Some Biogenetic-Type Transformations of Neoclerodane Diterpenoids from *Scutellaria* Species

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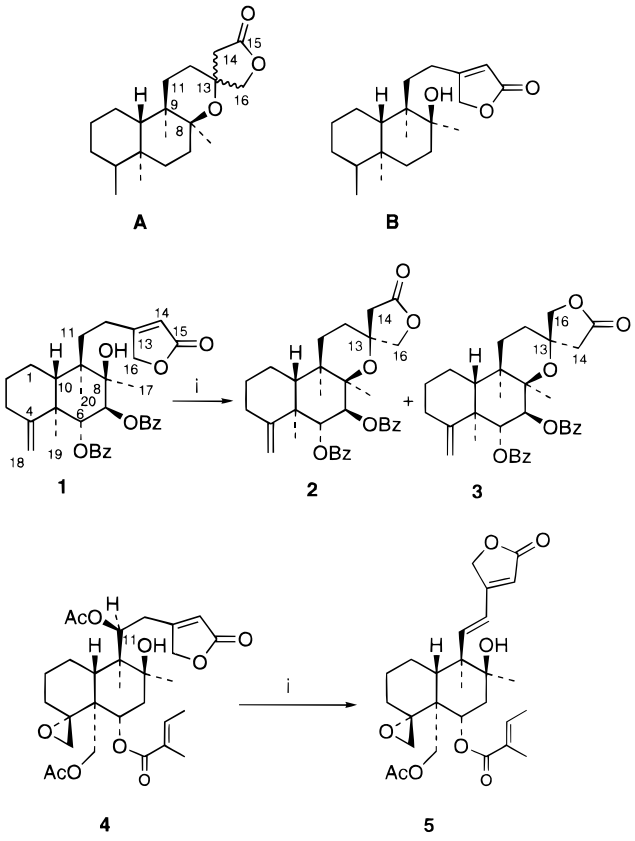
Treatment of scutebaicalin (**1**) with K-*t*-BuO yielded both the (13*S*)- and (13*R*)-8β,13-epoxyclerodanes **2** and **3**, respectively, by a Michael-type heterocyclization reaction. Identical treatment of scutalpin B (**4**) gave the corresponding (11*E*)-11-deacetoxy-12-dehydro derivative **5** by an elimination reaction. Side chains at C-9, such as those of compounds **1**−**5**, are frequent among the neoclerodanes found in *Scutellaria* species, and these transformations suggest a plausible biogenetic pathway for these diterpenoids.

A large number of neoclerodane[1] diterpenoids have been isolated from plants and microorganisms in the past few years.[2−4] These compounds have attracted interest because of their biological activity as insect antifeedants.[5] This behavior makes them potentially useful as ecologically acceptable agents for pest control. Species of the genus *Scutellaria* (family Labiatae) are the source of the most potent neoclerodane insect antifeedants known so far,[6,7] and efforts toward the total synthesis of such compounds have been made recently.[8,9]

Several neoclerodanes found in *Scutellaria* species possess in their structures a *cis*-fused 8β,13-tetrahydropyran ring system and a 13-spiro-15,16-γ-lactone[2−4,7,10−16] involving the C-8, C-9, and C-11−C-16 carbons of the neoclerodane framework (Scheme 1, compounds such as **A**). From a biogenetic point of view, the tetrahydropyran moiety of these substances (**A**) may arise from 8β-hydroxyneoclerod-13-en-15,16-olide derivatives (Scheme 1, compounds of type **B**, also found in *Scutellaria* species[2−4,12]) by an intramolecular hetero-Michael addition. This pathway has been suggested to produce the tetrahydropyranyl ring of some polyketide-type metabolites.[17]

Treatment of scutebaicalin[18] (**1**, Scheme 1) with equimolecular amounts of K-*t*-BuO in anhydrous THF solution (see Experimental Section) yielded the C-13 epimers **2** and **3** (1:1.7 ratio, respectively) by an intramolecular hetero-Michael reaction, in which the attack of the C-8 alkoxide from the C-13 *re* face of the α,β-unsaturated γ-lactone is slightly favored, because the (13*R*)-epimer **3** was the major product of the reaction. This stereoselectivity should be due to the existence of a preferred rotamer of the C-9 side chain of **1**. The structures of **2** and **3** were in agreement with their ^{1}H and ^{13}C NMR spectra (see Table 1) and other spectroscopic data (see Experimental Section). In particular, the stereochemistry at the C-13 stereogenic center was firmly supported by NOE experiments, because **2** showed NOE enhancements in the signals of the H_A-16 (δ 4.10, 2% enhancement) and H_B-16 (δ 4.20, 4%) protons when the Me-17 protons (δ 1.21) were irradiated, whereas in **3** irradiation at δ 1.27 (Me-17) caused NOE enhancements in both protons of the C-14 methylene group (δ 2.56 and 2.70, 1% and 3% NOE enhancement, respectively).[7,10,13−16]

Scheme 1[a]



[a] Key: (i) K-*t*-BuO, THF, 0 → 70 °C.

When scutalpin B (**4**, Scheme 1), which possesses an acetoxyl substituent at the C-11 position, was treated in the same manner as **1**, however, it gave **5** in 86% yield as the sole detectable product of the reaction. The physical (mp, $[\alpha]_D$) and spectroscopic (^{1}H NMR, IR, and MS) data of **5** were identical to those reported for a neoclerodane previously isolated from *Scutellaria al-*

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Table 1. ^{1}H and ^{13}C NMR Spectral Data of Compounds **2** and **3**

proton(s)	**2**	**3**	$J_{H,H}$ (Hz)	**2**	**3**	carbon(s)	**2**	**3**
H-1α	1.68 (dddd)	1.68 (dddd)	1α,1β	13.0	12.9	1	21.4 (t)	21.5 (t)
H-1β	1.60[a]	1.60[a]	1α,2α	4.1	4.0	2	28.6 (t)	28.7 (t)
H-2α	1.97 (m)	1.97 (m)	1α,2β	13.2	13.4	3	33.0 (t)	33.1 (t)
H-2β	1.37 (ddddd)	1.36 (ddddd)	1α,10β	12.2	12.3	4	154.0 (s)	154.2 (s)
H-3α	2.28 (tdd)	2.28 (tdd)	1β,2α	1.5	1.5	5	46.0 (s)	46.1 (s)
H-3β	2.11 (ddd)	2.10 (ddd)	1β,2β	4.3	4.3	6	73.7 (d)	73.7 (d)
H-6β	6.04 (d)	6.02 (d)	1β,10β	2.9	3.0	7	75.0 (d)	75.2 (d)
H-7α	5.67 (d)	5.67 (d)	2α,2β	13.4	13.4	8	81.1 (s)	81.4 (s)
H-10β	2.10 (dd)	2.08 (dd)	2α,3α	4.5	4.5	9	38.4 (s)	38.4 (s)
H-11α	1.60[a]	1.60 (ddd)	2α,3β	1.4	1.4	10	44.4 (d)	43.1 (d)
H-11β	1.75[a]	1.77 (ddd)	2β,3α	13.2	13.4	11	27.5 (t)	27.4 (t)
H-12α	1.75[a]	1.60[a]	2β,3β	4.3	4.3	12	28.6 (t)	29.0 (t)
H-12β	1.75[a]	1.83 (td)	3α,3β	13.2	13.5	13	76.3 (s)	75.6 (s)
H_A−14	2.56 (d)	2.56 (d)	6β,7α	10.2	10.3	14	42.9 (t)	42.7 (t)
H_B−14	3.10 (d)	2.70 (d)	11α,11β	*a*	15.0	15	173.8 (s)	174.8 (s)
H_A−16	4.10 (d)	4.20 (d)	11α,12α	*a*	3.8	16	76.6 (t)	79.9 (t)
H_B−16	4.20 (d)	4.40 (d)	11α,12β	*a*	14.8	17	20.2 (q)	20.3 (q)
Me-17	1.21 (s)	1.27 (s)	11β,12α	*a*	1.6	18	104.9 (t)	104.9 (t)
H_A−18	4.58 (br s)[b]	4.57 (br s)[b]	11β,12β	*a*	4.4	19	16.8 (q)	16.8 (q)
H_B−18	4.78 (br s)[c]	4.77 (br s)[c]	12α,12β	*a*	14.8	20	20.5 (q)	20.6 (q)
Me-19	1.48 (s)	1.48 (s)	14A,14B	17.5	16.7	C′OO	165.8 (s)	165.8 (s)
Me-20	1.04 (s)	1.04 (s)	16A,16B	8.9	9.0	1′	130.1 (s)	130.2 (s)
H-2′,6′	7.85 (dd)	7.84 (dd)	18A,18B	<0.5	<0.5	2′,6′	129.8 (2C, d)	129.8 (2C, d)
H-3′,5′	7.30 (br t)	7.29 (br t)	18A,3α	0.6	0.5	3′,5′	128.1 (2C, d)	128.1 (2C, d)
H-4′	7.44 (tt)	7.43 (tt)	OBz			4′	132.9 (d)	132.9 (d)
H-2″,6″	7.69 (dd)	7.69 (dd)	ortho	8.5−7.8	8.5−7.8	C″OO	166.5 (s)	166.5 (s)
H-3″,5″	7.19 (br t)	7.19 (br t)	meta	1.2	1.2	1″	129.2 (s)	129.3 (s)
H-4″	7.35 (tt)	7.35 (tt)	para	ca 0	ca 0	2″,6″	129.4 (2C, d)	129.4 (2C, d)
						3″,5″	128.0 (2C, d)	128.0 (2C, d)
						4″	132.5 (d)	132.5 (d)

[a] This is an overlapped signal. [b] This signal shows a $W_{1/2} = 4$ Hz. [c] This signal shows a $W_{1/2} = 2$ Hz.

pina.[19] In this case, we suppose that the 8β-alkoxide could produce an intramolecular abstraction of a proton from the close C-12 position, forming a stable carbanion, which may undergo the loss of the C-11 acetate, giving the (11*E*)-neoclerod-11-ene derivative **5**. An elimination of the C-11 acetate of **4** by a direct E_1 or E_2 pathway, without participation of the 8β-alkoxide, however, could not be excluded. Although, in the case of **4**, the heteroannelation does not take place, its transformation into **5** could suggest a biogenetic relationship between these natural compounds.

Besides these biogenetic relationships, the chemical transformations reported here can be useful for establishing chemical correlations between other related diterpenoids as well as for the synthesis of these biologically interesting compounds.

Experimental Section

General Experimental Procedures. Melting points were determined on a Kofler block and are uncorrected. Optical rotations were measured on a Perkin−Elmer 241 MC polarimeter. IR spectra (KBr) were obtained on a Perkin−Elmer 681 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution using a Varian Unity-500 apparatus at 500 and 125.7 MHz, respectively, and chemical shifts are reported with respect to residual $CHCl_3$ (δ 7.25) for ^{1}H and to solvent signals (δ_{CDCl_3} 77.0) for ^{13}C. ^{13}C NMR assignments were determined by HMQC and HMBC spectra. MS were recorded in the positive EI mode on a Hewlett−Packard HP 5989A instrument. Elemental analyses were made with a Carlo Erba EA 1108 apparatus. Merck Si gel no. 7734 (70−230 mesh) deactivated with 10% H_2O, w/v, was used for column chromatography. Starting materials [scutebaicalin (**1**) and scutalpin B (**4**)] were available from previous studies.[7,10,18]

Preparation of (13*S*)- and (13*R*)-6α,7β-Bis(benzoyloxy)-8β,13-epoxyneoclerod-4(18)-en-15,16-olides (2 and 3, Respectively) from Scutebaicalin (1). A solution of **1** (26 mg, 0.046 mmol) and K-*t*-BuO (5.2 mg, 0.046 mmol) in dry THF (5 mL) was stirred at 0 °C for 2 h under Ar. Then, the temperature was slowly raised to 70 °C. After 4 h, an aqueous NH_4Cl saturated solution (5 mL) was added to the reaction, and the mixture was extracted with EtOAc (4 × 10 mL). The EtOAc extract was dried (Na_2SO_4), filtered, and evaporated, giving a residue that was subjected to column chromatography [Si gel, EtOAc−petroleum ether (1:1) as eluent] yielding a mixture of the C-13 epimers **2** and **3** (19 mg, 1:1.7, respectively, established from the ^{1}H NMR spectrum) and starting material (**1**, 4 mg). Rechromatography of the mixture [Si gel column, petroleum ether−EtOAc (4:1) as eluent] gave **2** (6 mg, less polar constituent) and **3** (10 mg).

Compound **2**: mp 115−117 °C (EtOAc−petroleum ether); $[\alpha]^{18}_D$−182.8° (*c* 0.19, $CHCl_3$); IR (KBr) ν_{max} 3080, 1635, 910 (exocyclic methylene), 3050, 1730, 1610, 1590, 1280, 710, 690 (OBz), 1790 (spiro γ-lactone), 3000, 2960, 2870, 1455, 1380, 1320, 1180, 1110, 1070, 1030, 970, 850 cm^{-1}; UV (MeOH) λ_{max} (log ε) 203 (4.31), 228 (4.42), 275 (3.31) nm; ^{1}H and ^{13}C NMR data, see Table 1; positive EIMS *m*/*z* 558 $[M]^+$ (3), 543 (2), 453 (4), 436 (8), 421 (15), 331 (5), 314 (10), 307 (7), 299 (6), 203 (3), 105 (100), 77 (17); *anal*. C 72.94%, H 6.78%, calcd for $C_{34}H_{38}O_7$, C 73.09%, H 6.86%.

Compound **3**: mp 137−140 °C (EtOAc−petroleum ether); $[\alpha]^{18}_D$−160.7° (*c* 0.34, $CHCl_3$); IR (KBr) ν_{max} 3080, 1640, 910 (exocyclic methylene), 3040, 1730, 1610, 1590, 1280, 710, 690 (OBz), 1790 (spiro γ-lactone), 3000, 2950, 2860, 1455, 1375, 1320, 1180, 1150, 1110, 1100, 1075, 1040, 1030, 975, 860, 850 cm^{-1}; UV (MeOH) λ_{max} (log ε) 203 (4.26), 228 (4.39), 230 (4.40), 274 (3.26) nm; ^{1}H and

^{13}C NMR data, see Table 1; positive EIMS *m*/*z* 558 $[M]^+$ (4), 543 (3), 453 (5), 436 (9), 421 (9), 331 (6), 314 (10), 307 (9), 299 (7), 203 (4), 105 (100), 91 (2), 77 (17); *anal*. C 73.14%, H 6.80%, calcd for $C_{34}H_{38}O_7$, C 73.09%, H 6.86%.

Preparation of (11*E*,13*Z*)-19-Acetoxy-6α-(tigloyloxy)-4α,18-epoxy-8*β*-hydroxyneocleroda-11,13-dien-15,16-olide (5) from Scutalpin B (4). Treatment of **4** (81 mg, 0.147 mmol) with K-*t*-BuO (16.6 mg, 0.147 mmol) in THF solution (7 mL) as described above yielded **5** [62 mg after chromatographic purification, Si gel, $CHCl_3$−MeOH (49:1) as eluent; yield 86%]. Compound **5** showed mp and $[\alpha]_D$, and IR, ^{1}H NMR, and MS identical with those reported for a natural diterpenoid previously found in *S. alpina*.[19]

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References and Notes

(1) Although the hydrocarbon skeleton of these diterpenoids is biogenetically derived from an *ent*-labdane, and they should be named *ent*-clerodanes, we prefer to use the term *neoclerodane* proposed by Rogers et al. (Rogers, D.; Unal, G. G.; Williams, D. J.; Ley, S. V.; Sim, G. A.; Joshi, B. S.; Ravindranath, K. R. *J. Chem. Soc., Chem. Commun*. **1979**, 97−99) because it is the nomenclature used in the majority of the articles published on this subject since 1979.

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