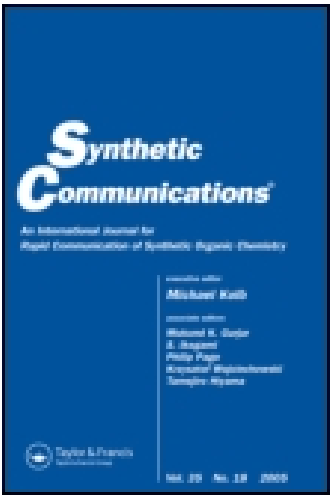

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CONVERSION OF (+)-CONFERTIFOLIN INTO 11,12-BISNORDRIMAN-9-ONE AND (+)-8αH,9αH-11,12-DIACETOXYDRIMANE*

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CONVERSION OF (+)-CONFERTIFOLIN INTO 11,12-BISNORDRIMAN-9-ONE AND (+)-8α*H*,9α*H*-11,12-DIACETOXYDRIMANE*

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ABSTRACT

A short synthesis of naphthalenone (−)-**1** and natural drimanic diacetate (**(+)-3**), from confertifolin (**(+)-4**), is reported. The proposed absolute configuration of **(+)-3** was confirmed.

INTRODUCTION

Naphthalenone **1** has been widely used as a key intermediate in the syntheses of a variely of biologically important terpenes, such as warburganal,[1] albicanol,[2] atisirene,[3] pallescensin A,[4] and recently, racemic **1** was converted into (±)-hispanolone.[5] Optically pure (−)-**1** was previously prepared from (+)-Wieland-Miescher ketone (**2**) in a six-step sequence.[3]

On the other hand, the drimanic diacetate **3** has been recently isolated from the sponge, *Dysidea fusca*.[6] Its absolute configuration (normal drimane skeleton) was assigned only by biosynthetic reasons. Compound **3** was

*Dedicated to Prof. E. A. Rúveda on the occasion of his retirement.

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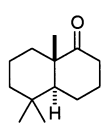
previously prepared from zamoranic acid methyl ester, but the sign of the specific rotation was not reported.[7]



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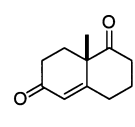

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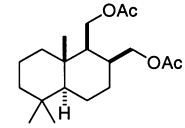

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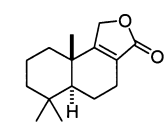


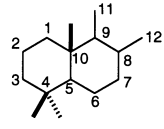
4

Continuing our interest in the synthesis of terpenoids and related compounds from natural drimanic sesquiterpenes,[8–10] we report here a short alternative synthesis of (−)-**1** and (+)-**3**, to confirm the proposed absolute stereochemistry of the latter, by using natural (+)-confertifolin (**4**) as starting material. Confertifolin ((+)-**4**) has been prepared in a three-step sequence from commercially available manool,[11] and also from abietic acid.[12]

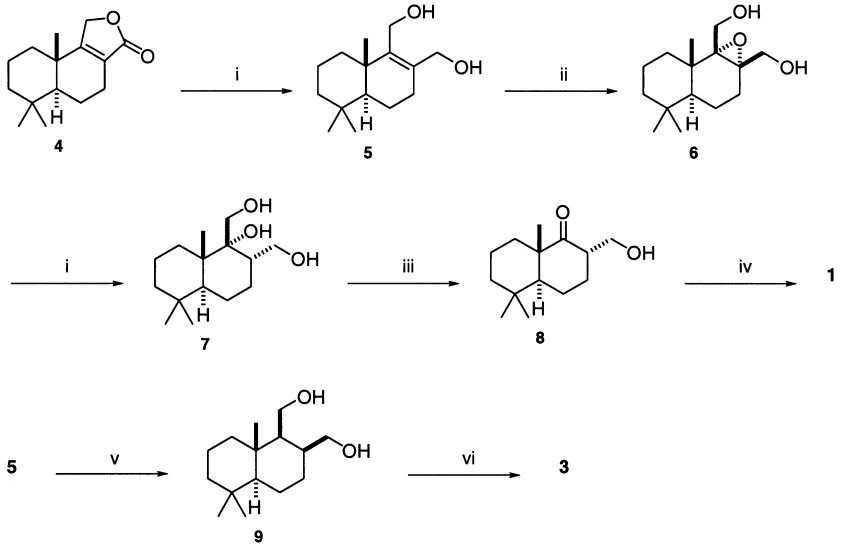
RESULTS AND DISCUSSION

The syntheses of (−)-**1** and (+)-**3** are shown in Scheme 1. Lactone (+)-**4** was reduced with $LiAlH_4$ in THF at reflux, to give enediol (+)-**5** (85% yield)[13]. Epoxidation of (+)-**5** with mCPBA in CH_2Cl_2 at room temperature gave the α-epoxide (+)-**6** (85% yield). As the reagent should attack from the less hindered α-face of the double bond, the stereochemistry of the epoxide was consequently assigned as α-.

Reduction of (+)-**6** with $LiAlH_4$ afforded triol (+)-**7** in 65% yield. Oxidation of (+)-**7** with $NaIO_4$ in THF/water gave the corresponding ketone (−)-**8 in** 77% yield. Transformation of **(−)-8** into (−)-**1** was carried out by treatment with Jones reagent. The carboxylic acid could not be isolated because of spontaneous decarboxylation. A retro-aldol process was discarded, because when (−)-**8** was treated with a mixture of sulfuric acid, water, and acetone (same conditions as for a Jones reaction, without oxidant), the starting material was recovered unchanged. The specific rotation and spectral data of (−)-**1** were concordant with those previously reported[3] (*vide infra*, Tab. 1 and 2, and Experimental).



Compounds numbering



Scheme 1. i) $LiAlH_4$, THF, reflux, 2.5 h; ii) mCPBA, CH_2Cl_2, r.t., 2 h; iii) $NaIO_4$, THF/H_2O, r.t., 20 m; iv) Jones reagent, acetone; v) H_2, PtO_2, EtOAc, 40°, 2 h; vi) Ac_2O, Pyr, r.t., overnight.

Hydrogenation of (+)-**5** to give (+)-**9** was accomplished in 80% yield, by using PtO_2 in EtOAc. Finally, acetylation of (+)-**9** with Ac_2O and pyridine gave (+)-**3** (86% yield). The specific rotation of this synthetic product was: $[\alpha]_D^{24} = +46.8$ (c = 2.5, $CHCl_3$), while the value reported in the literature for the natural (+)-**3** was $[\alpha]_D^{20} = +37$ (c = 1.4, $CHCl_3$)[6]. Consequently, the absolute configuration of (+)-8α*H*,9α*H*,11,12-diacetoxydrimane is established as shown in the formula.

EXPERIMENTAL

Melting points were measured on a Stuart-Scientific SMP3 apparatus and are uncorrected. Optical rotations were obtained for $CHCl_3$ solutions on a Perkin-Elmer 241 polarimeter, and their concentrations are expressed in g/100 mL. NMR spectra were recorded on a Bruker AM-200 spectrometer. Chemical shifts are expressed in ppm downfield relative to TMS (δ scale) in $CDCl_3$ solutions. Carbon multiplicity was established by a DEPT pulse sequence. IR spectra were recorded as KBr disks in a Bruker FT-IR Vector-22 and frequencies are in cm^{-1}. Elemental analyses were obtained on a Fisons-Carlo-Erba FA-1108 Automost microanalyzer.

Table 1. IR and ^{1}H NMR Chemical Shifts ($CDCl_3$, 200.13 MHz)

Compound	IR (cm^{-1})	^{1}H NMR (δ, ppm)
1	1707	2.67–2.50 (m, 1H, H-8a), 2.24–2.16 (m, 1H, H-8b), 2.15–1.98 (m, 1H, H-7a), 1.79–1.06 (m, 10H), 1.14 (s, 3H, 10-Me), 0.92 (s, 3H, 4-Me-(), 0.88 (s, 3H, 4-Me-)
3	1741, 1237	4.26 (dd, J=5.2, 11.3 Hz, 1H, H-11a), 4.12 (t, J = 10.8 Hz, 1H, H-12a), 4.07–4.00 (m, 2H, H-11b(H-12b), 2.19–2.13 (m, 1H, H-8), 2.02 (s, 3H, AcO), 2.01 (s, 3H, AcO), 1.91–1.75 (m, 1H) 1.72–0.90 (m, 11H), 0.83 (s, 3H, 4-Me-β), 0.81 (s, 3H, 10-Me), 0.78 (s, 3H, 4-Me-β).
5	3356, 2993, 1452, 978	4.24–3.97 (m, 4H, H11(H12), 2.71 (bs, 2H, 2×OH), 2.26–2.20 (m, 2H, H-7), 1.89–1.09 (m, 9H), 0.98 (s, 3H, 10-Me), 0.90 (s, 3H, 4-Me-β), 0.84 (s, 3H, 4-Me-β)
6	3320, 1036, 914, 903	4.05 (dd, J=4.6, 11.7, 1H, H-11), 3.70–3.35 (m, 5H, H-11b+H12 + 2 ×OH), 2.16–1.10 (m, 11H), 1.09 (s, 3H, 10-Me), 0.81 (s, 3H, 4-Me-(), 0.78 (s, 3H, 4-Me-β)
7	3440, 1063	4.06 (bs, 1H, OH) 3 73–3.43 (m, 4H, H-11(H-12). 3.23 (bs, 1H, OH), 3.00 (bs, 1H, OH), 1.93–1.11 (m, 12H), 0.88 (s, 3H, 10-Me), 0.87 (s, 3H, 4-Me-α), 0.82 (s, 3H, 4-Me-β)
8	3443, 1699, 1461, 1058	($CDCl_3$+D_2O) 3.65 (dd, J=7.1, 11.5 Hz, 1H,H-12), 3.52 (dd, J=3.9, 11.5 Hz, 1H, H-12), 2.87–272 (m, 11H, H-8), 2.06–1.08 (m, 11H), 1.13 (s, 3H, 10-Me), 0.90 (s, 3H, 4-Me-β), 0.86 (s, 3H,4-Me-α)
9	3331, 1016	3.97–3.54 (m, 4H, H-11(H-12), 2.18–0.92 (m, 15H), 0.86 (s, 3H, 4-Me-α), 0.85 (s, 3H, 10-Me), 0.80 (s, 3H, 4-Me-β)

For analytical TLC, Merck silica gel 60 in 0.25 mm layer was used. Chromatographic separations were carried out by conventional column on Merck silica gel 60 (230–400 Mesh) using hexane-EtOAc gradients of increasing polarity.

All reactions were routinely run under a N_2 atmosphere. All organic extracts were dried over anhydrous magnesium sulfate and evaporated under reduced pressure, at a temperature below 65°C.

(+)-Confertifolin (**4**) was obtained from an hexane extract of the bark of *D. winteri* [13].

8,9-Drimen-11,12-diol (5)

To a suspension of $LiAlH_4$ (0.4 g, 10.5 mmol) in dry THF (20 mL) was added dropwise a solution of confertifolin (1.0 g, 4.2 mmol) solution in THF

Table 2. ^{13}CNMR Chemical Shifts ($CDCl_3$, 50.13 MHz)

Carbon	1	3	5	6	7	8	9
C-1	33.06	39.14	36.19	34.45	31.51	32.81	39.38
C-2	18.11	18.40	18.85	18.34	18.69	18.03	18.47
C-3	41.62	41.79	41.52	41.26	41.49	41.51	41.87
C-4	34.18	33.17	33.28	32.85	33.38	34.29	33.18
C-5	53.51	56.17	51.33	43.32	46.13	53.87	56.41
C-6	20.97	17.56	18.71	17.16	21.22	20.65	18.34
C-7	26.35	29.11	31.26	25.85	26.07	29.26	30.02
C-8	37.64	34.89	136.01	65.55	42.88	47.18	37.87
C-9	216.03	51.43	146.16	72.12	75.35	218.41	54.53
C-10	49.11	37.14	38.19	37.29	41.53	49.09	37.33
C-11	—	62.64	57.89	61.42	63.56	—	60.40
C-12	—	63.94	63.98	66.02	64.91	63.01	16.44
10-Me	18.61	16.44	20.40	16.41	15.36	18.61	16.44
4-Me-	33.16	33.43	33.19	33.63	33.56	33.06	33.52
4-Me-β	22.09	21.47	21.56	21.50	22.10	22.06	21.61
AcO	—	21.03	—	—	—	—	—
AcO	—	21.03	—	—	—	—	—
AcO	—	171.17	—	—	—	—	—
AcO	—	171.17	—	—	—	—	—

(10 mL). The reaction mixture was refluxed for 2 h, then AcOEt (10 mL) and 1 N HCl (10 mL) were successively added to decompose the excess $LiAlH_4$. After extraction with AcOEt (3×25 mL), the combined organic extracts were washed with saturated $NaHCO_3$ solution, water, dried, and concentrated. The crude product was purified by column chromatography to afford diol **5** (0.86 g, 85%) as a colorless solid: m.p. 123°–124°C (AcOEt); $[\alpha]_D^{24}+120.0^\circ$ ($c = 1.1$); analysis: found C, 75.38%, H, 10.80%, $C_{15}H_{26}O_2$ requires C, 75.58%, H, 11.00%.

8α,9α-Epoxidriman-11,12-diol

To a solution of diol **5** (1.00 g, 4.20 mmol) in CH_2Cl_2 (30 mL), mCPBA (0.94 g, 5.4 mmol) was added. The resulting solution was stirred for 1 h at room temperature, diluted with CH_2Cl_2 (20 mL), washed with saturated solution of $NaHCO_3$ (3×25 mL), water (50 mL), dried, and evaporated. The residue was chromatographed, providing epoxide **6** (0.91 g, 85%) as

white crystals: m.p. 81°–82°C (AcOEt), $[\alpha]_D^{24}$+45.29 (c, 1.9); analysis found C, 70.53%, H, 10.07%, $C_{15}H_{26}O_3$ requires C, 70.83%, H, 10.30%.

(8βH)-9α,11,12-Drimantriol (7)

To a stirred suspension of $LiAlH_4$ (200 mg, 5.25 mmol) in dry THF (20 mL), a solution of epoxide **6** (200 mg, 0.8 mmol) in dry THF (10 mL) was added, and the reaction mixture was heated at reflux temperature under nitrogen for 4 h. The excess of reagent was decomposed by addition of AcOEt and aqueous 10% HCl solution. The mixture was then extracted with AcOEt (3×25 mL), and the organic phase was washed with saturated $NaHCO_3$ (25 mL), water (25 mL), dried, and evaporated. The residue was chromatographed, affording triol **7** (202 mg, 64%), as a white solid: m.p. 54°–55°C (AcOEt); $[\alpha]_D^{24}$+24.1 (c, 1.9); analysis found C, 69.90%, H, 11.30%, $C_{15}H_{28}O_3$ requires C, 70.27%, H, 11.01%.

12-Hydroxy-(8βH)-11-nordriman-9-one (8)

To a stirred solution of $NaIO_4$ (107 mg, 0.5 mmol) in a mixture of THF (0.2 mL) and water (0.6 mL), triol **7** (90 mg, 0.35 mmol) was added and the solution stirred at room temperature. The reaction was completed after 15 min. The reaction mixture was extracted with hexane (4 × 5 mL) and the combined extracts were washed with saturated $NaHCO_3$ solution, water, dried and concentrated to give a yellowish oil. The crude product was purified by column chromatography to provide ketol **8** (60 mg, 77%) as a colorless oil: $[\alpha]_D^{24}$−25.54 (c, 1.1).

11,12-Bisnordriman-9-one (1)

To a stirred solution of compound **8** (160 mg, 0.71 mmol) in acetone (15 mL), Jones reagent (5 mL) was added dropwise at 10°C. The reaction was monitored by TLC until disappearance of the starting material. The excess reagent was destroyed by addition of MeOH. The resulting solution was extracted with AcOEt (3 × 25 mL), and the organic phase was washed with saturated $NaHCO_3$ solution (25 mL), water (25 mL), dried, and evaporated. The residue was chromatographed, affording **1** (100 mg, 72%) as an oil: $[\alpha]_D^{17}$−39.1 (c, 0.44).

8αH,9αH-11,12-Drimantriol (9)

To a hydrogenation vessel containing a solution of diol **5** (230 mg, 0.97 mmol) in AcOEt (10 mL), PtO_2 (21 mg) was added. The vessel was then pressurized to 30 psi with hydrogen, and shaken for 2 h at 40°C. The resulting suspension was filtered through a short silica gel plug, and the filtrate was concentrated. The residue was chromatographed, affording diol **9** (185 mg, 80%) as a white solid: m.p. 149°–150°C (AcOEt); $[\alpha]_D^{24}$+24.62 (c, 1.8); analysis: found C, 75.03%, H, 11.90%, $C_{15}H_{28}O_2$ requires C, 74.95%, H, 11.74%.

8αH,9αH-11,12-Diacetoxydrimane (3)

Diol **9** (150 mg, 0.62 mmol) was acetylated with Ac_2O (0.2 mL, 0.8 mmol) in pyridine (1 mL), using a standard procedure, to give diacetate **3** (350 mg, 86%), as an oil: $[\alpha]_D^{24}$+46.8 (c, 2.5).

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