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RELATIVE AND ABSOLUTE CONFIGURATIONS OF TWO NATURALLY OCCURRING ACETYLENIC SPIROKETAL ENOL ETHER EPOXIDES

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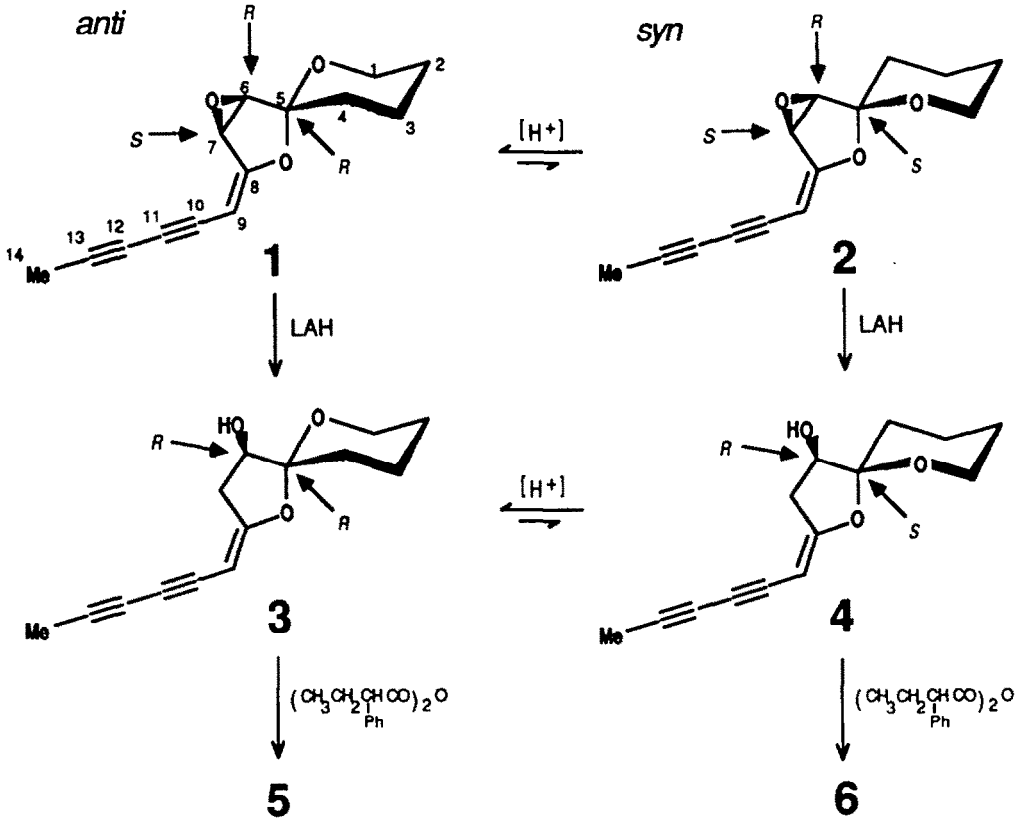
Abstract - The underground parts of *Artemisia selengensis* afforded a new C14 acetylenic six-ring spiroketal enol ether epoxide. A closely related diastereomeric compound has been isolated previously, however, the relative configuration of the epoxy ring (*anti* or *syn* to a reference oxygen) could not be established. The relative stereochemistries of the *anti-syn* pair were elucidated by ^{1}H-lanthanide induced shifts and comparison of ^{13}C NMR data. The absolute configurations were deduced via the corresponding carbinols using the method of *Horeau*. The results were confirmed by CD measurements and equilibration experiments of *anti* ⇌ *syn* pairs.

From the extensive studies of *Bohlmann* and his collaborators [1] it is known that the accumulation of polyacetylenes represents a typical chemical trend of the plant family *Asteraceae*. The different tribes of that family may be distinguished on the basis of distinct structural types of polyacetylenes. The very characteristic acetylenic spiroketal enol ethers have only been found so far in the tribe *Anthemideae*. They comprise a stereochemically interesting group of C13 and C14 acetylenes where a twofold ring closure of an intermediate keto-alcohol gives, depending on the chain length, either "5-ring spiroketal enol ether" (C13, two 5-rings) or "6-ring spiroketal enol ether" (C14, one 5-ring, one 6-ring) [2-5]. Additional oxidation of the C14-6-ring spiroketal enol ether leads to compounds of type **1** or **2** with three oxa-ring systems (3-, 5- and 6-ring: oxirane, oxolane and oxane). Further oxygenated derivatives with acetoxy groups at the oxane ring were also isolated [1].

In the course of our current comparative studies on polyacetylenes of the tribe *Anthemideae*, particularly within the large genus *Artemisia*, we have already isolated a large number of spiroketal enol ether derivatives [6,7]. From the underground parts of *Artemisia selengensis* Turcz. ex Bess. belonging to the East Asiatic allies of the *A.vulgaris* group, a series of spiroketal enol ether epoxides has now been isolated which chromatographically clearly deviates from the corresponding closely related derivatives. The elucidation of the stereochemistries of the parent compounds of the two epoxide series (epoxy bridge *anti* or *syn* to the oxygen of the oxane ring) is reported in this paper.

The occurrence of either *anti* or *syn* epoxides of type **1** or **2** seems to be very characteristic for certain *Artemisia* species. So we could not detect any *anti* epoxide **1** (or further substituted derivatives [8]) in *Artemisia selengensis*. On the



other hand no *syn* derivatives of type **2** were detected in all other epoxy-spiroether containing *Anthemideae* genera investigated so far.

Several stereochemical questions arise for the diyn-ene-spiro system (compare formulas **1** and **2**): (i) *cis* or *trans* (*E* or *Z*) orientation of the 8,9-double bond, (ii) the relative configuration of the epoxy bridge, *anti* or *syn* to the oxygen of the oxane 6-ring, (iii) the absolute configurations at C5, C6, and C7, (iv) the conformations of the ring systems (e.g. axial / equatorial position of the two substituents at C5 of the oxane chair).

The question whether the -C≡C-C≡C-Me rest points towards the oxolane-O or towards C7 is usually answered by the chemical shift of the 9-H proton. A broad s at ∂= 5.20 ppm indicates a stereo- chemistry usually denoted as "*cis*" [3,4]. "*Cis*" refers here to the carbon-skeleton of the compound (compare **1**); however, using the unambiguous *Z/E* nomenclature, "*cis*" corresponds to *E* (and not as usually to *Z*), since the priorities in both types of nomenclature are reversed in this special case. *Z*-configuration is indicated by a chemical shift of ca. ∂= 4.9 ppm for 9-H. The assignments are based on ^{1}H NMR arguments and results of UV irradiation of the *Z* ⇌ *E* isomers [2,3]. The LIS (lanthanide induced shifts) calculation of (*E*)-**3** (and its *Z*-isomer) fully support these assignments (*vide infra*).

The relative configuration of the epoxy bridge in previously isolated derivatives of that type is still unknown. Neither in the parent compound **1** [4], nor in further oxygenated derivatives (axial -OCOMe or -OCOCH$_2$-CHMe$_2$ at position C2 [8]) the stereochemistry of the epoxy ring could be elucidated.

Concerning the absolute configurations no published data were available on spiroketal enolethers with en-yne chromophors. In Ref.[8] X-ray analysis and CD measurements of "this

Table 1. ^{1}H NMR data for compounds **1** - **4** ($CDCl_3$, TMS, ∂/ppm, 250 MHz) and ^{13}C NMR for **1**, **2**, and **7** (*J*-modulated spectra, $CDCl_3$, TMS, ∂/ppm, 250 MHz)

	^{1}H NMR				^{13}C NMR		
No.	**1**	**2**	**3**	**4**	**1**	**2**	**7**[c]
1	3.75-3.93 *m*[a]	3.86-3.94 *m*	ax: 3.78 *ddd* eq: 3.68 *ddd*	3.85-3.90 *m*	63.3 *t*	64.7 *t*	64.6 *t*
2					24.9 *t*	24.5 *t*	66.5 *d*
3	1.60-1.95 *m*	1.55-1.85 *m*	1.55-1.85 *m*	1.60-1.90 *m*	18.7 *t*	18.0 *t*	22.9 *t*
4			(4eq: 2.00 *m*)		28.9 *t*	30.7 *t*	23.6 *t*
5	-	-	-	-	106.0 *s*	106.0 *s*	105.4 *s*
6	3.81 *d*	3.80 *d*	4.03 br *d*	3.90 *t*	51.9 *d*	52.2 *d*	51.9 *d*
7	4.30 *d*	4.29 *d*	cis: 2.79 *d*[d] tr.: 3.14 *ddd*	cis: 2.68 *ddd* tr.: 3.15 *dd*	60.0 *d*	58.9 *d*	59.7 *d*
8	-	-	-	-	165.0 *s*	163.7 *s*	164.5 *s*
9	5.18 *br s*	5.15 *br s*	5.01 *br s*	4.93 *br s*	85.9 *d*	85.4 *d*	86.5 *d*
10-13[b]	-	-	-	-	79.6 *s*	79.7 *s*	79.8 *s*
(-C≡)	-	-	-	-	69.9 *s*	69.7 *s*	69.5 *s*
14	2.00 *s*	1.99 *s*	1.99 *s*	1.99 *s*	4.6 *q*	4.6 *q*	4.6 *q*

J (Hz) 1,2: 6,7 = 3; 3: 1ax,1eq = 1ax,2ax = 12; 1ax,2eq = 4; 6,7tr. = 5; 6,7cis < 0.5; 7tr.,9 = 2.3; 7cis,7tr. = 18; 4: 6,7tr. = 7.5; 6,7cis = 8.8; 7cis,9 = 2.7; 7tr.,9 = 0.5; 7cis,7tr. = 17

[a] A broad pseudo *t* is centered at 3.89 (*ddd*, J gem ≈ J ax,ax ≈ 12 Hz, axial 1-H), a broad pseudo *d* at 3.78 (*ddd*, Jgem ≈ 12 Hz, equatorial 1-H); [b] Only two of the four -C≡ resonances are detectable in the diluted solutions (ca. 6 mg in 0.5 ml); [c] Acetyl group: 170.5 (*s*, CO), 21.2 (*q*, Me); [d] 7cis and 7tr. refer to the positions relative to the OH group at C6

type of spiro ketal" were mentioned as unpublished results, however, no data, arguments or explicit assignments were given in the text [9]. The optical rotatory dispersion (ORD) of bicyclic spiroketals *without* special chromophors is well documented [10]. However, attempts to eliminate the en-diyne chromophor of **1** or **2** by catalytic reduction failed; in all hydrogenation experiments we obtained open chain products (compare [2]). Therefore, a correlation of chiroptical properties with the corresponding dioxaspiranes [10,11] was not possible.

From the roots of *Artemisia selengensis* Turcz. ex Bess. we have now isolated the second diastereomer **2** of the *anti-syn* epoxide pair. ^{13}C and ^{1}H NMR LIS data for compounds **1** / **2** and their LAH-reduction products **3** / **4** allowed to determine the relative configurations and the conformations of the ring systems. Kinetic racemate resolution of 2-phenyl butanoic anhydride with the optically active secondary carbinols **3** and **4** (*Horeau* 's method) together with data for the circular dichroism (CD) of compounds **1** - **4** were used to deduce the absolute configurations.

Relative Configurations and Conformation

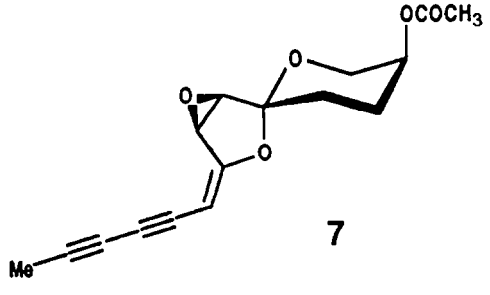
The spectral data for the *anti* / *syn* pair **1** / **2** are very similar and do not allow a clear cut discrimination between both isomers. The ^1H NMR spectra of **1** and **2** differ only in the somewhat closer chemical shifts for the ax and eq protons at C1 (see Table 1, narrower m for **2**), in the ^{13}C NMR all corresponding chemical shifts for both isomers are within 2 ppm. The assigments of the ^{13}C resonances (J-modulated spectra) are straightforward with the exception of the CH_2-carbon atoms C2, C3, and C4. A comparison of the spectrum of **1** with that of the naturally occurring C2-acetyl derivative **7** (Ref. [9]) allowed to assign these resonances. For C3 a shift difference of +4.6 ppm is expected upon substitution of 2-H with -OCOMe, C4 should show a $\Delta\partial$ of -3.2 (or more negative due to the *van der Waals* interaction of the axial 2-OCOMe group with the γ-carbon atom C4)[12]. The observed values are +4.2 for C3 and -5.3 ppm for C4. The hope that a comparison of the ^{13}C NMR shifts for atom C4 might allow a safe decision between isomers **1** and **2** failed. The values ∂= 28.9 ppm for **1** and 30.7 for **2** are slightly in favour of the *anti*-epoxide structure for **1**: due to steric compression, C4 should be more shielded in compound **1** (the epoxide bridge points towards C4). However, the shift difference of $\Delta\partial_{(2\text{-}1)}$ of 1.8 ppm is not very striking.

A further argument that **1** should be the *anti* and **2** the *syn* isomer was furnished by the lanthanide induced shift (LIS) data of these compounds. Since three ether type oxygens are present in **1** and **2**, we chose the more selectively coordinating $Eu(dpm)_3$ reagent [13]. Table 2 shows the observed LIS values (extrapolated to a 1:1 concentration ratio of substrate and reagent, which is not identical to a 1:1 complex in the case of weakly coordinating substrates [13]). Complexation is not very strong and the values are rather low. The LIS values for the protons at C6 and C7 deserve some comment. The values 1.22 and 1.28 ppm for 6-H and 7-H for compound **1** are almost equal (±0.03 ppm or ±2.4%). This must be due to a complex geometry which is rather symmetric in the close vicinity of the coordination site. For compound **2** the corresponding values for 6-H and 7-H are 1.20 and 0.88 ppm. In the latter case the LIS value for 6-H is larger and the values differ significantly (±0.24 ppm or ±15%). A reasonable explanation would be that in the *syn*-isomer **2** some kind of bidentate complexation (at the oxirane and oxane oxygen) participates in the complex equilibrium [13] and moves the average lanthanide ion position closer to 6-H.

Table 2. ^1H NMR LIS data of compounds **1** - **4**; values extrapolated to a substrate : reagent ratio of 1:1; $Eu(dpm)_3$ for **1** and **2**; $Eu(fod)_3$ for **3** and **4**; $\Delta\partial$ / ppm (calculated values for **3** in brackets)

No.	1	2	3	4
1 ax	0.32	0.37	0.38 (0.34)	4.35[a]
1 eq	0.37	0.41	0.27 (0.22)	4.97[a]
2 ax	0.17[a]	[b]	0.24 (0.23)	3.94[a]
2 eq	0.19[a]	[b]	0.20 (0.20)	1.71[a]
3 ax	0.30[a]	[b]	0.48 (0.45)	0.63[a]
3 eq	0.35[a]	[b]	0.26 (0.33)	1.13[a]
4 ax	0.48[a]	[b]	0.93 (0.91)	5.56[a]
4 eq	0.71[a]	[b]	1.31 (1.35)	5.37[a]
6-H	1.22	1.80	1.73 (-)	4.87
7	1.28	1.32	cis: 1.28 (1.24) tr.: 0.63 (0.70)	4.48 3.27
9	0.33	0.30	0.46 (0.39)	1.89
14	-0.06	-0.06	-0.03 (-0.05)	-0.24

[a] Tentative assignments; [b] 0.20 - 0. 72 (unresolved)



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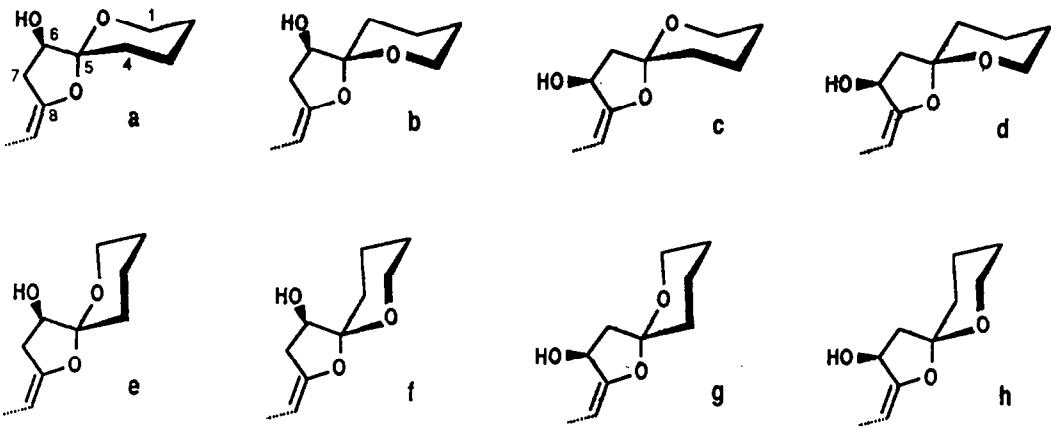

The LIS data for the reduction products (carbinols **3** and **4**) allowed an unambiguous decision concerning the relative stereochemistries of the parent compounds **1** and **2**. LAH reduction of **1** gave a single product. In the ^{1}H NMR the C7 methylene protons (vicinal to >CHOH) appear as well separated d and ddd! This means that one of the two C7 protons exhibits only a geminal coupling constant of 17 Hz, the other one a geminal coupling of 17 Hz, a vicinal of 5 Hz, and an additional long range coupling of 2.5 Hz. This information should help to support a geometry derived from a computational LIS simulation.

The OH group coordinates much better to shift reagents than ether functions [13]. The LIS values obtained with $Eu(fod)_3$ were simulated in a *McConnell-Robertson* type calculation [14], testing different possible substrate geometries and varying the lanthanide ion position to obtain best agreement between experimental and calculated values. Substrate geometries **a-h** were checked for compound **3**. The proposed geometries include different -OH positions at C6 or C7, *anti-* or *syn-* OH, and the two possible chairs for the oxane ring. For the oxolane 5-ring three conformations were checked for all cases **a-h**: (i) a flat 5-ring, (ii) a conformation with a torsional angle of 10° for C5 above and C6 10° below the O-C8-C7 plane, and (iii) a conformation with C5 10° below and C6 10° above O-C8-C7. The non-planar geometries correspond to a twisted envelope conformation, avoiding eclipsed atoms at C5 and C6 (O, C7, C8, and C9 were kept planar due to the double bond C8=C9). From the 24 proposed substrate geometries 22 gave a very bad fit with an average deviation of >40% between the calculated and the experimental value. The flat 5-ring structure **a** gave a fit with R= 17.5% (which is still bad), but for the twisted envelope conformation of the oxolane ring with C6 up and C5 down, the fit was 8.5% (which is already fairly good). Further refinement of the torsional angles lowered the R-factor [13,14] to 6.6% (see Tab.2 for the best fit).

The resulting structure proves that the OH position at C6 is *anti* relative to the oxygen of the oxane ring (corresponding to pseudo-axial *trans* conformations of the C6-OH and the C5-OCH_2- groups and therefore a favoured pseudo-equatorial conformation for the C5-CH_2- group of the oxolane ring). Concerning the 6-ring system of spiro compound **3**, -O-C8 occupies the axial, -C6 the equatorial position at C5 of the oxane chair. The results for the geometries of both ring systems are reasonable, since the alkyloxy substituents should adopt the unfavoured (pseudo)axial positions much easier than the alkyl rests (ax-eq "conformational energy" for OCH_3 2.9 kJ/mol, for -CH_2-CH_3 7.5 kJ/mol [15]). The decision in favour of C6-*anti* OH is very clear (confidence level >99.5% [16]); the parent epoxide **1** must therefore be the *anti* isomer. The reliability of the derived geometry of **3** is further supported

by the coupling pattern of the $H_2C(7)$-C(6)H(OH) ABX system. In the LIS calculation the C7-proton *cis* to OH (larger LIS value than the *trans* one) shows a dihedral angle Θ of ca. 95±5° with the C6-proton. $\Theta_{(H\text{-}C6\text{-}C7\text{-}Hcis)} \approx 90°$ explains the lack of a measurable vicinal coupling $J_{6\text{-}H,7Hcis}$ in the ^{1}H NMR spectrum of **3**.

Reduction of epoxide **2** with LAH yielded a uniform product **4**. The ^{1}H-NMR spectrum of carbinol **4** is entirely different from the spectrum of **3**. The C7 methylene protons give a dd (geminal and vicinal coupling) and a ddd (including an allylic long range coupling); in the case of **4** the C7-proton *cis* to the C6-OH group shows an appreciable allylic coupling (not the *trans* one, like in **3**). These results are compatible with basically the same 5-ring geometry in **3** and **4**, the only difference being the *anti* or *syn* OH at C6. The LIS data of alcohol **4** are very interesting. The values, extrapolated for a reagent to substrate ratio of 1:1, are much larger for **4** compared to **3**. Although the absolute LIS values depend on many factors (presence of traces of water in the substrate or on the glass surface of the NMR tube, quality of reagent, concentration of substrate in the solution), the differences in the complexing behaviour of **3** and **4** are striking. In compound **3** 6-H, 4-Heq, and 7-H*cis* are the farthest shifted protons, in **4** 1Hax, 1Heq, 2-Hax, 4-Hax, 4Heq, 6-H, and 7H*cis* are all within the maximum values of 3.9-5.6 ppm. The only reasonable explanation is the assumption of a strong multidentate (bi- or even tridentate) complex where all above mentioned protons lie within the strongest shifting region of the magnetic field of the paramagnetic Eu(III) ion. No quantitative evaluation of the LIS data of **4** was possible, but the qualitative results indicate clearly a *syn*-configuration for 6-OH and therefore for the parent epoxide **2** as well.

For both compounds **3** and **4** the negative LIS values for the terminal methyl groups deserve some attention. A negative LIS value is only possible if the angle O(substrate)-Eu(III)-H(i) is > 56°. This condition needs a "U" or at least "L" form arrangement of these atoms in the complex [13a]. These requirements are only fulfilled for the 8,9-(*E*) orientated double bond. In the *Z*-isomer the acetylenic side chain points away from 6-OH ("I" shape of the complex) and a positive LIS value is expected. The LIS value of the methyl groups of the *Z*-isomer of **3** is +0.08 ppm compared to -0.03 ppm for **3** (all other values, including 8-H are practically the same; the LIS of the *Z* -isomer were taken from a *Z*/*E* mixture obtained by exposure of a solution of **3** to light). The corresponding value for Me in **4** (*E* -isomer) is -0.24 (see Table 2).

Absolute Configurations

The absolute configurations were determined using the kinetic method of *Horeau* [17,18]. Optically active secondary alcohols react with racemic 2-phenylbutanoic anhydride giving diastereomeric ester mixtures. Depending on the absolute configuration of the secondary alcohol either the (*R*)- or (*S*)-phenylbutanoic acid moiety is kinetically favoured during esterification. After workup the activity of the remaining phenylbutanoic acid is checked: (+)-(*S*)-acid indicates (*R*)-configuration of the alcohol, (-)-(*R*)-acid results after reaction of the racemic anhydride with (*S*)-alcohol. The method is rather reliable, especially for high optical yields due to high selectivity of the reaction. The alcohols **3** and **4** should be very well suited for the determination of the absolute configuration at C6, because the groups attached to this carbon atom are very different in size [H, CH_2, C(O,O,C)], which is an important requirement for the selectivity of the esterification.

In the case of reaction **3** → **5** (+)-(*S*)-phenylbutanoic acid was set free in the reaction. This corresponds to (*R*)-configurated C6. The optical yield was 46% which is very good (optical yields >20% are considered to give safe results). The optical yield was determined from the ^{1}H NMR spectrum of the crude diastereomeric ester mixture **5** (no chromatographic purification to avoid changes in the product composition).

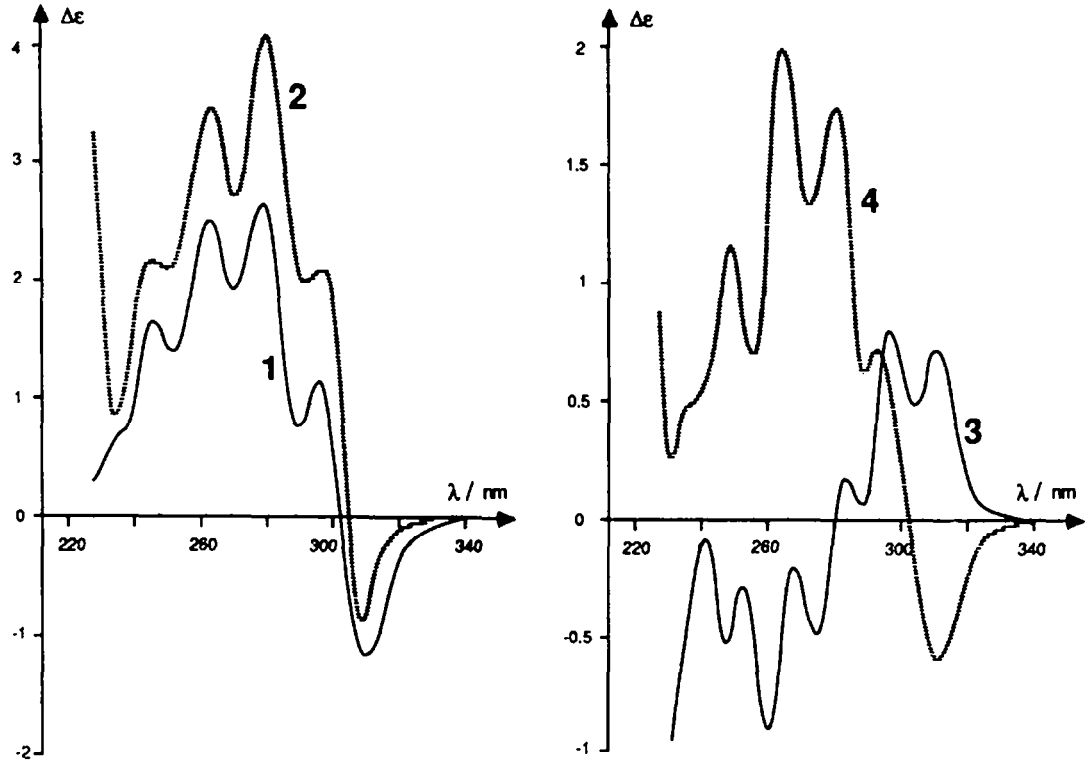

Figure 1. CD spectra of compounds 1 - 4

Especially the resonances of the C7-H *cis* to the oxygen atom at C6 were completely separated (shift difference 0.15 ppm) and allowed an accurate analysis of the ratio of the diastereomeric esters **5** : 73% (6*R*)-alcohol-(2*R*)-2-phenylbutanoic ester and 27% (6*R*)-alcohol-(2*S*)-ester. The absolute configuration at C5 of **3** (and **1**) follows from the known relative configurations derived in the previous section.

The reaction of carbinol **4** with the racemic anhydride yielded again (+)-(*S*)-phenylbutanoic acid, the (-)-acid was incorporated preferentially in the ester. ^{1}H NMR analysis of the diastereomeric ester mixture **6** (shift difference for 7H*trans* 0.12 ppm) showed a ratio (6*R*)-alcohol-(2*R*)-2-phenylbutanoic ester : (6*R*)-alcohol- (2*S*)-ester of 67 : 33 , corresponding to an optical yield of 34%. The result is C6-(*R*) and C5-(*S*) for alcohol **4** and epoxide **2**.

The above derived results, identical absolute configuration for the epoxide group (C6 and C7) in **1** and **2** and opposite configuration at the spiro center C5, is supported by the circular dichroism (CD) data. In the CD spectra of compounds **1** and **2** all bands between 250 and 300 nm are very similar, which may be explained by identical configurations of the epoxide atoms C6 and C7 which are close to the diyn-ene chromophor; especially C7 is of importance, since the influence of a chiral element on the chiroptical properties of a symmetrical chromophor decreases rapidly with the distance. The CD spectra of alcohols **3** and **4** show that several bands are reversed in sign (Fig.1). This is due to the fact that there are two centers of chirality (C5 and C6) about equidistant from the chromophor. These results furnish independent arguments for equal absolute configurations for the epoxide bridges in **1** and **2** but opposite absolute configurations for the spiro centers (C5).

Final proof for the identical absolute configurations of the epoxide bridges in compounds **1** and **2** was furnished by isomerization experiments allowing a chemical correlation between the two series **1** → **3** → **5** and **2** → **4** → **6**. Treatment of compound **2** with an acidic catalyst (*p*-toluenesulfonic acid) should isomerize **2** to compound **1** due to the ketal nature of this type of compounds; an isomerization at the spiro carbon atom should take place. It turned out that the synthetic compound **1** obtained in the equilibrium **2** ⇌ **1** is identical with natural **1** (^{1}H NMR and CD). This result proofs unambiguously that **1** and **2** differ only in the absolute configurations at the spiro center C5. The same result was obtained in all equilibration experiments **1** ⇌ **2** and **3** ⇌ **4** using compounds **1** - **4** as starting materials (see Experimental). Since material got lost in side reactions the isomerizations had to be stopped before the final equilibria could be reached. However, the observed product ratios (see Exp.) indicate that the *anti*-isomers **1** and **3** are the favoured ones.

As a concluding remark it should be emphasized again that an equilibration (or isomerization) during the isolation of compounds **1** and **2** from plant material can be excluded , since in *A.selengensis* we could only find the *syn*-compound, whereas in *A.douglasiana* only the *anti*-product could be detected (using the same experimental procedure). The accumulation of either (5*R*) or (5*S*) spiro ketals seems to be a biogenetically determined trend.

Experimental

IR: Perkin-Elmer 398. - UV: Perkin-Elmer Lambda 5. - MS: Varian MAT CH-7 and 311A (high resolution). - NMR: Bruker WM-250. - CD: Jobin-Yvon Mark III. - Optical Rotations: Perkin Elmer 241 Polarimeter. For the determination of the LIS values increasing amounts of either $Eu(fod)_3$ or $Eu(dpm)_3$ were added to a solution of ca. 3 mg of substrate in 0.5 ml $CDCl_3$. The LIS for the concentration ratio R_0:S_0 = 1:1 ("1:1 complex") were obtained by extrapolation of 4-6 different reagent concentrations. The experimental data were simulated using a combined COORD and LIS programme COOLIS, allowing a convenient variation of internal molecular parameters (especially torsional angles) for direct input in the LIS calculation (COOLIS written in BASIC for a MacIntosh PC).

Compound **1** was obtained from the underground parts of *Artemisia douglasiana* Bess. in Hook (compare [8]).

1: $[\alpha]_D^{20}$ = -14°; $[\alpha]_{436}^{20}$ = -21° (c= 0.5, $CHCl_3$). UV [EtOH, λ/nm (ε)]: 293 (14 700), 279 (17 200), 267 (12 200), 253 (sh, 7 200), 225 (28 400), 218 (21 300). CD [EtOH, λ/nm (Δε)]: 310 (-1.17), 295 (+1.12), 280 (+2.65), 265 (+2.50), 253 (+1.70), 238 (sh, +1.10).

300 g fresh air dried underground parts of *A. selengensis* Turcz. ex Bess. afforded after the usual workup [7] 150 mg of epoxide **2**.

(+)-(3S,4R,5S) - (2E)- 3,4-Epoxy-(2,4-hexadiynyliden) - 1,6-dioxaspiro[4.5]decane (**2**) : Colourless crystals, m.p. 121-122°C. $[\alpha]_D^{20}$ = +259°; $[\alpha]_{436}^{20}$ = +626° (c= 0.5, $CHCl_3$). IR (CCl_4, cm^{-1}): 2942 s, 2909m, 2882w, 2865w, 2844w, 2146m, 1645s, 1466w, 1438m, 1384s, 1355m, 1334w, 1297w, 1283s, 1268s, 1231s, 1195s, 1158m, 1138s, 1100s, 1080m, 1063m, 1047s, 1009s, 967s, 944m, 920m, 890s, 856s, 848m, 688m. UV [EtOH, λ/nm (ε)]: 293 (14 500), 279 (17 000), 266 (12 300), 252 (sh, 6 600), 224 (28 900), 217 (sh, 24 000). CD [EtOH, λ/nm (Δε)]: 305 (-0.92), 297 (+2.12), 280 (+4.10), 263 (+3.53), 253 (+2.20), 225 (+8.2), 216 (+12.0). MS [70 eV, 50°C, m/z (rel.int.)]: 230.094. (21%, M^+, $C_{14}H_{14}O_3$ affords 230.0943), 127 (18), 126 (100, $C_7H_{10}O_2^+$, comp.Ref.[19]), 125 (11), 104 (5), 97 (6), 76 (16), 71 (15); no other peaks >4%. ^{1}H and ^{13}C NMR see Table 1.

3: A solution of 20 mg **1** in dry ether was treated with a small amount of LAH. After 5-10 min TLC showed a complete reaction. After

addition of a small amount of water the Al-hydroxide precipitate was filtered off. The clear solution contained 15 mg of pure carbinol **3**. $[\alpha]_D^{20}$ = -41°; $[\alpha]_{436}^{20}$ = -81° (c= 0.3, $CHCl_3$). UV [EtOH, λ/nm (ε)]: 292 (12 400), 278 (15 900), 264 (12 500), 250 (sh, 6 600), 222 (26 300), 214 (24 200). CD [EtOH, λ/nm (Δε)]: 309 (+0.71), 294 (+0.77), 284 (+0.30), 273 (-0.46), 260 (-0.91), 247 (-0.55).

4: LAH reduction of **2**. $[\alpha]_D^{20}$ = +123°; $[\alpha]_{436}^{20}$ = +270° (c= 0.5, $CHCl_3$). UV [EtOH, λ/nm (ε)]: 292 (12 700), 277 (16 500), 263 (12 100), 252 (sh, 6 400), 222 (24 500), 216 (23 800). CD [EtOH, λ/nm (Δε)]: 310 (-0.68), 291 (+0.67), 280 (+1.75), 265 (+1.95), 250 (+1.20), 237 (sh, +0.50).

Horeau esterification of carbinols **3** and **4**: A mixture of 4 mg carbinol and 30 mg of freshly prepared racemic 2-phenylbutanoic anhydride in 1 ml dry pyridine was allowed to stand 2 days in the dark. After hydrolyzation (aqu.$NaHCO_3$) the neutral components were extracted with ether. From the acidified aqueous layer 2-phenylbutanoic acid was isolated by extraction with benzene and the optical rotation determined in a minimum amount of this solvent [17,18]. In both cases the sign of the rotation was positive (+0.023 in the case of **3** and +0.011 in the case of **4**) indicating *R*-configuration for C6 in both compounds. The neutral components (diastereomeric ester mixtures **5** and **6**) were analyzed by ^{1}H NMR to obtain information on the optical yield of the reaction.

Diastereomeric mixture **5** [73% (*R*)-2-phenylbutanoic ester and 27% (*S*)-ester of **3**; corresponding to an optical yield of 46%]: ^{1}H NMR ($CDCl_3$, ∂/ppm) 7.25-7.35 (m, aromat.H), 5.10 and 5.07 (d, 0.27+0.73 H, J= 5 Hz, 6-H), 4.99 (br.s, 1H, 9-H), 3.60-3.80 (m, 2H, 1-H), 3.50 and 3.44 (t, 0.27+0.73 H, J=7 Hz, -CO-CH<), 3.19 and 3.12 (ddd, 0.73+0.27 H, J= 18, 5, and 2.3 Hz, 7-H*trans*), 2.79 and 2.64 (d, 0.73+0.27 H, J= 18 Hz, 7-H*cis*), 2.00-2.20 (m, 2H, >CH-CH_2-CH_3), 1.98 (s, 3H, =C-CH_3), 1.2-1.9 (m, 6H), 0.88 (t, 3H, -CH_2-CH_3).

Diastereomeric mixture **6** [67% (*R*)-2-phenylbutanoic ester and 33% (*S*)-ester of **3**; corresponding to an optical yield of 34%]: ^{1}H NMR ($CDCl_3$, ∂/ppm) 7.27-7.37 (m, aromat.H), 4.86-5.03 (m, 2H, 6-H + 9-H), 3.63-3.90 (m, 2H, 1-H), 3.57 and 3.49 (t, 0.67+0.33 H, J= 7 Hz, -CO-CH<), 3.26 and 3.14 (ddd, 0.67+0.33 H, J= 17, 7.5, and 0.5 Hz, 7-H*trans*), 2.82-2.93 (m, 1H, 7-H*cis*), 2.00-2.20 (m, 2H, >CH-CH_2- CH_3), 1.98 (s, 3H, ≡C-CH_3), 1.3-1.9 (m, 6H), 0.88 (t, 3H, -CH_2-CH_3).

Equilibrations **1** ⇌ **2** and **3** ⇌ **4**: 4 mg of each of the compounds **1-4** were dissolved in MeOH/Et_2O = 3:1 and 2-4 small crystals (~1mg) of *p*-toluenesulfonic acid were added. The progress of the reaction was controlled by TLC (petrol ether/ether 8:2 for **1** ⇌ **2** and 6:4 for **3** ⇌ **4**; in both cases the *anti*-isomers were less polar). After 6 h the equilibrations were stopped since increasing amounts of polar decomposition products were formed. Run 1: ~0.2 mg **2**, 2.8 mg **1**. Run 2: ~1.2 mg **1**, 1.8 mg **2**. Run 3: ~0.2 mg **4**, 2.7 mg **3**. Run 4: ~1 mg **3**, 2 mg **4**. The components of the four runs were isolated by TLC and the identity of the compounds was checked by ^{1}H NMR (for purity), UV (determination of the concentrations), and CD (for correlation of the absolute configurations of **1**, **3** with **2**, **4**).

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