

DITERPENES FROM *NARDOPHYLLUM LANATUM*

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Abstract—The aerial parts of *Nardophyllum lanatum*, collected in northern Chile, gave in addition to a *seco*-diterpene isolated from an Argentinian collection two new *cis*-clerodanes and an acid derived from geranyl geraniol. The structures were elucidated by high field NMR techniques and by partial synthesis.

INTRODUCTION

Nardophyllum is a small genus which occurs south of the tropics in South America. It is placed in the tribe Asteraceae, subtribe Solidagininae. The shrubs are characterized by homomous heads as in *Chrysocoma* [1]. One species from a collection in Argentina gave some unusual diterpenes [2]. We have now studied a sample from northern Chile.

RESULTS AND DISCUSSION

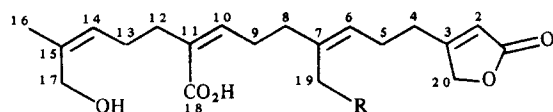
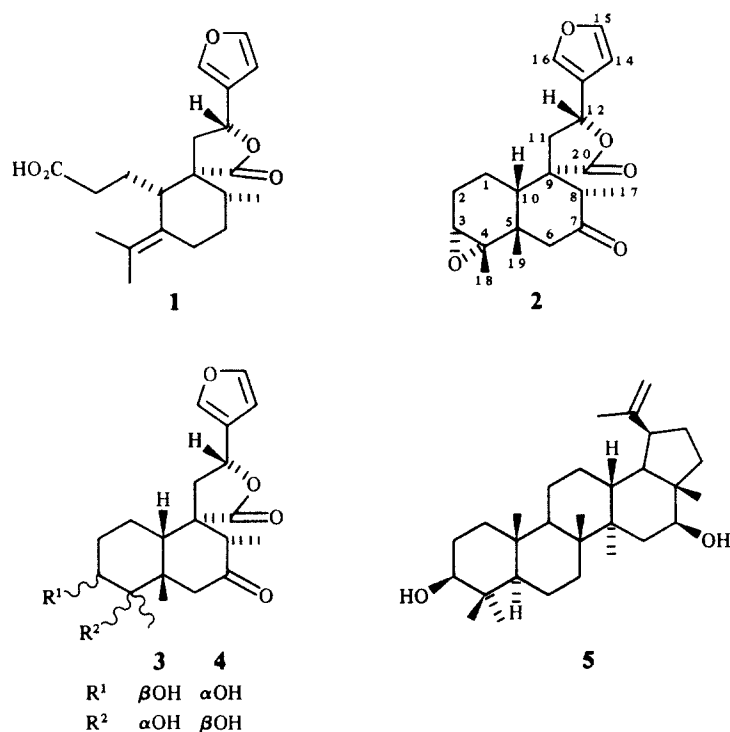
The extract of the aerial parts of *N. lanatum* (Meyen) Cabr. gave in addition to dammadienylacetate, caryophyllenepoxide, lup-20-ene-3 β ,16 β -diol (**5**), **1** [2] and, as the main constituent, the clerodane **2**. In addition the diterpenes **3** and **6** as well as the known Δ^{10} *E/Z*-isomeric 17-hydroxygutesolbriolides **7** and **8** [3] were present.

The molecular formula of **2** was C₂₀H₂₄O₅ and the ¹H NMR spectrum (Table 1) indicated the presence of a diterpene with a β -substituted furan ring (δ 6.36, 7.43 and 7.44 *br s*), two tertiary methyl groups and one secondary methyl group. A pair of double doublets at δ 3.47 and 2.49 indicated the presence of a methylene group adjacent to a keto group and a doublet at δ 3.10 was attributed to an epoxide proton. The methyl doublet was coupled with a proton which exhibited a broadened quartet at δ 2.55. Accordingly, a furanoclerodane with a 7-keto group was present. This was supported by comparison of the ¹H NMR spectrum with that of similar clerodanes which further indicated the presence of a 20,12-olide. In deuteriobenzene all signals could be assigned by spin decoupling. In particular a *W*-coupling between H-6 α and H-19 as well as between H-6 β and H-10 were observed. Inspection of models showed that these couplings required a *cis*-clerodane. This and the stereochemistry were established by the observed NOEs (H-19 with H-6 β (4%), H-8 (11%), H-18 (6%) and H-10 (6%), H-18 with H-3 (7%), H-6 β (5%) and H-19 (5%), H-10 with H-11' (4%), H-17 with H-14 (3%), H-2 β with H-3 (4%), H-12 with H-14 (2%) and H-16 (4%) as well as H-8 with H-19 (5%) and H-11 (3%). These effects and the observed

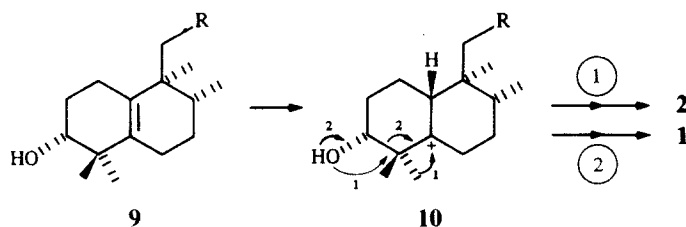
couplings required the presence of a *cis*-clerodane with ring **B** in a boat conformation. This was further supported by the geminal coupling of H-6 which is always smaller in cyclohexanones in a boat form. The presence of a *cis*-clerodane with a 3 α ,4 α -epoxide group explained the downfield shift of H-6 α . The ¹³C NMR data (see Experimental), which were assigned by a hetero COSY spectrum, also supported the structure. The observed positive Cotton-effect agreed with the proposed absolute configuration.

The ¹H NMR spectrum of **3** in deuteriobenzene (Table 1) again could be fully assigned by spin decoupling. The resulting sequences indicated the presence of a 3 β -hydroxy-*cis*-clerodane closely related to **2**. This was established by the observed NOEs [H-17 with H-11' (4%), H-18 with H-2 β (3%), H-19 with H-11 (8%) and H-6 β (5%), H-6 α with H-3 (4%), H-8 with H-6 β (2%) and H-12 with H-16 (2%) and H-11 (5%)]. These effects also led to the complete stereochemistry. Accordingly, lactone **3** was derived from **2** by hydrolytic attack at C-3 from the β -face. Reaction of **2** in dioxane with acid afforded a 3:2 mixture of **3** and **4**. While compound **3** was identical with the isolated diol the ¹H NMR spectrum of **4** (Table 1) indicated that a 3 α ,4 β -diol was formed. As the latter could not be detected in the extract the diol **3** was probably not an artifact.

The ¹H NMR spectrum of **6** and of its methyl ester **6a** (Table 2) was in part similar to that of 17-hydroxygutesolbriolide (**7**) [3]. The presence of an additional acetoxy group followed from the replacement of one olefinic methyl signal by that of an acetate methyl and a broadened singlet at δ 4.58. In deuteriobenzene all signals in the spectrum of **6a** could be assigned by spin decoupling. This also indicated the relative position of the three oxygen functions. Irradiation of H-2 sharpened the broadened triplet at δ 1.60 which itself was coupled with the broadened quartet at δ 1.88. As irradiation at δ 5.08 sharpened the singlet at δ 4.55 and collapsed the signal at δ 1.88 to a triplet the position of the acetoxy group was settled as the relative chemical shift of H-19 and H-17 defined the assignment. Irradiation of H-6 also sharpened the triplet at δ 2.17 which itself was coupled with the broadened quartet at δ 2.66. The latter was also coupled



6* R = OAc 7* R = H, Δ^{10E} 8* R = H, Δ^{10Z}



*6a–8a are the corresponding methyl esters

with the low field triplet at δ 5.68 which therefore was H-10. The chemical shift of the latter required the carbomethoxy group at C-11 on a Z-configured Δ^{10} -double bond. The remaining hydroxy group had to be placed at C-17 as the chemical shift of the olefinic methyl excluded a 16-hydroxy group.

Comparison of the constituents of the species from Chile and Argentina shows that there are significant differences though the general type of the compounds is the same. Most likely all the cyclic diterpenes are derived from a common precursor, a partly rearranged labdane like **9**. Protonation at C-10 then could induce rearrangement to a 3 α ,4 α -epoxide which by oxidation would give the keto lactone **2**, or could lead by fragmentation to an aldehyde, a precursor of **1**. Similar *cis*-clerodanes have

been isolated from *Solidago* [4], *Pteronia* [5] and *Chilictrichium* species [2].

The geranyl geraniol derivatives with a butenolide end group may be chemotaxonomically important. They have been isolated from several genera of the tribe Astereae, three of them also placed in the subtribe Solidagininae (*Solidago* [6], *Gutierrezia* [3, 7], *Pteronia* [5]).

EXPERIMENTAL

The air-dried plant material (700 g, voucher Niemeyer 8907, deposited in the Herbarium of the University of Concepcion, Chile, collected in February 1989 in the Region del Libertador Bernardo O'Higgins) was extracted and worked-up as reported

Table 1. ¹H NMR spectral data of compounds 2–4 (400 MHz, CDCl₃, δ-values)

H	2	C ₆ D ₆ -MeOD	3	C ₆ D ₆	4
1α	1.88 m	1.95 dq	} 2.05 m	} 1.70 m	2.23 dq
1β	1.49 m	1.04 dq			1.50 dq
2α	2.22 m	1.86 dq			1.71 dq
2β	1.95 m	1.39 ddd	1.45 m	1.14 dq	2.11 br dd
3	3.10 d	2.75 d	3.83 dd	3.30 dd	3.57 t
6α	3.47 br d	3.81 br d	2.69 br d	2.21 br d	3.48 br d
6β	2.49 dd	2.59 dd	2.45 br d	2.49 dd	2.03 dd
8	2.55 br q	2.15 br q	3.18 br q	3.07 br q	3.19 br q
10	1.70 m	1.16 ddd	1.78 m	1.60 m	2.31 br d
11	2.60 dd	2.01 dd	2.62 dd	2.10 dd	2.60 dd
11'	2.49 dd	1.59 dd	2.21 dd	1.92 dd	2.17 dd
12	5.44 br t	4.88 br t	5.43 br dd	4.84 br dd	5.47 br dd
14	6.36 br s	6.13 dd	6.37 br s	6.08 br s	6.33 dd
15	7.43 br s	7.11 t	7.44 t	7.04 t	7.40 t
16	7.44 br s	7.27 dt	7.49 br s	7.07 br s	7.46 br s
17	1.18 d	1.18 d	0.99 d	1.09 d	0.95 d
18	1.25 s	0.99 s	1.22 s	0.92 s	1.22 s
19	1.21 br s	0.82 br s	1.10 br s	0.83 br s	1.05 br s

J [Hz]: 6α,6β=13; 6α,19~1; 6β,10=1; 8,17=7; 11,11'=14; 11,12=11',12=8.5; 12,16=14,15=14,16=15,16~1; compound 2: 1α,1β=1α,2β=1α,10=2α,2β~13; 1α,2α=1β,2α=1β,2β=1β,10~3; 2α,3=3.5; compound 3: 1α,2β=2α,2β=2β,3=12; 2α,3=4; 1β,2β=5; 11,12=5; 11',12=11; compound 4: 1α,1β=1α,2β=1α,10=2α,3=13; 1β,2α=1β,2β=1β,10~3; 2α,3=2β,3=1.5.

Table 2. ¹H NMR spectral data of compounds 6 and 6a (400 MHz, CDCl₃, δ-values)

H	6*	6a*	C ₆ D ₆
2	5.82 tt	5.86 tt	5.50 tt
4	2.38 br t	2.44 br t	1.60 br t
5	2.23 br q	2.18 br q	1.88 br q
6	5.33 br t	5.37 br t	5.08 br t
8	2.13 br t	2.18 br t	2.17 br t
9	2.50 br q	2.51 br q	2.66 br q
10	5.75 br t	5.80 br t	5.68 br t
12	2.13 br t	2.28 br t	2.37 br t
13	2.44 br q	2.48 br q	2.22 br q
14	5.19 br q	5.23 br q	5.24 br t
16	1.72 br s	1.78 br s	1.85 br s
17	3.99 br s	4.04 br s	4.06 br s
19	4.53 br s	4.58 br s	4.55 br s
20	4.71 d	4.73 d	3.92 d
OAc	2.01 s	2.06 s	1.80 s
OMe	—	3.73 s	3.46 s

*Signal between 2.5 and 2.0 not assigned with certainty.

J [Hz]: 2,4=2,20=1.5; 4,5=5,6=8,9=9,10=12,13=13,14=7.

previously [8]. CC gave four fractions. The first one gave by TLC (petrol-Et₂O, 9:1) 20 mg dammadienyl acetate and 15 mg carophyllenepoxide. The second fraction (Et₂O-petrol, 3:1) gave 800 mg 5 and the third one gave after esterification with CH₂N₂ by TLC (Et₂O-petrol, 3:1) 500 mg 1a and 30 mg 5. The last CC fraction gave by repeated CC 1.5 g 2 and two mixtures (4/2 and 4/3). HPLC of 4/2 (MeOH-H₂O, 7:3, always RP 8, flow rate 3

ml/min, ca 100 bar) gave 3 mg 3 (*R_f*, 1.2 min) and 10 mg 2. HPLC (MeOH-H₂O, 17:3) of one-tenth of fraction 4/3 gave 5 mg 6 (*R_f*, 1.2 min) and mixtures. Esterification of fraction 4/3 with CH₂N₂ gave by HPLC (MeOH-H₂O, 4:1) 90 mg 6a (*R_f*, 1.5 min), 90 mg 7a and 90 mg 8a. Known compounds were identified by comparing the 400 MHz ¹H NMR spectra with those of authentic material.

3α,4α,15,16-Bisepoxy-cis-8βH-clerodane-31(16),14-dien-6-one (2). Crystals, mp 198°; IR ν_{max}^{CHCl₃} cm⁻¹: 1770 (γ-lactone), 1710 (C=O), 885 (β-subst. furan); MS *m/z* (rel. int.): 344.162 [M]⁺ (5) (calc. for C₂₀H₂₄O₅: 344.162), 326 [M-H₂O]⁺ (2), 316 [M-CO]⁺ (2), 273 (14), 124 (52), 109 (100), 95 (32), 94 (56), 81 (26); [α]_D²⁴+86 (CHCl₃; *c* 0.73); CD (MeOH): Δε₂₈₈+2.2, Δε₂₁₅-3.1; ¹³C NMR (CDCl₃, C-1-C-20): 20.5, 24.1, 60.4, 61.4, 35.6, 44.1, 210.2, 47.0, 53.7, 51.9, 44.7, 72.0, 124.7, 107.8, 144.1, 139.5, 11.1, 30.4, 19.9, 177.0 (assigned by hetero COSY).

Compound 2 (50 mg) in dioxane (3 ml) and dil H₂SO₄ (1 ml) were heated for 5 min at 70°. Usual work-up gave after TLC (CHCl₃-C₆H₆-Et₂O-MeOH, 30:30:30:1) 25 mg 3 (*R_f*, 0.36), identical with the isolated diol (¹H NMR) and 17 mg 4 (*R_f*, 0.45); crystals, mp 225°; MS *m/z* (rel. int.): 362.173 [M]⁺ (5) (calc. for C₂₀H₂₆O₆: 362.173), 344 [M-H₂O]⁺ (14), 318 (7), 301 (10), 229 (10), 179 (100), 161 (30), 133 (30), 95 (34), 94 (42), 81 (24).

3β,4α-Dihydroxy-15,16-epoxy-cis-8βH-clerodane-13(16),14-dien-6-one (3). Crystals, mp 221°; IR ν_{max}^{CHCl₃} cm⁻¹: 3600 (OH), 1780 (γ-lactone), 1720 (C=O); MS *m/z* (rel. int.): 362.173 [M]⁺ (3) (calc. for C₂₀H₂₆O₆: 362.173), 344 [M-H₂O]⁺ (4), 319 (4), 301 (6.5), 273 (4), 252 (15), 229 (11), 179 (100), 161 (28), 133 (21), 105 (26), 95 (30), 94 (39), 81 (24); [α]_D²⁴+17 (MeOH; *c* 0.24).

19-Acetoxy-17-hydroxygutiesolbriolide (6). Gum, purified as its methyl ester 6a, gum; IR ν_{max}^{CHCl₃} cm⁻¹: 3500 (OH), 1790 (γ-lactone), 1755 (OAc), 1720, 1640 (C=CCO₂R); MS *m/z* (rel. int.): 370.215 [M]⁺ (5.5) (calc. for C₂₃H₃₂O₇: 370.215), 310 [M-HOAc]⁺ (10), 295 [310-Me]⁺ (8), 213 [310-C₃H₅O₂]⁺ (39), 147 (51), 119 (50), 98 [3-methylbutenolide]⁺ (100).

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