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CONFIRMATION OF THE ABSOLUTE CONFIGURATION OF DOLICHANTOSIDE AND ISODOLICHANTOSIDE BY SYNTHESIS FROM (−)-SECOLOGANIN*

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Key Word Index—(−)-Isodolichantoside; (−)-dolichantoside; absolute configuration; partial synthesis; strictosidine derivatives; vincoside derivatives; circular dichroism.

Abstract—Determination of the absolute configuration of (−)-dolichantoside and (−)-isodolichantoside was achieved by their preparation via the hydrochlorides of strictosidine and vincoside and their corresponding lactams from (−)-secologanin and tryptamine hydrochloride. Copyright © 1997 Elsevier Science Ltd

INTRODUCTION

During our phytochemical investigations of the Central American *Psychotria correae* (Rubiaceae) [2] and our structural work on its alkaloidal constituents, the new correantines [3, 4], correantosides [3, 4] and the already known isodolichantoside (**1**) [5, 6], an Australian group questioned the absolute configuration established for **1** [7]. For the dolichantoside/isodolichantoside series they doubted that the Cotton effect in the 270–300 nm range would be sufficient evidence to establish the configuration at C-3. They suggested from the published positive Cotton effect at 220 nm, the reverse 3*R*-configuration for dolichantoside (**2**) and, consequently, the 3*S*-configuration for **1**.

To settle the controversial discussions on the stereochemical arguments from the CD curves, we decided to establish the absolute configurations of **1** and **2** unambiguously by synthesis starting from (−)-secologanin (**3**).

RESULTS AND DISCUSSION

(−)-Secologanin (**3**) was subjected to a Pictet–Spengler-like condensation with tryptamine hydrochloride according to the method described by Battersby [8]. The mixture of the hydrochlorides of vincoside (**4**) and strictosidine (**5**) produced, which are epimeric at C-3, was separated chromatographically. Furthermore, both alkaloids were converted to the corresponding lactams **6** and **7**, respectively. NMR studies and particularly NOE measurements with these lactams (Fig. 1) connected the configuration of the proton at C-3 in the β-carboline system to the secologanin moiety of the molecules and thereby revealed the absolute configurations at that centre for both compounds.

The results allowed us to distinguish **4**, for which the 3*R*-configuration had already been determined by X-ray analysis [9], from **5** independently from published physico-chemical data.

N-Methylation converted **5** to dolichantoside (**2**) and **4** to isodolichantoside (**1**); the latter had been shown to be identical with the natural product isolated from *P. correae*. These results, therefore, determined the absolute configuration of isodolichantoside at C-3 to be *R* and corroborated our recent reports [3, 4].

Since the chemical stability of the free bases from **4** and **5** is rather limited, CD measurements were done with their hydrochlorides and, in addition, with the corresponding lactams **6** and **7**. In these studies compounds **4** and **5** showed very similar CD curves (Table 1), which did not allow an unambiguous distinction between the two epimers.

However, the CD curves of the corresponding lactams **6** and **7**, and also of the *N*-methylated alkaloids **1** and **2**, exhibited characteristic maxima in the 270–300 nm region. The compounds with the 3*R*-configuration—the lactam of vincoside (**6**) and isodolichantoside (**1**)—are characterized by negative Cotton effects in this region. Consequently, the CD curves of the compounds with the 3*S*-configuration, like the lactam of strictosidine (**7**) and dolichantoside

* Part 81 in the series 'Constituents of Tropical Medicinal Plants'. For part 80 see ref. [1].

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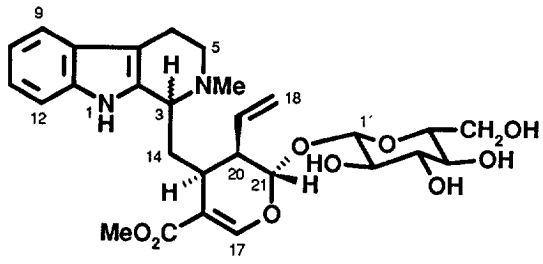
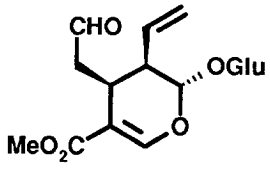


1: (3 R)
2: (3 S)



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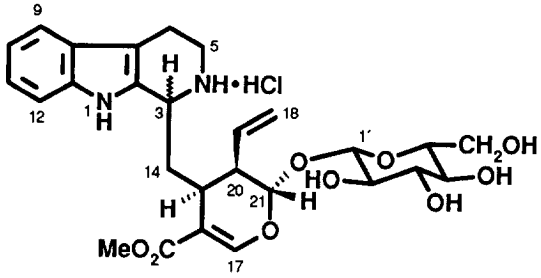
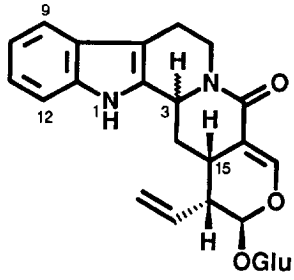


4: (3 R)
5: (3 S)



6: (3 R)
7: (3 S)

(**2**), exhibited a positive Cotton effect in the 270–300 nm range.

The Cotton effects at shorter wave lengths were also different but they obviously are less significant for the determination of the absolute configuration.

Therefore, our results determine the absolute configuration of isodolichantoside (**1**) to be 3*R* and corroborate the results of Angenot [5] and also the general rule of Klyne *et al.* [10].

EXPERIMENTAL

General. Mps: uncorr. Analytical TLC was performed on precoated plates (HPTLC plates, silica gel 60 F_{254}, Merck) using CH_2Cl_2–MeOH (4:1); detection: UV, anisaldehyde reagent [11]. Unless otherwise stated, $[\alpha]_D$ in MeOH at 21°, CD and UV in MeOH, IR in $CHCl_3$. Unless otherwise stated, ^1H NMR at 360 MHz and ^{13}C NMR at 62.9 MHz in CD_3OD with TMS as int. standard. EIMS at 70 eV. Unless key ions, only ions are given for $m/z \geqslant 100$ if rel. intensities $\geqslant 20\%$ and for $m/z < 100$ if rel. intensities $\geqslant 50\%$.

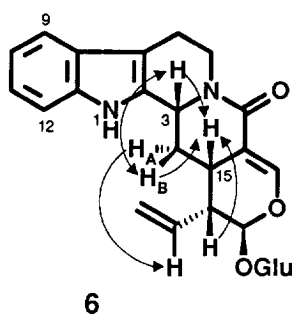
Origin of compounds

Isodolichantoside (**1**) was isolated from leaves of *P. correae* [3, 4]. Synthetic **1** was prepd from **4** by methylation using $NaBH_3CN$ and CH_2O [12].

Dolichantoside (**2**), isolated from *Strychnos gossweileri* [13], was a generous gift from Prof. L. Angenot, University of Liège, Faculté de Médecine, Institut de Pharmacie, Liège, Belgium. Synthetic **2** was prepd by methylation of **5** using $NaBH_3CN$ and CH_2O [12].

(−)-*Secologanin* (**3**) was kindly supplied by Dr R. T. Brown, University of Manchester, Department of Chemistry, Manchester, U.K. [14].

Vincoside hydrochloride (**4**). Partial synthesis was carried out with 50 mg of (−)-secologanin (**3**) and 25.2 mg tryptamine HCl according to ref. [8]. Sepn of



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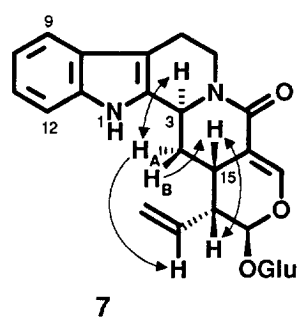

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Fig. 1. Important NOE enhancements observed for compounds **6** and **7**.

Table 1. Characteristic Cotton effects in the CD curves of compounds **1**, **2** and **4**–**7**

3*R*-Series		3*S*-Series	
Vincoside hydrochloride (**4**)		Strictosidine hydrochloride (**5**)	
λ (nm)	Δε	λ (nm)	Δε
217	+11.32	220	+24.33
235	−12.17	234	−28.30
265	−3.40	280	−1.13
		288	−1.47
Lactam of vincoside (**6**)		Lactam of strictosidine (**7**)	
λ (nm)	Δε	λ (nm)	Δε
220	+14.94	225	−6.47
234	−23.41		
268	−3.49	270	+10.46
295	−1.99	295	+2.49
Isodolichantoside (**1**)		Dolichantoside (**2**)	
λ (nm)	Δε	λ (nm)	Δε
226	−3.8	222	+0.60
240	+3.8	236	−2.18
270	−2.2		
280	−2.7	283	+0.27
290	−4.3		

the reaction mixt. by CC using Fractogel TSK HW-40 (S) (MeOH–0.1 N HCl (4:1)) and then HPLC on Lichrosorb RP18 (MeOH–H_2O–0.1 N HCl (2:1:1)) yielded **4** (14 mg) and **5** (16.5 mg). TLC: R_f 0.29; anisaldehyde: blue. $[\alpha]_D$ −133° (*c* 1.12) (ref. [8] $[\alpha]_D$ −143° (MeOH; for *c*: no data)). For IR and UV see ref. [8]. ^{1}H NMR: δ 2.51 (1H, *ddd*, J_1 = 15, J_2 = 7, J_3 = 4 Hz, H-14A), 2.18 (1H, *ddd*, J_1 = 15, J_2 = 10, J_3 = 5 Hz, H-14B), 2.83 (1H, *m*, H-20), 3.00–3.19 (3H, *m*, H-6A, H-6B, H-15), 3.20–3.45 (4H, *m*, H-2′, H-3′, H-4′, H-5′), 3.52 (1H, *m*, H-5A), 3.65 (3H, *s*, OMe), 3.69 (1H, *dd* (partly overlapped by signal of OMe), J_1 = 12, J_2 = 6.5 Hz, H-6A), 3.77 (1H, *m*, H-5B), 3.99 (1H, *dd*, J_1 = 12, J_2 = 2 Hz, H-6B′), 4.77 (1H, *d*, *J* = 8 Hz, H-1′), 4.77–4.85 (1H, *m* (partly overlapped by signals of H-1′ and H_2O), H-3), 5.37 (1H, *br d*, *J* = 10.5 Hz, H-18A), 5.43 (1H, *br d*, *J* = 17.5 Hz, H-18B), 5.69 (1H, *d*, *J* = 7 Hz, H-21), 6.00 (1H, *ddd*, J_1 = 17.5, J_2 = 10.5, J_3 = 8.5 Hz, H-19), 7.05 (1H, *br dd*, J_1 = J_2 = 8 Hz, H-10), 7.15 (1H, *br dd*, J_1 = J_2 = 8Hz, H-11), 7.37 (1H, *br d*, *J* = 8 Hz, H-12), 7.47 (1H, *br d*, *J* = 8 Hz, H-9), 7.54 (1H, *s*, H-17). ^{13}C NMR: δ 19.5 (C-6), 31.2 (C-15), 34.3 (C-14), 42.9 (C-5), 45.4 (C-20), 52.1 (OMe), 54.6 (C-3), 62.9 (C-6′), 71.7 (C-4′), 74.7 (C-2′), 78.0 (C-5′), 78.6 (C-3′), 97.5 (C-21), 100.5 (C-1′), 107.4 (C-7), 110.2 (C-16), 112.4 (C-12), 119.1 (C-9), 120.6 (C-10 or C-18), 120.8 (C-18 or C-10), 123.6 (C-11), 127.4 (C-8), 129.5 (C-2), 135.0 (C-19), 138.3 (C-13), 154.6 (C-17), 169.6 (C-22). EIMS *m/z* (rel. int.): 530 $[M]^+$ (0.7), 350 (20), 329 (21), 281 (22), 279 (41), 267 (23), 265 (25), 264 (20), 263 (33), 235 (22), 221 (36), 185 (51), 184 (22), 171 (75), 170 (26), 169 (37), 156 (23), 154 (22), 144 (36), 143 (27), 130 (22), 129 (22), 128 (21), 103 (20), 73 (81), 44 (96), 43 (100).

Strictosidine hydrochloride (**5**). From the partial synthesis mentioned above. TLC: R_f 0.34; anisaldehyde: violet. $[\alpha]_D$ −204° (*c* 1.31) (ref. [8] $[\alpha]_D$ −112° (MeOH; for *c*: no data)). For IR and UV see ref. [8]. ^{1}H NMR: δ2.23 (1H *br dd*, J_1 = J_2 = 14 Hz, H-14A), 2.36 (1H, *br dd*, J_1 = 14, J_2 = 11 Hz, H-14B), 2.75 (1H, *m*, H-20), 3.0–3.18 (3H, *m*, H-6A, H-6B, H-15), 3.19–3.27 (2H, *m*, H-2′, H-4′), 3.33–3.52 (3H, *m*, H-5A, H-3′, H-5′), 3.64 (1H, *dd*, J_1 = 12, J_2 = 7 Hz, H-6A′), 3.70–3.82 (1H, *m*, H-5B), 3.80 (3H, *s*, OMe), 3.97 (1H, *dd*, J_1 = 12, J_2 = 2 Hz, H-6B′), 4.67 (1H, *br d*, *J* = 11 Hz, H-3), 4.80 (1H, *d*, *J* = 8 Hz, H-1′), 5.28 (1H, *br d*, *J* = 11 Hz, H-18A), 5.36 (1H, *br d*, *J* = 17.5 Hz, H-18B), 5.80–5.92 (1H, *m*, H-19) within 5.86 (1H, *d*, *J* = 9 Hz, H-21), 7.04 (1H, *br dd*, J_1 = J_2 = 8 Hz, H-10), 7.14 (1H, *br dd*, J_1 = J_2 = 8 Hz, H-11), 7.33 (1H, *br d*, *J* = 8Hz, H-12), 7.47 (1H, *br d*, *J* = 8 Hz, H-9), 7.80 (1H, *s*, H-17). ^{13}C NMR: δ 19.5 (C-6), 32.4 (C-15), 34.8 (C-14), 42.7 (C-5), 45.4 (C-20), 52.6 (OMe), 53.1 (C-3), 63.0 (C-6′), 71.7 (C-4′), 74.7 (C-2′), 78.0 (C-5′), 78.8 (C-3′), 97.3 (C-21), 100.4 (C-1′), 107.1 (C-7), 109.0 (C-16), 112.3 (C-12), 119.1 (C-9), 119.8 (C-18), 120.6 (C-10), 123.5 (C-11), 127.4 (C-8), 130.1 (C-2), 135.4 (C-19), 138.2 (C-13), 156.9 (C-17), 171.2 (C-22). EIMS *m/z* (rel. int.): 530 $[M]^+$ (0.40), 350 (35), 329 (20), 322 (32), 307 (24), 291 (23), 281 (30), 279 (81), 265 (38), 264 (34), 263 (92), 249 (31), 235 (21), 223 (27), 221 (77), 209 (34), 185 (30), 184 (30), 171 (55), 170 (33), 169 (43), 168 (25), 167 (23), 156 (27), 154 (26), 145 (21), 144 (37), 143 (27), 136 (31), 130 (27), 129 (36), 128 (30), 127 (22), 115 (27), 110 (25), 73 (96), 50 (52), 44 (83), 43 (100).

Lactam of vincoside (**6**). Compound **6** (6.6 mg) was prepd from **4** according to ref. [8]. TLC: R_f 0.59; anisaldehyde: grey-brown. $[\alpha]_D$ −46° (*c* 0.18) (ref. [8] $[\alpha]_D$ −71° (MeOH; *c* 1.4)). For IR and UV see ref. [8]. ^{1}H NMR: δ 1.46 (1H, *ddd*, J_1 = J_2 = 13, J_3 = 12 Hz, H-14A), 2.47 (1H, *ddd*, J_1 = 13, J_2 = J_3 = 4 Hz, H-14B), 2.68–2.81 (3H, *m*, H-6A, H-6B, H-20), 2.95 (1H, *ddd*, J_1 = J_2 = 12.5, J_3 = 4.5 Hz, H-5A), 3.21 (1H, *dd*, J_1 = 9, J_2 = 8 Hz, H-2′), 3.20–3.42 (4H, *m*, H-15, H-3′, H-4′, H-5′), 3.68 (1H, *dd*, J_1 = 12, J_2 = 6 Hz, H-6A′), 3.90 (1H, *dd*, J_1 = 12, J_2 = 2 Hz, H-6B′), 4.70 (1H, *d*, *J* = 8Hz, H-1′), 4.94 (1H, *dm*, *J* = 12 Hz, H-3), 5.07 (1H, *ddd*, J_1 = 12.5, J_2 = 4.5, J_3 = 2 Hz, H-5B), 5.19 (1H, *dd*, J_1 = 10, J_2 = 2 Hz, H-18A), 5.29 (1H, *dd*, J_1 = 17.5, J_2 = 2 Hz, H-18B), 5.51 (1H, *d*, *J* = 2 Hz, H-21), 5.54 (1H, *ddd*, J_1 = 17.5, J_2 = J_3 = 10 Hz, H-19), 6.99 (1H, *ddd*, J_1 = J_2 = 8, J_3 = 1 Hz, H-10), 7.08 (1H, *ddd*, J_1 = J_2 = 8, J_3 = 1 Hz, H-11), 7.30 (1H, *br d*, *J* = 8 Hz, H-12), 7.42 (1H, *br d*, *J* = 8 Hz, H-9), 7.45 (1H, *d*, *J* = 2.5 Hz, H-17). ^{13}C NMR: δ 22.0 (C-6), 27.3, 32.6 (C-14 and C-15), 41.2, 44.5 (C-5 and C-20), 54.8 (C-3), 62.7 (C-6′), 71.6 (C-4′), 74.8 (C-2′), 78.0 (C-5′), 78.3 (C-3′), 97.4 (C-21), 99.6 (C-1′), 109.0 (C-16), 109.3 (C-7), 112.0 (C-12), 118.8 (C-9), 120.9 (C-10), 120.5 (C-18), 122.5 (C-11), 127.9 (C-8), 133.9 (C-19), 134.6 (C-2), 138.3 (C-13), 149.0 (C-17), 166.0 (C=O). EIMS *m/z* (rel. int.): 498 $[M]^+$ (4), 336 (24), 267 (100), 266 (59), 265 (71),

263 (20), 235 (27), 171 (74), 170 (22), 169 (55), 168 (22), 156 (23), 144 (33), 143 (49).

Lactam of strictosidine (**7**). **7** (2.9 mg) was prepd from **5** as described in ref. [8]. Mp 200° (from MeOH–H_2O) (ref. [8] mp 201–202°). TLC: R_f 0.56; anisaldehyde: yellow–brown. $[\alpha]_D$ −33° (*c* 0.17) (ref. [8] $[\alpha]_D$ −118° (MeOH; *c* 2.8)). For IR and UV see ref. [8]. ^{1}H NMR: δ 2.05 (1H, *ddd*, $J_1 = J_2 = 14$, $J_3 = 5.5$ Hz, H-14A), 2.47 (1H, *ddd*, $J_1 = 14$, $J_2 = 4.5$, $J_3 = 2$ Hz, H-14B), 2.64–2.72 (2H, *m*, H-6A, H-20), 2.80 (1H, *m*, H-15), 2.89–3.01 (1H, *m*, H-6B), 2.96 (1H, *dd*, $J_1 = 9$, $J_2 = 8$ Hz, H-2′), 3.11 (1H, *ddd*, $J_1 = J_2 = 12.5$, $J_3 = 4.5$ Hz, H-5A), 3.15–3.32 (3H, *m*, H-3′, H-4′, H-5′), 3.62 (1H, *dd*, $J_1 = 12$, $J_2 = 6$ Hz, H-6A′), 3.86 (1H, *dd*, $J_1 = 12$, $J_2 = 2$ Hz, H-6B′), 4.57 (1H, *d*, $J = 8$ Hz, H-1′), 4.95 (1H, *dd*, $J_1 = 12.5$, $J_2 = 5.5$ Hz, H-5B), 5.08 (1H, *m*, H-3), 5.32 (1H, *dd*, $J_1 = 10.5$, $J_2 = 2$ Hz, H-18A), 5.37 (1H, *dd*, $J_1 = 17.5$, $J_2 = 2$ Hz, H-18B), 5.41 (1H, *d*, $J = 2$ Hz, H-21), 5.66 (1H, *ddd*, $J_1 = 17.5$, $J_2 = J_3 = 10.5$ Hz, H-19), 6.99 (1H, *ddd*, $J_1 = 8$, $J_2 = 7$, $J_3 = 1.5$ Hz, H-10), 7.08 (1H, *ddd*, $J_1 = 8$, $J_2 = 7$, $J_3 = 1.5$ Hz, H-11), 7.33 (1H, *dm*, $J = 8$Hz, H-12), 7.37 (1H, *d*, $J = 2$ Hz, H-17), 7.39 (1H, *m*, H-9). ^{13}C NMR (90 MHz): δ 22.1 (C-6), 24.9 (C-15), 27.3 (C-14), 44.8 (C-5, C-20), 55.1 (C-3), 62.6 (C-6′), 71.4 (C-4′), 74.3 (C-2′), 78.0 (C-5′), 78.2 (C-3′), 98.1 (C-21), 100.5 (C-1′), 109.2 (C-16), 110.3 (C-7), 112.2 (C-12), 118.7 (C-9), 120.1 (C-10), 120.5 (C-18), 122.5 (C-11), 128.7 (C-8), 134.4 (C-19), 134.8 (C-2), 137.8 (C-13), 149.2 (C-17), 167.1 (C=O). EIMS *m/z* (rel. int.): 498 $[M]^+$ (3), 267 (52), 266 (79), 265 (100), 264 (24), 263 (24), 237 (24), 236 (30), 235 (54), 171 (41), 169 (33), 144 (30), 143 (27), 127 (21).

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