -57.3$ ($c = 1.03$, $CHCl_3$). CI-MS: 254 (67, $[M+NH_4]^+$), 236 (35, $[M-H_2O+NH_4]^+$), 219 (100, $[M-OH]^+$). Anal. calc. for $C_{16}H_{28}O$ (236.39): C 81.29, H 11.94; found: C 81.25, H 11.86.

Data of **16**: TLC (silica gel, hexane/Et_2O 3:1): R_f 0.10. Colorless crystals from hexane/Et_2O. M.p. 86°. $[\alpha]_D^{21} = -66.5$ ($c = 1.01$, $CHCl_3$).

X-Ray Crystal-Structure Determinations of **10** *and* **13**–**15**[3]). The data collection and refinement parameters are given in *Table 3*, and views of the molecules are shown in *Figs. 1* and *3–5*. All measurements were made on a *Nonius Kappa CCD* diffractometer [31] with graphite-monochromated MoK_α radiation (λ 0.71073 Å). Data reduction was performed with HKL Denzo and Scalepack [32]. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. Equivalent reflections, other than *Friedel* pairs, were merged. Each structure was solved by direct methods with SIR92 [33] (SHELXS97 [34] for **13**), which revealed the positions of all non-H-atoms, and the non-H-atoms were refined anisotropically. All of the H-atoms bonded to C were fixed in geometrically calculated positions (d(C–H) = 0.95 Å), and each was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{eq} of its parent C-atom. For **13** and **15**, the H-atoms of the OH groups were placed in the positions indicated by a difference electron density map, and their positions were allowed to refine together with individual isotropic displacement parameters. The refinement of each structure was carried out on F by using full-matrix least-squares procedures, which minimized the function $\Sigma w(|F_o|-|F_c|)^2$. Corrections for secondary extinction were applied, except in the case of **14**. For **15**, two reflections, whose intensities were considered to be extreme outliers, were omitted from the final refinement. Neutral-atom scattering factors for non-H-atoms were taken from [35a], and the scattering factors

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[3]) Crystallographic data (excluding structure factors) for the structures of **10** and **13**–**15** have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publications no. CCDC-185023 to CCDC-185026, resp. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. (fax: +44-(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk).

Table 3. *Crystallographic Data for Compounds* **10** *and* **13**–**15**

	10	**13**	**14**	**15**
Crystallized from	$CDCl_3$	hexane/Et_2O	hexane/Et_2O	$Et_2O/CHCl_3$
Empirical formula	$C_{45}H_{72}O_3 \cdot CDCl_3$	$C_{16}H_{28}O$	$C_{16}H_{28}O$	$C_{16}H_{28}O$
Formula weight [g mol^{-1}]	781.45	236.40	236.40	236.40
Crystal color, habit	colorless, prism	colorless, plate	colorless, prism	colorless, prism
Crystal dimensions [mm]	$0.20 \times 0.20 \times 0.25$	$0.08 \times 0.25 \times 0.25$	$0.25 \times 0.30 \times 0.40$	$0.10 \times 0.12 \times 0.20$
Temperature [K]	298 (1)	160 (1)	298 (1)	160 (1)
Crystal system	trigonal	tetragonal	triclinic	tetragonal
Space group	*R*3	$I4_1$	*P*1	*I*4
Z	3	16	4	8
Reflections for cell determination	7753	3540	6970	1417
2θ Range for cell determination [°]	2–58	2–55	2–58	2–50
Unit-cell parameters *a* [Å]	21.0628 (6)	26.9848 (4)	7.5017 (1)	19.855 (1)
b [Å]	21.0628 (6)	26.9848 (4)	14.4539 (2)	19.855 (1)
c [Å]	8.5623 (6)	7.9181 (2)	15.3996 (3)	7.4897 (4)
α [°]	90	90	111.7153 (6)	90
β [°]	90	90	89.0912 (6)	90
γ [°]	120	90	103.4926 (6)	90
V [Å^3]	3289.7 (3)	5765.8 (2)	1503.85 (4)	2952.7 (3)
D_x [g cm^{-3}]	1.182	1.089	1.044	1.063
μ(Mo $K\alpha$) [mm^{-1}]	0.246	0.0648	0.0622	0.0633
$2\theta_{(max)}$ [°]	57.4	55	58	50
Total reflections measured	14667	39327	26683	10738
Symmetry-independent reflections	3633	6567	12394	2465
Reflections used ($I > 2\sigma(I)$)	2756	5333	8703	1825
Parameters refined	157	315	610	158
Final *R*	0.0492	0.0489	0.0627	0.0442
wR	0.0458	0.0405	0.0606	0.0438
Weights: *p* in $w = [\sigma^2(F_o) + (pF_o)^2]^{-1}$	0.010	0.005	0.005	0.005
Goodness-of-fit	1.806	1.951	2.459	1.382
Secondary extinction coefficient	$5.4(9) \cdot 10^{-7}$	$6.2(7) \cdot 10^{-7}$	–	$1.7(2) \cdot 10^{-6}$
Final Δ_{max} / σ	0.0004	0.0005	0.0002	0.0001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.25; −0.30	0.29; −0.22	0.17; −0.22	0.16; −0.16

for H-atoms from [36]. Anomalous dispersion effects were included in F_c [37]; the values for f' and f'' were those of [35b]. The values of the mass-attenuation coefficients were those of [35c]. All calculations were performed with the teXsan crystallographic software package [38].

In **10**, the trioxane molecule sits about a crystallographic three-fold axis, and there are an equivalent number of $CDCl_3$ molecules in the structure, which also sit on three-fold axes. Refinement of the absolute structure parameter [39] yielded a value of −0.05(8), which independently confirms that the refined coordinates represent the true enantiomorph. For the remaining structures, the absolute configuration was not determined crystallographically because of the low anomalous scattering power of the compound. Instead, the enantiomer used in each refinement was chosen by means of the known configuration of the polycyclic skeleton.

In **13**, there are two symmetry-independent molecules of the same enantiomer in the asymmetric unit, and the only significant difference between their conformations is the orientation of the OH H-atom. The atomic coordinates of the two molecules were tested carefully for a relationship from a higher symmetry space group with the program PLATON [40], but none could be found.

In **14**, there are four symmetry-independent molecules of the same enantiomer in the asymmetric unit, but there are no significant differences in their conformations, although the positions of the OH H-atoms could not be determined reliably, and these atoms were omitted from the model. The atomic coordinates of the four molecules were also tested for a relationship from a higher symmetry space group with PLATON, but none could be found.

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