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CIRCULAR DICHROISM OF C-7, C-6 *TRANS*-FUSED GUAIANOLIDES OF *CENTAUREA SCOPARIA**

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Key Word Index—*Centaurea scoparia*; Asteraceae; sesquiterpene lactones; C-7, C-6 *trans*-fused guaianolides; absolute configuration; CD; extension of Geissman rule.

Abstract—The CD spectra of eight guaianolides from the aerial parts of *Centaurea scoparia* have been investigated. Most of these compounds contain a C-7, C-6 *trans*-fused α-methylene γ-lactone moiety and display negative cotton effects in the range of 252–271 nm for the nπ* transition of the α-methylene γ-lactone chromophore and a positive Cotton effect between 216–225 nm in case of a second chromophore in 8*S*-position for 4′-hydroxymethacrylates and between 241–246 nm for 4′-hydroxytiglates, which may be used for the determination of the absolute configuration of such guaianolides on the basis of spectral correlations with chlorojanerin, the absolute configuration of which was established by X-ray analysis.

INTRODUCTION

In the course of our phytochemical investigation of the aerial parts of *Centaurea scoparia* Sieb. we have already reported the isolation and structure elucidation of eight guaianolides **1–8** [1, 2]. Their structures and relative stereochemistries were mainly established by NMR-spectroscopic methods. These studies led to the assignment of a *trans*-fusion between the α-methylene γ-lactone moiety and the seven-membered carbocyclic ring at C-7 and C-6 [1, 2].

An early attempt to relate the position and absolute stereochemistry of the α-methylene γ-lactone ring of the sesquiterpene lactones to the sign of its Cotton effect in CD curves in the range 246–261 nm was made by Geissman *et al.* [3, 4]. In his well-known general rule Geissman suggested for sesquiterpene lactones with this chromophore in position C-7 that, regardless of the structural type of the sesquiterpene lactone, *cis*-fused lactones closed toward C-8 as well as those *trans*-fused closed toward C-6 give negative Cotton effects, whereas those *cis*-fused closed toward C-6 as well as those *trans*-fused closed toward C-8 show positive values [3, 4]. Exceptions were observed for ambrosiol, ambrosiol diacetate, apoludin, psilostachyin and psilostachyin C [4]. The given explanations are not all convincing in the light of our findings and will be discussed subsequently. Geissman was mainly concerned with the nπ* transition of the α-methylene γ-lactone chromophore, whereas its ππ* transition had been neglected. Other chromophores also present were cyclic ketones and enones as well as *trans*-annularly conjugated C=C bonds [4]. The first mention of the ππ* transition of the α-methylene γ-lactone chromophore was that of the guaianolide dehydrocostus lactone (**9**) which exhibits a negative Cotton effect at 223 nm (Δε − 3.64) in addition to that of the nπ* transition at 265 nm (Δε − 0.25) [5]. The germacranolide jurineolide (**10**) contains in addition to the unsaturated lactone moiety a second chromophore, a 4-hydroxyangelate, at the chiral centre C-8. Its CD spectrum displays a negative band at 263 nm (Δε − 1.48) for the nπ* transition, a strong positive band at 221 nm (Δε + 44.8) together with a negative band at 199 nm (Δε − 34.2) which were assigned to the unsaturated lactone and to the overlapping nonconjugated C=C bonds in the ten-membered ring. The positive, instead of the expected negative sign for this maximum at 221 nm, was ascribed to the overlap of the ππ* transitions of the unsaturated lactone and the transannular conjugation system. Strangely enough the 4-hydroxyangelate chromophore at C-8 was not taken into consideration at all.

Meanwhile the Geissman rule has frequently been applied to the determination of the absolute configuration of C-7 in the α-methylene γ-lactone ring of sesquiterpene lactones [6–11], but with the exception of [12] the influence of additional unsaturated ester chromophores at adjacent chirality centres on the principal α-methylene γ-lactone chromophore has not been described.

Therefore, in this work both chromophores contributing to the CD curves of the eight guaianolides **1–8** with such unsaturated sesquiterpene ester lactone structural features have been thoroughly studied with the aim of determining their absolute configurations.

*Dedicated to Professor Hans Möhrle on the occasion of his 65th birthday.

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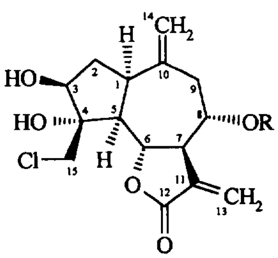

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2: B
3: C
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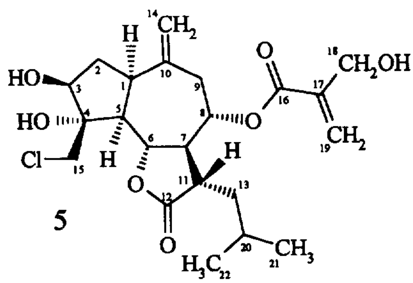

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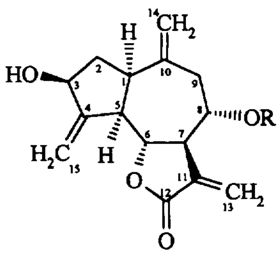

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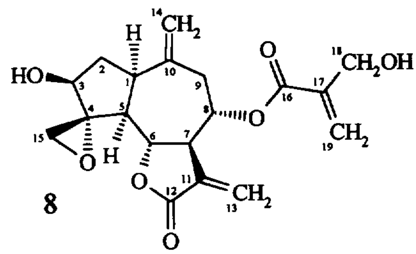

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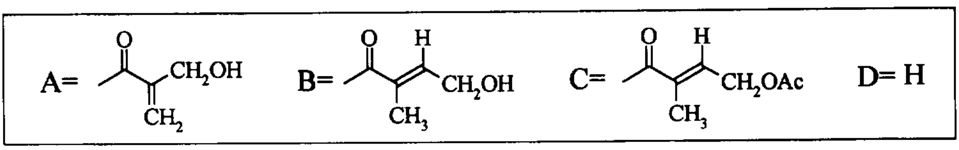

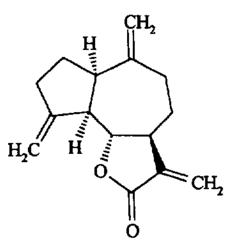

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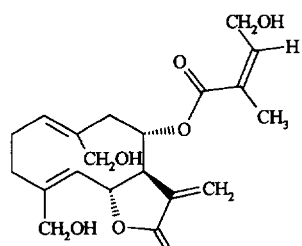

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The CD spectrum of **2** has been measured earlier [13] without interpretation and strong deviations in the short wave range from our findings. Recently the CD data for **1** and **8** were published by Budesinsky *et al.* [14]. Comparison with our data shows similarity for the negative Cotton effect of the $n\pi^*$ transition of the α-methylene γ-lactone chromophore in the range of 259–267 nm, whereas Cotton effects at shorter wave lengths are missing with the exception of one strong positive Cotton effect for **1** at 209 nm in contrast to our findings.

RESULTS AND DISCUSSION

Chlorojanerin (**1**) is a chlorine-containing crystalline guaianolide. Its structure and absolute configuration were established prior to the CD study by means of a single crystal X-ray crystallographic analysis. Thus it has a *trans/anti/cis*-fusion of the α-methylene γ-lactone moiety and the seven-membered carbocyclic ring at C-7 and C-6 and the five-membered ring at C-5 and C-1, respectively, with the absolute configuration (1*R*,3*S*,4*R*,5*S*,6*S*,7*R*,8*S*) [12].

Chlorojanerin (**1**) contains, as a second chromophore a 4-hydroxymethacrylate at C-8 in addition to that of the α-methylene γ-lactone. Its CD curve (Figure 1) shows two Cotton effects. The negative Cotton effect at 260 nm for the $n\pi^*$ transition of α-methylene γ-lactone chromophore is in accordance with the Geissman's rule, which relates this negative Cotton effect to the C-7,C-6 *trans*-fusion of the γ-lactone ring with 7*R* configuration [3, 4].

However the strong Cotton effect at 225 nm is positive and opposite in sign to that expected for the $\pi\pi^*$ transition of α-methylene and γ-lactone chromophore [5]. This inconsistency in the range of the $\pi\pi^*$ transition can only result from overlap of the maxima of the 4-hydroxymethacrylate and the α-methylene γ-lactone chromophores with a strong positive contribution of the ester chromophore, which is missing in the corresponding alcohol chlorohyssopifolin B (**4**). The latter's CD spectrum (Figure 1) gives evidence of this explanation. The contribution of the $\pi\pi^*$ transition of the α-methylene γ-lactone chromophore of **4** is nearly zero in the range of the $n\pi^*$ transition of the unsaturated ester chromophore

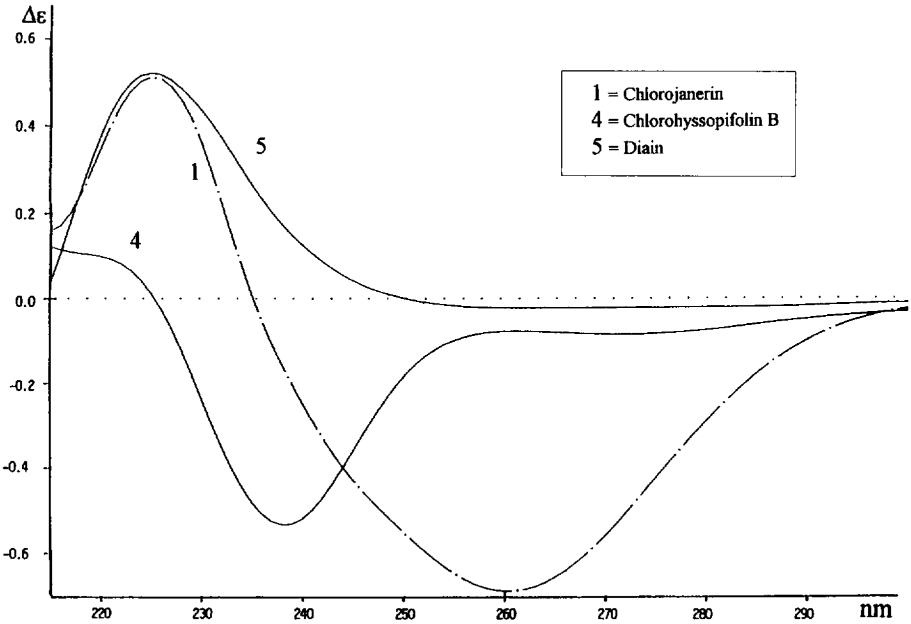

Fig. 1. CD spectra of compounds **1**, **4** and **5** (MeOH).

around 225 nm, but with a bathochromically shifted negative Cotton effect at 238 nm.

Moreover the CD curve of diain (**5**) (Figure 1), which is an α,β-saturated lactone (C-7), shows in comparison with the CD curve of **1** only one strong positive Cotton effect at 225 nm. This effect can only result from the 4-hydroxymethacrylate chromophore at C-8 with *S*-configuration. This result supports our interpretation of the CD curve of **1**. In conclusion the CD curve of **1** can be used as a standard for deriving the absolute configurations of our C-7, C-6 *trans*-fused guaianolide (*S*)-8-*O*-(4-hydroxymethacrylates).

Both cynaropicrin (**6**) and janerin (**8**) contain, in addition to the α-methylene γ-lactone moiety, the 4-hydroxymethacrylate chromophore at C-8. They display the typical negative Cotton effect at 259 and 263 nm, respectively (Figure 2) together with a positive maximum at 216 and 222 nm, respectively. Spectral correlation with **1** leads to the (7*R*)-configuration with *trans*-lactone fusion at C-6 and with a (8*S*)-4-hydroxymethacrylate moiety. The complete configurations at the remaining asymmetric centres are determined as (1*R*,3*S*,5*S*,6*S*,7*R*,8*S*) for **6** and as (1*R*,3*S*,4*R*,5*S*,6*S*,7*R*,8*S*) for **8**, respectively.

Chlorohyssopifolin B (**4**) and deacylcynaropicrin (**7**) as *trans*-fused α-methylene γ-lactones closed toward C-6 exhibit a weak but distinct negative Cotton effect for their nπ* transition at 271 nm for **4** hypsochromically shifted to 252 nm for **7**. The negative Cotton effect for the ππ* transition of this chromophore is observed at 238 nm and again hypsochromically shifted to 230 nm for **7**, respectively (Figure 2). The loss of the C-4-chirality centre influences the position but not the sign of the Cotton effect for both transitions. The absolute configuration of C-7 of **4** and **7** may therefore be deduced by spectral correlation with **1** as (7*R*) with *trans*-junction of the lactone moiety to C-6 if one considers the missing influence of the second chromophore 8-*O*-(4-hydroxymethacrylate). The configurations at the remaining chirality centres are derived in the usual manner as (1*R*,3*S*,4*R*,5*S*,6*S*,7*R*,8*S*) for **4** and as (1*R*,3*S*,5*S*,6*S*,7*R*,8*S*) for **7**.

In contrast 8-deacylcentaurepensin 8-*O*-(4-hydroxy)-tiglate (**2**) and chloroscoparin (**3**) contain, in addition to the standard chromophore of the unsaturated γ-lactone, the 4-hydroxytiglate and the 4-acetoxytiglate ester functions at C-8 as the second chromophore. Additionally to the negative Cotton effects at 269 or 271 nm for the nπ* transition of the α-methylene γ-lactone chromophore (Figure 2) they display bathochromically shifted positive Cotton effects at 241 and 246 nm, respectively, for the nπ* transition of the 4-hydroxytiglic ester chromophores, which cause bathochromic shifts of 16–21 nm compared to the CD curve of **1** (see Experimental).

Additionally are observed a negative band at 223 nm for **2**, which is associated with the ππ* transition of the unsaturated lactone, and a positive second band at 218 nm for **3** resulting from overlap of the two ππ* transitions of both the unsaturated lactone and ester moiety. The signs of the maxima in the range from 260–270 nm of **2** and **3** are in accord with that of **1** indicating their 7*R*-configuration with a *trans*-fused lactone linkage to C-6. The positive band may conceivably be an indicator for the (8*S*)-4-hydroxytiglate substitution. The stereochemistry at the remaining stereo centres could be deduced on (7*R*) as (1*R*,3*S*,4*R*,5*S*,6*S*,7*R*,8*S*) for **2** and as (1*R*,3*S*,4*R*,5*S*,6*S*,7*R*,8*S*) for **3**.

Diain (**5**) with a saturated γ-lactone moiety contains only the 4-hydroxymethacrylate chromophore at the C-8-chirality centre. It gives rise to a remarkably strong

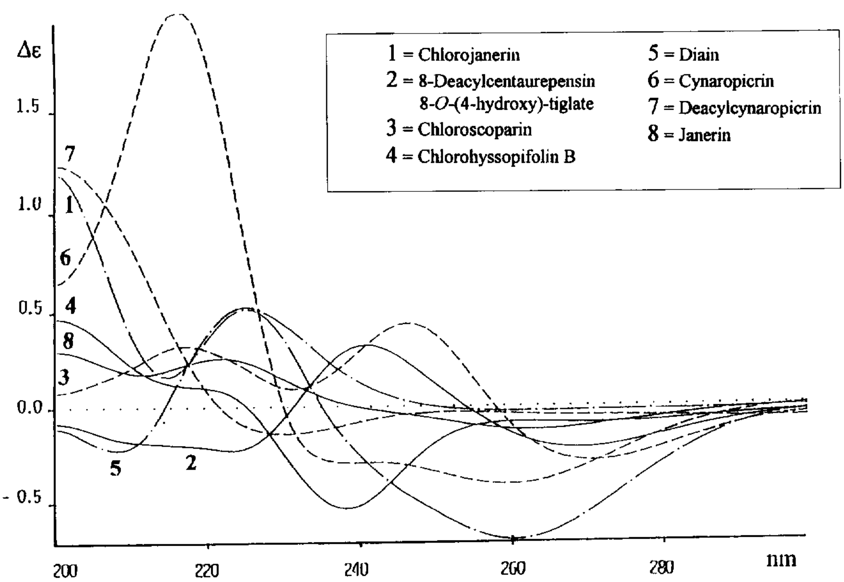

Fig. 2. CD spectra of compounds **1**–**8** (MeOH).

positive Cotton effect at 225 nm for the $n\pi^*$ transition with a negative Cotton effect at 208 nm for the $\pi\pi^*$ transition (Figures 1 and 2), the former of which matches perfectly with the corresponding positive band of **1** indicating the (8*S*)-configuration. The configuration at the other asymmetric centres could be determined relative to (8*S*). Of no diagnostic significance but observable is a very weak broad negative Cotton effect without a maximum in the range from 250 to 300 nm for the $n\pi^*$ transition of the lactone carbonyl group.

The Geissman rule has been shown to be generally applicable for elucidating the absolute configuration of carbon C-7 of seven 6,7-*trans*-fused α-methylene γ-lactone ester sesquiterpene lactones with the range of the maxima arising from the $n\pi^*$ transition of α,β-unsaturated lactones having to be widened up to 271 nm. The position of the Cotton effect is clearly influenced by the type of the second chromophore adjacent to the crucial chirality centre C-7. The $n\pi^*$ band is found between 260–263 nm in lactones with 4-hydroxymethacrylates at C-8 and is shifted to 269–271 nm in lactones with 4-hydroxytiglates in position C-8. This might be due to a differing chiral overlap of the two C=C double bonds in the two separated chromophores. The $\pi\pi^*$ transition maximum of the unsaturated lactone is negative in sign but often hidden under the strong positive Cotton effect of the unsaturated ester in the range 215–240 nm and therefore of limited value. Irregularities in the sign of the Cotton effect associated with the $n\pi^*$ transition of α,β-unsaturated sesquiterpene lactones as observed in ref. [4] cannot be solely correlated with an oxygen function near the ring oxygen of the C-6 fused lactone but also with the *trans*-junction of their A/B rings, since all but one of our investigated compounds are oxygenated in the 4α-position, whereas the A/B ring junction is *cis*.

In extension of the Geissman rule we have found a second chiral indicator for α,β-unsaturated 6,7-*trans*-fused sesquiterpene lactone with an unsaturated ester moiety in position C-8. This chromophore exhibits a positive Cotton effect in the case of 8*S*-4-hydroxymethacrylates in the range 216–225 nm and for 8*S*-4-hydroxytiglates between 241–246 nm. This holds also true for α,β-saturated 6,7-*trans*-fused sesquiterpene lactones containing one of these unsaturated ester moieties, i.e. the absolute configuration of this class of constituents may be correlated via the C-8 instead of the C-7 chirality centre.

EXPERIMENTAL

Details for collection and identification of plant materials, a voucher specimen, extraction, isolation and identification of the investigated guaianolides are reported elsewhere [1, 2]. CD curves were measured on a CD 6, Jobin Yvon Instruments S.A. in MeOH sols at 20° and in cells of 0.5 cm bath length.

CD data of compounds **1–8**. Chlorojanerin (**1**): $\sim \Delta\varepsilon_{200} + 1.20$, $\Delta\varepsilon_{215} + 0.158$ (min), $\Delta\varepsilon_{225} + 0.510$, $\Delta\varepsilon_{260} - 0.688$ (MeOH; $c\,2.5 \times \mathrm{E}10^{-3}\,\mathrm{mol\,l^{-1}}$); 8-Deacylcentaurepensin 8-*O*-(4-hydroxy)-tiglate (**2**): $\Delta\varepsilon_{223} - 0.221$, $\Delta\varepsilon_{241} + 0.320$, $\Delta\varepsilon_{269} - 0.213$ (MeOH; $c\,1.4 \times \mathrm{E}10^{-3}\,\mathrm{mol\,l^{-1}}$); Chloroscoparin (**3**): $\Delta\varepsilon_{217} + 0.320$, $\Delta\varepsilon_{246} + 0.432$, $\Delta\varepsilon_{271} - 0.282$ (MeOH; $c\,2.2 \times \mathrm{E}10^{-3}\,\mathrm{mol\,l^{-1}}$); Chlorohyssopifolin B (**4**): $\Delta\varepsilon_{238} - 0.532$, $\Delta\varepsilon_{271} - 0.0845$ (MeOH; $c\,2.5 \times \mathrm{E}10^{-3}\,\mathrm{mol\,l^{-1}}$); Diain (**5**): $\Delta\varepsilon_{208} - 0.519$, $\Delta\varepsilon_{225} + 0.521$ (MeOH; $c\,1.2 \times \mathrm{E}10^{-3}\,\mathrm{mol\,l^{-1}}$); Cynaropicrin (**6**): $\Delta\varepsilon_{216} + 2.010$, $\Delta\varepsilon_{259} - 0.407$ (MeOH; $c\,0.29 \times \mathrm{E}10^{-3}\,\mathrm{mol\,l^{-1}}$); Deacylcynaropicrin (**7**): $\Delta\varepsilon_{230} - 0.136$, $\Delta\varepsilon_{252} - 0.0269$ (MeOH; $c\,0.84 \times \mathrm{E}10^{-3}\,\mathrm{mol\,l^{-1}}$); Janerin (**8**): $\Delta\varepsilon_{211} + 0.172$, $\Delta\varepsilon_{222} + 0.254$, $\Delta\varepsilon_{263} - 0.116$ (MeOH; $c\,2.89 \times \mathrm{E}10^{-3}\,\mathrm{mol\,l^{-1}}$).

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REFERENCES

1. Youssef, D. and Frahm, A. W. (1994) *Planta Med.* **60**, 267.
2. Youssef, D. and Frahm, A. W. (1994) *Planta Med.* **60**, 572.
3. Waddell, T. G., Stöcklin, W. and Geissman, T. A. (1969) *Tetrahedron Letters* **17**, 1313.
4. Stöcklin, W., Waddell, T. G. and Geissman, T. A. (1970) *Tetrahedron* **26**, 2397.
5. Suchy, M., Dolejs, L., Verout, V., Sorm, F., Snatzke, G. and Himmelreich, J. (1969) *Coll. Czech. Chem. Comm.* **34**, 229.
6. Herz, W., Bhat, S. V., Crawford, H., Wagner, H., Maurer, G. and Faraks, L. (1972) *Phytochemistry* **11**, 371.
7. Vichnewski, W. and Gilbert, B. (1972) *Phytochemistry* **11**, 2563.
8. Irwin, M. A. and Geissman, T. A. (1973) *Phytochemistry* **12**, 863.
9. Corbella, A., Gariboldi, P. and Jommi, G. (1974) *Phytochemistry* **13**, 459.
10. Lee, K. H., Ibuka, T., Kozuka, M., McPhail, A. T. and Onan, K. D. (1974) *Tetrahedron Letters* **26**, 2287.
11. Osawa, T., Taylor, D., Suzuki, A. and Tamura, S. (1977) *Tetrahedron Letters* **13**, 1169.
12. Youssef, D. (1995) *Ph.D. Thesis*, Freiburg University, Freiburg, Germany.
13. Rustaiyan, A., Sharif, Z., Tajarodi, A., Ziesche, J. and Bohlmann, F. (1984) *Planta Med.* **50**, 193.
14. Budesinsky, M., Nowak, G., Rychlewska, U., Hodgson, D., Saman, D., Daniewski, W. M., Drozdz, B. and Holub, M. (1994) *Collect. Czech. Chem. Commun.* **59**, 1175.