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ABSOLUTE CONFIGURATION OF FOUR CLEISTANTHANE DITERPENES FROM VELLOZIACEAE

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Key Word Index—*Vellozia* spp.; Velloziaceae; diterpenes; cleistanthanes; absolute configuration.

Abstract—The absolute configurations of four cleistanthane diterpenes isolated from several species of *Vellozia* were determined by circular dichroism measurements.

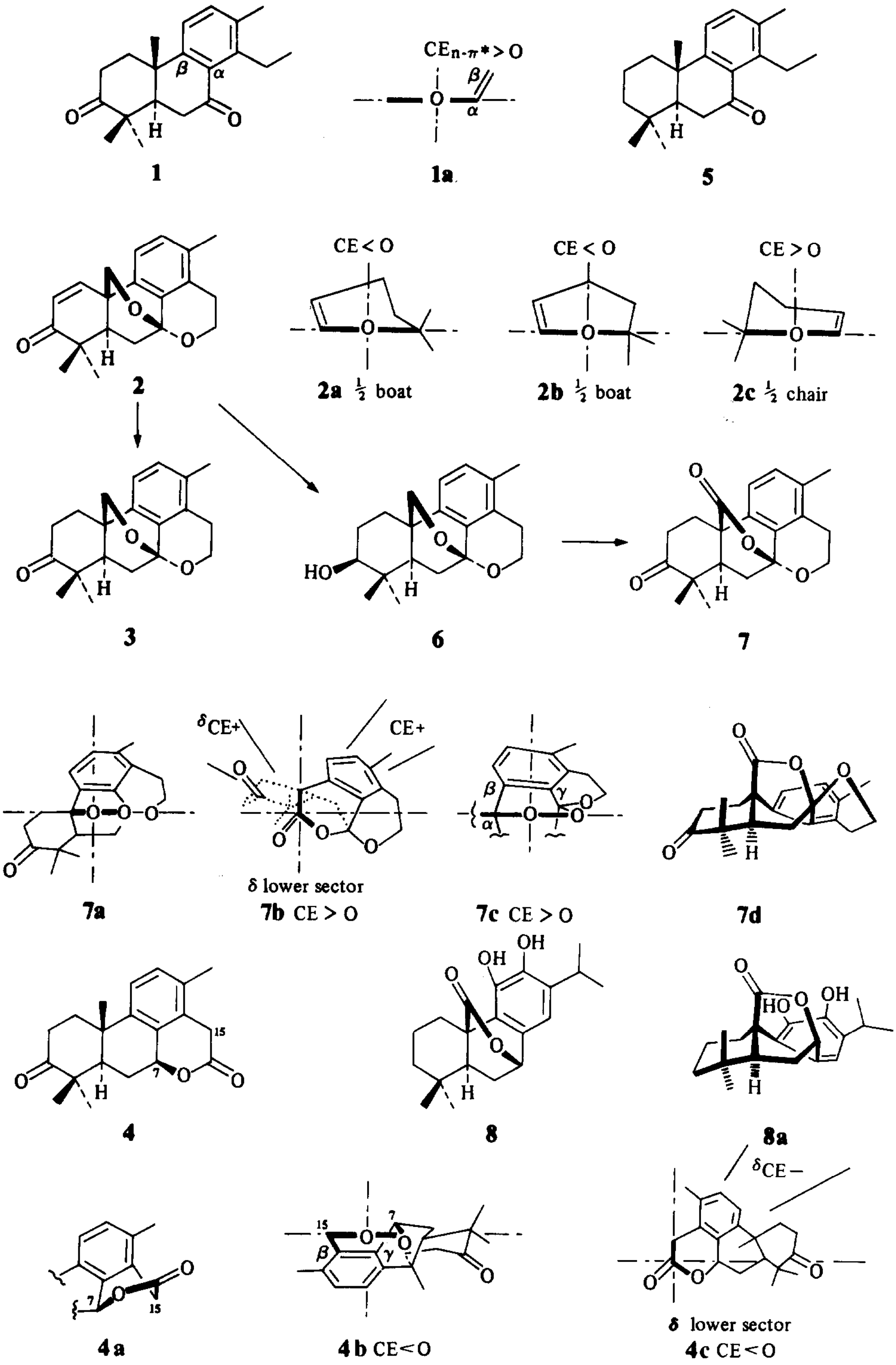
INTRODUCTION

Cleistanthane and pimarane diterpenes are common constituents of the Velloziaceae family [1]. We showed recently that both classes of diterpenes from *Vellozia flavicans* and *V. leptopetala* belong to the normal series [1], *in contrast to the pimaranes and cleistanthanes from* the Euphorbiaceae that are all members of the antipodal series [2]. In previous communications [3–6] we described the isolation and structure determination of various new cleistanthane derivatives (**1**–**4**) obtained from several *Vellozia* species. Only the relative stereochemistries were reported. This work reports on the absolute configurations of these compounds.

RESULTS AND DISCUSSION

Determination of the absolute configuration of cleistantha-8,11,13-triene-3,7-dione (**1**) [3] came directly from the positive Cotton effect ($[\theta]_{338} + 9924$) associated with the n–π^* transition of the α,β-unsaturated keto chromophore (**1a**) (see Scheme 1) [7]. This showed that **1** belongs to the normal series as does diterpene **5** reported earlier ($[\theta]_{336} + 4005$) [1]. Compound **1** is, thus, [5*S*,10*S*]-cleistantha-8,11,13-triene-3,7-dione.

Catalytic controlled reduction of 7α,16; 7β,20-diepoxycleistantha-1,8,11,13-tetraen-3-one (**2**) into **3** has already been briefly described [4]. It seemed, therefore, straightforward to determine the absolute configurations of **2** and **3** by CD measurements of the latter compound. However, the conformation of ring-A in **3** could not be assumed *a priori* since it is known that 4,4-dimethyl-3-keto steroids display anomalies in their CD and ORD spectra [8, 9]. In addition, there is a lack of CD studies on suitable models. Therefore, direct determination of the absolute configuration of **3** by application of the octant rule was not reliable enough. In addition, examination of Dreiding models of **2** showed that ring-A may exist in three stable conformations, two half-boats (**2a** and **2b**) and one half-chair (**2c**). Here again, CD studies might be helpful for conformational analysis, but were ruled out for unambiguous determination of the absolute configuration of **2**. Hence, the use of a chromophore in a rigid system should be the best way for determination, by CD techniques, of the absolute stereochemistries of cleistanthanes **2** and **3**. In both compounds, ring-A presents conformational flexibility, whereas the remaining part of the molecule is extremely rigid, due to the presence of the pyrane and epoxymethane rings. Thus, the introduction of a suitable chromophore in the rigid part of the molecule became of particular interest. This was achieved by catalytic hydrogenation of **2** into **6** followed by Jones oxidation to afford **7** [4] in which the lactone moiety fulfilled the above requirements. The chiroptical properties of lactones have not been studied as extensively as have those of the saturated keto chromophore since the absorption maximum of lactones occurs in a less accessible region of the UV spectrum. Klyne's lactone sector rule [10] and Snatzke's sector comet rule [11] consider that the Cotton effect of lactones originates in asymmetrization of the chromophore by substitution. Projections **7a** (comet) and **7b** (sector) show that a positive Cotton effect may be predicted if **7** belongs to the normal series of diterpenes, whereas a negative Cotton effect should be observed for the antipodal series [10, 11]. The CD curve of **7** showed a positive Cotton effect ($[\theta]_{236} + 63\,074$); one may, thus, conclude that **7** is a diterpene of the normal series. However, it has also been suggested that the Cotton effects associated with a lactone should be interpreted in terms of ring chirality [12, 13]. Bridged γ-lactones, particularly of the (3, 2, 1)-type, have been studied in that way and the sign of the associated Cotton effect has been shown to assist in the determination of absolute configurations [14]. δ-Lactones bridging an unsaturated ring (as in **7**) [14] and β,γ-unsaturated acid derivatives [15] have received special treatment. Application of these rules [15] to the conformer **7c** corroborated our former conclusion on the absolute configuration of **7**. However, since the values of the CD maximum of **7** is an order of magnitude greater than the values usually obtained for lactones, the observed CD is probably due to the chiral interaction between the lactone and the ^1L_a aromatic absorption [16]. Hence, final interpretation of the positive Cotton effect of lactone **7** came from comparison with the CD curve of the model compound carnosol (**8**), which is known, by



Scheme 1.

chemical correlation with (+)-ferruginol to belong to the normal series [17]. The lactone ring of 7 forces ring-B to adopt a boat conformation (7d) and, on the whole, the chromophore of 7 is identical to that of 8 (see 8a). The CD curve of 8 presented a positive Cotton effect ($[\theta]_{242}$ +57 895), proving that 7 and 8 possess the same absolute configuration. Consequently, diterpenes 2 and 3 belong to the normal series, as concluded above on the basis of Klyne's or Snatzke's treatments and also on the basis of ring chirality analysis. Hence, 2 is [5*S*,7*S*,10*R*]-7α,16;

7β,20-diepoxycleistantha-1,8,11,13-tetraen-3-one and **3** is [5*S*,7*S*,10*R*]-7α,16; 7β,20-diepoxycleistantha-8,11,13-trien-3-one.

The fourth diterpene, 3-oxo-cleistantha-8,11,13-trien-(16 → 7β)-olide (**4**), had its structure and relative configuration deduced from spectral and chemical evidence [6]. Again, due to the 4,4-dimethyl effect [8], the 3-keto chromophore cannot be used for absolute configuration purposes. It seemed, therefore, more convenient to use the lactone as a chromophore. Dreiding models showed that the lactone ring is more stable in a slightly flattened boat conformation, with C-7 and C-15 at the flagpole positions (**4a**). In addition, an X-ray study of **4** proved that this is also the preferred conformation in the crystalline state [18]. Application of the ring chirality rule for γ-lactones [14] or of the rule for β,γ-unsaturated acid derivatives [15] to lactone **4** gave identical conclusions and showed that the observed negative Cotton effect of **4** ($[\theta]_{213}$ − 93 600) corresponds to projection **4b**, meaning that **4** is [5*S*,7*S*,10*S*] -3 -oxo -cleistantha -8,11,13 -trien -(16 → 7β)-olide, also a member of the normal series. Interpretation of the Cotton effect in terms of the comet (**4b**) and sector rules (**4c**) afforded an identical conclusion. Here again, the observed CD maximum corresponds more probably to chiral interaction between the lactone and the aromatic ^1L_a maximum [16]. The negative chirality observed is in agreement with the proposed absolute configuration.

These results are in total agreement with our previous work on other cleistanthane diterpenes from Velloziaceae [1] and, by extension, one may now assume that probably all the cleistanthanes from the family Velloziaceae are of the normal series.

Now that the absolute configurations have been determined, our CD studies on the 3-keto chromophore allow for the conformational analysis of ring-A. This will be the subject of another paper.

EXPERIMENTAL

All the equipment used for this work has been previously described [1].

CD spectra of diterpenes **1**, **4** *and* **8**. Compound **1** (3.66×10^{-4} M/l., C_6H_{12}): $[\theta]_{338}$ +9924, $[\theta]_{294}$ −9569. Compound **4** (6.41×10^{-4} and 6.41×10^{-5} M/l., MeOH); $[\theta]_{319}$ −624, $[\theta]_{285}$ +2496, $[\theta]_{213}$ −93 600. Compound **8** (3.45×10^{-5} M/l., MeOH): $[\theta]_{242}$ +57 894.

Catalytic hydrogenation of **2**. Compound **2** (1.0 g) in EtOAc (20 ml) was hydrogenated at 45 psi of H_2 on 10% Pd–C (100 mg). After 2 hr, the reaction medium was filtered and concd under red. pres. The solid thus obtained was crystallized several times from hexane–EtOAc (3:1) affording pure **6** (42 mg) as colourless plates: mp 104–106°; IR ν_{max}^{KBr} cm^{-1}: 3435, 2939, 2850, 1492, 1262, 1177, 1043, 910, 818; MS *m/z* (rel. int.): 314 $[M]^+$ (17), 284 (33), 283 (56), 265 (18), 258 (15), 241 (14), 227 (23), 199 (23), 199 (75), 197 (100), 185 (25), 181 (24), 160 (70); ^{1}H NMR (100 MHz, $CDCl_3$): δ1.06 (3H, *s*), 1.14 (3H, *s*), 2.18 (3H, *s*), 3.78–4.12 (3H, *m*), 4.28–4.52 (2H, *m*), 7.02 (2H, *s*); ^{13}C NMR (25.2 MHz, $CDCl_3$): δ18.0 (*q*), 18.7 (*q*), 26.7 (*q* + *t*), 27.3 (*t*), 29.2 (*t*), 34.7 (*t*), 36.7 (*s*), 40.1 (*s*), 41.6 (*d*), 65.5 (*t*), 72.4 (*t*), 76.0 (*d*), 98.8 (*s*), 123.9 (*d*), 128.3 (*d*), 130.5 (*s*), 134.1 (*s*), 134.4 (*s*), 135.0 (*s*).

Jones oxidation of **6**. Compound **6** (85 mg) in Me_2CO (5 ml) was stirred for 5 min at room temp. in the presence of Jones reagent (2 ml). Excess oxidizing reagent was then destroyed by adding a satd aq. soln of sodium bisulphite. The reaction medium was extracted exhaustively with $CHCl_3$. The organic layer was washed with H_2O and dryed over Na_2SO_4. Filtration and evaporation of the solvent furnished an oily residue which was purified by silica gel CC. The fraction eluted with hexane–EtOAc (85:15) afforded, after several crystallizations from hexane–EtOAc (9:1), colourless crystals of **7** (40 mg): mp 168–170°; IR ν_{max}^{KBr} cm^{-1}: 2947, 1745, 1702, 1464, 1257, 1202, 1182, 890, 833; MS *m/z* (rel. int.): 326 $[M]^+$ (1), 282 (14), 197 (100); ^{1}H NMR (100 MHz, $CDCl_3$): δ1.00 (3H, *s*), 1.22 (3H, *s*), 2.32 (3H, *s*), 3.10–3.40 (2H, *m*), 4.10 (1H, *ddd*, *J* = 3, 11, 12 Hz), 4.36 (1H, *ddd*, *J* = 2, 5, 12 Hz), 7.03 (1H, *d*, *J* = 8 Hz), 7.20 (1H, *d*, *J* = 8 Hz), ^{13}C NMR (25.2 MHz, $CDCl_3$): δ17.9 (*q*), 19.5 (*q*), 23.4 (*q*), 24.5 (*t*), 25.8 (*t*), 33.6 (*t*), 34.2 (*t*), 46.4 (*s*), 47.0 (*s*), 47.9 (*s*), 63.1 (*t*), 101.8 (*s*), 119.4 (*d*), 129.8 (*s*), 130.0 (*d*), 132.3 (*s*), 134.2 (*s*), 173.4 (s), 213.6 (*s*); CD ($7.05\ 10^{-5}$ and $4.90\ 10^{-4}$ M/l., MeOH): $[\theta]_{273}$ +2100, $[\theta]_{266}$ +2650, $[\theta]_{236}$ +63 074.

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