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Transformation of Montanin A into Isocrotocaudin. A Revision of the Structures of Crotocaudin and Isocrotocaudin#

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Key Words: *Neo*-clerodane diterpenoids; partial synthesis; formation of β,γ-unsaturated γ-lactones; revision of the C-8 stereochemistry of crotocaudin and isocrotocaudin.

Abstract: *Starting from montanin A (**3**) compound **11** was obtained by opening of the C-20,C-12 γ-lactone (**6**), oxidation of the C-12 hydroxyl group (**9**), relactonization to the β,γ-unsaturated γ-lactone (**10**) via the C-12 enol form, and final selective air oxidation of the α,β,β'-trialkyl furan to the corresponding α,β-unsaturated γ-lactone (**11**). Compound **11** was identical to isocrotocaudin, to which structure **1** has previously been assigned only on spectroscopic grounds. The above transformation establishes that the previous 8S configuration of isocrotocaudin (**1**) and its related C-6,C-10 stereoisomer crotocaudin (**2**) must be corrected to 8R.*

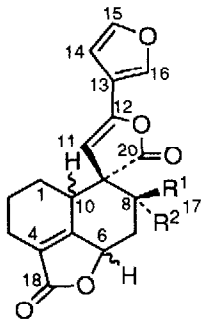
Some years ago[1] Chatterjee, Banerjee and Bohlmann isolated from the petrol extract of the stem-bark of *Croton caudatus* (Euphorbiaceae) two new diterpenoids, isocrotocaudin (**1**) and crotocaudin (**2**). The structures of these compounds were established by spectroscopic methods and both substances were chemically correlated by treating crotocaudin (**2**) with $NaBH_4$ in methanol, which caused the epimerization of the C-6 and C-10 asymmetric centres, giving isocrotocaudin (**1**)[1].

From a biogenetic point of view, the 8*S* configuration of compounds **1** and **2** is highly surprising. It is well known[2] that the *neo*-clerodane diterpenoids are biogenetically derived from *ent*-labdanes through an 8,4-friedo backbone rearrangement, as result of that the C-17 methyl group adopts an 8α-configuration (8*R* stereochemistry). Furthermore, the vast majority of the *neo*-clerodanes isolated from plants possesses the C-17 methyl group in α-configuration[2a], and the few exceptions having the opposite stereochemistry, such as teuvincentins B and C, are due to the acid character of the C-8 proton when C-7 bears a carbonyl function[2b].

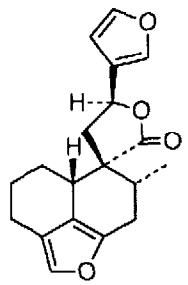
In order to elucidate conclusively the C-8 stereochemistry of isocrotocaudin (**1**), and hence of crotocaudin (**2**)[1], we undertook a partial synthesis of this compound starting from the natural 19-nor-*neo*-clerodane montanin A (**3**)[3a], the 8*R* configuration of which is well known by its chemical correlations with teucvin,[3b,c]

Dedicated to Professor F. Martín Panizo, CSIC, Madrid, on the occasion of his 80th birthday.

gnaphalin (**4**) and 19-acetylgnaphalin (**5**)[3d,e], whose structures have been firmly established from X-ray diffraction analyses[3b,e].



		R^1	R^2
1	(H-6β, H-10β)	Me	H
2	(H-6α, H-10α)	Me	H
11	(H-6β, H-10β)	H	Me
12	(H-6α, H-10α)	H	Me



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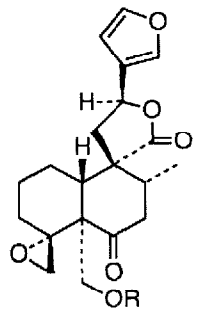
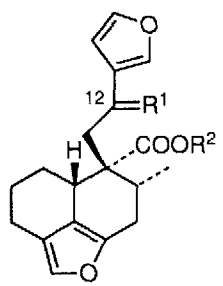
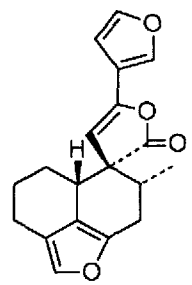


4 R=H
5 R=Ac



6 R^1=H,OH (12*S*), R^2=H
7 R^1=H,OH (12*S*), R^2=Me
8 R^1=O, R^2=Me
9 R^1=O, R^2=H



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Montanin A (**3**) was obtained[3d,e] in large amounts from compounds **4** and **5**. It was transformed[4] into the hydroxy ester **7**, via the unstable hydroxy acid **6**, by successive treatment with $KOBu^t$ in *t*-BuOH at 130°C for 30 minutes, acidification (pH~5) with 0.1N H_2SO_4, extraction with EtOAc and reaction with diazomethane (94% overall yield). Compound **7** was oxidized to the corresponding C-12 keto derivative[4] (**8**) in moderate yield (47%) by using the CrO_3-pyridine complex in pyridine solution. The hindered methyl ester **8** was hydrolized by Gassman's procedure[5], giving the unstable keto acid **9** (63% yield) besides minor quantities (3%) of the derivative[4] **10** and starting material (**8**, 25%). The formation of the β,γ-unsaturated γ-lactone **10** in alkaline solution[5] may be rationalized by an attack of the C-12 enolate form of compound **8** on the C-20 ester

group and loss of a methoxyl anion. On the other hand, treatment of the keto acid **9** with N,N'-dicyclohexylcarbodiimide in dry pyridine solution[6] (reflux under Ar, 2 hours) also yielded compound **10** (64%) via a dehydration between the C-20 carboxyl group and the C-12 ketone in its enol form.

Finally, when an ethanol free chloroform solution of the derivative **10** was exposed to air and daylight for 18 hours at room temperature[3a,d,e], a selective oxidation occurred and the furan involving the C-4, C-5, C-6 and C-18 carbons was transformed into the 4,5-unsaturated 18,6α-γ-lactone moiety of compound **11**, in a very poor yield (5%)[7].

The physical (mp, $[\alpha]_D$) and spectroscopic (IR, UV, ^{1}H NMR, CD and MS) data of compound **11** were identical[4] with those reported[1] for isocrotocaudin, to which structure **1** has been attributed only on spectroscopic reasons[1]. From all the above data, it is evident that the previous 8β-configuration of the C-17 methyl group of isocrotocaudin (**1**) and crotocaudin (**2**)[1] must be changed to an α-configuration. Thus, isocrotocaudin and crotocaudin possess structures **11** and **12**, respectively.

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4. All compounds gave satisfactory elemental analyses and correct MS.
   7: mp 85-88°C (espontaneously on cooling). $[\alpha]_D^{18}$ + 63.9° ($CHCl_3$, *c* 0.155). IR ν_{max} (KBr) cm^{-1}: 3460, 3360 (OH), 3120, 1555, 1505, 875 (furans), 1720 (COOMe). ^{1}H NMR (300 MHz, $CDCl_3$), *J* in Hz, δ: 3.19 *ddd*, *J*=11.9, 4.4, 2.2 (H-10β); 2.03 *dd*, *J*= 15.5, 2.1 (H_A-11); 2.55 *dd*, *J*= 15.5, 9.9 (H_B-11); 4.94 *dt*, *J*= 9.9, 2.1 (H-12); 6.45 *dd*, *J*= 1.9, 0.9 (H-14); 7.40 *t*, *J*= 1.9 (H-15); 7.43 *m* (H-16); 1.04 *d*, *J*= 6.8 (3H, Me-17); 7.03 *br s* (H-18); 3.53 *s* (3H, COOMe). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ, DEPT multiplicity (C number assignment); 24.1 *t* (1), 25.9 *t* (2), 19.3 *t* (3), 120.3 *s* (4), 118.7 *s* (5), 147.2 *s* (6), 30.9 *t* (7), 36.2 *d* (8), 51.7 *s* (9), 38.4 *d* (10), 41.0 *t* (11), 63.5 *d* (12), 130.8 *s* (13), 108.4 *d* (14), 143.4 *d* (15), 138.5 *d* (16), 17.3 *q* (17), 135.6 *d* (18), 174.5 *s* (20), 51.2 *q* (COOMe).
   8: mp 129-131°C (EtOAc - *n*-hexane). $[\alpha]_D^{18}$ +77.2° ($CHCl_3$, *c* 0.132). IR ν_{max} (KBr) cm^{-1}: 3140, 1600, 1560, 1510, 875 (furans), 1730 (COOMe), 1670 (ketone). UV λ_{max} (EtOH), nm (log ε): 215

(3.10), 258 (3.33). ^{1}H NMR δ: 3.05 *br dd*, *J*= 12.2, 4.5 (H-10$_\beta$); 3.26 *d* and 3.34 *d*, *J*= 17.5 (H$_A$-11 and H$_B$-11); 6.76 *dd*, *J*= 1.9, 0.8 (H-14); 7.43 *dd*, *J*= 1.9, 1.4 (H-15); 8.08 *m* (H-16); 1.07 *d*, *J*= 6.5 (3H, Me-17); 6.99 *br s* (H-18); 3.55 *s* (3H, COOMe). ^{13}C NMR δ: 24.0 *t* (1), 25.5 *t* (2), 19.2 *t* (3), 120.1 *s* (4), 118.1 *s* (5), 147.7 *s* (6), 30.8 *t* (7), 35.9 *d* (8), 51.5 *s* (9), 39.1 *d* (10), 41.8 *t* (11), 192.8 *s* (12), 128.7 *s* (13), 108.6 *d* (14), 144.3 *d* (15), 146.9 *d* (16), 17.6 *q* (17), 135.5 *d* (18), 172.7 *s* (20), 51.1 *q* (COOMe).

10 : thick oil. $[\alpha]_D^{22}$ +88.7° ($CHCl_3$, *c* 0.142). IR ν_{max} (NaCl) cm^{-1}: 3140, 3120, 1600, 1560, 1510, 875 (furans), 1795, 1685 (β,γ-unsaturated γ-lactone). UV λ_{max} (EtOH), nm (log ε): 219 (4.12), 254 (4.14). ^{1}H NMR δ: 3.20 *m*, (H-10β); 5.36 *s* (H-11); 6.56 *dd*, *J*= 1.8, 0.9 (H-14); 7.45 *t*, *J*=1.8 (H-15); 7.67 *m* (H-16); 1.04 *d*, *J*= 6.8 (3H, Me-17); 7.08 *br s* (H-18). ^{13}C NMR δ: 23.4 *t* (1), 25.4 *t* (2), 19.0 *t* (3), 120.1 *s* (4), 116.3 *s* (5), 147.4 *s* (6), 28.7 *t* (7), 36.4 *d* (8), 56.2 *s* (9), 39.7 *d* (10), 105.4 *d* (11), 146.8 *s* (12), 115.6 *s* (13), 107.1 *d* (14), 143.9 *d* (15), 140.7 *d* (16), 17.4 *q* (17), 136.4 *d* (18), 175.3 *s* (20).

11: mp 216-218°C (EtOAc - *n*-hexane). $[\alpha]_D^{25}$ +151.2° ($CHCl_3$, *c* 0.041). Identical to isocrotocaudin[1] [mp 212°C (petrol-$CHCl_3$); $[\alpha]_D^{28}$ +152° ($CHCl_3$, *c* 0.11)]; superimposable IR, UV, CD, ^{1}H NMR and mass spectra.

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7. Apart from compound **11**, this reaction gave several minor products which were not investigated.

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