

100. From Colchicine and Some of Its Derivatives to 1,2,3,9,10-Pentamethoxybenzo[*a*]heptalenes

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Dedicated to *Albert Eschenmoser* on the occasion of his 70th birthday

*Schön ist, was wir sehen.
Schöner, was wir wissen;
am schönsten aber ist,
was sich unserem Verstehen verschliesst.*

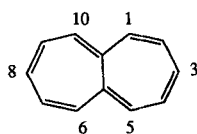
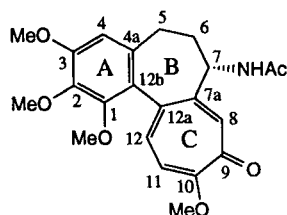
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A two-step synthesis of 4-methylcolchicine (**13**), starting from colchicine (**2**), has been developed (*Scheme 5*). In three steps, 4-ethylcolchicine (**28**) is also accessible from **2** (*Scheme 8*). Colchicine (**2**) and its derivatives **13** and **28** have been transformed into the benzo[*a*]heptalene derivatives **9**, **18**, and **34**, respectively, by *Hofmann* degradation of the corresponding deacetylcolchicine **3**, **19**, and **29**, respectively, followed by methylation of the two O-functions first with diazomethane and then with trimethoxonium tetrafluoroborate (*Scheme 2* and *6*). The thus formed tropylium salts gave, on deprotonation with Me₃N in CHCl₃, the expected pentamethoxybenzo[*a*]heptalenes **9**, **18**, and **34**, respectively. X-Ray crystal-structure analysis of **9** (*Fig. 3*) and **18** (*Fig. 7*), determination of the vicinal coupling constants of the H-atoms at the heptalene skeleton as well as the measurement of the racemization rate of the new benzo[*a*]heptalenes revealed a marked influence of the substituent at C(4) on the degree of twisting of the heptalene skeleton. The absolute configuration of the resolved heptalenes was deduced from their long-wavelength CD maxima around 350 nm. The heptalenes with a negative maximum in this range possess (7*aP*)-configuration.

1. Introduction. – If we neglect the fact that it was *Johannes Kepler* who displayed in 1619 in the first book of his famous work '*Harmonices Mundi*' the geometrical figure of two side-attached regular seven-membered polygons in order to exemplify his 18th statement which says that the plane space can completely be filled only in three ways, *i.e.*, with six triangles, four squares, or three hexagons [1], and what we may interpret in our views as the first connectivity graph of bicyclo[5.5.0]dodeca-1,3,5,6,8,10-hexaene (**1**), it seems that it had been *Wilson Baker* [2] in his *Tilden Lecture* on 'Non-benzenoid Aromatic Compounds' who first designed the formula **1** of two fused, fully unsaturated seven-membered rings in analogy to pentalene and azulene. Two years later, *i.e.*, in 1947, *Rapson* and coworkers [3] coined the name heptalene (**1**) for this structure from the drawing-board which became together with pentalene the progenitor of the '*alene*' class of structures (see *e.g.* [4]). It is worth recalling these events, since in their period of time fell '*after a time of misconception a brilliant inspiration of Dewar* [5] which set the stage for the

¹⁾ Part of the Ph.D. thesis of P.K., University of Zurich, 1993.

**1****2**

establishment of the correct structure of colchicine (**2**)², as Woodward [6] described the dramatic turning-point in the over 2000-year-old reported history of this molecule from nature and its biological action (see e.g. [7] and lit. cit. therein).

Both molecules had been the object of never-ceasing attraction to chemists at that early time as well as today. However, whereas **1** became one of the favorite molecules of physical organic chemists to deal with questions of aromaticity and antiaromaticity, and applicability of rapidly upcoming computational methods (see e.g. [8] [9] and lit. cit. there), it had been the unique annelation of the ring systems in **2**, including a novel type of aromatic ring system to which Dewar had given the name 'tropolone' [10], that became a challenge to the synthetic chemists³). Again, it should be noted that in the midst of the short period from 1959 to 1963, where the five classical colchicine synthesis of Eschenmoser and coworkers [11], van Tamelen *et al.* [12], Nakamura and coworkers [13], Scott *et al.* [14], and Woodward [6] were published (see also [15] [16]), fell also the first successful synthesis of heptalene by Dauben and Bertelli [17]³). Up to now, at least six further synthetic approaches to heptalene and its simple derivatives have been developed by Vogel *et al.* [20] [21], Hafner *et al.* [22], Paquette *et al.* [23], and others (see [24] [25]), and also the arsenal of colchicine syntheses has been enriched by at least nine further accesses to **2** or well-established relay compounds for **2** (*cf.* [26]).

The systematic name for colchicine (**2**) is (*S*)-*N*-(5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[*a*]heptalen-7-yl)acetamide. In the past of exciting colchicine chemistry and biology (see [27]), it seems—at least to our knowledge—that nobody has *expressis verbis* alluded to the heptalenic nature of colchicine and its derivatives. It was, therefore, the aim of this work which we started already in 1988 and concluded in 1993¹) to pick out of colchicine and of some of its 4-substituted derivatives their parent benzo[*a*]heptalene structure in order to throw a bridge across heptalene and colchicine chemistry, thereby also accomplishing first access to the scarcely known class of benzo[*a*]heptalenes⁴).

²) Eschenmoser [11b] mentions in the comprehensive treatise of his colchicine synthesis: 'In jenen Jahren musste dieses tropolonoide Ringsystem innerhalb des Rahmens der bisher aufgeklärten Pflanzenstoffe als eine unorthodoxe Struktur erscheinen; neben den besonderen biologischen Eigenschaften der Verbindung war denn auch dies der Gesichtspunkt, der das Colchicin als den prominentesten Vertreter tropolonoider Naturstoffe zu einem obligaten Ziel der organisch-chemischen Totalsynthese machte'.

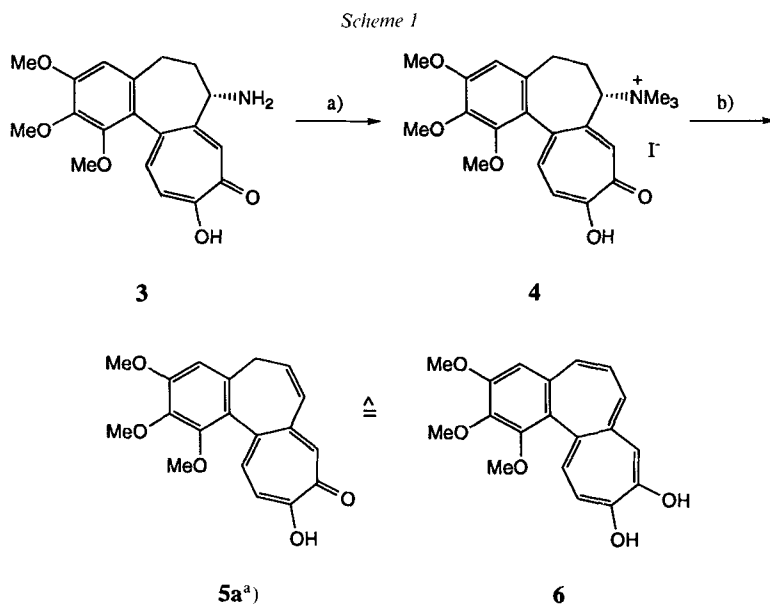
³) For earlier attempts of heptalene synthesis, see [18]. The first synthesis of an azulene-heptalene hybrid had been realized by Hafner and Schneider in 1959 [19b].

⁴) In the meantime, we succeeded in the synthesis of benzo[*a*]heptalene-6,7-dicarboxylates by thermal or catalyzed reaction of benz[*a*]azulenes with dimethyl acetylenedicarboxylate [28] [29] (see also [30]). Also benzo[*a*]heptalene itself is available [31] by a modification of Wenkert's colchicine synthesis [32].

Moreover, we were interested to study the possibly photochemically inducible double-bond shift (*cf.* [33]) in these compounds which should result in a strong positive photochromic effect, since the double-bond-shifted (DBS) form would possess a quinodimethane substructure. And last but not least, a new and most flexible approach to the synthesis of colchicinoid compounds may be an outcome of these structural associations⁴).

In the following, we report on the transformation of colchicine (**2**) and some of its 4-substituted derivatives into 1,2,3,9,10-pentamethoxybenzo[*a*]heptalenes.

2. 1,2,3,9,10-Pentamethoxybenzo[*a*]heptalene (9**) and Its Derivatives.** – Formal benzo[*a*]heptalene structures are already buried in the vast material of established colchicine chemistry. *Eschenmoser*, *e.g.*, reported on the *Hofmann* degradation of the quaternary ammonium salt **4**, derived from (–)-deacetylcolchicine (**3**), resulting in the formation of the dihydrobenzo[*a*]heptalene derivative **5a** (*Scheme 1*), following an unpublished procedure that had originally been worked out by *Woodward* (see [11b] and Footnote 62 therein)⁵). Compound **5a** (or **5b**), depicted in its tautomeric form **6**, already represents a heptalenic form of the colchicine skeleton. Therefore, we decided to follow the described *Hofmann* degradation and to investigate the *O,O*-dimethylation of **5b** and some of its 4-substituted derivatives.



a) MeI/2N NaOH, 50°. b) KOH/(CH₂OH)₂/H₂O, 185°.

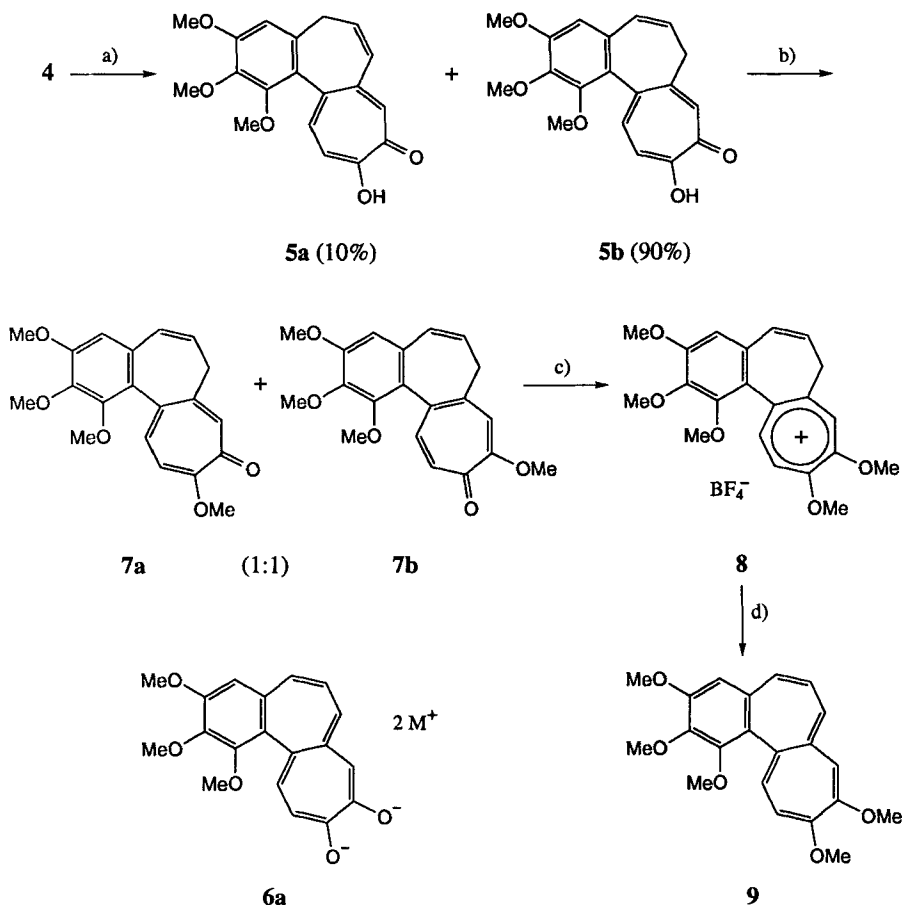
^a) See Footnote 5.

⁵) The position of the double bond in ring *B* (not ring *C* – we suppose – as it is said in Footnote 63 of [11b]) of **5a** was tentatively assigned. Indeed, *Brossi* and coworkers [34] (*cf.* [35]) showed later by ¹H-decoupling experiments of **5b** and of the corresponding 9- and 10-*O*-methyl derivatives **7a** and **7b** (see *Scheme 2*) that the double bond is in the 5,6-position.

2.1. *1,2,3,9,10-Pentamethoxybenzo[*a*]heptalene (9)*. When we repeated the *Hofmann* degradation of **4**, we found that indeed **5b** was the main product, however, accompanied by *ca.* 10% of **5a** according to $^1\text{H-NMR}$ analysis (*Scheme 2*)⁶.

The fact that the colchicine skeleton of **5b/5a** survives the strong alkaline conditions of the *Hofmann* degradation at 180–185°, whereas colchicine and its tetrahydro deriva-

Scheme 2



a) See *Scheme 1*; pure **5b** was obtained after crystallization in a yield of 51%. b) CH₂N₂ in Et₂O/MeOH, 0° (*cf.* [35]); the 1:1 mixture of **7a/7b** was obtained in a yield of 87%. c) Me₃O⁺BF₄⁻/CH₂Cl₂, 20°, 80%. d) Me₃N/CHCl₃, 0°, 73%.

⁶) We deduce the presence of **5a** from additional signals in the $^1\text{H-NMR}$ spectrum (CDCl₃) of the reaction mixture of **5b** at 7.81 ppm (*d*, *J* = 12.6 Hz) and 7.21 (*d*, *J* = 12.6 Hz) for H–C(12) and H–C(11), respectively, which are close to those of **5b** (*cf. Exper. Part*). There are also 3s, observed at 3.90, 3.88, and 3.53 ppm, which can be attributed to the 3 MeO groups of **5a**. The other signals of **5a** were obscured by those of **5b**. The mixture was not separated nor did we attempt to enrich **5a** by chromatography or crystallization. The presence or absence of **5a** in the reaction mixture was irrelevant for the further planned steps (*cf. 6* in *Scheme 1*).

tives, under strong alkaline conditions, easily undergo a contraction of ring *C* (cf. [27]), indicates the occurrence of the benzo[*a*]heptalene 9,10-dioxide **6a** in the reaction mixture⁷⁾.

The methylation of the tropolone moiety in **5b** with CH_2N_2 in $\text{Et}_2\text{O}/\text{MeOH}$ posed no problems (cf. [35]). The resulting 1:1 mixture of the *O*-methyl derivatives of tropolone **7a/7b** was not separated, but directly transformed into the dimethoxy-substituted tropylium ion **8**.

Its ^1H -NMR spectrum ((D_6) DMSO) was in accordance with the proposed structure, displaying 5s at 3.89, 3.85, 3.81, 3.58, and 3.16 ppm for 5 MeO groups and a well separated *AB* system for $\text{CH}_2(7)$ at 3.34 and 2.40 ppm with $^2J_{AB} = 12.3$ Hz, and additional vicinal and allylic couplings with $\text{H}-\text{C}(6)$ and $\text{H}-\text{C}(5)$ (cf. *Exper. Part*).

For the final step leading to **9**, we followed the deprotonation procedure ($\text{Me}_3\text{N}/\text{CHCl}_3$), originally developed by *Dauben* and *Bertelli* [17], for such tropylium ions. Compound **9** was obtained in a yield of 73%. It deposited from acetone/hexane in pale yellow crystals (m.p. 146–148°).

The UV and the ^1H -NMR spectrum of **9** are shown in *Figs. 1* and *2*. The UV spectrum exhibits a broad long-wavelength absorption band around 350 nm with a tailing above 400 nm, typical for heptalenes with at least one substituent at the *peri*-positions (cf. [36]). (All heptalenes of this type have a pale-yellow-to-orange color.)

More evidence of the heptalenic structure of **9** is delivered by its ^1H -NMR spectrum. As expected, $\text{H}-\text{C}(4)$ and $\text{H}-\text{C}(8)$ appear as *s* at 6.52 and 5.50 ppm, respectively. The observed vicinal coupling constants between $\text{H}-\text{C}(6)$ and $\text{H}-\text{C}(7)$ of 6.4 Hz is quite typical and of the same order as those found in alkyl-substituted heptalene-4,5-dicarboxylates, which exhibit in their peripheral *s-cis*-butadiene subunits torsional angles of *ca.* 30° (cf. [37] [38]). The vicinal coupling constant between $\text{H}-\text{C}(11)$ and $\text{H}-\text{C}(12)$ of 7.6 Hz is too large and not typical for heptalenes.

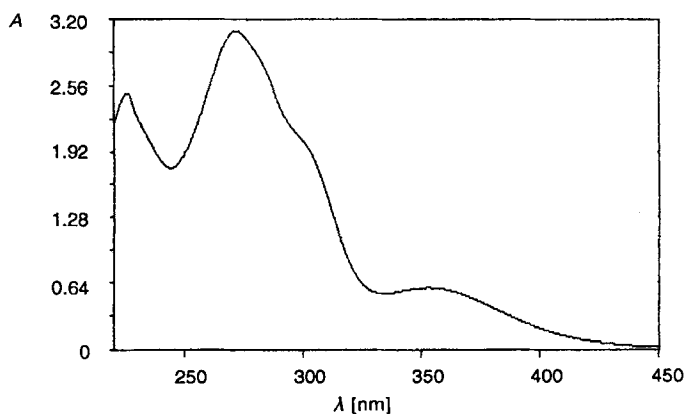


Fig. 1. UV Spectrum (cyclohexane) of 1,2,3,9,10-pentamethoxybenzo[*a*]heptalene (**9**)

⁷⁾ However, all attempts to trap the dianion **6a** directly in the original reaction mixture by *O*-methylation failed. It may be that the KOH concentration was too high (see *Exper. Part*). Similarly, deprotonation of **5a/5b** with LDA or *t*-BuLi at low temperatures, followed by addition of Me_2SO_4 or MeI, did not lead to **9** (Scheme 2). AM1 calculations of the dianion **6a** show an appreciably larger electron density at C(5) (−0.41) as compared with C(7) (−0.31). This might be an indication that **5b** does not arise from a kinetically controlled protonation of **6a**. We thank Dr. R. W. Kunz for these calculations.

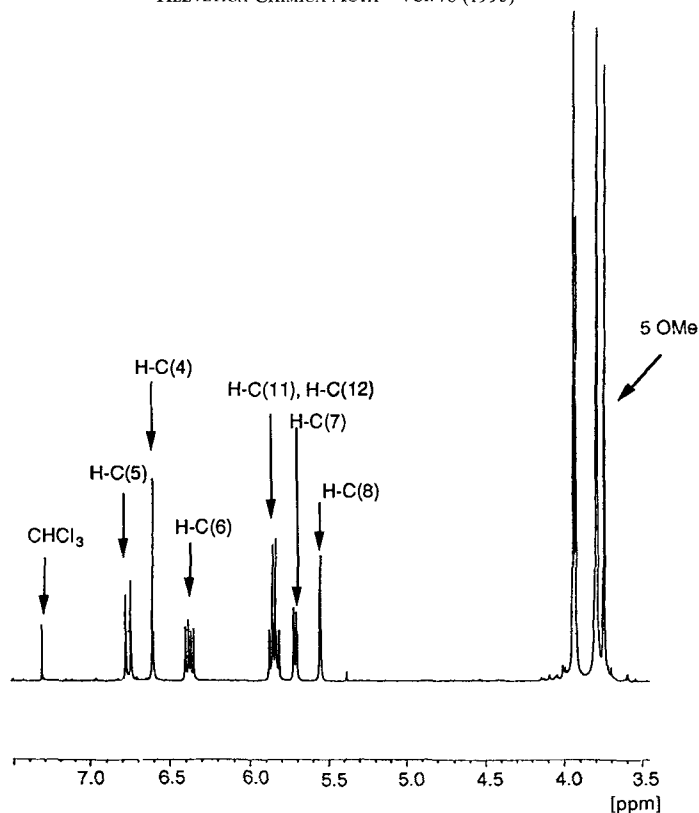


Fig. 2. ^1H -NMR Spectrum (CDCl_3) of 1,2,3,9,10-pentamethoxybenzo[a]heptalene (**9**)

However, it might be influenced by the MeO substituent at C(10). On the other hand, it might be an indication that the ring *C* in **9** is flatter than ring *B* (with $^3J = 8.5 \cos^2 \theta - 0.28$ [37]; the calculated torsion angle $\text{H-C}(9)\text{--C}(10)\text{--H}$ amounts to 16°). Again, quite typical for heptalenes is the vicinal coupling constant of 11.7 Hz for $\text{H-C}(5)$ and $\text{H-C}(6)$, also allowing to assign the position of the $\text{C}=\text{C}$ bonds in **9**. The spatial neighborhood of $\text{H-C}(4)$ and $\text{H-C}(5)$ as well as of $\text{H-C}(7)$ and $\text{H-C}(8)$ is indicated by strong ^1H -NOE effects between these H-atoms. Moreover, between $\text{H-C}(7)$ and $\text{H-C}(8)$ exists a weak coupling with a constant in the order of 0.1 to 0.2 Hz. The ^{13}C -NMR spectrum of **9** is in accordance with the structure deduced from the ^1H -NMR spectrum (*cf. Exper. Part*).

A more detailed insight into the structure of **9** is obtained by inspecting its X-ray crystal structure (*cf. Fig. 3*)⁸⁾. The heptalene torsion around the central $\text{C}(7a)\text{--C}(12a)$ bond is clearly recognizable. The main torsion angles are collected in *Table 1*.

At first glance, one already recognizes that the torsion angles are indeed comparable with those of heptalene-4,5-dicarboxylates which carry at best one further substituent in their *peri*-positions [37] [38]. *Fig. 4* shows two examples from literature which clearly demonstrate the influence of one *peri*-substituent on the central heptalene torsion angles. The *gauche* torsion angles of **9** and dimethyl heptalene-4,5-dicarboxylate are quite simi-

⁸⁾ The X-ray crystal-structure analysis of **9** revealed the presence of solvent molecules in the crystals which were not further resolved (*see Exper. Part*).

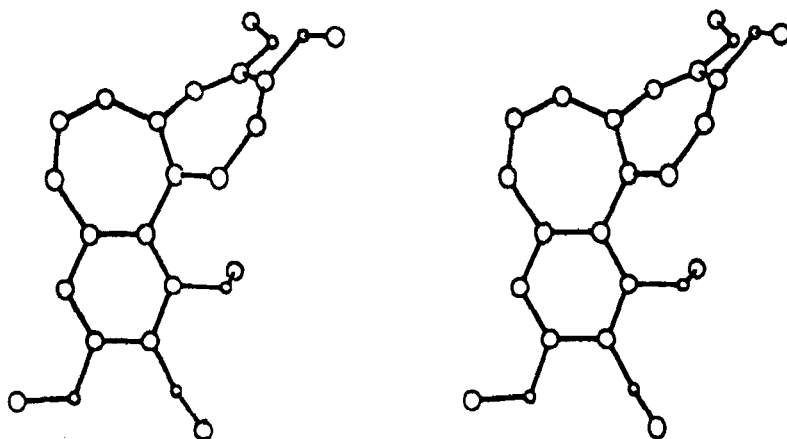


Fig. 3. Stereoscopic view of the X-ray crystal structure of 1,2,3,9,10-pentamethoxybenzo[a]heptalene (9). Only the C- and O-atoms are shown. The (7aP)-configuration of the heptalene skeleton is displayed.

Table 1. Torsion Angles θ from the X-Ray Crystal Structure of 1,2,3,9,10-Pentamethoxybenzo[a]heptalene (9).
In parentheses, e.s.d.'s.

Atoms	θ [°]	Remarks
C(7)–C(7a)–C(12a)–C(12)	–130(1)	Heptalene torsion angles around the central σ bond C(7a)–C(12a)
C(7)–C(7a)–C(12a)–C(12b)	52(1)	
C(8)–C(7a)–C(12a)–C(12)	51(1)	
C(8)–C(7a)–C(12a)–C(12b)	–127(8)	
C(1)–C(12b)–C(12a)–C(7a)	124(1)	'Colchicinoid' torsion angles around the aromatic σ bond C(12a)–C(12b)
C(1)–C(12b)–C(12a)–C(12)	–54(1)	
C(4a)–C(12b)–C(12a)–C(7a)	–59(1)	
C(4a)–C(12b)–C(12a)–C(12)	123(1)	
C(5)–C(6)–C(7)–C(7a)	–26(2)	s-cis-Butadiene torsion angles of the heptalene perimeter
C(8)–C(9)–C(10)–C(11)	24(2)	
C(10)–C(11)–C(12)–C(12a)	–27(2)	
C(12b)–C(4a)–C(5)–C(6)	29(2)	Benzo part

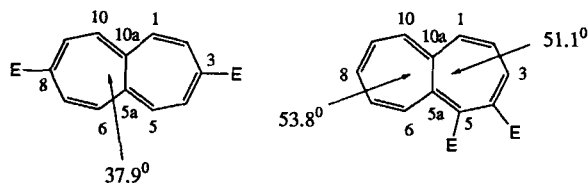
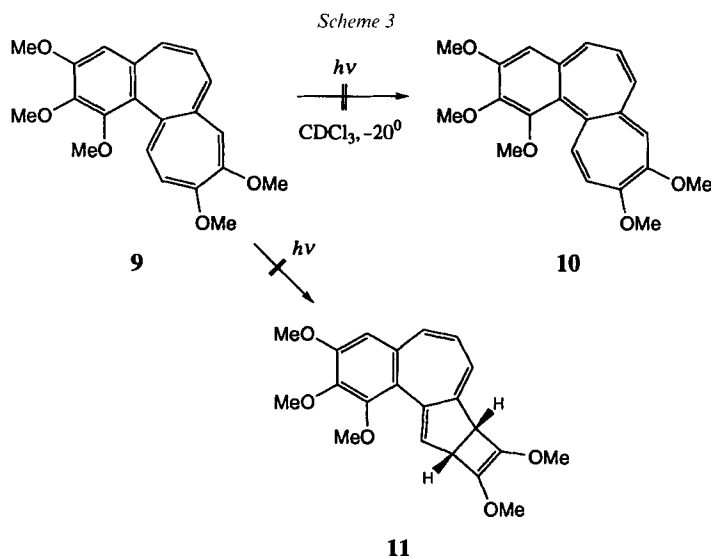


Fig. 4. Gauche torsion angles at the C(5a)–C(10a) bond of dimethyl heptalene-3,8- [39] and -4,5-dicarboxylate [40] (taken from the corresponding X-ray crystal data)

lar⁹⁾. The torsion of the *s-cis*-butadiene units of the heptalene perimeter are actually slightly below 30°. The corresponding torsion angles including the H-atoms, namely $\theta(\text{H}-\text{C}(6)-\text{C}(7)-\text{H})$ and $\theta(\text{H}-\text{C}(11)-\text{C}(12)-\text{H})$, amount to 28° and 16°, respectively. They agree very well with the θ values calculated with the *Karplus-Conroy* relation, *i.e.*, the structure of **9** in solution must be close to that determined in the crystal. The MeO substituents at C(1) to C(3) give way to each other, and their Me groups assume positions which are orthogonal to the plane of the benzo moiety and *anti* to each other for MeO–C(1) and MeO–C(2). The Me group of MeO–C(3) lies in the plane of the benzo moiety. One also can recognize that the Me group of MeO–C(1) is *anti*-oriented to C(12) of the heptalene part, *i.e.*, its spatial orientation is determined by the configuration of the heptalene skeleton. The MeO groups at C(9) and C(10) show an in-plane *anti*-orientation to each other¹⁰⁾.

We were disappointed when we investigated the photochemical behavior of **9**. We expected, as mentioned already, the formation of the quinoid compound **10**, the DBS isomer of **9** (Scheme 3) which might undergo thermal reversion to **9**. However, the irradiation of **9** with a high-pressure Xe lamp in an O₂-free CDCl₃ solution at –20° in NMR tubes (diameter 5 mm)¹¹⁾ led neither to the formation of **10** nor could we observe a



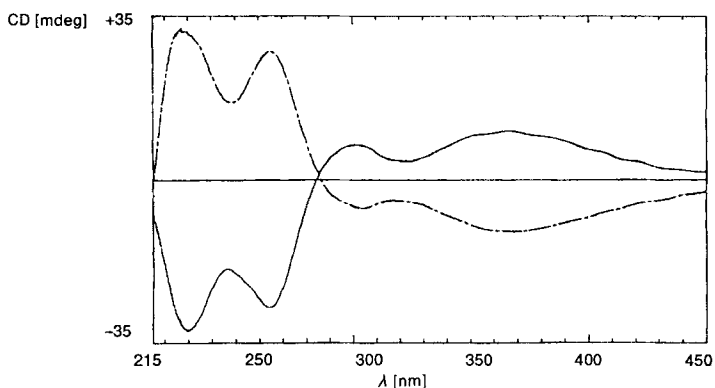
⁹⁾ Structure calculations of benzo[*a*]heptalene with a modified MM3 force field give *gauche* torsion angles around the C(7a)–C(12a) bond which are nearly identical with those determined for **9** [41]. This means that not the MeO substituent at C(1) is responsible for the strength of the torsion around C(7a)–C(12a) bond. On the contrary, it is rather the steric interaction with C(1) that causes the torsion.

¹⁰⁾ A closer inspection of Fig. 3 also reveals that **9** possesses two axes of helicity. One coincides with the C(7a)–C(12a) bond and determines the heptalene configuration of benzo[*a*]heptalenes, and the other one runs along the C(12a)–C(12b) bond thereby characterizing the 'colchicinoid' configuration of benzo[*a*]heptalenes. On structural grounds, the sense of helicity of both axes is opposite (*cf.* Table 1). Therefore, it is sufficient to describe the chirality of benzo[*a*]heptalenes with only one stereochemical descriptor, namely that of the heptalene helicity (see (7a*P*)-**9** instead of (7a*P*, 12b*M*)-**9** in Fig. 3).

¹¹⁾ ¹H-NMR Spectra were recorded at –20° at 360 MHz. For a detailed description, see [33b]. We thank Prof. Dr. T. Jenny, Institut de chimie organique, Université de Fribourg, for these experiments.

photochemical behavior similar to that of colchicine and its derivatives (*cf.* [27b] [27c]), which, in the case of **9**, could result in the formation of **11**. Benzo[*a*]heptalene **9** was photochemically stable, also after several hours of irradiation.

Since we found no indication for a DBS process in **9**, we assumed that the configuration of **9** might be stable enough to resolve **9** at room temperature. Of course, the main contribution of the activation energy of racemization has to be expected from the steric interaction of MeO–C(1)/H–C(12). However, the other *peri*-interactions H–C(4)/H–C(5) and H–C(7)/H–C(8) as well as the vicinal interaction of MeO–C(9)/MeO–C(10), which form a torsion angle of 22(1)° (see *Exper. Part*) that should be strongly diminished in the transition state of racemization, will also contribute to the activation energy of racemization¹²). Indeed, we could separate the antipodes of **9** on an analytical *Chiracel OD* column at 0° with a precooled mixture of hexane and *i*-PrOH (85:15). Both antipodes of **9** racemized rapidly at room temperature ($\tau_{1/2}(22^\circ) = 3.6$ h; see later). Qualitative CD spectra of (+)- and (–)-**9** are shown in *Fig. 5*¹³). The antipode with the shorter retention time on the *Chiracel OD* column, *i.e.*, (–)-**9**, is characterized by two negative maxima at 369 and 305 nm and two positive maxima at 264 and 229 nm. Two



*Fig. 5. Qualitative CD spectra (EtOH) of the antipodes of 1,2,3,9,10-pentamethoxybenzo[*a*]heptalene (**9**) after separation on a analytical Chiracel OD column with hexane/*i*-PrOH 85:15 ($t_R((+)\text{-}\mathbf{9})/t_R((-)\text{-}\mathbf{9}) = 1.40$)*

negative maxima above 300 nm are due to all (*P*)-configured heptalenes which we have separated so far (*cf.* [36]; see also [25]), and whose absolute configuration is well established. *Fig. 6* shows as an example the CD spectrum of (–)-(*P*)-6,7,9,11-tetramethylheptaleno[1,2-*c*]furan ((–)-(*P*)-**11**) [42] which is structurally close to **9** and chemically correlated with (–)-(*P*)-5,6,8,10-tetramethylheptalene-1,2-dimethanol ((–)-(*P*)-**12**), whose absolute configuration, in turn, is correlated with (+)-(*R*)-1-phenylethanol [36] (see also [43]). Therefore, we assign the (*P*)-configuration to (–)-**9** which has the shorter retention time on the *Chiracel OD* column.

¹²) For a more detailed discussion of the energies of activations of the racemization of the 1,2,3,9,10-pentamethoxybenzo[*a*]heptalenes, see [41]. Indeed, the transition state of racemization is not planar according to calculations with a modified MM3 force field [41].

¹³) According to the small amounts of (+)- and (–)-**9** that were available to us, we refrained from measuring quantitative CD spectra.

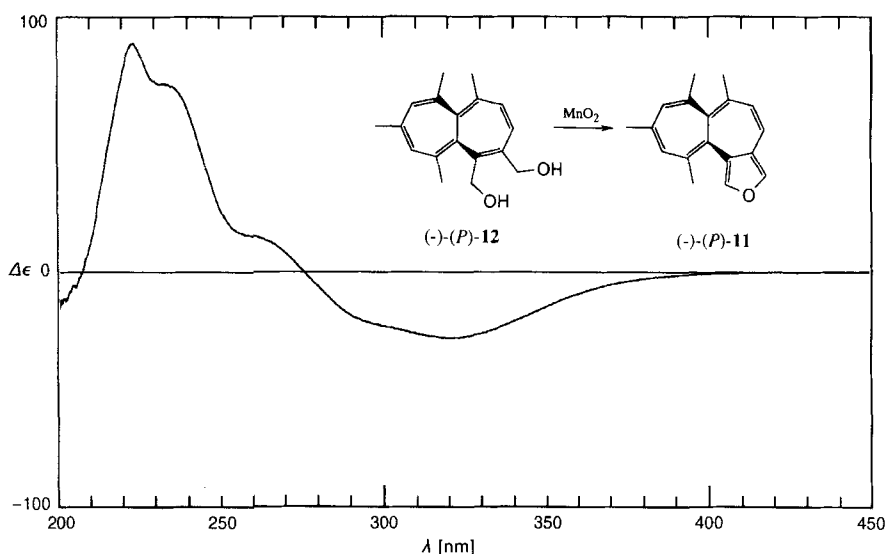
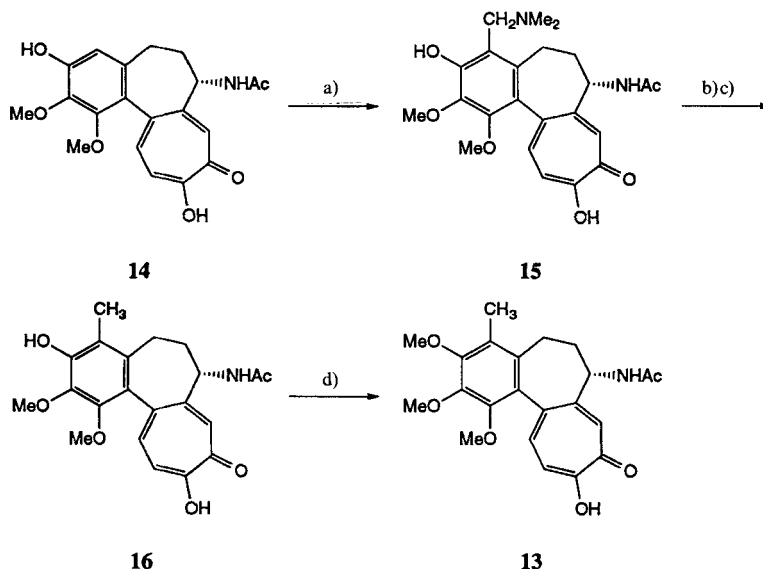


Fig. 6. CD Spectrum (EtOH) of $(-)-(P)$ -6,7,9,11-tetramethylhepteno[1,2-*c*]furan $(-)-(P)$ -11 [42]

It should be noted that colchicine (**2**), deacetamidocolchicine, and deacetamidoisocolchicine with (*M*)-configuration at the C(12a)–C(12b) bond, *i.e.*, which corresponds to the (*P*)-configuration of **9**¹⁰, possess nearly mirror-image CD spectra as compared to that of $(-)$ -**9** (*cf.* Fig. 5) [44]. However, their long-wavelength absorption at *ca.* 360 nm is determined by the tropolone part of these molecules which is no longer present in **9**. Nevertheless, a direct chemical correlation of the configuration of colchicine and its derivatives with that of benzo[*a*]heptalenes has not yet been realized.

2.2. 1,2,3,9,10-Pentamethoxy-4-methylbenzo[*a*]heptalene (18). There are in principle five *peri*-positions available for the introduction of substituents in **9**. We presumed that the aromatic position at C(4) would be most promising for electrophilic aromatic substitutions due to the π -donor substituents at ring *A*. First attempts showed, however, that neither the *Vilsmeier* formylation nor the reaction with dichloromethyl methyl ether in the presence of SnCl_4 led to the formation of the expected 4-formyl derivative of **9**. Likewise, we had no success with *Friedel-Crafts* reactions with AcCl in the presence of AlCl_3 or SnCl_4 as well as with Ac_2O and polyphosphoric acid. All these reactions led mostly to decomposition of **9**. Also, metalation of **9** at C(4) with BuLi or *t*- BuLi in the presence of TMEDA in cyclohexane or THF were not successful. We could observe in all metalation reactions of **9** a change of the color of the reaction mixture from yellow to red indicating a deprotonation of **9**. However, we were not able to establish a deprotonation at C(4) by the addition of D_2O or MeI . Heptalene **9** was recovered unchanged, and incorporation of deuterium at C(4) or any other position could not be detected by $^1\text{H-NMR}$ spectroscopy.

Therefore, we decided to introduce a Me and Et group at C(4) already in **2** and follow then the procedure developed for the synthesis of **9** (Scheme 2). Roussel-UCLAF has described the synthesis of 4-methylcolchicine (**13**) in two patents [45]. 3-*O*-Demethylcol-

Scheme 4^{a)}

a) Me₂NH/CH₂O. b) MeI. c) NaBH₄. d) CH₂N₂.

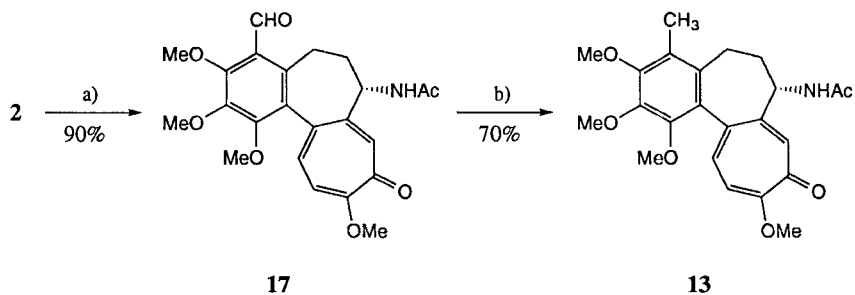
^{a)} Synthesis of **13** according to *Roussel-UCLAF* [45].

chicine (**14**) is transformed by a *Mannich* reaction into 3-*O*-demethyl-4-[(dimethylamino)methyl]colchicine (**15**) which, in turn, after quaternization is reduced with NaBH₄ to give 3-*O*-demethyl-4-methylcolchicine (**16**; *Scheme 4*). In the final step, **16** is methylated with CH₂N₂. The greatest disadvantage of this synthesis is the availability of **14**. It cannot easily be synthesized from **2** (*cf.* the discussion in [34]). However, it can be obtained by hydrolysis from its glucoside [34] which occurs besides **2** (*ca.* 1%) [46a] in the seeds of *Colchicum autumnale* L. to an extent of 0.25% [46].

With respect to the poor access to **14**, we looked for a more efficient synthesis of **13** with **2** as starting material. Apparently, there are only two positions in **2** which are prone to substitution reactions, namely C(4) to electrophilic reactions and C(10) to nucleophilic exchange reactions (*cf.* [27d]). Moreover, the formylation of **2** at C(4) under the conditions described by *Rieche et al.* [47] seems to be the only electrophilic reaction that can be performed with unprotected **2** leading to the formation of 4-formylcolchicine (**17**) in yields up to 80% [48] (*Scheme 5*). We obtained **17** in a yield of 90% by following the procedure described in [48]. Again, our first attempts to reduce **17** directly to **13** were not successful. For example, the reaction of **17** with diborane, which efficiently reduces azulene-1-carbaldehydes to 1-methylazulenes [47], gave only the corresponding alcohol in low yields. Reactions with BH₃·SMe₂ [50], *Raney*-Ni (type *W 6*) in aqueous EtOH [51], ZnI₂, and Na[BH₃CN] [52], and the *Huang-Minlon* reaction [53]¹⁴⁾ run similarly. Therefore, we sought for a completely different reduction concept. *Kursanow et al.* [54] have

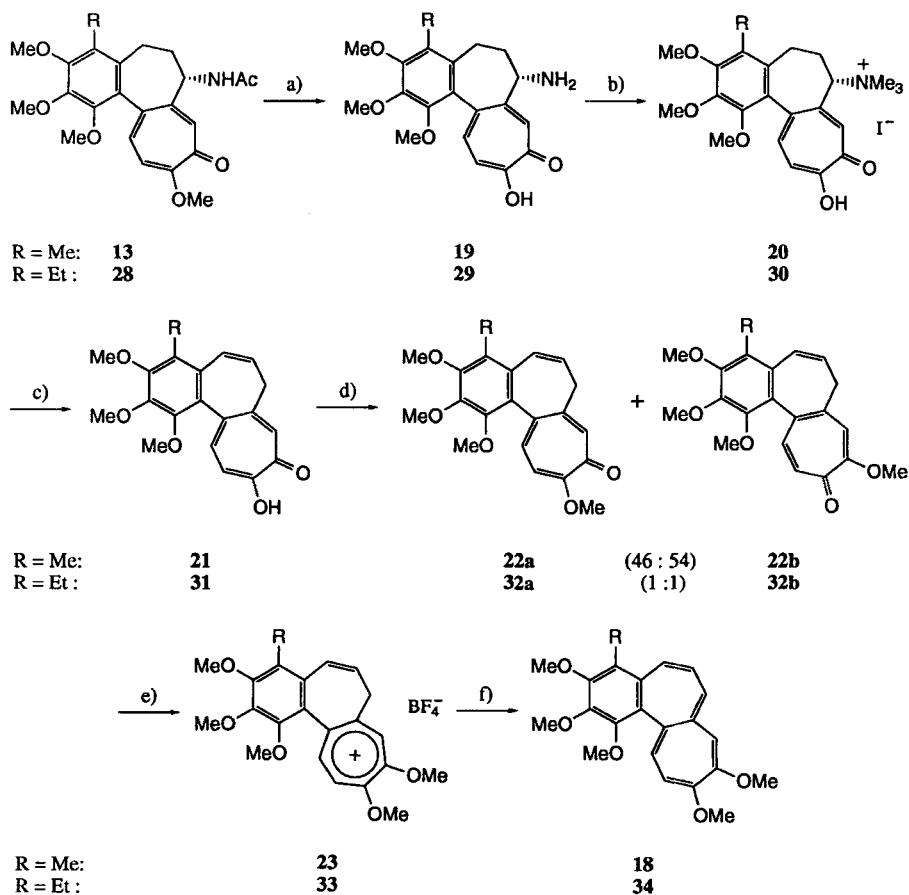
¹⁴⁾ Established reduction procedures such as *Clemmensen* or *Wolff-Kishner* reactions have not been tried on account of the strong acidic or basic conditions that have to be applied.

Scheme 5



a) $\text{Cl}_2\text{CHOMe}/\text{SnCl}_4$ in CH_2Cl_2 , $0^\circ \rightarrow 20^\circ$ (cf. [48]). b) $\text{Et}_3\text{SiH}/\text{CF}_3\text{COOH}$, $50^\circ/15$ h.

Scheme 6



a) 20% H_2SO_4 , reflux/24 h (15 h for **28**). b) 2N NaOH , MeI , $50^\circ/20$ h. c) $\text{KOH}/(\text{CH}_2\text{OH})_2/\text{H}_2\text{O}$, $185^\circ/30$ min.
 d) CH_2N_2 in $\text{Et}_2\text{O}/\text{MeOH}$, 0° . e) $\text{Me}_3\text{O}^+\text{BF}_4^-/\text{CH}_2\text{Cl}_2$, 20° . f) $\text{Me}_3\text{N}/\text{CHCl}_3$, 0° .

shown that benzyl cations that are stabilized by π -donor substituents at the aromatic ring can be reduced with silanes, preferably with Et_3SiH . In this way, benzylic alcohols as well as corresponding carbaldehydes and other carbonyl compounds can successfully be reduced to the alkyl compounds in the presence of $\text{CF}_3\text{COOH}/\text{Et}_3\text{SiH}$. When we applied this procedure to 4-formylcolchicine (**17**), we observed the smooth formation of **13** in good yields (*Scheme 5*).

The synthesis of **18** followed that of **9** (*Scheme 6*). Hydrolysis of **13** with 20% aqueous H_2SO_4 gave de-*N*-acetyl-4-methylcolchicine (**19**) in 59% yield. Quaternization of **19** with MeI led to the formation of the ammonium salt **20** in 66% yield. The *Hofmann* degradation of **20** delivered only de-7-acetamido-5,6-didehydro-4-methylcolchicine (**21**) in 44% yield. The prototropic analogue to **5a** (*cf. Scheme 2*) could not be detected by ^1H -NMR spectroscopy. Methylation of **21** with CH_2N_2 gave in 62% yield a 46:54 mixture **22a/22b** (^1H -NMR). The tropylium salt **23** was obtained in a yield of 75%. Its transformation into the heptalene **18** with Me_3N in CHCl_3 was realized in a yield of 68%. Recrystallization from hexane/AcOEt gave **18** in yellow crystals which melted at 124° .

The ^1H -NMR spectrum (C_6D_6) of **18** showed the *d* of $\text{H}-\text{C}(5)$ shifted by 0.23 ppm to lower field, as compared with **9**, due to the presence of $\text{Me}-\text{C}(4)$. $^3J(\text{H}-\text{C}(5), \text{H}-\text{C}(6))$ amounted to 12.0 Hz, *i.e.*, it was by 0.3 Hz larger than that of **9**. Correspondingly, $^3J(\text{H}-\text{C}(6), \text{H}-\text{C}(7))$ was with 6.1 Hz distinctly lower than that of **9** (6.4 Hz). The second 3J value of the *s-cis*-butadiene subunit C(10) to C(12) is comparable (7.4 Hz) with that of **9**. Noteworthy is also that **18** displays a clearly larger and measurable 4J value of 1.3 Hz between $\text{H}-\text{C}(7)$ and $\text{H}-\text{C}(8)$ as **9** (0.1–0.2 Hz). The slightly smaller vicinal coupling between $\text{H}-\text{C}(6)$ and $\text{H}-\text{C}(7)$ in **19** as compared with **9** indicates a somewhat larger torsion angle between $\text{H}-\text{C}(6)$ and $\text{H}-\text{C}(7)$ and the corresponding torsion angle of C(5) to C(7).

The latter deduction was fully supported by the X-ray crystal-structure analysis of **18** (*Fig. 7* and *Table 2*). One recognizes that the Me group at C(4) in **18** exerts a distinct influence on the degree of twisting of the heptalene skeleton as compared to **9** (*cf. Table 1*). In average, the *s-trans* and *s-cis* torsion angles of the central C(7a)–C(12a) bond in **18** are *ca.* 7° smaller and larger, respectively, than in **9**. The corresponding trend is established for the ‘colchicinoid’ torsion angles around the C(12a)–C(12b) bond. The torsion angle between the $\text{H}-\text{C}(6)$ and $\text{H}-\text{C}(7)$ amounts to 33° , *i.e.*, it is by 8° larger than the corresponding angle in **9**. The torsion angle, calculated for the found coupling constant of 6.1 Hz for **18**, amounts to 29° (*vide supra*).

As expected, the Me group at C(4) has also an influence on the spatial arrangement of the MeO groups at ring A, mainly on $\text{MeO}-\text{C}(3)$. This group lies not longer – as in **9** – in the plane of the aromatic ring. It assumes a nearly orthogonal position with respect to the aromatic plane and is situated on the same side of this plane as $\text{MeO}-\text{C}(2)$. However, this group is markedly turned in direction of the plane of ring A – again, if we compare its position with that of $\text{MeO}-\text{C}(2)$ in **9**. Only $\text{MeO}-\text{C}(1)$ in **18** still occupies an orthogonal position to the plane of the aromatic ring with an *anti*-relation to C(12) of the twisted heptalene skeleton. That the situation must be similar in solution shows a comparison of the chemical shifts of the *s* of the MeO groups in **9** and in **18** (*Table 3*). As one can see, four MeO signals of **18** show a shift increment of $+0.10 \pm 0.03$ ppm (as compared with **9**) and only one, namely $\text{MeO}-\text{C}(3)$, a shift increment of $+0.43$ ppm.

The observed more pronounced torsion of the heptalene skeleton of **18** should also lead to a higher barrier for its racemization. Indeed, we had no problems in the resolution of **18** on the analytical *Chiracel OD* column at room temperature. The (–)-(7a*P*)-enantiomer of **18** showed again the shorter retention time (hexane/*i*-PrOH 85:15). Both

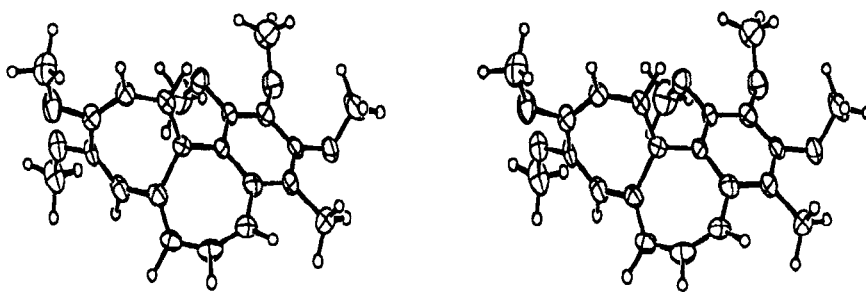


Fig. 7. Stereoscopic view of the X-ray crystal structure of 1,2,3,9,10-pentamethoxy-4-methylbenzo[a]heptalene (**18**) (ORTEP presentation)

Table 2. Torsion Angles Θ from the X-Ray Crystal Structure of 1,2,3,9,10-Pentamethoxy-4-methylbenzo[a]heptalene (**18**). In parentheses, e.s.d's.

Atoms	Θ [°]	Remarks
C(7)–C(7a)–C(12a)–C(12)	–125.8(5)	Heptalene torsion angles around the central σ bond C(7a)–C(12a)
C(7)–C(7a)–C(12a)–C(12b)	59.0(6)	
C(8)–C(7a)–C(12a)–C(12)	58.5(6)	
C(8)–C(7a)–C(12a)–C(12b)	–116.7(5)	
C(1)–C(12b)–C(12a)–C(7a)	117.8(5)	'Colchicinoid' torsion angles around the aromatic σ bond C(12a)–C(12b)
C(1)–C(12b)–C(12a)–C(12)	–57.3(6)	
C(4a)–C(12b)–C(12a)–C(7a)	–61.3(6)	
C(4a)–C(12b)–C(12a)–C(12)	123.6(5)	
C(5)–C(6)–C(7)–C(7a)	–32.7(8)	<i>s-cis</i> -Butadiene torsion angles of the heptalene perimeter
C(8)–C(9)–C(10)–C(11)	32.6(7)	
C(10)–C(11)–C(12)–C(12a)	–32.8(7)	
C(12b)–C(4a)–C(5)–C(6)	29.9(7)	Benzo part

Table 3. Comparison of the Chemical Shifts [ppm] (C_6D_6) of the MeO Groups in **9** and **18**

Benzo[a]heptalene	MeO–C(2)	MeO–C(1)	MeO–C(3)	MeO–C(9)	MeO–C(10)
9 ^{a)}	3.84	3.69	3.33	3.21	3.16
18 ^{b)}	3.90	3.80	3.76	3.33	3.28

^{a)} Assignments based on 1H -NOE measurements (see *Exper. Part*).

^{b)} Tentative assignments in analogy to those of **9**.

antipodes of **18** were stable at room temperature (calc. $\tau_{1/2}(22^\circ) = 35.6$ h; see later). The qualitative CD spectra of (–)-(7a*P*)- and (+)-(7a*M*)-**18** are shown in Fig. 8.

Enantiomer (7a*P*)-**18** displays the longest-wavelength negative maximum at 357 nm, i.e., in comparison to (7a*P*)-**9**, it is hypsochromically shifted by 12 nm. The pronounced second negative maximum of (7a*P*)-**9** at 305 nm appears for (7a*P*)-**18** only as a barely detectable shoulder in the same spectral region. The two positive maxima at 263 and 227 nm are comparable with those of (7a*P*)-**9**, which appear at 264 and 229 nm. The more pronounced twisting of the heptalene skeleton in **18** has thus mainly an influence on the heptalene absorption at > 300 nm. We have made similar observations with heptalene-4,5-dicarboxylates and their derivatives (*cf.* [33] [36]).

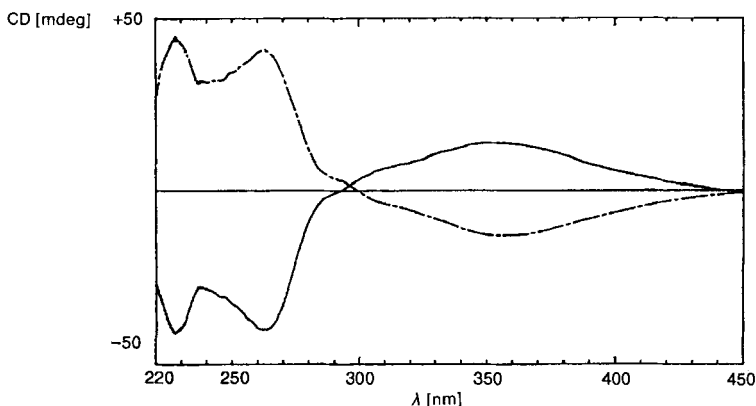
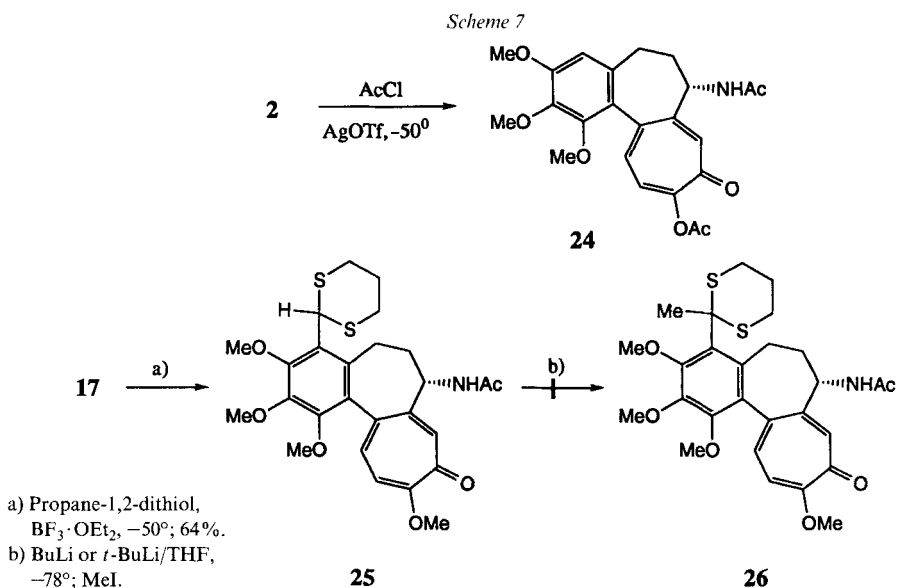


Fig. 8. Qualitative CD spectra (EtOH) of the antipodes of 1,2,3,9,10-pentamethoxy-4-methylbenzo[a]heptalene (**18**) after separation on an analytical Chiracel OD column with hexane/*i*-PrOH 85:15 ($t_R((+)\text{-}\mathbf{18})/t_R((-)\text{-}\mathbf{18}) = 1.22$)

2.3. 4-Ethyl-1,2,3,9,10-pentamethoxybenzo[a]heptalene (**34**). We were interested in the synthesis of this homologue of **18**, because we expected a further restriction of the conformational space of the MeO groups at ring *A* and conversely also of the Et group at C(4).

Friedel-Crafts acetylations of colchicine (**2**) at C(4) had not been successful so far. On the other hand, the acetylation of the model compound 1,2,3-trimethoxybenzene takes place without problem. *Effenberger et al.* have shown that the mixed anhydride of acetic and trifluoromethanesulfonic acid, generated at low temperature *in situ* from AcCl and AgOTf, is a most powerful agent for acetylations [55]. When we applied this procedure to **2**, we observed that acetylation had only occurred at the MeO group at C(10) (Scheme 7).



Since 4-formylcolchicine (**17**) was easily available from **2**, we decided to test it as starting material for the synthesis of 4-ethylcolchicine (**28**). First attempts in line with the well established 'umpolung' of the CHO group showed that we indeed could prepare the dithiane derivative **25** of **17** (*Scheme 7*). However, the methylation of deprotonated **25** failed. The ¹H-NMR spectra of the crude reaction mixtures indicated that the tropolone ring had been attacked by the strong bases, necessary for the deprotonation of **25**. Signals that would have indicated the presence of **26** in the reaction mixture could not be detected. Experiments to methylenate the CHO group of **17** by *Wittig* or *Tebbe* reactions [56] have also not been successful.

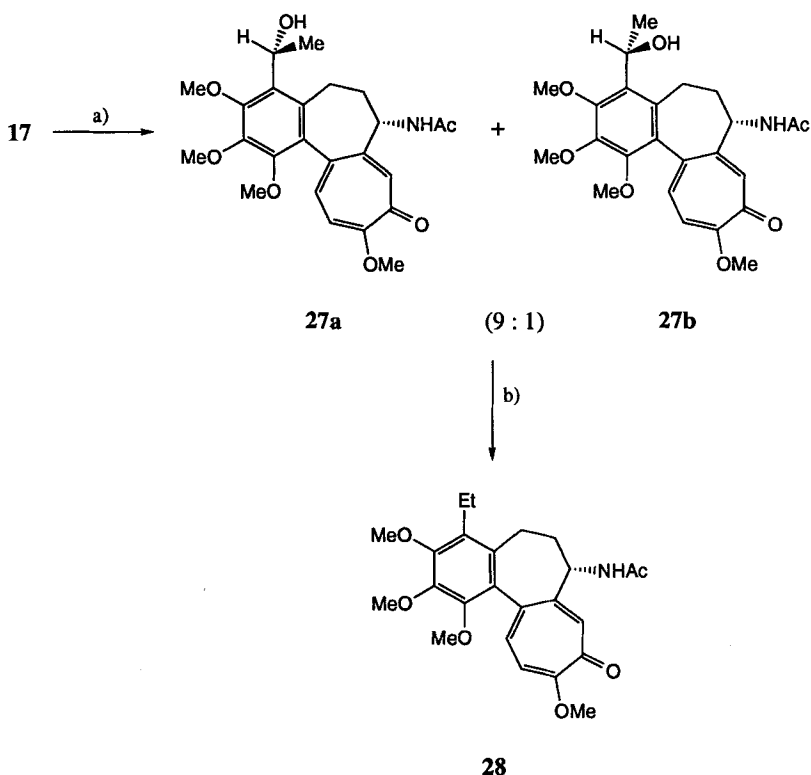
Therefore, we investigated the addition of metal-organic reagents of the type RM (R = alkyl residue, M = metal part) to the CHO group. Again, we had to learn that colchicine chemistry is a chemistry on its own. The typical metal-organic reagents (MeMgBr, MeLi, MeMgBr/CeCl₃), which owe their reactivity mainly to their strong basicity, gave no reaction at all at the CHO group at C(4) of **17**. We assume that, in these cases, the deprotonation of the AcNH group at C(7) takes place. The thus created negative charge on the Ac group shields, in the twisted colchicine structure, the CHO group at C(4) against an attack by nucleophiles¹⁵).

Indeed, when we changed to the much less basic MeZr(OBu)₃ reagent, for which *Seebach* and coworkers have shown that it transfers its Me group to most acidic carbonyl systems such as β-tetralone [58], we observed a smooth diastereoselective Me transfer to the CHO group of **17** (*Scheme 8*). It is noteworthy that, also in the presence of an excess of 2 mol-equiv. of MeZr(OBu)₂, we recovered 8% of **17**. The development of a pink color during the reaction indicated that also deprotonation at the AcNH group had taken place to a certain extent. The main diastereoisomer **27a** could be obtained in pure form by two crystallizations from MeOH and then from acetone. The crystals were, however, not suitable for an X-ray crystal-structure analysis. The ¹H-NMR spectrum (CDCl₃) of the 9:1 mixture **27a/27b** showed comparable chemical shifts for both isomers except for the NH signal which appeared for the main product at markedly lower field (8.18 ppm) as for the by-product (7.67 ppm). Molecular models show that an intramolecular H-bridge between the OH group of the MeCHOH group at C(4) and the AcNH group at C(7) in **27** is only possible in an *syn*-arrangement of both substituents. Therefore, we assign the (*R*)-configuration to the MeCHOH group at C(4) in the main diastereoisomer **27a**. This assignment is in agreement with the fact that the *Si*-side of the CHO group in **17** should be shielded by the bent colchicine skeleton and the AcNH substituent at C(7), *i.e.*, the CHO group should preferentially be attacked on its *Re*-side by the spacious Zr reagent (*cf.* also [58]).

The reduction of the 9:1 mixture **27a/27b** with Et₃SiH/CF₃COOH gave the expected 4-ethylcolchicine (**28**) in a yield of 64% (*Scheme 8*). The transformation of **28** into 4-ethyl-1,2,3,9,10-pentamethylbenzo[*a*]heptalene (**34**) could be realized without difficulties (*Scheme 6*). The hydrolysis of **28** gave de-*N*-acetyl-4-ethylcolchicine (**29**) in a yield of 44%. Quaternization of **29** led to the ammonium salt **30** (57%), the *Hofmann* degradation of which could only be realized in a yield of 25%. Nevertheless, the methylation of **31** with CH₂N₂ was attained in a yield of 84% and resulted in a 1:1 mixture **32a/32b** (¹H-NMR). The mixture **32a/32b** gave in the usual way the tropylium salt **33** (56%). The

¹⁵) The X-ray crystal structure of 4-acetylcolchicine is in accordance with this reasoning [57].

Scheme 8



a) 3 mol-equiv. of $\text{MeZr}(\text{OBu})_3$ in $\text{Et}_2\text{O}/\text{CH}_2\text{Cl}_2$; 72%. 8% of **17** were recovered. b) $\text{Et}_3\text{SiH}/\text{CF}_3\text{COOH}$, $50^\circ/15\text{ h}$; 64%.

deprotonation of **33** to the expected heptalene **34** took place in a yield of 78%. The latter crystallized from MeOH in large yellow crystals and melted at $128\text{--}129^\circ$.

The $^1\text{H-NMR}$ spectrum (C_6D_6) of **34** is similar to that of **18** in C_6D_6 . The size of $^3J(\text{H-C}(6), \text{H-C}(7))$, which is a good indicator for the degree of twisting of the heptalene skeleton as we have seen, was of the same order (6.0 Hz) as for **18** (6.1 Hz). The inherent chirality of the heptalene skeleton is clearly indicated by the diastereotopy of the two H-atoms of the CH_2 group of the Et substituent at C(4). They appear in C_6D_6 as an ABX_3 system with $\Delta\delta = 45\text{ Hz}$ and $^2J_{\text{AB}} = 13.1\text{ Hz}$ (see Fig. 9). In CDCl_3 , there is nearly no shift difference between the two anisochronous H-atoms of the CH_2 group of Et-C(4). We tested some other solvents for discrimination of the diastereotopic H-atoms. We found, however, that C_6D_6 gave the strongest effects. On the other hand, other H-atoms of **34** showed appreciable solvent effects, especially H-C(11) and H-C(12). The observed chemical shifts for the H-atoms at the heptalene skeleton for the different solvents are collected in Table 4.

The resolution of **34** on the analytical *Chiracel OD* column at room temperature and with hexane/*i*-PrOH (95:5) created no problems. As expected in view of our experiences with **9** and **18**, the (7a*P*)-enantiomer of **34** showed again the shorter retention time. The configurational stability of the antipodes of **34** turned out to be distinctly larger than that of **18** ($\tau_{1/2}(34^\circ)$ of **34**/ $\tau_{1/2}(34^\circ)$ of **18** = 1.4; see later). The CD spectra of the antipodes of **34** are shown in Fig. 10. They resemble – as expected – very much those of **18** (cf. Fig. 5).

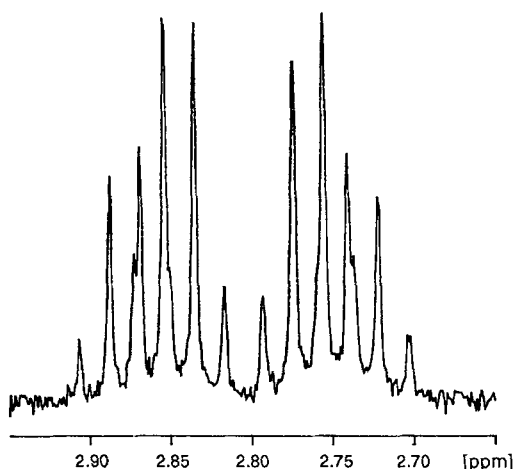


Fig. 9. Segment of the methylene H-atoms of the Et group in the ^1H -NMR spectrum (400 MHz, C_6D_6) of 4-ethyl-1,2,3,9,10-pentamethoxybenzo[a]heptalene (**34**)

Table 4. ^1H -NMR Solvent Shifts [ppm] of the Heptalene H-Atoms of 4-Ethyl-1,2,3,9,10-pentamethoxybenzo[a]heptalene (**34**)^{a)}

H-Atom	CDCl_3	$(\text{D}_6)\text{Aceton}$	CD_3OD	C_6D_6	$\text{C}_6\text{D}_5\text{NO}_2$	$\text{C}_6\text{D}_5\text{Br}$
H-C(5)	6.93 (12.1)	6.92 (12.0)	6.87 (12.1)	7.01 (12.0)	7.01 (11.8)	6.96 (12.1)
H-C(6)	6.33 (12.1, 6.0)	6.30 (12.1, 5.9, 1.0)	6.27 (12.1, 6.0)	6.33 (12.0, 6.0)	6.45 (11.6, 5.8)	6.32 (12.1, 5.8)
H-C(7)	5.64 (6.1, 1.5)	5.60 (6.3)	5.59 (6.3)	5.66 (5.9)	5.76 (5.9)	5.63 (6.5)
H-C(8)	5.53	5.61	5.61	5.38	5.74	5.43
H-C(11)	5.79	5.68 (7.9)	5.64 (7.4)	5.51 (7.4)	5.89 (7.1)	5.58 (7.5)
H-C(12)	5.79	5.81 (7.4)	5.81 (7.4)	6.00 (7.3)	5.95 (7.4)	5.84 (7.4)

^{a)} In parentheses are the coupling constants in Hz.

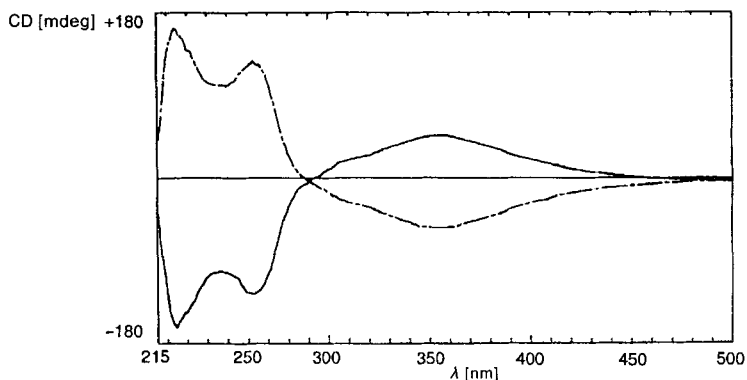
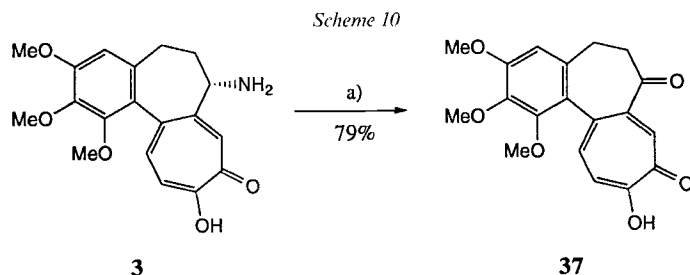
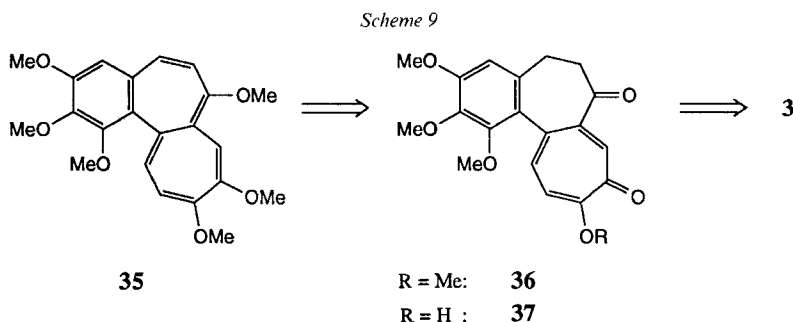


Fig. 10. Qualitative CD spectra (EtOH) of the antipodes of 4-ethyl-1,2,3,9,10-pentamethoxybenzo[a]heptalene (**34**) after separation on an analytical Chiracel OD column with hexane/*i*-PrOH 95:5 ($t_R((+)\text{-34})/t_R((-)\text{-34}) = 1.21$)

2.4. *Attempted Synthesis of 1,2,3,7,9,10-Hexamethoxybenzo[a]heptalene (35)*. The title benzo[a]heptalene **35** can retrosynthetically be linked to colchicone (**36**) or de-7-acetamido-7-oxocolchicine (**37**; Scheme 9). The latter two compounds are synthetically available from de-*N*-acetylcolchicine (**3**; see e.g. [59] [60]). Formation of the methyl enoether at C(7) of **36** would allow to apply our procedure for benzo[a]heptalene formation to this 6,7-didehydro compound. However, the procedures for the synthesis of **36** or **37** from **3** are tedious, or by-products are formed. *Brossi* and coworkers have shown [60]



a) 1. 1-Formyl-4-methylpyridinium benzenesulfonate/ CH_2Cl_2 /DMF 3:1, r.t./2 h; 2. DBU, r.t./10 min; 3. sat. aq. oxalic acid, r.t./17 h.

that the *Schiff* base of **3** with PhCH_2NH_2 undergoes, on heating with KOH in MeOH (96 h under reflux), a reversible prototropic shift at C(7) which leads to racemization and, on hydrolysis, to the formation of racemic **3** and **37**. In the meantime, *Buckley* and *Rapoport* [61], as well as *Otha* and *Okamoto* [62], based on earlier work of *Corey* and *Achiwa* [63], have developed biomimetic transamination reactions which take place already at room temperature under very mild conditions. The bad solubility of **3** needed a slight modification in *Rapoport's* protocol. Indeed, the transamination of **3** occurred then smoothly in a yield of 79 % in a one-pot reaction (Scheme 10)¹⁶⁾¹⁷⁾.

¹⁶⁾ *Corey's* procedure, applied to **3**, was unsuccessful.

¹⁷⁾ We developed the synthesis of **37**, based on *Rapoport's* procedure, at the beginning of our work. Since then, *Banwell et al.* [64] reported on the synthesis of colchicone (**36**) and isocolchicone by transamination reaction with 4-formyl-1-methylpyridinium *p*-toluenesulfonate.

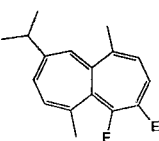
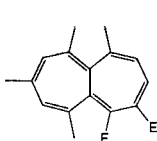
The 7-oxo group in **37**, however, could not be reacted with metal-organic reagents. In most cases, only enolization was achieved. No reaction at all was observed with carbonylphilic organotitanium and organozirconium reagents. Transformation of **37** in the mixture of **36** and isocolchicone did not change the situation. The organotitanium and organozirconium reagents led only to an exchange of the MeO group at C(10) and C(9), respectively¹⁸⁾.

The reaction of the mixture of **36** and isocolchicone with an excess of trimethoxonium tetrafluoroborate led to the formation of a salt which, on treatment with Me₃N in CHCl₃, gave a probe which readily decomposed. A rapidly isolated probe showed in the ¹H-NMR spectrum (CDCl₃) in the olefinic region two AB systems which could correspond to H–C(5,6) and H–C(11,12) in **35**. However, we were not able to improve the procedure of isolation, due to the instability of the compound which might be **35**.

3. Kinetics of the Racemization of the 1,2,3,9,10-Pentamethoxybenzo[*a*]heptalenes. –

It is known that the number of substituents in the *peri*-position of heptalenes have a decisive influence on the configurational stability of heptalenes as well as on their π -skeletal stability as expressed by the DBS process in heptalenes [33] [36] [66] (see also [25]). However, the DBS process takes place at lower temperatures than racemization¹⁹⁾ which is characterized by a double ring inversion (DRI). Heptalene-4,5-dicarboxylates need, in general, two further substituents in *peri*-position to be resolvable at room temperature. The first heptalene which we could resolve was the dimethyl heptalene-4,5-dicarboxylate **38** [36]. It has a half-life time ($\tau_{1/2}$) of 18 h at room temperature. One further Me substituent in the *peri*-position dramatically increases the configurational stability as shown by the data of the comparable heptalene-4,5-dicarboxylate **39** [66] (Tables 5), i.e., heptalenes such as **39** are configurationally stable up to 120°. Therefore, we were quite surprised to learn from our resolved benzo[*a*]heptalenes that one substituent at C(1) is sufficient for a reasonable configurational stability at room temperature. To get more insight into the process of their racemization which is not superimposed by a DBS

Table 5. Activation Parameters for the Racemization of Me-Substituted Heptalene-4,5-dicarboxylates

Parameter	 	
	38 ^{a)}	39 ^{b)}
$\Delta H_{25}^\ddagger$ [kcal mol ⁻¹]	21.4 ± 0.6	28.3 ± 0.4
$\Delta S_{25}^\ddagger$ [cal deg ⁻¹ mol ⁻¹]	-8.8 ± 1.9	-11.6 ± 0.9
$\Delta G_{25}^\ddagger$ [kcal mol ⁻¹]	24.0 ± 1.1	31.8 ± 0.6

^{a)} Data taken from [36].

^{b)} Data taken from [66].

¹⁸⁾ We will report on this interesting exchange reaction that can also be realized with colchicine (**2**) later in this journal [65] (*cf. Footnote 1*).

¹⁹⁾ The situation is just opposite to the processes that take place in cyclooctatetraenes. In general, the ring inversion occurs here with lower activation energies than the DBS process (*cf.* [67] [68]).

process, we followed the kinetics of the racemization of **9**, **18**, and **34** by measuring the decrease of their most-intense CD band at 260–265 nm in dependence of time and temperature. Since we had only very small quantities available, we measured the kinetics in the eluent solution of the HPLC separations. The racemization reactions followed in all cases strict first-order kinetics. The calculated activation parameters for **9**, **18**, and **34** are collected in *Table 6*.

Table 6. Activation Parameters for the Racemization of the Benzo[*a*]heptalenes **9**, **18**, and **34** in Hexane/*i*-PrOH^{a)}

Parameter	9	18	34
Temp. ranges [°]	6–30	34–58	34–58
E_a [kcal mol ⁻¹]	19.1	21.3	23.5
$A \cdot 10^{10}$ [s ⁻¹]	2.1	3.0	89
$\Delta H^\ddagger$ [kcal mol ⁻¹]	19.1	20.7	22.4
$\Delta S^\ddagger$ [cal deg ⁻¹ mol ⁻¹]	-13.3	-12.6	-5.8
$\Delta G^\ddagger$ [kcal mol ⁻¹]	23.1	24.4	24.7
$\tau_{1/2}$ (25°) [h]	2.65	25.0	39.3

a) Margins of error are less than $\pm 3\%$ in all cases.

What we have already seen qualitatively, namely that the order of configurational stability is **9** < **18** < **34**, is reflected here quantitatively. The introduction of a Me substituent at C(4) increases $\Delta H^\ddagger$ by 1.6 kcal mol⁻¹ ($\Delta G^\ddagger$ by 1.3 kcal mol⁻¹). Taking into account that the *peri*-strain difference (allylic $A^{(1,3)}$ strain) between naphthalene and 1-methylnaphthalene amounts to 1.6 kcal mol⁻¹ [69], the observed difference in $\Delta H^\ddagger$ between **9** and **18** indicates a fully developed $A^{(1,3)}$ strain in the transition state of racemization of **18**, i.e., Me–C(4) and H–C(5) must be in a coplanar arrangement in the transition state²⁰⁾. On the other hand, we observe nearly the same difference in $\Delta H^\ddagger$ between **18** and **34** (1.7 kcal mol⁻¹), but only a small increase in $\Delta G^\ddagger$ (0.3 kcal mol⁻¹). The entropy values show that this effect is mainly attributed to a change in $\Delta S^\ddagger$. Whereas **9**

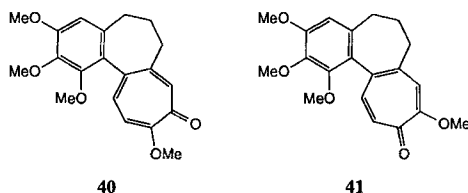


Table 7. Activation Parameters for the Racemization of *De*-7-acetamidocolchicine (**40**) and *De*-7-acetamidoisocolchicine (**41**)^{a)}

Parameter	40	41
$\Delta H^\ddagger$ [kcal mol ⁻¹]	17.1 $\pm$ 0.3	19.3 $\pm$ 0.3
$\Delta S^\ddagger$ [cal deg ⁻¹ mol ⁻¹]	-16.4 $\pm$ 1.1	-13.7 $\pm$ 2.1
$\Delta G^\ddagger$ [kcal mol ⁻¹]	22.1 $\pm$ 0.2	23.4 $\pm$ 0.2

a) In EtOH; values are taken from [44].

²⁰⁾ This observation does not imply that all three rings of the benzo[*a*]heptalenes must be coplanar in the transition state of racemization (see *Footnote 12*).

and **18** exhibit, within the margins of error, the same activation entropy, it is much more positive for **34**. This is a clear indication for the restriction of the conformational space of the Et group already in the ground state due to the buttressing effect that is exerted by the MeO substituents at C(1) to C(3) (see Fig. 7).

Recently, a study of the racemization of de-7-acetamidocolchicine (**40**) and de-7-acetamidoisocholchicine (**41**) has been published [44]. As can be seen from the activation parameters in Table 7, the values are very close to ours. The slightly lower average $\Delta H^\ddagger$ value for **40** and **41** as compared with that of **9** may be an indication for greater stiffness of the heptalene skeleton. Also the slightly more negative average $\Delta S^\ddagger$ value for **40** and **41** points in this direction. The higher flexibility of the partially saturated ring *B* in **40** and **41** needs a higher degree of order in the transition state of racemization.

We thank Dr. B. Vincent and Dr. A. Linden for the X-ray diffraction analyses. We also thank Prof. M. Hesse and his coworkers for mass spectra, Prof. W. von Philipsborn and his coworkers for NMR support and ¹H-NOE measurements, and H. Frohofer for elemental analyses. Technical assistance in experiments by Jacqueline Kessler and financial support by the Swiss National Science Foundation is gratefully acknowledged.

Experimental Part

General. Solvents and reagents of the grade 'puriss.' were used without further purification. Solvents of the grade 'purum' were distilled and, where necessary, dried before distillation. Colchicine (**2**) was taken from Fluka (quality: BioChemica > 98%) and Janssen (quality: 97%). M.p. Mettler apparatus, type FP5/52; uncorrected. TLC: on silica gel 60 *F*₂₅₄ on Al foils, thickness 0.2 mm or on Al₂O₃ 60 *F*₂₅₄, neutral (type E), thickness 0.2 mm; Merck. Prep. TLC: on silica gel 60 *F*₂₅₄ thickness 2 mm and on Al₂O₃ 150 *F*₂₅₄ (type T), thickness 1.5 mm; Merck. Column chromatography (CC): on silica gel 60 (0.063–0.200 mm or 0.040–0.063 mm; Merck) or on Al₂O₃ basic, act. III (JCN Biochemicals). Anal. HPLC: pump: Kontron 410; detector: Uvicon 725 (Kontron); column: Chiracel OD (DAICEL), 25 × 0.46 cm, equipped with a removable cooling aid; cooling medium: MeOH; kryostate: Lauda K4R. Polarimetry: Perkin-Elmer 241 MC polarimeter; [α]_D, at room temperature; *c* in g/100 ml. UV/VIS Spectra: Perkin-Elmer spectrograph 552 and Lambda 9 spectrophotometer; λ in nm (log ϵ). CD Spectra: Jasco J-500A spectrophotometer; λ in nm (rel. mdeg.). IR Spectra: Perkin-Elmer spectrograph 297 and FT-IR, Series 1600 (NaCl); main bands in cm⁻¹. ¹H-NMR Spectra: Bruker AM-400, AM-300, and Varian XL 200; δ in ppm (TMS = 0); *J* in Hz. ¹³C-NMR Spectra: Varian XL 200; δ in ppm (CHCl₃ at 76.9 ppm). Mass Spectra: Varian 112S spectrometer and Finnigan MAT 90; 70 eV; *m/z* (rel. %).

1. 1,2,3,9,10-Pentamethoxybenzo[*a*]heptalenes. – 1.1. *1,2,3,9,10-Pentamethoxybenzo[*a*]heptalene* (**9**). 1.1.1. *De-N-acetylcolchicine* (**3**; cf. [70]). Colchicine (**2**, 30.27 g, 75 mmol) was dissolved in H₂O (600 ml), and 150 ml of conc. H₂SO₄ slowly added, whereby the color of the soln. changed from yellow to orange. The mixture was heated under N₂ at reflux for 5 h. The hot soln. was cautiously neutralized with solid Na₂CO₃ leading to the precipitation of **3**. It was filtered at r.t., washed with ice-cooled H₂O and recrystallized from EtOH. Compound **3** (20.3 g, 80.5%) was obtained in fine yellow needles. M.p. 153–157° ([70]: 155–157°). [α]_D = –110.8 (*c* = 0.28; CHCl₃). For spectral data, see [71]. Anal. calc. for C₁₉H₂₁NO₅ (343.39): C 66.46, H 6.16; found: C 66.19, H 6.40.

1.2.1. *Quaternary Ammonium Iodide 4 of 3* (cf. [11b]). Compound **3** (3.6 g, 10.5 mmol) was dissolved in 2N NaOH (315 ml) and MeI (180 ml) added. The two-phase mixture was intensely stirred overnight under N₂ at 50°. The excess MeI was separated and the aq. phase extracted with CH₂Cl₂ (3 × 50 ml). The aq. phase was acidified with 50% of H₂SO₄ under cooling and then **4** extracted with CHCl₃ (5 × 100 ml). After drying, the CHCl₃ was distilled off and the residual yellow oil crystallized by addition of CH₂Cl₂/Et₂O. Iodide **4** (3.79 g, 70%) was obtained in brownish crystals. M.p. 223–226° (dec.) ([11b]: 228–231°). For spectral data, see [70].

1.1.3. *5,6- and 6,7-Didehydro-7-deacetamidocolchicine* (**5b** and **5a**, resp.; cf. [11b] [34] [35]). Iodide **4** (5.08 g, 9.9 mmol) was dissolved in 2N NaOH (25 ml) and ethyleneglycol (50 ml). To this soln. was added a soln. of KOH (170 g) in H₂O (100 ml) and ethyleneglycol (50 ml). The mixture was heated at 180° during 20 min. A vivid evolution of Me₃N could be observed during this time, and some of the product mixture was separated already as a yellow mass. After cooling, the mixture was acidified with 50% H₂SO₄. The product that contained a lot of inorg. salts was dissolved, after filtration, in CHCl₃. The CHCl₃ soln. was washed with H₂O, sat. NaHCO₃ soln.

and, again, H_2O . The residual brown oil of the CHCl_3 phase was distilled in a 'Kugelrohr' (230°/0.02 Torr) to yield a honey-like distillate which, on treatment with Et_2O /hexane, solidified. Recrystallization from AcOEt /EtOH gave deep-yellow crystals (160 g, 51 %) of **5b**. M.p. 144–145° ([11b]: 143–144°). UV/VIS (99 % EtOH): λ_{max} 354 (4.22), 284 (sh, 4.08), 243 (4.58); λ_{min} 304 (3.90). IR (CHCl_3): 3100 (br.), 3005s, 2970m, 2940m, 2857w, 2840w, 1617s, 1595s, 1550s, 1480s, 1455s, 1447s, 1432s, 1400s, 1385s, 1336s, 1288s, 1267s, 1140s, 1097s, 1045m, 1003m, 850m. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 7.61 (d, $J = 12.3$, H–C(12)); 7.41 (s, H–C(8)); 7.18 (d, $J = 12.3$, H–C(11)); 6.62 (s, H–C(4)); 6.56 (dd, $^3J = 9.7$, $^4J = 2.0$, H–C(5)); 6.23 (ddd, $^3J = 9.6$, 7.9, 6.4, H–C(6)); 3.96 3.93, 3.63 (3s, 3 MeO); 3.16 (dd, $^2J = 12.4$, $^3J = 7.9$, H–C(7)); 2.76 (ddd, $^2J = 12.4$, $^3J = 6.1$, $^4J = 2.1$, H–C(7)); OH not recognizable. EI-MS: 326 (100, M^+), 283 (17, $[M - \text{CO}]^+$), 267 (18), 240 (15), 169 (13). Anal. calc. for $\text{C}_{19}\text{H}_{28}\text{O}_5$ (326.35): C 69.93, H 5.56; found: C 69.65, H 5.51.

The distillate showed **5a** (10 %) in the presence of **5b** (90 %) according to $^1\text{H-NMR}$ (400 MHz, CDCl_3): 7.81 (d, $J = 12.6$, H–C(12)); 7.61 (d, $J = 12.6$, H–C(11)); 3.90 3.88, 3.53 (3s, 3 MeO). The other signals of **5a** were covered by those of **5b**.

1.1.4. *5,6-Didehydrode-7-acetamidocolchicine (7a) and -isocolchicine (7b; cf. [34] [35])*. CH_2N_2 in Et_2O , generated from *N*-methyl-*p*-toluenesulfonylnitrosamide (4.25 g) in Et_2O /EtOH with KOH (3.18 g; cf. [71]), was directly distilled into an ice-cooled soln. of **5b**, which was only partly dissolved at the beginning. It had been dissolved completely after the addition of CH_2N_2 under evolution of N_2 . The mixture was stirred for additional 60 min at 0° and then 30 min at r.t. The residue of the soln. was subjected to CC (Al_2O_3 N, act. III; $\text{CH}_2\text{Cl}_2/\text{AcOEt}$ 1:1). The 1:1 mixture **7a**/**7b** was obtained as a pale-yellow foam. IR (CHCl_3): 3010m, 2940m, 2840w, 1614s, 1587s, 1565s, 1490s, 1465m, 1402m, 1375m, 1335m, 1260s, 1155m, 1140s, 1100m. $^1\text{H-NMR}$ (200 MHz, CDCl_3): 7.41 (d, $J = 13.0$, H–C(12) of **7b**); 7.30 (s, H–C(8) of **7a**); 7.21 (d, $J = 11.0$, H–C(12) of **7b**); 7.03 (d, $J = 12.9$, H–C(11) of **7b**); 6.82 (s, H–C(8) of **7b**); 6.70 (d, $J = 11.2$, H–C(11) of **7a**); 6.63, 6.56 (2s, H–C(4) of **7a** and **7b**); 6.55–6.49 (superimposed dd, H–C(5) of **7a** and **7b**); 6.39–6.13 (superimposed ddd, H–C(6) of **7a** and **7b**); 4.00, 3.96, 3.95, 3.93, 3.92, 3.68, 3.58 (7s, 8 OMe); 3.16–3.04 (superimposed dd, H–C(7) of **7a** and **7b**); 2.71–2.61 (superimposed ddd, H–C(7) of **7a** and **7b**). EI-MS: 340 (100, M^+), 312 (69), 297 (36), 281 (48), 254 (37), 238 (14).

1.1.5. *Formation of the Tropylium Salt 8 (cf. [72])*. To a suspension of trimethyloxonium tetrafluoroborate 0.55 g, 3.72 mmol) in dry CH_2Cl_2 (20 ml) was added, dropwise under stirring and under N_2 , a soln. of **7a**/**7b** (1.10 g, 2.23 mmol) in CH_2Cl_2 (15 ml). The orange-colored mixture was stirred for additional 1.5 h at r.t. and then heated 2 h under reflux. During this time, a yellow precipitate had separated from the mixture. After cooling to –20°, the precipitate was filtered off through a *Schlenk* tube under a slight pressure of N_2 . The product was washed with Et_2O and then dried in a stream of N_2 and afterwards in high vacuum. The salt **8** (1.00 g, 80 %) was obtained in small, yellow, moisture-sensitive crystals. M.p. 213–216° (dec.). IR (KBr): 2940m, 2870w, 1595s, 1540s, 1490s, 1475s, 1470s, 1405m, 1378m, 1350m, 1333s, 1295s, 1085s, 1055s. $^1\text{H-NMR}$ (400 MHz, (D_6)DMSO): 7.26 (d, $J = 12.9$, H–C(12)); 7.09 (s, H–C(8)); 6.85 (s, H–C(4)); 6.78 (d, $J = 12.7$, H–C(11)); 6.63 (dd, $^3J = 9.6$, $^4J = 1.6$, H–C(5)); 6.28 (ddd, $^3J = 9.5$, 7.9, 6.1, H–C(6)); 3.89, 3.85, 3.81, 3.58, 3.16 (5s, 5 MeO); 3.34 (dd, $^2J = 12.3$, $^3J = 8.0$, H–C(7)); 2.40 (ddd, $^2J = 12.3$, $^3J = 6.0$, $^4J = 1.9$, H–C(7)). EI-MS: 354 (100 [$M - \text{HBF}_4$] $^+$), 340 (76), 339 (53), 312 (51), 297 (28), 281 (40), 254 (34). Anal. calc. for $\text{C}_{21}\text{H}_{23}\text{BF}_4\text{O}_5$ (422.22): C 57.04, H 5.25; found: C 56.65, H 5.31.

1.1.6. *Formation of 9*. Salt **8** (0.705 g, 1.60 mmol) was suspended in dry ice-cooled CHCl_3 (250 ml), and a soln. of Me_3N (2.5 g) in CHCl_3 (15 ml) was added dropwise within 20 min under N_2 . The deep-yellow color of the suspension changed to orange. After 30 min stirring at 0°, the formed trimethylammonium tetrafluoroborate was removed by filtration through a *Schlenk* tube under a slight pressure of N_2 . The orange filtrate was distilled and the residue crystallized from hexane/acetone: **9** crystallized in yellow crystals (0.41 g, 73 %). M.p. 146–148°²¹⁾. UV/VIS (99 % EtOH): λ_{max} 351 (3.73), 271 (4.40), 211 (4.42); λ_{min} 335 (3.84), 243 (4.36). UV/VIS (cyclohexane): λ_{max} 351 (3.66), 271 (4.37), 217 (4.33); λ_{min} 332 (3.75), 244 (4.28). UV/VIS (conc. H_2SO_4): λ_{max} 366 (sh, 4.07), 348 (sh, 4.13), 255 (4.58), 200 (4.33); λ_{min} 294 (4.01), 218 (4.18). IR (CHCl_3): 3007s, 2965m, 2940m, 2835w, 1588s, 1490s, 1465m, 1455m, 1417m, 1380w, 1335s, 1320s, 1192m, 1157m, 1138s, 1100s. $^1\text{H-NMR}$ (400 MHz, CDCl_3): 6.65 (d, $J = 11.7$, H–C(5)); 6.52 (s, H–C(4)); 6.25 (dd, $^3J = 11.7$, $^3J = 6.5$, H–C(6)); 5.79 (d, $J = 7.6$, H–C(12)); 5.75 (d, $J = 7.6$, H–C(11)); 5.60 (d, $J = 6.3$, H–C(7)); 5.50 (s, H–C(8)); 3.90, 3.87, 3.73, 3.71 (4s, ratio 1:1:2:1, 15 H, 5 MeO). $^1\text{H-NMR}$ (400 MHz, C_6D_6): 6.65 (d, $J = 11.5$, H–C(5)); 6.38 (s, H–C(4)); 6.26 (dd, $^3J = 11.7$, $^3J = 6.4$, H–C(6)); 5.95 (d, $J = 7.4$, H–C(12)); 5.61 (d, $J = 6.6$, H–C(7)); 5.50 (d, $J = 7.4$, H–C(11)); 5.33 (s, H–C(8)); 3.84

²¹⁾ The yellow crystals of **9** were in a first run contaminated with some orange-red crystals (m.p. 132–134°). The X-ray crystal-structure analysis (see 4.1) of the yellow crystals showed that they contained a certain amount of solvent molecules. A $^1\text{H-NMR}$ spectrum (CDCl_3) of the orange-red crystals revealed that they consist of 96 % of **9** and of 4 % of **7a**. When CDCl_3 solns. of pure **9** were stored over a longer period (4 weeks) at r.t., they also showed the presence of **7a**, i.e., **7a** seems to be the controlled product of ether cleavage of **9**.

(s, MeO–C(2)); 3.69 (s, MeO–C(1)); 3.33 (s, MeO–C(3)); 3.21 (s, MeO–C(9)); 3.16 (s, MeO–C(10)). ¹H-NOE (400 MHz, C₆D₆): 3.16 (MeO–C(10))→5.50 (s, H–C(11)); 3.21 (MeO–C(9))→5.33 (s, H–C(8)); 3.33 (MeO–C(3))→6.38 (m, H–C(4)); 3.69 (MeO–C(1))→3.84 (w, MeO–C(2)); 3.84 (MeO–C(2))→3.69 (w, MeO–C(1)). ¹³C-NMR (50 MHz, CDCl₃): 154.45 (s); 154.26 (s); 152.25 (s); 150.67 (s); 143.92 (s); 136.48 (s); 134.68 (s); 131.86 (d); 128.70 (s); 127.92 (d); 127.75 (d); 125.19 (d); 125.07 (s); 107.37 (d); 105.05 (d); 104.35 (d); 61.12 (q); 61.08 (q); 56.01 (q); 55.86 (q); 55.07 (q). EI-MS: 354 (100, M⁺), 339 (45), 311 (25), 295 (13), 281 (8). Anal. calc. for C₂₁H₂₂O₅ (354.41): C 71.17, H 6.26; found: C 71.00, H 6.52.

1.1.6.1. *Separation of 9 into Its Antipodes (7aP)- and (7aM)-9*. Column temp. 0–5°; mobile phase; hexane/i-PrOH 85:15; flow rate: 0.5 ml/min; detector wavelength: 350 nm; *t*_R ((7aP)-9) 21.6 min, *t*_R ((7aM)-9) 29.8 min. CD (99% EtOH, qual.) of (7aP)-9 (cf. Fig. 5): 369 (–0.31), 305 (–15), 286 (0.0), 264 (0.87), 229 (1.00). CD (99% EtOH, qual.) of (7aM)-9 (cf. Fig. 5): 368 (0.30), 302 (0.21), 285 (0.0), 264 (–0.85), 230 (–1.00).

1.2. 1.2.3.9.10-Pentamethoxy-4-methylbenzo[a]heptalene (18). 1.2.1. 4-Formylcolchicine (17; cf. [48]). Colchicine (2; 6.62 g, 15.3 mmol), in dry CH₂Cl₂ (60 ml), was reacted with dichloromethyl methyl ether (16.5 ml, 186 mmol) and SnCl₄ (5.3 ml, 45 mmol) under ice-cooling. Evolution of HCl took place and a red, highly viscous oil separated. Stirring was continued for 30 min at 0° and then for 15 h at r.t. Ice-water and CH₂Cl₂ were added. After dissolution of the precipitates, the CH₂Cl₂ phase was separated, washed with 0.5N NaOH and H₂O. The residue of the CH₂Cl₂ phase was filtered through a column of silica gel (AcOEt/EtOH 7:3): 17 was obtained as a pale-yellow foam (5.88 g, 90%). A probe was crystallized from acetone. M.p. 247° ([48]: 250°). [α]_D = +6.2 (c = 0.43, CHCl₃). UV/VIS (99% EtOH): λ_{max} 344 (4.17), 237 (4.46); λ_{min} 287 (3.49). IR (CHCl₃): 3440m, 3270 (br.), 3005s, 2940m, 1680s (CHO), 1617s, 1590s, 1565s, 1505s, 1470s, 1420m, 1348m, 1325s, 1257s, 1107s, 1075m, 1036s, 993s. ¹H-NMR (400 MHz, CDCl₃): 10.45 (s, CHO); 7.77 (d, *J* = 6.4 NH); 7.53 (s, H–C(8)); 7.22 (d, *J* = 10.7, H–C(12)); 6.84 (d, *J* = 10.9, H–C(11)); 4.52 (quint.-like *m*, recognizable (*J* = 6.5, 12.4, H–C(7))); 4.05, 4.01, 3.97, 3.68 (4s, 4 MeO); 2.30 (sept.-like *m*, recognizable *J* = 6.4, *J* = 13.0, H_A–C(6)); 2.00 (s, NHCOCH₃); 2.05–1.79 (*m*, H_B–C(6), 2 H–C(5)). EI-MS: 427 (49, M⁺), 399 (8, [M – CO]⁺), 384 (17), 340 (100). Anal. calc. for C₂₃H₂₅NO₇ (427.26): C 64.63, H 5.90, N 3.28; found: C 64.43, H 6.11, N 3.09.

1.2.2. 4-Methylcolchicine (13). Compound 17 (5.13 g, 12.0 mmol) was dissolved in CF₃COOH (12 ml, 157 mmol), and Et₃SiH (12 ml, 75 mmol) was added. The mixture was stirred for 15 h at 50° and under N₂. The cooled mixture was neutralized with sat. NaHCO₃ soln. and extracted with CH₂Cl₂ (3 × 100 ml). The combined CH₂Cl₂ extracts were washed with sat. NaCl soln. H₂O, and then dried (MgSO₄). The residue of the CH₂Cl₂ extracts was chromatographed on silica gel (AcOEt/EtOH 7:3) to give 13 as a yellow foam (3.45 g, 70%). UV/VIS (99% EtOH): λ_{max} 345 (4.13), 232 (4.41); λ_{min} 286 (3.55). CD (99% EtOH, qual.): 335 (–0.56), 262 (–0.81), 247 (0.00), 231 (1.00). IR (CHCl₃): 3442m, 3273 (br.), 3000s, 2940m, 2841m, 1675s, 1615s, 1588s, 1557s, 1504s, 1462s, 1411s, 1348s, 1249s, 1102s. ¹H-NMR (300 MHz, CDCl₃): 8.10 (d, *J* = 6.2, NH); 7.61 (s, H–C(8)); 7.33 (d, *J* = 10.7, H–C(12)); 6.88 (d, *J* = 10.9, H–C(11)); 4.58 (quint.-like *m*, recognizable *J* = 6.2, 11.8, H–C(7)); 4.01, 3.96, 3.88, 3.59 (4s, 4 MeO); 2.86–2.80 (*m*, aliphat. H); 2.19 (s, Me–C(4)); 1.97 (s, NHCOMe), 2.20–1.70 (*m*, 3 aliphat. H). ¹³C-NMR²²⁾ (50 MHz, CDCl₃): 179.54 (s, C(9)); 170.20 (s, NHCOCH₃); 164.04 (s, C(10)); 152.46 (s, C(3)); 152.21 (s, C(7a)); 148.87 (s, C(1)); 145.45 (s, C(2)); 137.10 (s, 12a); 135.58 (d, C(12)); 132.43 (s, C(4a)); 130.11 (d, C(8)); 129.07 (s, C(12b)); 123.96 (d, C(11)); 61.39, 61.17, 60.69, 56.39 (4q, 4 MeO); 52.74 (d, C(7)); 35.18 (t, C(6)); 25.07 (t, C(5)); 22.71 (q, NHCOMe); 11.46 (q, Me–C(4)). EI-MS: 413 (100, M⁺), 385 (44), 370 (99), 326 (88), 311 (49), 295 (42). Anal. calc. for C₂₃H₂₇NO₆ (413.48): C 66.81, H 6.58, N 3.39; found: C 66.53, H 6.71, N 3.20.

1.2.3. 4-Methylde-N-acetylcolchicine (19). Colchicine 13 (3.43 g, 8.30 mmol) was dissolved in 20% aq. H₂SO₄ (100 ml) and heated to reflux under N₂ for 24 h. The still hot soln. was neutralized with solid Na₂CO₃ and the precipitating yellow mass filtered off, washed with ice-cooled H₂O and crystallized from EtOH: 19 was obtained in brownish needles (1.75 g, 59%). It was sensitive to air. M.p. 179–180°. UV/VIS (99% EtOH): λ_{max} 350 (4.21), 240 (4.45); λ_{min} 289 (3.62). IR (CHCl₃): 3514 (br.), 3006s, 2939s, 2837m, 1614s, 1550s, 1451s, 1407s, 1346s, 1278s, 1104s, 1080s, 1046s, 1009m. ¹H-NMR (300 MHz, CDCl₃): 8.08 (s, H–C(8)); 7.50 (d, *J* = 11.6, H–C(12)); 7.31 (d, *J* = 11.9, H–C(11)); 3.93, 3.88, 3.60 (3s, 3 MeO), 3.74 (*m*, H–C(7)); 2.74 (*m*, 1 aliphat. H); 2.23 (s, Me), 2.05 (*m*, 2 aliphat. H), 1.68 (*m*, 1 aliphat. H). NH₂ and OH signals were not detected.

1.2.4. *Formation of the Quaternary Ammonium Salt 20*. Compound 19 (1.75 g, 4.90 mmol) was dissolved in 2N NaOH (160 ml) and stirred together with MeI (90 ml) as a two-phase system under N₂ for 20 h at 50°. The excess of MeI was separated and the aq. phase extracted with CHCl₃ (5 × 70 ml). The CHCl₃ phases were dried (MgSO₄) and CHCl₃ distilled off. The residual oil was crystallized with hexane/Et₂O. The salt 20 formed small, yellow-brownish crystals (1.70 g, 66%). M.p. 205–208°. The salt was sensitive to air, light, and moisture. It was degraded without further characterization.

²²⁾ Assignment of the ¹³C resonance lines according to published data of 'colchicinoids' [73] [74].

1.2.5 *Hofmann Degradation of 20*. Salt **20** (1.70 g, 3.20 mmol) was dissolved in 8 ml 2N NaOH and ethyleneglycol (16 ml). A soln. of KOH (90 g) in H₂O (32 ml) and ethyleneglycol (16 ml) was added under N₂ and the mixture was heated for 30 min at 185°. Me₃N evolved and a yellow-colored mass precipitated. The mixture was acidified under cooling with 50% aq. H₂SO₄. The following workup was the same as for **5b** (see 1.1.3). The brown oil of **21** was solidified with hexane and recrystallized from acetone. 4-Methyl-5,6-didehydrode-7-acetamidocolchicine (**21**) was obtained on brown crystals (0.48 g, 44%). M.p. 159–161°. UV (99% EtOH): $\lambda_{\max}$ 350 (4.21), 242 (4.41); $\lambda_{\min}$ 304 (3.93). IR (CHCl₃): 3202 (br.), 3005s, 2964s, 2939s, 1658m, 1616s, 1549s, 1479s, 1465s, 1418s, 1401s, 1379s, 1333s, 1296s, 1284s, 1263s, 1174m, 1105s. ¹H-NMR (300 MHz, CDCl₃): 7.60 (d, *J* = 12.1, H-C(12)); 7.41 (s, H-C(8)); 7.17 (d, *J* = 12.2, H-C(11)); 6.57 (dd, ³*J* = 9.8, ⁴*J* = 1.7, H-C(5)); 6.28 (ddd, ³*J* = 9.9, 7.6, 6.6, H-C(6)); 3.99, 3.91, 3.56 (3s, 3 MeO); 3.13 (dd, ²*J* = 12.2, ³*J* = 7.7, H-C(7)); 2.76 (ddd, ²*J* = 12.1, ³*J* = 5.7, ⁴*J* = 1.8, H-C(7)); 2.27 (s).

Signals of the 6,7-didehydro isomer of **21** could not be detected in the ¹H-NMR spectrum.

1.2.6 *Mixture of 4-Methyl-5,6-didehydrode-7-acetamidocolchicine (22a) and -isocolchicine (22b)*. The procedure was the same as described for **7a/7b**. Colchicine **21** (0.48 g, 1.40 mmol), in ice-cooled MeOH (15 ml), was reacted with CH₂N₂/Et₂O, liberated from *N*-methyl-*p*-toluenesulfonylnitrosamide (2.87 g, 13.4 mmol) with KOH in EtOH/H₂O. The 46:54 mixture **22a/22b** was purified by CC (Al₂O₃/N, act. III, CH₂Cl₂) to give the mixture as a yellow foam (0.31 g, 62%). ¹H-NMR (300 MHz, CDCl₃): 7.39 (d, *J* = 12.9, H-C(12) of **22b**); 7.27 (s, H-C(8) of **22a**); 7.18 (d, *J* = 10.7, H-C(12) of **22a**); 7.00 (d, *J* = 13.0, H-C(11) of **22b**); 6.82 (s, H-C(8) of **22b**); 6.67 (d, *J* = 11.06, H-C(11) of **22a**); 6.60 (dd, ³*J* = 9.87, ⁴*J* = 1.78) and 6.51 (dd, ³*J* = 9.9, ⁴*J* = 1.6, each 1 H, H-C(5) of **22a** and **22b**); 6.40–6.17 (superimposed ddd, H-C(6) of **22a** and **22b**); 4.00, 3.98, 3.97, 3.95, 3.90, 3.89, 3.62, 3.50 (8s, 8 MeO); 3.10–2.97 (superimposed dd, H-C(7) of **22a** and **22b**).

1.2.7 *Formation of the Tropylium Salt 23*. The mixture **22a/22b** (0.24 g, 0.68 mmol) was reacted in dry CH₂Cl₂ (5 ml) with a suspension of Me₃O⁺BF₄[–] (0.112 g, 0.82 mmol) in dry CH₂Cl₂ (5 ml) under N₂. The mixture was stirred for 1.5 h at r.t. and heated at reflux for additional 1.5 h. Et₂O (10 ml) was added and the mixture kept overnight at –20°. The salt was filtered and dried as described for **8** (see 1.1.5). Salt **23** was obtained in yellow-to-brownish crystals (0.23 g, 57%) which were very sensitive to moisture. They were subjected to deprotonation.

1.2.8 *Deprotonation of 23 to 18*. The salt **23** (0.23 g, 0.50 mmol) was dissolved in dry CHCl₃ (90 ml), and, under ice-cooling and N₂, treated with a soln. of Me₃N in CHCl₃ (see 1.1.6). The heptalene **18** was purified over a short column (Al₂O₃ 90, CH₂Cl₂) and crystallized from hexane/AcOEt. It was obtained in large, yellow crystals (0.125 g, 68%). M.p. 124°. UV (99% EtOH): $\lambda_{\max}$ 348 (sh, 3.85), 302 (sh, 4.22), 265 (4.50); $\lambda_{\min}$ 241 (4.26). IR (CHCl₃): 3007s, 2982s, 2937s, 2834m, 1586s, 1415s, 1385s, 1334s, 1288m, 1261s, 1156s, 1104s, 1043s, 1014s. ¹H-NMR (300 MHz, C₆D₆): 6.91 (d, *J* = 12.0, H-C(5)); 6.32 (dd, ³*J* = 12.0, ³*J* = 6.2, H-C(6)); 5.99 (d, *J* = 7.3, H-C(12)); 5.65 (dd, *J* = 6.0, 1.3, H-C(7)); 5.52 (d, *J* = 7.4, H-C(11)); 5.38 (d, *J* = 1.3, H-C(8)); 3.92, 3.80, 3.76 (3s, 3 MeO); 3.33 (s, MeO-C(9)); 3.28 (s, MeO-C(10)); 2.34 (s, Me). EI-MS: 368 (100, *M*⁺), 353 (55), 325 (14), 295 (9), 279 (7), 224 (5).

1.2.8.1 *Separation of 18 into the Antipodes (7aP)-18 and (7aM)-18*. Column temp.: r.t.; mobile phase: hexane/*i*-PrOH 85:15; flow rate: 0.5 ml/min; detection wavelength: 350 nm; *t*_R((7aP)-**18**) 13.6 min; *t*_R((7aM)-**18**) 16.5 min. CD (99% EtOH, qual.) of (7aP)-**18**: 357 (–0.31), 296 (0.0), 263 (0.88), 227 (1.00); CD (99% EtOH, qual.) of (7aM)-**18**: 352 (0.41), 296 (0.0), 264 (–0.94), 226 (–1.00).

1.3 *4-Ethyl-1,2,3,9,10-pentamethoxybenzo[a]heptalene (34)*. 1.3.1. 4-[(*R*)-1-Hydroxyethyl]- and 4-[(*S*)-1-Hydroxyethyl]colchicine (**27a** and **27b** resp.). Preparation of 1M [Zr(OBn)₃Cl] in Et₂O (cf. [58a]): The content of a 100-ml flask of commercial [Zr(OBn)₄] (Aldrich®, 80% in BuOH) was distilled in a 'Kugelrohr' to give, after a forerun of BuOH, a brownish viscous substance (at ca. 250°/10^{–4} Torr). The viscous oil (76.3 g, 0.2 mol) was dissolved in dry Et₂O (200 ml) under Ar. ZrCl₄ (15.6 g, 0.067 mol) was added portionwise at 0°. Stirring was continued for 20 h at r.t. The brown soln. was adjusted to 200 ml, so that the prepared solution was 1M with respect to [Zr(OBu)₃Cl]. A portion of this soln. (16 ml, 16 mmol) was placed in a flame-dried apparatus and diluted with dry Et₂O (50 ml). At 0°, a 1.6M soln. of MeLi in Et₂O (10 ml, 16 mmol) was added dropwise, whereby the content of the apparatus turned turbid. After 60 min stirring at 0°, a soln. of **17** (2.08 g, 4.9 mmol) in CH₂Cl₂ (20 ml) was added within 20 min and the mixture stirred for 15 h at 0 to 20°. The pink-colored soln. was added to ice and then extracted with CH₂Cl₂. After drying (MgSO₄), the residue of the CH₂Cl₂ extracts was subjected to CC (silica gel, AcOEt/EtOH 7:3) to yield recovered **17** (0.16 g, 8%) and a 9:1 mixture **27a/27b** (1.55 g, 72%; ¹H-NMR) as a beige powder. Pure **27a** was obtained by recrystallization first from MeOH and then from acetone. M.p. 244–245°. [α]_D = +41.4 (c = 0.125, CHCl₃). UV (99% EtOH): $\lambda_{\max}$ 343 (4.22), 234 (4.50); $\lambda_{\min}$ 283 (3.70). IR (CHCl₃): 3442m, 3267(br.), 3005s, 2940s, 2842m, 1673s, 1616s, 1589s, 1562s, 1502s, 1463s, 1445s, 1418s, 1369s, 1347s, 1331s, 1289s, 1257s, 1157s, 1136s, 1118s, 1082s, 1056s, 1037s, 1007s. ¹H-NMR (300 MHz, CDCl₃) of crystallized **27a**: 7.68 (d, *J* = 6.7,

NH); 7.52 (s, H–C(8)); 7.26 (d, $J = 10.7$, H–C(12)); 6.87 (d, $J = 10.9$, H–C(11)); 5.20 (*quint.*-like *m*, H–C(4)); 4.58 (*quint.*-like *m*, recognizable $J = 6.1$, 12.1, H–C(7)); 4.06, 4.02, 3.93, 3.60 (4s, 4 MeO); 3.02 (*m*, OH); 2.16 (*m*, 2 aliphatic H); 2.00 (s, NHCOMe); 1.85 (*m*, 2 aliphatic H); 1.55 (d, $J = 6.7$, MeCHOH). $^1\text{H-NMR}$ (300 MHz, CDCl_3) of **27b** (mixture with **27a**): 7.69 (d, $J = 6.5$, NH²³); 7.54 (s, H–C(8)); 7.34 (d, $J = 10.8$, H–C(12)); 6.85 (d, $J = 10.8$, H–C(11)); 5.18 (*quint.*-like *m*, H–C(4)); 4.58 (*quint.*-like *m*, H–C(7)); 4.01, 3.96, 3.94, 3.65 (4s, 4 MeO); 3.02 (*m*, OH); 2.17 (*m*, 2 aliphatic H); 1.97 (s, NHCOMe); 1.87 (*m*, 2 aliphatic H); 1.24 (d, $J = 7.0$, MeCHOH). EI-MS: 443 (83, M^+), 400 (11, $[M - \text{COMe}]^+$), 382 (14), 351 (15), 338 (100), 323 (37), 307 (14), 91 (88).

1.3.2. *4-Ethylcolchicine* (**28**). The 9:1 mixture **27a/27b** (1.40 g, 3.20 mmol) was stirred for 15 h at 50° under N_2 in a mixture of CF_3COOH (10 ml) and Et_3SiH (3 ml, 19 mmol). The orange soln. was neutralized with sat. aq. NaHCO_3 soln. and then extracted with CH_2Cl_2 . The CH_2Cl_2 phases were washed with sat. NaCl soln., then with H_2O and, after drying (MgSO_4), evaporated. Excess Et_3SiH was removed in high vacuum and the residue subjected to CC (silica gel, AcOEt/EtOH 7:3): **28** was obtained as a yellowish foam (0.865 g, 64%). $[\alpha]_D = -104.8$ ($c = 0.25$, CHCl_3). UV (99% EtOH): λ_{max} 344 (4.22), 232 (4.53); λ_{min} 286 (3.67). IR (CHCl_3): 3442*m*, 3264 (br.), 3005*s*, 2971*s*, 2938*m*, 1677*s*, 1615*s*, 1589*s*, 1556*s*, 1502*s*, 1462*s*, 1416*s*, 1369*m*, 1348*s*, 1256*s*, 1105*s*, 1050*s*, 1030*s*. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.64 (br. *s*, NH); 7.55 (s, H–C(8)); 7.31 (d, $J = 10.7$, H–C(12)); 6.87 (d, $J = 11.0$, H–C(11)); 4.64 (*quint.*-like *m*, recognizable $J = 6.2$, $J = 11.8$, H–C(7)); 4.01, 3.96, 3.93, 3.60 (4s, 4 MeO); 2.85 (*m*, 1 aliphatic H); 2.65 (*oct.*-like *m*, recognizable $^3J = 7.7$, $^2J = 15.3$, MeCH_2); 2.28–2.13 (*m*, 2 aliphatic H); 1.99 (s, NHCOMe); 1.87 (*m*, 1 aliphatic H); 1.14 (t, $J = 7.5$, MeCH_2). EI-MS: 427 (100, M^+), 399 (62, $[M - \text{CO}]^+$), 384 (19), 356 (13), 340 (97), 325 (41), 311 (54), 297 (20), 282 (17).

1.3.3. *4-Ethylde-N-acetylcolchicine* (**29**). Colchicine **28** (0.865 g, 2.02 mmol) was dissolved in a mixture of H_2O (15 ml) and conc. H_2SO_4 (4 ml) and heated at reflux for 15 h under N_2 . The usual workup (see 1.2.2) gave **29** which was dissolved in hot EtOH for crystallization. However, a gel formed in this solvent. Therefore, it was recrystallized from H_2O . The microcrystalline compound was isolated by centrifugation. In this way, **29** was obtained in fine, yellow-to-brown crystals (0.33 g, 44%). M.p. 205–208°. UV/VIS (99% EtOH): λ_{max} 351 (4.22), 243 (4.50); λ_{min} 289 (3.64). IR (CHCl_3): 3400(br.), 3005*s*, 2968*s*, 2938*s*, 2875*s*, 2847*m*, 1615*s*, 1549*s*, 1451*s*, 1409*s*, 1372*s*, 1345*s*, 1262*s*, 1106*s*, 1032*s*. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 8.06 (s, H–C(8)); 7.48 (d, $J = 11.7$, H–C(12)); 7.30 (d, $J = 11.7$, H–C(11)); 3.93 (s, 2 MeO); 3.79 (*q*-like *m*, recognizable $J = 6.5$, 11.2, H–C(7)); 3.60 (s, MeO); 2.79–2.57 (2 superimposed *m*, MeCH_2 , 1 aliphatic H); 2.32–2.19 (*m*, 1 aliphatic H); 2.05 (*m*, 1 aliphatic H); 1.70 (*m*, 1 aliphatic H); 1.14 (t, $J = 7.5$, MeCH_2); NH_2 and OH signals were not detected. $^1\text{H-NMR}$ (300 MHz, C_6D_6): 8.17 (s, H–C(8)); 7.22 (d, $J = 11.6$, H–C(12)); 7.18 (d, $J = 11.7$, H–C(11)); 3.78, 3.74, 3.37 (3s, 3 MeO); 3.38 (*q*-like *m*, recognizable $J = 5.9$, 11.8, H–C(7)); 2.68 (*quint.*-like *m*, recognizable $J = 7.5$, 13.2, diastere. H of MeCH_2); 2.53 (*quint.*-like *m*, recognizable $J = 7.6$, 13.4, diastere. H of MeCH_2); 2.37 (*m*, 1 aliphatic H); 1.94–1.84 (*m*, 2 aliphatic H); 1.26–1.15 (*m*, 1 aliphatic H); 1.11 (t, $J = 7.5$, MeCH_2); NH_2 and OH signals were not detected. CI-MS: 372 (100, $[M + 1]^+$), 368 (25), 358 (15), 344 (7).

1.3.4. *Quaternization of 29* was performed in the usual way with **29** (0.32 g, 0.86 mmol) and MeI (15 ml) in 2*N* NaOH at 50° under N_2 . The usual workup gave the iodide **30** as a foam which crystallized, when a small amount of Et_2O was added (0.264 g, 57%).

1.3.5. *4-Ethyl-5,6-didehydrode-7-acetamidocolchicine* (**31**). The Hofmann degradation of **29** (0.26 g, 0.48 mmol) was performed in the usual manner in 2*N* NaOH (5 ml), H_2O (6 ml), ethyleneglycol (in total 6 ml) in the presence of KOH (12.1 g) at 185° during 30 min. The usual workup gave **31** as a brown oil which solidified in the presence of hexane. Recrystallization from acetone gave **31** in yellow-brown crystals (0.042 g, 25%). M.p. 177–180°. UV/VIS (99% EtOH): λ_{max} 351 (4.21), 244 (4.51); λ_{min} 303 (3.89). IR (CHCl_3): 3007*m*, 2966*m*, 2937*m*, 1616*s*, 1576*s*, 1550*s*, 1522*s*, 1506*s*, 1478*s*, 1457*s*, 1419*s*, 1402*s*, 1379*s*, 1333*s*, 1285*s*, 1262*s*, 1107*s*, 1032*s*, 951*m*. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.59 (d, $J = 12.1$, H–C(12)); 7.41 (s, H–C(8)); 7.17 (d, $J = 12.1$, H–C(11)); 6.62, (dd, $^3J = 9.8$, $^4J = 1.8$, H–C(5)); 6.3 (ddd, $^3J = 9.8$, 7.6, 6.5, H–C(6)); 3.99, 3.95, 3.55 (3s, 3 MeO); 3.12 (dd, $^2J = 12.2$, $^3J = 7.7$, H–C(7)); 2.83–2.73 (ddd, recognizable $^2J = 13.0$, $^3J = 6.5$, $^4J = 1.8$, superimposed with *q*, $J = 7.4$, H–C(7), MeCH_2); 1.14 (t, $J = 7.5$, MeCH_2). EI-MS: 354 (100, M^+), 325 (34), 297 (39), 265 (12), 91 (41). Anal. calc. for $\text{C}_{21}\text{H}_{22}\text{O}_5$ (354.44): C 71.17, H 6.26; found: C 70.88, H 6.52.

1.3.6. *Mixture of 4-Ethyl-5,6-didehydrode-7-acetamidocolchicine* (**32a**) and **32b**. Methylation of **31** (0.040 g, 0.11 mmol) in ice-cooled MeOH (5 ml) with CH_3N_2 in Et_2O was performed in the usual manner (see 1.2.6). CC (Al_2O_3 90, CH_2Cl_2) of the 1:1 mixture **32a/32b** gave the purified mixture as a yellowish foam (0.035 g, 84%). $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.40 (d, $J = 13.0$, H–C(12)); of **32b**): 7.30 (s, H–C(8) of **32a**); 7.19 (d, $J = 10.7$, H–C(12) of **32a**); 7.02 (d, $J = 12.9$, H–C(11) of **32b**); 6.84 (s, H–C(8) of **32b**); 6.69 (d, $J = 10.8$, H–C(11) of **32a**);

²³) The NH signal of **27a** appeared in the $^1\text{H-NMR}$ of the 9:1 mixture at 8.18 ppm.

6.67 (*dd*, $^3J = 9.8$, $^4J = 1.7$) and 6.58 (*dd*, $^3J = 10.0$, $^4J = 1.7$, each 1 H, H–C(5) of **32a** and **32b**); 6.57–6.18 (superimposed *ddd*, H–C(6) of **32a** and **32b**); 4.01, 3.99, 3.98, 3.96, 3.95, 3.94, 3.62, 3.50 (8s, 8 MeO); 3.08–2.97 (superimposed *dd*, H–C(7) of **32a** and **32b**); 2.74 (superimposed *ddd*, H–C(7) of **32a** and **32b**, recognizable *oct.*-like *m*, $J = 7.5$, MeCH₂ of **32a** and **32b**); 1.27 (*t*, $J = 7.2$), 1.16 (*quint.*-like *m*, recognizable $J = 7.5$), CH₂CH₃ of **32a** and **32b**).

1.3.7. *Formation of the Tropylium Salt 33.* The reaction was performed with the 1:1 mixture **32a/32b** (0.035 g, 0.095 mmol) and Me₃O⁺BF₄[–] (0.016 g, 0.11 mmol) in dry CH₂Cl₂ (7 ml in total). After 1 h heating at reflux, CH₂Cl₂ was distilled off and the residue directly deprotonated.

1.3.8. *Formation of 4-Ethyl-1,2,3,9,10-pentamethoxybenzo[*a*]heptalene (34).* The residue from 1.3.7 was dissolved in dry CHCl₃ (15 ml) and treated with Me₃N in CHCl₃. The usual workup gave **34** which was purified by chromatography (Al₂O₃ 90, CH₂Cl₂) on a short column. Heptalene **34** was crystallized from MeOH and formed large, yellow crystals (0.016 g, 70%). M.p. 128–129°. UV/VIS (99% EtOH): $\lambda_{\max}$ 348 (sh, 3.70), 305 (sh, 4.16), 266 (4.35); $\lambda_{\min}$ 240 (4.25). IR (CHCl₃): 3004*m*, 2934*s*, 2855*m*, 1586*s*, 1462*s*, 1452*m*, 1415*s*, 1396*m*, 1333*m*, 1262*m*, 1156*m*, 1108*m*, 1108*s*, 1034*s*. ¹H-NMR (400 MHz, C₆D₆): 7.01 (*d*, $J = 12.0$, H–C(5)); 6.32 (*dd*, $^3J = 12.0$, $^3J = 6.0$, H–C(6)); 6.00 (*d*, $J = 7.3$, H–C(12)); 5.65 (*d*, $J = 5.9$, H–C(7)); 5.51 (*d*, $J = 7.4$, H–C(11)); 5.38 (*s*, H–C(8)); 3.78, 3.73, 3.66 (3*s*, arom. MeO); 3.21 (*s*, MeO–C(9)), 3.15 (*s*, MeO–C(10)); 2.89–2.72 (2 *sext.*-like *m*, $^3J = 7.4$, $^2J = 13.1$, diaster. MeCH₂); 1.17 (*t*, $J = 7.5$, MeCH₂). ¹H-DR (400 MHz, C₆D₆): 1.17 (*t*, CH₂CH₃)→2.86 (*A* of *AB* of MeCH₂, $J_{AB} = 13.2$); 2.75 (*B* of *AB* of MeCH₂, $J_{AB} = 13.1$). EI-MS: 382 (100, *M*⁺), 367 (18), 339 (6), 152 (9), 109 (9).

1.3.8.1. *Separation of 34 in the Antipodes (7aP)-34 and (7aM)-34.* Column temp.: r.t., mobile phase: hexane/*i*-PrOH 95:5; flow rate: 0.5 ml/min; detector wavelength: 345 nm; *t*_R((7aP)-**34**) 15.0 min, *t*_R((7aM)-**34**) 18.1 min. CD (99% EtOH, qual.) of (7aP)-**34**: 354 (–0.31), 290 (0.0), 263 (0.79), 224 (1.00). CD (99% EtOH qual.) of (7aM)-**34**: 359 (0.31), 290 (0.0) 264 (–0.77), 225 (–1.00).

2. *Biomimetic Synthesis of 7-Oxode-7-acetamidocolchicine (37) (cf. [60]).* – To a well stirred soln. of **3** (3.00 g, 8.74 mmol) in CH₂Cl₂/DMF 3:1 (90 ml) was added 4-formyl-1-methylpyridinium benzenesulfonate (2.99 g, 10.7 mmol) at r.t. under N₂. The color of the soln. changed from yellow to brown. After 2 h stirring at r.t., DBU (3 ml, 20 mmol) was added dropwise. The color of the mixture changed thereby from brown to red. After 10 min stirring, a sat. aq. oxalic-acid solution (100 ml) was added for hydrolysis. The two-phase mixture was stirred for 17 h at r.t. to complete hydrolysis. The org. layer was separated, and the aq. phase was extracted with CH₂Cl₂ (2 ×). The combined org. phases were washed with sat. NaCl soln. and dried (MgSO₄). The oily residue of the org. phases was solidified with Et₂O/AcOEt and recrystallized from MeOH to give **37** in yellow crystals (2.37 g, 79%). M.p. 154–155.5° ([59]: 154°). UV (99% EtOH): $\lambda_{\max}$ 356 (4.22), 247 (4.44); $\lambda_{\min}$ 295 (3.60). IR (CHCl₃): 3200(*br.*), 3005*m*, 2985*m*, 2970*m*, 1705*s*, 1622*s*, 1598*s*, 1555*s*, 1493*s*, 1450*s*, 1430*m*, 1405*m*, 1350*s*, 1330*m*, 1283*m*, 1240*m*, 1140*m*, 1105*m*. ¹H-NMR (400 MHz, CDCl₃): 7.57 (*d*, $J = 12.1$, H–C(12)); 7.39 (*d*, $J = 12.1$, H–C(11)); 7.19 (*s*, H–C(8)); 6.59 (*s*, H–C(4)); 3.91, 3.89, 3.59 (3*s*, 3 MeO); 3.14 (*td*, $J = 13.6$, 5.6, 1 aliphatic H); 2.96 (*ddd*, $J = 2.5$, 5.3, 16.5, 1 aliphatic H); 2.93 (*ddd*, $J = 5.5$, 13.6, 15.8, 1 aliphatic H); 2.69 (*ddd*, $J = 2.3$, 4.9, 16.0, 1 aliphatic H). EI-MS: 342 (100, *M*⁺), 314 (40, [*M* – CO]⁺), 299 (19), 271 (12), 256 (17). Anal. calc. for C₁₉H₁₈O₆ (342.35): C 66.66, H 5.30; found: C 66.47, H 5.40.

3. *Kinetic Measurements.* – 3.1. *Racemization of 9.* To avoid rapid racemization, (7aP)-**9** and (7aM)-**9** were stored after resolution in the eluant mixture of hexane/*i*-PrOH 85:15 at –20°. The soln. of *e.g.* (7aP)-**9** (0.2 ml) was diluted with the eluant mixture (0.8 ml) and filled in the thermostated CD cuvette. Measurements were performed

Table 8. Rates (*k*) of Racemization of (7aM)-**9**^{a)}

<i>T</i> [K]	<i>k</i> [s ^{–1}]	$\tau_{1/2}$ [s]
279.2	$8.04 \cdot 10^{-6}$	$8.62 \cdot 10^4$
283.2	$1.26 \cdot 10^{-5}$	$5.51 \cdot 10^4$
287.2	$1.99 \cdot 10^{-5}$	$3.50 \cdot 10^4$
291.2	$3.25 \cdot 10^{-5}$	$2.13 \cdot 10^4$
295.2	$5.40 \cdot 10^{-5}$	$1.28 \cdot 10^4$
299.2	$8.11 \cdot 10^{-5}$	$8.55 \cdot 10^3$
303.2	$1.33 \cdot 10^{-4}$	$5.22 \cdot 10^3$

^{a)} Correlation coefficients (*r*): 0.993–0.997.

after 15 min to allow the equilibrium of the temp. The margin of error in temp. measurements was $\pm 0.1^\circ$. The CD apparatus was flushed with dry N_2 during the measurements. The intervals of CD measurements were 12 min at 30° , 15 min at 26 and 22° , 20 min at 18° , 30 min at 14 and 10° , and 45 min at 6° . The decrease of the maximum at 265.0 nm was measured with a plot rate of 100 nm/min at the range of 290–240 nm. The obtained k values are collected in Table 8.

3.2. *Racemization of 18*. The procedure was the same as for **9**. The kinetics were followed at 7 temp. in intervals of 4° between 34 – 58° . At each temp., 11–15 CD measurements were performed in constant time intervals: $58^\circ/3$ min, $54^\circ/5$ min, $50^\circ/10$ min, $46^\circ/15$ min, $42^\circ/20$ min, 38 and $34^\circ/30$ min. The decrease of the maximum at 261.6 nm was followed. The obtained k values are collected in Table 9.

Table 9. Rates (k) of Racemization of (7aP)-**18** and (7aM)-**18**^{a)}

T [K]	k [s ⁻¹]	$\tau_{1/2}$ [s]
307.2	$2.41 \cdot 10^{-5}$	$2.87 \cdot 10^4$
311.2	$3.03 \cdot 10^{-5}$	$2.29 \cdot 10^4$
315.2	$5.92 \cdot 10^{-5}$	$1.17 \cdot 10^4$
319.2	$7.14 \cdot 10^{-5}$	$9.70 \cdot 10^3$
323.2	$1.46 \cdot 10^{-4}$	$4.74 \cdot 10^3$
327.2	$2.07 \cdot 10^{-4}$	$3.36 \cdot 10^3$
331.2	$2.52 \cdot 10^{-4}$	$2.76 \cdot 10^3$

^{a)} Correlation coefficients (r): 0.992–0.999.

Table 10. Rates (k) of Racemization of (7aP)-**34** and (7aM)-**34**^{a)}

T [K]	k [s ⁻¹]	$\tau_{1/2}$ [s]
307.2	$1.73 \cdot 10^{-5}$	$4.00 \cdot 10^4$
311.2	$2.53 \cdot 10^{-5}$	$2.74 \cdot 10^4$
315.2	$3.79 \cdot 10^{-5}$	$1.83 \cdot 10^4$
319.2	$6.55 \cdot 10^{-5}$	$1.06 \cdot 10^4$
323.2	$1.17 \cdot 10^{-4}$	$5.94 \cdot 10^3$
327.2	$1.68 \cdot 10^{-4}$	$4.13 \cdot 10^3$
331.2	$2.61 \cdot 10^{-4}$	$2.66 \cdot 10^3$

^{a)} Correlation coefficients (r): 0.992–0.999.

3.3. *Racemization of 34*. The procedure was the same as for **9** except that the eluant mixture consisted of hexane/*i*-PrOH 95:5. Temp. and time intervals as for **18**. The decrease of the maximum at 259.6 nm was followed. The obtained k values are collected in Table 10.

4. **Crystal Data** (Table 11). – *Structure Solution of 9*. All non-H-atoms were located by direct methods. No absorption corrections were applied. All H-atoms could be located in a difference map and were included in the refinement using a riding model. There is a molecule of solvent disordered around the three-fold axis, probably acetone, the nature of which could not be determined. Structure solution and refinement was performed with SHELXTL [75].

Table 11. Crystallographic Data for the Benzo[*a*]heptalenes **9** and **18**

Parameter	9	18
Crystallized from	hexane/acetone	hexane/AcOEt
Empirical formula	$C_{21}H_{22}O_5$ + solvent	$C_{22}H_{24}O_5$
Formula weight	354.41	369.43
Crystal color	yellow	yellow
Crystal temp. [K]	294	213
Crystal system	rhombohedral	orthorhombic
Lattice parameters		
Reflections for cell determination	25	18
2θ range [°]	$20 < 2\theta < 24$	$23 < 2\theta < 26$
a [Å]	18.678(4)	12.453(2)
b [Å]	–	8.867(3)
c [Å]	–	34.384(11)
α [°]	116.72(2)	–
V [Å ³]	2998(1)	3797(2)
Space group	$R\bar{3}$	$Pbca$
Z	6	8
D_x [g cm ⁻³]	1.178	1.292

Table 11 (cont.)

Parameter	9	18
Absorptions coefficient μ ($\text{MoK}\alpha$) [mm^{-1}]	0.078	0.085
2θ (max) [$^\circ$]	46	50
Total reflections measured	8777	4342
Symmetry independent reflections	2792	3311
Reflections observed ($I > 2.5\sigma(I)$)	1612	1665
Variables	262	274
Final R	0.0691	0.0660
R_w	0.0674 ^{a)}	0.0744 ^{b)}
Goodness-of-fit	1.719	1.199
$\Delta\rho$ (max; min) [$\text{e } \text{\AA}^{-3}$]	0.50; -0.39	0.26; -0.26

^{a)} $w = 1/(\sigma^2(F) + 0.0007 \cdot F^2)$.
^{b)} $w = 1/(\sigma^2(F) + 0.003714 \cdot F^2)$.

Structure Solution of 18. All non-H-atoms were located by direct methods. No absorption corrections were applied. The crystal (dimensions $0.14 \times 0.36 \times 0.46$ mm) diffracted weakly, and the number of observed reflections is thus relatively small (50% of the data). Therefore, although most of the H-atoms could be located in a difference Fourier map, in order to reduce the number of refined parameters, all H-atoms were placed in geometrically calculated positions and were included in the refinement using a riding model with C–H bond lengths of 1.08 Å. For the ring H-atoms individual isotropic temp. factors were refined, while, for the Me groups, an overall isotropic temp. factor was refined for the H-atoms of each group.

Structure solution was performed using the direct methods routine of SHELXS86 [76] and refinement was performed with SHELX76 [77]²⁴⁾.

REFERENCES

- [1] Ioannis Keppleri, 'Harmonices Mundi', Lincii Austriae, excudebat Ioannes Plancus; anno MDCXIX; see also the German translation by M. Caspar, Johannes Kepler, 'Weltharmonik', R. Oldenbourg Verlag, München–Wien, 1982, p. 67.
- [2] W. Baker, *J. Chem. Soc.* **1945**, 258.
- [3] D. H. S. Horn, J. R. Nunn, W. S. Rapson, *Nature (London)* **1947**, 160, 829.
- [4] I. Agranat, B. A. Hess, Jr., L. J. Schaad, *Pure Appl. Chem.* **1980**, 52, 1399.
- [5] M. J. S. Dewar, *Nature (London)* **1945**, 155, 141; see also *ibid.* **1945**, 155, 479.
- [6] R. B. Woodward, *The Harvey Lectures* **1963**, 31.
- [7] S.-B. Hastie, *Pharmac. Ther.* **1991**, 51, 377.
- [8] a) B. Pullman, A. Pullman, 'Les Théories Electroniques de la Chimie Organique', Masson et Cie., Paris, 1952; b) 'Non-Benzenoid Aromatic Compounds', Ed. D. Ginsburg, Interscience Publ., Inc., New York, 1959.
- [9] W. Bernhard, Ph. D. Thesis, Nr. 837, University of Fribourg, 1982.
- [10] M. J. S. Dewar, *Nature (London)* **1945**, 155, 50.
- [11] a) J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, A. Eschenmoser, *Angew. Chem.* **1959**, 71, 637; b) J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, T. Threlfall, A. Eschenmoser, *Helv. Chim. Acta* **1961**, 44, 540.
- [12] a) E. E. van Tamelen, T. A. Spencer, Jr., D. S. Allen, Jr., R. L. Orvis, *J. Am. Chem. Soc.* **1959**, 81, 6341; b) *Tetrahedron* **1961**, 14, 8.
- [13] a) S. Sunagawa, T. Nakamura, J. Nakazawa, *Chem. Pharm. Bull.* **1962**, 10, 291; b) T. Nakamura, Y. Murase, R. Hayashi, Y. Endo, *ibid.* **1962**, 10, 281; c) T. Nakamura, *ibid.* **1962**, 10, 299.

²⁴⁾ Atomic coordinates, and bond lengths and angles have been deposited with the *Cambridge Crystallographic Data Center*, 12 Union Road, Cambridge CB2 1EZ, England. They are also available from the authors.

- [14] a) A. I. Scott, F. McCapra, J. Nabney, D. W. Young, A. C. Day, A. J. Baker, T. A. Davidson, *J. Am. Chem. Soc.* **1963**, *83*, 3040; b) A. I. Scott, F. McCapra, R. L. Buchanan, A. C. Day, D. W. Young, *Tetrahedron* **1965**, *21*, 3605.
- [15] I. Fleming, 'Selected Organic Syntheses', John Wiley & Sons, London, 1973, p. 183 ff.
- [16] K. Nakanishi, T. Goto, S. Itô, S. Natori, S. Nozoe, 'Natural Products Chemistry', Kodansha Ltd., Academic Press, Inc., Tokyo, 1975, Vol. 2, p. 349 ff.
- [17] H. J. Dauben, Jr., D. J. Bertelli, *J. Am. Chem. Soc.* **1961**, *83*, 4657, 4659.
- [18] W. Baker, J. F. W. McOmie, in 'Progress in Organic Chemistry', J. W. Cook, ed., Butterworths Scient. Publ., London, 1955, Vol. 3, p. 44 ff.
- [19] a) K. Hafner, J. Schneider, *Justus Liebigs Ann. Chem.* **1959**, *624*, 37; b) E. G. Hoffmann, *ibid.* **1959**, *624*, 47.
- [20] a) E. Vogel, H. Königshofen, J. Wassen, K. Müllen, J. F. M. Oth, *Angew. Chem.* **1974**, *86*, 777; b) E. Vogel, D. Kerimis, N. T. Allison, R. Zellerhoff, J. Wassen, *ibid.* **1979**, *91*, 579.
- [21] E. Vogel, F. Hogrefe, *Angew. Chem.* **1974**, *86*, 779.
- [22] K. Hafner, H. Diehl, H. U. Süss, *Angew. Chem.* **1976**, *88*, 121.
- [23] L. A. Paquette, A. R. Browne, E. Chamot, *Angew. Chem.* **1979**, *91*, 581.
- [24] L. A. Paquette, *Isr. J. Chem.* **1980**, *20*, 233.
- [25] K. Hafner, G. L. Knaup, H. J. Lindner, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 155.
- [26] M. G. Banwell, *Aust. J. Chem.* **1991**, *44*, 1.
- [27] a) W. Cook, J. D. London, in 'The Alkaloids', Eds. R. H. F. Manske and H. L. Holmes, Academic Press, Inc., New York, 1952, Vol. 2, p. 261 ff.; b) W. C. Wildman, *ibid.*, Ed. R. H. F. Manske, New York, 1960, Vol. 6, p. 247 ff.; c) W. C. Wildman, B. A. Pursey, *ibid.*, Eds. R. H. F. Manske and H. L. Holmes, New York, 1968, Vol. 11, p. 407 ff.; d) H.-G. Capraro, A. Brossi, *ibid.*, Ed. A. Brossi, New York, 1984, Vol. 23, p. 1 ff.; e) O. Boyé, A. Brossi, *ibid.*, Eds. A. Brossi, G. A. Cordell, New York, 1992, Vol. 41, p. 125 ff.
- [28] A. J. Rippert, H.-J. Hansen, *Helv. Chim. Acta* **1993**, *76*, 2906.
- [29] R. Hunziker, D. Sperandio, H.-J. Hansen, *Helv. Chim. Acta* **1995**, *78*, 772.
- [30] M. Yasunami, T. Sato, M. Yoshifuyi, *Tetrahedron Lett.* **1995**, *36*, 103.
- [31] M. Laganà, R. Knecht, C. Weymuth, H.-J. Hansen, *Helv. Chim. Acta*, in preparation.
- [32] E. Wenkert, H.-S. Kim, in 'Studies in Natural Product Chemistry', Ed. Atta-ur-Rahman, Elsevier Science Publ., Amsterdam, 1989, Vol. 3, p. 287 ff.
- [33] a) W. Bernhard, P. Brügger, P. Schönholzer, R. H. Weber, H.-J. Hansen, *Helv. Chim. Acta* **1985**, *68*, 429, b) R. H. Weber, P. Brügger, T. A. Jenny, H.-J. Hansen, *ibid.* **1987**, *70*, 742.
- [34] M. Rösner, H.-G. Capraro, A. E. Jacobson, L. Atwell, A. Brossi, *J. Med. Chem.* **1981**, *24*, 257.
- [35] C. H. Hufford, H.-G. Capraro, A. Brossi, *Helv. Chim. Acta* **1980**, *63*, 50.
- [36] W. Bernhard, P. Brügger, J. J. Daly, P. Schönholzer, R. H. Weber, H.-J. Hansen, *Helv. Chim. Acta* **1985**, *68*, 415.
- [37] W. Bernhard, P. Brügger, J. J. Daly, G. Englert, P. Schönholzer, H.-J. Hansen, *Helv. Chim. Acta* **1985**, *68*, 1010.
- [38] Y. Chen, R. W. Kunz, P. Uebelhart, R. H. Weber, H.-J. Hansen, *Helv. Chim. Acta* **1992**, *75*, 2447.
- [39] J. Stegemann, H. J. Lindner, *Tetrahedron Lett.* **1977**, 2515.
- [40] H. J. Lindner, B. Kitschke, *Angew. Chem.* **1976**, *88*, 123; *ibid. Int. Ed.* **1976**, *15*, 106.
- [41] R. Knecht, Diploma Thesis, University of Zürich, 1995; b) R. Knecht, R. W. Kunz, H.-J. Hansen, *Helv. Chim. Acta*, in preparation.
- [42] P. Uebelhart, P. Mohler, R.-A. Fallahpour, H.-J. Hansen, *Helv. Chim. Acta*, in preparation.
- [43] R. H. Weber, Ph. D. Thesis, University of Basel, 1988.
- [44] U. Berg, J. Deinum, P. Lincolme, A. Kvassman, *Bioorg. Chem.* **1991**, *19*, 53.
- [45] Roussel-UCLAF, French Pat. No. 1,347,137, 1962, and No. 1,372,451, 1963 (*cf. CA*: **1964**, *60*, 15928g; *ibid.* **1965**, *62*, 16016f.).
- [46] a) F. Šantavý, T. Reichstein, *Helv. Chim. Acta* **1950**, *33*, 1606; b) P. Bellet, *Ann. Pharm. Fr.* **1952**, *10*, 81.
- [47] A. Riede, H. Gross, E. Höft, *Chem. Ber.* **1960**, *93*, 88.
- [48] G. Muller, A. Bladé-Font, R. Bardoneschi, *Liebigs Ann. Chem.* **1963**, *662*, 105.
- [49] A. J. Anderson, Jr., R. D. Breazeale, *J. Org. Chem.* **1969**, *34*, 2374.
- [50] R. O. Hutchins, F. Cistone, *Org. Prep. Proc. Int.* **1981**, *13*, 225.
- [51] H. R. Billica, H. Adkins, *Org. Synth. Coll. Vol.* **1967**, *3*, 176.
- [52] C. K. Lan, C. Dufresne, P. C. Bélanger, S. Piétre, J. Scheigetz, *J. Org. Chem.* **1986**, *51*, 3038.
- [53] Huang-Minlon, *J. Am. Chem. Soc.* **1946**, *68*, 2487.
- [54] D. N. Kursanow, Z. N. Parnes, N. M. Loim, *Synthesis* **1974**, 633.

- [55] F. Effenberger, E. Sohn, G. Eppe, *Chem. Ber.* **1983**, *116*, 1195.
- [56] F. N. Tebbe, G. W. Parshall, G. S. Reddy, *J. Am. Chem. Soc.* **1978**, *100*, 3611; see also: S. H. Pine, *Org. React.* **1993**, *43*, 1.
- [57] P. Kouroupis, A. Linden, H.-J. Hansen, *Helv. Chim. Acta*, in preparation.
- [58] a) B. Weidmann, C. D. Maycock, D. Seebach, *Helv. Chim. Acta* **1981**, *64*, 1552; b) B. Weidmann, D. Seebach, *Angew. Chem.* **1983**, *95*, 12; *ibid. Int. Ed.* **1983**, *22*, 31; c) D. Seebach, B. Weidmann, L. Widler, in 'Modern Synthetic Methods 1983', Ed. R. Scheffold, Salle + Sauerländer, Aarau, 1983, Vol. 3, p. 217 ff.
- [59] Roussel-UCLAF, French Pat. No. 1,375,049, 1963.
- [60] M. A. Iorio, A. Brossi, J. V. Silverton, *Helv. Chim. Acta* **1978**, *61*, 1213.
- [61] T. F. Buckley, H. Rapoport, *J. Am. Chem. Soc.* **1982**, *104*, 4446.
- [62] S. Otha, M. Okamoto, *Synthesis* **1982**, 756.
- [63] E. J. Corey, K. Achiwa, *J. Am. Chem. Soc.* **1969**, *91*, 1429.
- [64] M. G. Banwell, S. C. Peters, R. J. Greenwood, M. F. Mackay, E. Hamel, C. M. Lin, *Austr. J. Chem.* **1992**, *45*, 1577.
- [65] P. Kouroupis, J. Kessler, H.-J. Hansen, unpublished results.
- [66] K. Hafner, G. L. Knaup, H. J. Lindner, H.-C. Flöter, *Angew. Chem.* **1985**, *97*, 209; *ibid. Int. Ed.* **1985**, *24*, 212.
- [67] L. A. Paquette, *Pure Appl. Chem.* **1982**, *54*, 987.
- [68] L. A. Paquette, T.-Z. Wang, J. Luo, C. E. Cottrell, A. E. Clough, L. B. Anderson, *J. Am. Chem. Soc.* **1990**, *112*, 239.
- [69] J. Packer, J. Vaughan, E. Wong, *J. Am. Chem. Soc.* **1958**, *80*, 905; see also: G. Suld, A. P. Stuart, *J. Org. Chem.* **1964**, *29*, 2939.
- [70] R. F. Raffauf, A. L. Farren, G. E. Ullyot, *J. Am. Chem. Soc.* **1953**, *75*, 5292.
- [71] P. Kouroupis, Ph. D. Thesis, University of Zurich, 1993.
- [72] H. Meerwein, D. Borner, O. Fuchs, H.-J. Schrodt, J. Spille, *Chem. Ber.* **1956**, *89*, 2060.
- [73] B. Danieli, G. Palmisano, G. S. Ricca, *Gazz. Chim. Ital.* **1980**, *190*, 351.
- [74] J. Elguero, P. N. Muller, A. Bladé-Font, R. Faure, E. J. Vincent, *Bull. Soc. Chim. Belg.* **1980**, *89*, 193.
- [75] G. M. Sheldrick, SHELXTL, version 5.1, 1986.
- [76] G. M. Sheldrick, SHELXS86. *Acta Crystallogr., Sect. A* **1990**, *46*, 467.
- [77] G. M. Sheldrick, SHELX76. A program for crystal structure determination, Cambridge, England, 1976.