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Absolute Configurations and Circular Dichroism of Sesquiterpene-Coumarin Ethers

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The absolute stereochemistry of 14 naturally occurring sesquiterpene-coumarin ethers is discussed. In 13 cases the coumarin moiety is isofraxidin (7-hydroxy-6,8-dimethoxycoumarin), in one case scopoletin (7-hydroxy-6-methoxycoumarin). The sesquiterpene moieties belong either to the bicyclic drimenole series or to its consecutive products (methyl migration, ring opening). The CD spectra of all compounds are given. The assignments of the absolute configurations are based on the method of *Horeau*, chemical correlation by degradation reactions, extensive comparison of CD data, and biogenetic considerations.

(Keywords: Achillea; Artemisia; Chiroptical properties; Horeau's method; Natural constituents)

Absolute Konfigurationen und Circulardichroismus von Sesquiterpen-Cumarin-Ethern

Es wird die absolute Stereochemie von 14 natürlich vorkommenden Sesquiterpen-Cumarin-Ethern diskutiert. In 13 Fällen wird die Cumarineinheit von Isofraxidin (7-Hydroxy-6,8-dimethoxycumarin) repräsentiert, in einem Fall von Scopoletin (7-Hydroxy-6-methoxycumarin). Der Sesquiterpenteil ist entweder von Drimenol oder Folgeprodukten (Methylgruppenwanderung, Ringöffnung) abgeleitet. Die CD-Spektren aller Verbindungen sind angegeben. Die Zuordnung der absoluten Konfigurationen basiert auf der Methode von *Horeau*, chemischer Korrelation über Abbaureaktionen, Vergleich der CD-Spektren und biogenetischen Überlegungen.

Introduction

In a series of papers[1–5] we reported the isolation and structure elucidation of various sesquiterpene-isofraxidin (7-hydroxy-6,8-dimethoxycoumarin) ethers[1–4] and two sesquiterpene-scopoletin (7-hydroxy-6-methoxycoumarin) ethers[5] from *Achillea* and *Artemisia* species. However, in these papers we have confined ourselves to relative configurations only. Now we have accumulated enough material con-

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cerning the optically active compounds in this series to allow an extensive comparison of information on the absolute stereochemistry of these natural constituents.

The majority of the isolated compounds (**1**—**4**, **1a**—**5a**, **17**) belong to the drimenol type with a *trans* decaline structure and substituents at C1 (ax or eq —CH_2OAr), C2 (either methyl or methylene), C5 (two geminal methyl groups), C6 (ax or eq —OH), and C8a (ax methyl). A second smaller group represents products which may be derived biosynthetically from the drimenyl derivatives by methyl migration (**14**, **15**), eventually followed by ring cleavage (**18**, **19**). The absolute configurations of most of the compounds were determined by the method of *Horeau* and/or by chemical degradation to compounds of known absolute stereochemistry. The discussion includes the CD spectra of all optically active compounds described in Refs. [1–5] together with several additional derivatives.

Results and Discussion

Horeau's Method

Compounds **1**—**4** and **14** are secondary alcohols (ax or eq —OH at C6) and therefore well suited for the method of *Horeau*[6, 7]. In all cases the reaction of racemic 2-phenylbutanoic anhydride with **1**—**4** or **14** gave preferentially the (+)*S*-2-phenylbutanoic ester of the sesquiterpene alcohols thereby producing an excess of (−)*R*-2-phenylbutanoic acid. The absolute configuration at C6 is therefore *S* for all compounds investigated.

Usually we determined the ratio of (+)*S*:(−)*R* phenylbutanoic ester by NMR spectroscopy using separately prepared (+)*S*, (−)*R* ester mixtures of known composition as reference (see Exp.). This method needs a minimum of ca. 1.5 mg of the scarce natural material: 1 mg for the *Horeau* esterification and 0.5 mg for the synthesis of the reference esters. To obtain a sufficient amount of optically active phenylbutanoic acid for a reliable polarimetric measurement one needs at least 5–10 mg of natural product.

Since all relative configurations are known, the determination of one chiral center (6*S*) allows the assignment of all other centers as well. For compounds **1**, **2**, **4**, and **14** with an axial C6-OH this results in a (4a*S*, 8a*R*) configurated decaline system with (1*S*) configuration for axial —CH_2OAr (**1**, **2**) and (1*R*) for equatorial —CH_2OAr (**4**, **14**). However, since the equatorial C6-OH in **3** gave also (6*S*) the *trans* decaline system is of (4a*R*, 8a*S*) configuration, the axial —CH_2OAr results in (1*R*). Therefore the substituted decaline skeleton in drimartol B (**3**) is of opposite chirality to all other bicyclic terpenic moieties found so far in sesquiterpene-isofraxidin ethers. This finding is supported by all other methods as well (see below).

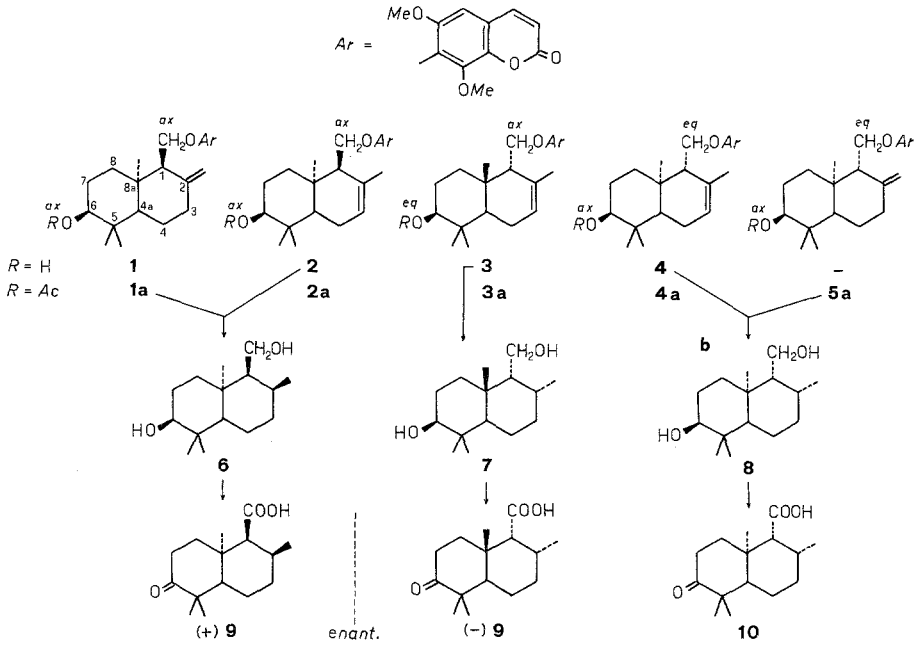
Chemical Correlation

The chemical degradation and correlation with compounds of known absolute configuration followed in principle the procedure given in Ref. [8] for the umbelliferone derived farnesiferol A. Catalytic reductive ether cleavage of alcohols **1**—**4** or acetyl derivatives **1a**—**5a** followed by treatment with KOH/*Me*OH/H_2O gave the diols **6**—**8** (see Scheme 1). These in turn were converted to the ketoacids **9** and **10** by *Jones* oxidation. The chiroptical data of the ketoacids may be compared with data reported in Refs. [8, 9] ($[\alpha]_D$ of **9** and **10**) or Ref. [10] ($[\alpha]_D$ and CD for **10**).

The alcohols **2**—**4**, and acetyl derivatives **1a** and **5a** were subjected to this degradation. **1a**—**3a**, and **4** were correlated by acetylation of **1**—**4** [1-3].

The keto acid **10** derived from **4** and **5a** is identical with the keto acid derived from coladonin [10]; (+)-**9** derived from **1** and **2** is identical with the keto acid derived from farnesiferol A [8]. However, (−)-**9** derived from drimartol B (**3**) is the enantiomer of the farnesiferol A derived keto acid. This proves again the different chirality of the terpenic unit in **3** as compared to all other comparable derivatives in the isofraxidin series (see Scheme 1).

Scheme 1



Circular Dichroism

The UV spectra of all sesquiterpene-isofraxidin ethers investigated are very similar. Especially the long wavelength part with two distinct maxima is nearly identical in all derivatives since it is mainly determined by the isofraxidin chromophore: 338–343 nm ($\varepsilon = 7\,000$–$8\,000$) and 295–300 nm ($\varepsilon = 10\,000$–$11\,000$). The two short wavelength bands at 225–228 nm ($\varepsilon = 17\,000$–$21\,000$) and 206–208 nm ($\varepsilon = 35\,000$–$45\,000$) form either shoulders or real maxima depending on the sesquiterpene part of the entire molecule [1–5, 11] (see schematical presentation in Fig. 1).

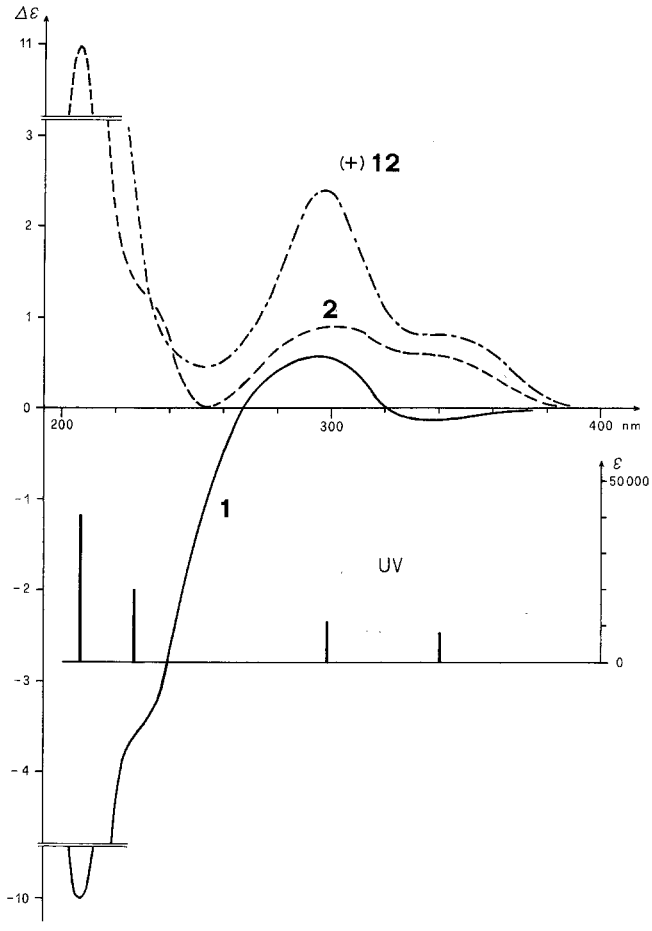


Fig. 1. CD curves for **1**, **2**, and (+)-**12**; the UV absorptions which are very similar for all sesquiterpene-isofraxidin ethers are presented schematically

All of these bands are exhibited in the CD spectra as well (Table 1). Additionally one finds in a few cases a less significant shoulder at about 250–260 nm which may as well result from the overlap of *Cotton* effects. However, these experimentally found shoulders are included in Table 1.

Using the information gained by means of the chemical methods (*Horeau* and chemical correlation) some stereochemical generalizations may be derived from the CD spectra for the different types of sequiterpene ethers. Especially the *Cotton* effects at 338–350 nm (usually weak), 290–305 nm (medium), and 205–210 nm (strong effect but sometimes the maximum is not reached by the measurement because of strong absorption) seem to be well suited for this discussion.

The exo-methylene type derivatives (**1**, **1a**, **5a**) show all a weak negative *Cotton* effect for the long wavelength band at 340–345 nm and a strong negative effect for the short wavelength band at 205–208 nm.

The short wavelength DC band has been already discussed[12] for a series of exo-methylene sesquiterpene-umbelliprenin (7-hydroxycoumarin) derivatives[13–15]. It was found that for axial —CH_2—O*Ar* (*Ar* = umbelliprenin) substituents the *Cotton* effects are larger ($\Delta\varepsilon > |-16|$) than for equatorially substituted ones ($\Delta\varepsilon < |-6|$). This is in agreement with our results for isofraxidin derivatives: **1** and **1a** (axial —CH_2O*Ar*) $\Delta\varepsilon = -10.0$ and -10.5; **5a** (equatorial —CH_2O*Ar*) $\Delta\varepsilon = -4.3$. The weaker effects at longer wavelength are not mentioned in Ref. [12].

In all cases of exo-methylene drimenol derived coumarin ethers the strong negative effect at ca. 205–210 nm is indicative for a (4a*S*, 8a*R*) decaline skeleton. The *Cotton* effect at about 300 nm is less significant since it may be reversed upon acetylation because an additional carbonyl chromophor is introduced. The long wavelength effect at about 350 nm is usually very weak and of the same sign as the dominant effect close to 200 nm.

In the drimenyl series **2**, **2a**, **3**, **3a**, **4**, **4a** the above mentioned rule concerning the short wavelength effect does not hold in the same form. In compounds with axial —CH_2O*Ar* (**2**, **2a**, **3**, **3a**) the *Cotton* effect at 205–208 nm is ca. + 12 for (4a*S*, 8a*R*) configurated derivatives (**2**, **2a**) and − 12 for the (4a*R*, 8a*S*) stereoisomers (**3**, **3a**). In the equatorially substituted compounds (**4**, **4a**) a less strong negative *Cotton* effect (− 3.4, − 4.0) is found for the (4a*S*, 8a*R*) configuration. It follows: axial —CH_2O*Ar* → strong positive *Cotton* effect, equatorial —CH_2O*Ar* → weaker negative effect for (4a*S*, 8a*R*) configuration.

The long wavelength band (345–350 nm) is in accord with the short wavelength band: ax —CH_2O*Ar* → positive *Cotton* effect, eq —CH_2O*Ar* → negative effect for (4a*S*, 8a*R*). However, these effects are weak compared with the short wavelength effects (see Table 1).

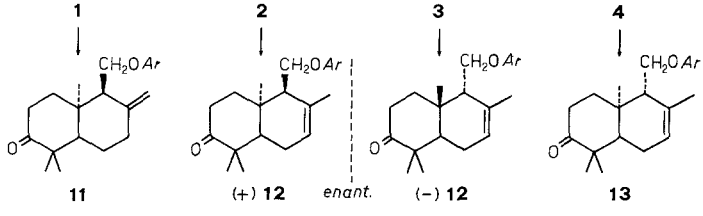
Table 1. *Chiroptical data for*

No.	Name[a]	Ref.	$[\alpha]_D$	Abs. config.
1	Pectachol	1	$-18°$	1*S*, 4a*S*, 6*S*, 8a*R*
1a	Acetylpectachol	1	$-7°$	1*S*, 4a*S*, 6*S*, 8a*R*
2	Drimartol A	1, 11	$+185°$	1*S*, 4a*S*, 6*S*, 8a*R*
2a	Acetyldrimartol A	2	$+110°$	1*S*, 4a*S*, 6*S*, 8a*R*
3	Drimartol B	1	$-140°$	1*R*, 4a*R*, 6*S*, 8a*S*
3a	Acetyldrimartol B	1	$-145°$	1*R*, 4a*R*, 6*S*, 8a*S*
4	Isodrimartol A	3	$-32°$	1*R*, 4a*S*, 6*S*, 8a*R*
4a	Acetylisodrimartol A	3	$-28°$	1*R*, 4a*S*, 6*S*, 8a*R*
5a	Albartin	2	$+2°$	1*R*, 4a*S*, 6*S*, 8a*R*
11	—	—	$-30°$	1*S*, 4a*S*, 8a*R*
12[c]	—	1, 11	$+140°$	1*S*, 4a*S*, 8a*R*
13	—	—	$-23°$	1*R*, 4a*S*, 8a*R*
14	Tripartol	4	$-36°$	1*R*, 2*S*, 6*S*, 8a*R*
15	Drimachone	4	$-38°$	1*R*, 2*R*, 4a*S*, 5*R*, 8a*R*
16	—	4	$+26°$	1*R*, 2*R*, 4a*S*, 5*R*, 6*S*, 8a*R*
17	Scopodrimol	5	$+160°$	1*S*, 4a*S*, 6*S*, 8a*R*
18	Secodriol	4	$-14°$	1*S*, 2*S*, 6*S*
19	Secodrial	4	$-11°$	1*S*, 2*S*, 6*S*

[a] Trivial names are listed for the naturally occurring compounds.
[b] The extremum of the short wavelength effect was not reached experimentally; however, (+) or (−) gives the sign of the slope between 210 and 220 nm (compare Figs. 1 and 2, **12**, **15**, and **16**).

The *Cotton* effect at ca. 295 nm is positive for all (4a*S*, 8a*R*) configurated compounds **2**—**4** and **2a**—**4a**, with one exception: An axial acetyl carbonyl (**2a**) reverses the sign of this effect (the same is observed for **1a**, see above).

Scheme 2



The 6-oxo derivatives **11**, (+)-**12**, (−)-**12**, and **13** of the alcohols **1**—**4** are rather interesting (Scheme 2 and Fig. 1). The short and long

sesquiterpene-coumarin ethers

CD Maxima and shoulders, *Et*OH, [nm ($\Delta\varepsilon$)]				
340 (−0.08),	296 (+0.54),		230 sh (−3.50),	208 (−10.0)
345 (−0.08),	295 (−0.36),		230 sh (−2.50),	207 (−10.5)
335 (+0.58),	300 (+0.88),		226 sh (+1.30),	208 (+11.0)
342 (+0.40),	290 (−1.80),	250 sh (+1.20),	228 (+4.85),	205 (+12.5)
338 (−0.73),	297 (−1.45),			208 (−12.0)
335 (−1.26),	295 (−2.86),			206 (−12.1)
350 (−0.20),	300 (+0.57),	250 sh (−0.33),	232 (−0.60),	205 (− 3.4)
345 (−0.41),	304 (+0.18),	260 sh (−0.35),	235 (−0.75),	207 (− 4.0)
345 (−0.08),	305 (+0.22),		232 (+0.50),	205 (− 4.3)
338 (−0.10),	298 (+0.87),	250 sh (−0.60),	230 sh (−1.55),	(−)[b]
340 (+0.80),	295 (+2.40),			(+)
345 (−0.44),	299 (+1.12),	250 sh (−0.80),	225 sh (−1.20),	210 (− 4.4)
330 (+0.16),	309 (+0.33),	259 (−0.20),	230 sh (+0.84),	210 (+ 6.1)
335 (+0.05),	290 (−2.53),		230 sh (−1.00),	(−)
340 (+0.16),	295 (+0.45),		227 (−1.50),	(−)
345 (+1.20),	295 (+0.70),	258 (+0.80),	228 (−1.20),	(+)
345 (−0.33),	295 (−0.91),		238 (+0.40),	212 (−15.0)
350 (−0.24),	293 (−0.85),		243 (+0.37),	(−)

[c] Data for (+)-**12**, obtained by oxidation of **2**; the enantiomeric product (−)-**12** was obtained from **3**[1] [for (−)-**12** all signs are reversed, the experimental CD curve gave a perfect mirror image].

wavelength *Cotton* effects are in full agreement with the above outlined rules. The effect at about 300 nm should be strongly influenced by the n → π* transition of the C6-carbonyl group. Indeed one observes in all cases an "anti-octant behavior" which is typically for 5,5-*gem.*-dimethyl substituted 6-oxo derivatives of the decaline type[16, 17]. The reason for this "*gem.*-dimethyl effect" is a ring flattening caused by crowding[18, 19].

The natural 6-oxo compound **15** is a product of methyl migration (C5-*Me* ax → C4a-*Me* ax, C8a-*Me* ax → C1-*Me* ax) and reduction of the double bond in the B ring. The compound exhibits a very clear negative n → π* carbonyl *Cotton* effect (290 nm, $\Delta\varepsilon = -2.53$). Reduction of the carbonyl to a hydroxyl group (**16**) results in a drastically lower positive effect in this region (295 nm, $\Delta\varepsilon = +0.45$); all other transitions remain essentially unchanged (see Fig. 2). **15** has no geminal dimethyl arrangement, there is only one equatorial C5-*Me* left. Therefore the octant rule must be valid as in numerous similar cases for terpenes and steroids[16, 17]: **15** belongs to the (4a*S*, 8a*R*) series (Scheme 3).

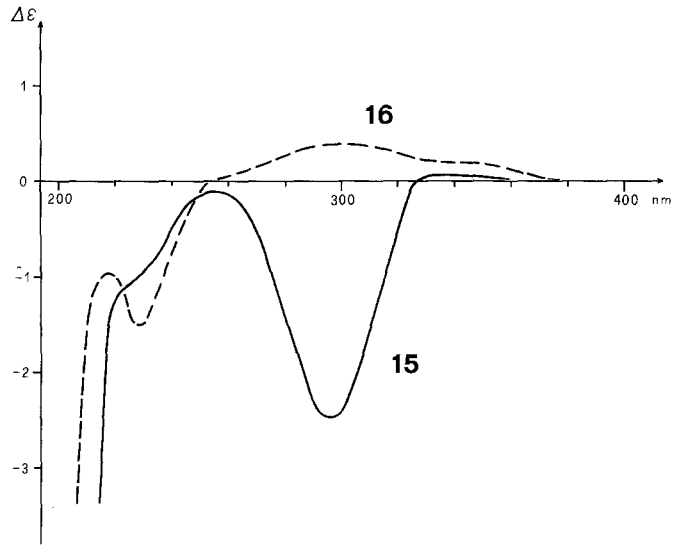
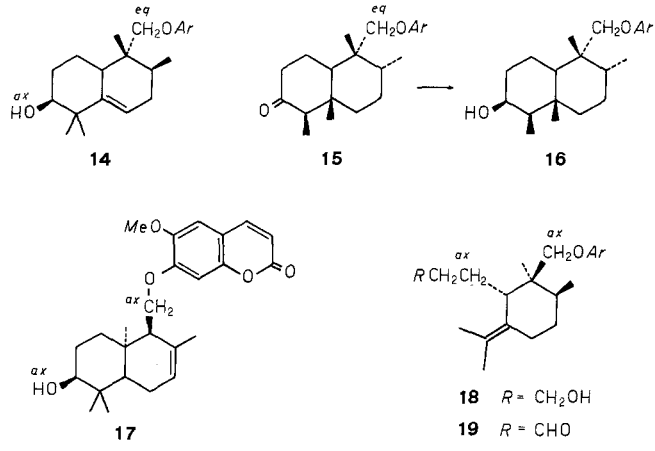


Fig. 2. CD curves for keto compound **15** and the corresponding alcohol **16**

Scheme 3



Compound **17** is the scopoletin analog to **2**. Since the UV spectra of scopoletin derivatives differ somewhat from isofraxidins, the CD spectrum of **17** shows some different features as well (in comparison to **2**). However, the two long wavelength *Cotton* effects (345 and 295 nm) are both positive in **2** and **17**. The intensities of these *Cotton* effects are

proportional to the UV extinctions[5, 11] in both cases: **17**, $\Delta\varepsilon$ (345) : $\Delta\varepsilon$ (295) = +1.2 : +0.7 (= 1 : 0.58), ε (343) : ε (295) = 11300 : 6700 (= 1 : 0.59); **2**, $\Delta\varepsilon$ (335) : $\Delta\varepsilon$ (300) = +0.58 : +0.88 (= 1 : 1.51), ε (337) : ε (294) = 6900 : 10500 (= 1 : 1.52). This striking analogy in the relation of UV to CD spectra allows the save conclusion that the absolute configuration of the sesquiterpene moiety is identical for **17** and **2**, namely (4a*S*, 8a*R*).

In the shorter wavelength region the CD spectrum of **17** shows a positive *Cotton* effect at 258 nm and a negative effect at 228 nm. In scopoletins there are three distinct UV absorptions[5] in the region of 225–260 nm whereas only one is observed for isofraxidins; this part of the CD spectrum is therefore not suited for a correlation between the two series. The significant short wavelength effect close to 200 nm is strongly positive for **17** and **2**.

The absolute configurations of the monocyclic sesquiterpene derivatives **18** and **19** isolated from *Achillea ochroleuca*[4] are derived from biogenetic evidence: These compounds are the products of C8a-*Me* ax → C1-*Me* ax methyl migration followed by C5–C6 bond cleavage and ring inversion of the resulting cyclohexane derivative. Now the —$CH_2CH_2CH_2OH$ chain (for **18**, see Scheme 3) is axial (previously equatorial in the parent decaline structure), —CH_2OAr is axial as well. Products of methyl migration are rather scarce as natural products compared to the usual bicyclic 8a-*Me* ax substituted derivatives[15]. However, from *Achillea ochroleuca* we could isolate two bicyclic compounds of that type (**14** and **15**) and both belong to the (4a*S*, 8a*R*) series. Starting from (4a*S*, 8a*R*) the above outlined biosynthetic pathway results in a configuration (1*S*, 2*S*, 6*S*) for both **18** and **19**. The CD spectra of the alcohol **18** and aldehyde **19** are nearly identical.

A further argument is in agreement with this absolute configuration: A parent compound with C1-CH_2OAr in an equatorial position is required to allow the usual C8a-*Me* ax → C1-*Me* ax migration[20] (compare **14** and **15**). So far all isofraxidin derivatives with —CH_2OAr eq belong to the (4a*S*, 8a*R*) series. The only exception for all sesquiterpene-isofraxidin ethers isolated to date is drimartol B (**3**) but since —CH_2OAr is there in an axial position, compound **3** may be excluded as a possible parent compound for **18** and **19**.

Acknowledgements

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Experimental Part

The CD spectra were recorded on a Jobin-Yvon Dichrograph Mark III (CNRS-Roussel-Jouan), for the NMR spectra a Bruker WM-250 spectrometer equipped with a 80K Aspect computer was used.

For the already known sesquiterpene-coumarin ethers see the Refs. listed in Table 1.

Horeau Esterifications

General procedure for **1**, **2**, **4**, and **14**: A mixture of 1–2 mg of the carbinols (0.0025–0.005 mmol) and 15–30 mg freshly prepared racemic 2-phenylbutanoic acid anhydride (0.05–0.1 mmol) in 1 ml dry pyridine was allowed to stand 1–3 days in the dark. After hydrolysation (aqu. $NaHCO_3$) the neutral components were isolated by extraction with ether. The resulting diastereomeric esters were usually contaminated with some 2-phenylbutanoic anhydride. However, this does not disturb the analysis of the NMR spectra (DC purification may result in a change of the $R:S$ ratio).

For NMR reference the 2-phenylbutanoic esters of **1**—**4** and **14** were also prepared from optically active 2-phenylbutanoyl chloride of known $R:S$ composition. (+)-(*S*)- and (−)-(*R*)-2-phenylbutanoic acid [optical resolution via (+)-phenethylamine salt] was mixed in the desired ratio and converted to the acid chloride by thionyl chloride (10 min, 40°). The crude 2-phenylbutanoyl chloride was evaporated 2 times with dry benzene and 0.03 ml of this product was added to 0.5–2 mg of the alcohols **1**–**4**, or **14**. After 10 min at 40° the mixture was hydrolyzed with aqueous $NaHCO_3$ solution and the neutral products were isolated by extraction with ether. Usually the NMR spectra were taken from the crude esters.

In the following only the NMR signals which show a clear difference of corresponding signals for the diastereomeric (*R*)- and (*S*)-2-phenylbutanoic esters of the alcohols **1**–**4**, and **14** are listed.

1: $CDCl_3$: 4.00 (s, 3 H, C8′-O*Me*, *S*), 3.96 (*R*). C_6D_6: 6.61 (d, 1 H, C4′-H, $J = 9.5$ Hz, *R*), 6.57 (*S*); 6.07 (s, 1 H, C5′-H, *R*), 6.05 (*S*); 5.96 (d, 1 H, C3′-H, $J = 9.5$ Hz, *R*), 5.93 (*S*); 3.79 (s, 3 H, C8′-O*Me*, *S*), 3.75 (*R*). Average signal intensity $S:R = 68:32\%$, optical yield 34%.

2: $CDCl_3$: 6.64 (s, 1 H, C5′-H, *S*), 6.62 (*R*); 5.35 (br. ps. t, 1 H, C3-H, *R*), 5.32 (*S*); 4.68 (br. ps. t, 1 H, C6-H, *R*), 4.63 (*S*); 4.92 (s, 3 H, C8′-O*Me*, *S*), 4.83 (*R*); 4.82 (s, 3 H, C6′-O*Me*, *S*), 4.78 (*R*). C_6D_6: 6.59 (d, 1 H, C4′-H, $J = 10$ Hz, *R*), 6.58 (*S*); 6.04 (s, 1 H, C5′-H, *S*), 6.03 (*R*); 4.95 (d, 1 H, C3′-H, $J = 10$ Hz, *R*), 4.93 (*S*); 5.36 (br. ps. t, C3-H, *R*), 5.31 (*S*); 4.95 (br. ps. t, 1 H, *R*), 4.91 (*S*); 3.77 (s, 3 H, C8′-O*Me*, *S*), 3.67 (*R*); 3.32 (s, 3 H, C6′-O*Me*, *S*), 3.28 (*R*). $S:R = 70:30\%$, optical yield 40%.

3: Neither in $CDCl_3$ nor in C_6D_6 any significant differences in the spectra of the diastereomeric esters.

4: $CDCl_3$: 6.68 (s, 1 H, C5′-H, *S*), 6.67 (*R*); 4.67 (br. ps. t, 1 H, C6-H, *R*), 4.64 (*S*); 3.99 (s, 3 H, C8′-O*Me*, *S*), 3.95 (*R*); 3.85 (s, 3 H, C6′-O*Me*, *S*), 3.82 (*R*). $S:R = 68:32\%$, optical yield 34%.

14: $CDCl_3$: 5.33 (br. ps. t, 1 H, C4-H, *R*), 5.30 (*S*). C_6D_6: 5.45 (br. ps. t, 1 H, C4-H, *R*), 5.35 (*S*); 4.89 (br. ps. t, 1 H, C6-H, *R*), 4.86 (*S*); 4.05 (d, 1 H, —CH_2O—, $J = 8$ Hz, *S*), 4.03 (*R*); 3.90 (d, 1 H, —CH_2O—, $J = 8$ Hz, *S*), 3.87 (*R*). $S:R = 65:35\%$, optical yield 30%.

Horeau esterification of **3**: 22 mg **3** (0.05 mmol) and 155 mg racemic 2-phenylbutanoic acid anhydride (0.5 mmol) in 2 ml dry pyridine gave after 2 days in the dark and proper workup[6,7] 35 mg 2-phenylbutanoic acid with

$\alpha_D = -0.065 \pm 0.005$ in 1 ml benzene → (−)-(*R*)-2-phenylbutanoic acid → therefore (6*S*)-**3**. The chemical yield of the reaction was 25%, the optical yield 35%.

Diols **6–8**

Catalytic reductive ether cleavage (**1a**, **2** → **6**, **3** → **7**, **4**, **5a** → **8**, see Scheme 1), general procedure: 5–10 mg of the natural products in 10 ml *Et*OH-*Ac*OH (3 : 1) were hydrogenated with Pt/H_2 (10–20 mg PtO_2, room temp., atm. pressure, 15 h). The solvent was evaporated under reduced pressure (catalyst removed) and the residue was heated to reflux (0.5 h) with 5% KOH in $MeOH/H_2O$ (2 : 1). The neutral products were isolated by extraction with ether. After evaporation of the solvent the remaining oil was treated with small amounts of petrol ether. In all cases a white crystalline precipitate (2–5 mg) of pure diol was obtained (**6–8**).

6: M.p. 117–119°; $[\alpha]_D^{20} = +115°$ ($c = 0.2$, $CHCl_3$); NMR ($CDCl_3$): 3.97 (dd, 1 H, —C**H**$_2$OH, $J = 11$ and 5 Hz), 3.65 (dd, 1 H, —C**H**$_2$OH, $J = 11$ and 7 Hz), 3.42 (br. m, 1 H, C6-H, $w_{1/2} = 7$ Hz), 2.10–1.95 (m, 2 H), 1.65–1.30 (m, 10 H), 1.14 (d, 3 H, C2-*Me*, $J = 7.5$ Hz), 1.12 (s, 3 H, C8a-*Me*), 0.95 (s, 3 H, C5-*Me*), 0.86 (s, 3 H, C5-*Me*).

7: M.p. 182–184° (Ref.[8] 183–185°); $[\alpha]_D^{20} = -32°$ ($c = 0.5$, $CHCl_3$) (Ref.[8] + 29°); NMR ($CDCl_3$): 3.91 (dd, 1 H, —C**H**$_2$OH, $J = 11$ and 5 Hz), 3.54 (dd, 1 H, —C**H**$_2$OH, $J = 11$ and 7 Hz), 3.20 (dd, 1 H, C6-H, $J = 10$ and 7 Hz), 2.08 (m, 1 H), 1.75–1.25 (m, 11 H), 1.16 (d, 3 H, C2-*Me*, $J = 7.5$ Hz), 1.12 (s, 3 H, C8a-*Me*), 0.98 (s, 3 H, C5-*Me*), 0.80 (s, 3 H, C5-*Me*).

8: M.p. 149–151°; $[\alpha]_D^{20} = +70°$ ($c = 0.4$, $CHCl_3$); NMR ($CDCl_3$): 3.89 (dd, 1 H, —C**H**$_2$OH, $J = 10.5$ and 4.5 Hz), 3.60 (dd, 1 H, —C**H**$_2$OH, $J = 10.5$ and 9.5 Hz), 3.42 (dd, 1 H, C6-H, $J = 3$ and 3 Hz), 2.18 (m, 1 H), 1.70–1.35 (m, 10 H), 0.97 (d, 3 H, C2-*Me*, $J = 7.5$ Hz), 0.95 (s, 3 H, C5-*Me*), 0.88 (s, 3 H, C8a-*Me*), 0.85 (s, 3 H, C5-*Me*). The *Me* signals were assigned by comparison of the four diols: C6-OH ax/C1-CH_2OH ax (**6**), OH ax/CH_2OH eq (**8**), OH eq/CH_2OH ax (**7**), and OH eq/CH_2OH eq (Ref.[10]).

Keto Acids (+)-**9**, (−)-**9**, *and* **10**

Jones reagent was added in excess to a solution of 2–5 mg of the diols **6–8** in 1 ml acetone[10]. After 10 min at room temp. 10 ml ether was added and the acidic products were isolated (extraction with bicarbonate). Without further purification rather pure keto acids **9** and **10** were obtained.

9: M.p. 92–94° (Ref.[8] 94–95°); $[\alpha]_D^{20} = +12.5°$ (from **6**, see Scheme 1, $c = 0.5$, $CHCl_3$), $[\alpha]_D^{20} = -13°$ (from **7**, $c = 0.6$, $CHCl_3$) (Ref.[8] −11.8°); CD (*Et*OH): 319 nm ($\Delta\varepsilon = +0.05$), 289 (−0.26) (from **6**, reversed signs for the keto acid derived from **7**, see Scheme 1); NMR ($CDCl_3$): 2.67 (ddd, 1 H, C7-H ax, $J = 16$, 11.5, and 7 Hz), 2.40 (ddd, 1 H, C7-H eq, $J = 16$, 6.5, and 4 Hz), 2.22 (d, 1 H, C1-H, $J = 5$ Hz), 2.17–2.07 (m, 2 H), 2.00 (m, 1 H), 1.85–1.70 (m, 2 H), 1.60–1.45 (m, 3 H), 1.28 (s, 3 H, C8a-*Me*), 1.14 (d, 3 H, C2-*Me*, $J = 8$ Hz), 1.10 (s, 3 H, C5-*Me*), 1.05 (s, 3 H, C5-*Me*).

10: M.p. 163–165° (Ref.[10] 164–166°); $[\alpha]_D^{20} = -17°$ ($c = 0.5$, $CHCl_3$) (Ref.[10] − 16°); CD (*Et*OH): 318 nm ($\Delta\varepsilon = 0.04$), 289 (−0.23); NMR ($CDCl_3$): 2.65 (ddd, 1 H, C7-H ax, $J = 16$, 12, and 7 Hz), 2.45–2.30 (m, 3 H), 2.20 (m, 1 H), 2.08–1.57 (m, 2 H), 1.80–1.50 (m, 3 H), 1.38 (s, 3 H, C8a-*Me*), 1.12 (d, 3 H, C2-*Me*, $J = 8$ Hz), 1.10 (s, 3 H, C5-*Me*), 1.07 (s, 3 H, C5-*Me*).

Oxo Derivatives **11** *and* **13**

3 mg of the alcohol (**1** or **4**) was stirred for 15 h at room temp. with 30 mg CrO_3 in 1 ml dry pyridine. After workup (acidification with HCl, ether extraction) and purification by TLC (silica gel, Merck, methylene chloride/ethanol 98.5 : 1.5) ca. 2 mg of the pure ketones were obtained.

11: M.p. 136–137°; $[\alpha]_D^{20} = -30$, $[\alpha]_{436}^{20} = -57°$ ($c = 0.2$, acetone); UV (*Et*OH, nm, ε): 336 (7700), 294 (11200), 225 (24000), 204 (50500); MS (70 eV, 110°): 440 (M^+, 7.5%), 222 (100%, isofraxidine); NMR ($CDCl_3$): 7.60 (d, 1 H, C4′-H, $J = 10$ Hz), 6.65 (s, 1 H, C5′-H), 6.35 (d, 1 H, C3′-H, $J = 10$ Hz), 4.91 and 4.85 (two br. s, 2 H, $=CH_2$, $w_{1/2} = 5$ Hz), 4.28 (dd, 1 H, C1-CH_2O*Ar*, $J = 9.5$ and 5.5 Hz), 4.08 (dd, 1 H, C1-CH_2O*Ar*, $J = 9.5$ and 7 Hz), 3.96 (s, 3 H, C8′-O*Me*), 3.85 (s, 3 H, C6′-O*Me*), 2.79 (ddd, 1 H, C7-H ax, $J = 15$, 15, and 6 Hz), 2.40–2.25 (m, 4 H), 2.10 (ddd, 1 H, C3-H ax, $J = 14$, 14, and 4 Hz), 1.80 (dd, 1 H, C4a-H ax, $J = 13$ and 4 Hz), 1.75–1.55 (m, 3 H), 1.21 (s, 3 H, *Me*), 1.10 (s, 3 H, *Me*), 1.05 (s, 3 H, *Me*).

13: Colourless oil; $[\alpha]_D^{20} = -23°$, $[\alpha]_{436}^{20} = -65°$ ($c = 0.5$, acetone); UV (*Et*OH, nm, ε): 337 (8000), 295 (10800), 225 (22000), 205 (48500); MS (70 eV, 100°): 440 (M^+, 5%), 222 (100%, isofraxidin); NMR ($CDCl_3$): 7.62 (d, 1 H, C4′-H, $J = 10$ Hz), 6.68 (s, 1 H, C5′-H), 6.35 (d, 1 H, C3′-H, $J = 10$ Hz), 5.60 (br. s, 1 H, C3-H, $w_{1/2} = 11$ Hz), 4.20 (pseudo d with $J = 10$ Hz, 2 H, narrow AB part of an ABX, C1-CH_2—O*Ar*), 4.00 (s, 3 H, C8′-O*Me*), 3.87 (s, 3 H, C6′-O*Me*), 2.78 (ddd, 1 H, C7-H ax, $J = 14.5$, 14.5, and 5 Hz), 2.45–2.25 (m, 3 H), 2.15–2.00 (m, 2 H), 1.95 (br. s, 3 H, C2-*Me*), 1.75–1.60 (m, 2 H), 1.12 (s, 6 H, 2 *Me*), 1.08 (s, 3 H, *Me*).

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