Partial Synthesis of (−)-11,12-Dinordriman-8-one and the (−)-Enantiomer of Polywood†

J. Chem. Research (S), 1998, 36–37†

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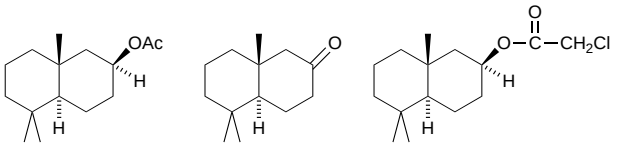
A chiral sequiterpene diol **6**, readily available from the natural product polygodial (**4**), has been used for the first partial synthesis of the title compounds.

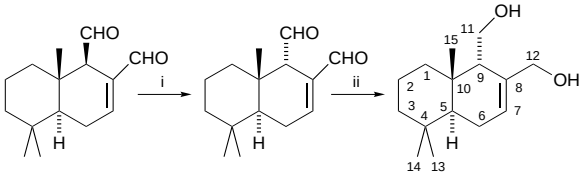
In a study of the odour evaluation of *trans*-decalins, the secondary acetate (±)-**1** and the ketone (±)-**2** have been reported to possess a woody tonality.[1,2]



(–)-**1** (–)-**2** **3**

Racemic **1** (known as Polywood) and **2** have been previously synthesized by acid-catalysed cyclization of acyclic or monocyclic precursors.[3,4] Later, the acetate (−)-**1** and ketone (−)-**2** were prepared using enzyme-catalysed kinetic resolution of (±)-**3**.[5] Pursuing our interest in the synthesis of terpenoids and related products from naturally chiral compounds,[6–8] we report here the first partial syntheses of (−)-**1** and (−)-**2**, using readily available starting material and cheap reagents.

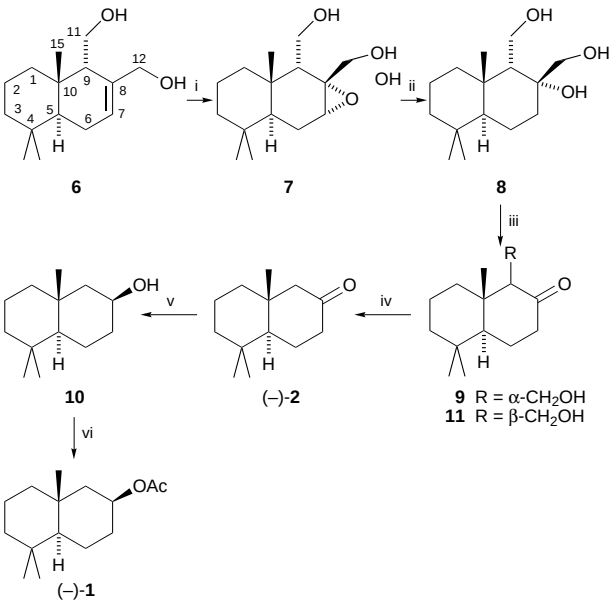
The starting material was the chiral diol **6**[9–10] derived from isopolygodial (**5**) which in turn was obtained by basic isomerization of polygodial (**4**), available from various natural sources[11–13] (Scheme 1). The synthetic sequence is shown in Scheme 2.



4 **5** **6**

Scheme 1 *Reagents:* i, KOH, MeOH (50%); ii, $NaBH_4$, MeOH (80%)

Epoxidation of **6** with *m*-chloroperbenzoic acid produced a single epoxide (**7**) in 75% yield. the α-stereochemistry of the epoxide was determined by means of both ^1H and ^{13}C NMR spectroscopy. Comparison of the 7-H signal in the ^1H NMR spectrum of **7** (δ 3.3, dd, $W_{1/2}$ 5.2 Hz) with that of 11-acetoxy-7α,8-epoxydrimane (δ 3.04, dd, $W_{1/2}$ 4.6 Hz)[14] indicated that both compounds have the same epoxide stereochemistry. On the other hand the signal for C-5, appearing at a field of 15.2 ppm higher than that corresponding to **6** in the ^{13}C NMR spectrum, confirmed the α configuration of the epoxide as reported for similar compounds.[15] This stereochemistry is explained by considering that the hydrogen bonding between the hydroxy group at C-11 and the peracid directs the epoxidation reactions.[16] The epoxide **7** was refluxed with $LiAlH_4$ in tetrahydrofuran (THF) to afford the triol **8** in 85% yield. Oxidative degradation of **8** with sodium periodate gave the ketol **9** in 75% yield. Transformation of **9** into (−)-**2** was carried out by treatment with Jones reagent. The carboxylic



6 **7** **8**

9 R = α-CH_2OH
11 R = β-CH_2OH

10 (–)-**2**

(–)-**1**

Scheme 2 *Reagents:* i, *m*-chloroperbenzoic acid, CH_2Cl_2, 15 °C (75%); ii, $LiAlH_4$, THF (85%); iii, $NaIO_4$, MeOH (75%); iv, CrO_3, H_2SO_4, acetone (72%); v, DIBALH, THF (80%); vi, Ac_2O, Py (97%)

acid could not be isolated because decarboxylation was spontaneous. The retro-aldol process was discarded because when the ketol **9** was treated with a mixture of sulfuric acid, water and acetone (Jones reagent without CrO_3), the starting material was recovered exclusively. The physical constants and spectral data of (−)-**2** were in accord with the values described by Gautier *et al.*[5]

Compound (−)-**2** was reduced with DIBALH to give the β-alcohol **10** in 80% yield. Finally, acetylation of **10** with Ac_2O in pyridine gave (−)-**1** in 97% yield.

It is important to note that attempted oxidation of the epimeric ketol **11** (prepared by the same sequence starting with the diol derived from polygodial) gave a large number of products, none of which could be identified. We have no explanation for the difference in reactivity between the two epimers.

Experimental

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Optical rotations were obtained for solutions in chloroform (g/100 mL) on a Perkin Elmer 241 polarimeter. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 200 spectrometer. Chemical shifts are reported in ppm downfield relative to tetramethylsilane (δ scale) in $CDCl_3$ solutions. Carbon substitution degrees were established by DEPT pulse sequence. For analytical TLC, Merck silica gel 60G in 0.25 mm thick layers was used. Chromatographic separations were carried out by conventional column on Merck silica gel 60 (70–230 mesh) using hexane–EtOAc mixtures of increasing polarity.

All organic extracts were dried over anhydrous sodium sulfate and evaporated under reduced pressure, below 65 °C. (−)-Polygodial (**4**) was purified from a light petroleum extract of the bark of *Drimys winteri*.[11]

7α,8-*epoxy*-(9β-*H*)-*drimane*-11,12-*diol* (**7**).—To a solution of the diol **6** (1 g, 4.2 mmol) in CH_2Cl_2 (30 mL) *m*-chloroperbenzoic acid

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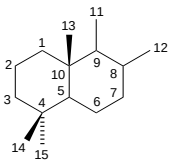
†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 1 ^{13}C NMR data ($CDCl_3$, 50.3 MHz)



Carbon	Compound **6**	**7**	**8**	**9**	(−)-**2**	**10**	(−)-**1**
C-1	36.5	36.3	37.4	39.3	42.0	42.4	42.1
C-2	18.8	18.3	20.1	18.5	18.8	18.3	18.3
C-3	42.7	42.4	42.2	42.2	42.3	42.5	42.4
C-4	33.1	32.8	33.4	33.4	33.2	33.0	33.0
C-5	54.1	38.9	56.7	46.0	52.2	54.3	53.9
C-6	24.3	22.8	18.8	23.2	23.1	17.0	17.6
C-7	127.5	56.9	33.1	36.8	42.0	35.2	32.2
C-8	137.2	61.9	76.5	214.7	211.7	67.9	70.6
C-9	43.3	48.4	48.5	67.1	59.6	51.3	47.8
C-10	36.0	34.8	37.6	40.0	38.4	34.2	34.2
C-11	63.1	60.3	60.9	60.7	—	—	—
C-12	67.7	66.7	69.4	—	—	—	—
C-13	21.7	22.1	21.8	22.0	19.4	21.4	20.8
C-14	22.0	22.8	23.7	22.0	21.4	21.4	21.3
C-15	33.0	32.9	33.1	33.5	33.3	33.1	33.1
*C*OCH$_3$							170.6
CO*C*H$_3$							21.6

(0.94 g, 5.4 mmol) was added in small portions at room temperature during 10 min. Stirring was continued at room temperature for 35 min. The reaction mixture was washed with $NaHCO_3$ and water, dried and concentrated. The residue was chromatographed over silica gel to afford the (unstable) epoxide **7** (0.79 g, 75%), mp 105–107 °C (from acetone–hexane); $[\alpha]_D^{25}$ −69.2 (1.01, $CHCl_3$) δ_H 0.84 (s, 3 H), 0.87 (s, 3 H), 0.94 (s, 3 H) and 3.3 (dd, $W_{1/2}$ 5.2 Hz) (Found: C, 69.90; H, 10.60. $C_{15}H_{26}O_3$ requires C, 70.83; H, 10.30%).

(8R)-(9*β*-*H*)-*Drimane*-8,11,12-*triol* (**8**).—To a stirred mixture of $LiAlH_4$ (0.6 g, 16 mmol) in dry THF (50 mL) a solution of the epoxide **7** (1.15 g, 4.5 mmol) in dry THF (30 mL) was added and the mixture was heated at reflux temperature under nitrogen for 4 h. The excess of reagent was decomposed by the addition of EtOAc and an aqueous solution of HCl (10%). The mixture was extracted with EtOAc and the organic phase was washed with $NaHCO_3$ and water, dried and concentrated to give the *triol* **8** (0.99 g, 85%) mp 117–120 °C (from EtOAc); $[\alpha]_D^{25}$ −41.6 (*c*, 1.12), δ_H 0.75 (s, 3 H), 0.82 (s, 3 H) 1.01 (s, 3 H) and 3.5–4.0 (m, 4 H) (Found: C, 69.90; H, 11.09. $C_{15}H_{28}O_3$ requires C, 70.27; H, 11.01%).

11-*Hydroxy*-(9*β*-*H*)-12-*nordriman*-8-*one* (**9**).—To a stirred solution of $NaIO_4$ (0.76 g, 3.53 mmol) in water (15 mL) a solution of the triol **8** (0.86 g, 2.54 mmol) in MeOH (10 mL) was added at room temperature during 1.5 h. The reaction solution was extracted with EtOAc and the organic phase was washed with $NaHCO_3$, water and dried. The crude product was purified by column chromatography to provide *compound* **9** (0.5 g, 75%), mp 111–112 °C (from acetone–hexane); $[\alpha]_D^{25}$ −22.1 (*c*, 0.68 in $CHCl_3$); δ_H 0.92 (s, 3 H), 0.94 (s, 3 H), 0.94 (s, 3 H), 2.1–2.4 (m, 2 H) and 3.93 (m, 2 H) (Found: C, 74.80; H, 10.80. $C_{14}H_{24}O_2$ requires C, 74.95; H, 10.78%).

11,12-*Dinordriman*-8-*one* [(−)-**2**].—To compound **9** (3.2 g, 15.4 mmol) in acetone (50 mL) Jones reagent (11.5 mL, 2.6 M; 30.8 mmol) was added while swirling and the reaction was monitored by TLC. Usual work-up gave the *ketone* (−)-**2** (2.2 g, 72%), mp 90–92 °C (from hexane) (lit.,[5] 88–90 °C); $[\alpha]_D^{25}$ −81.8 (*c*, 1.1 in $CHCL_3$) {lit.,[5] $[\alpha]_D^{20}$ −81.6 (*c*, 1.23 in $CHCl_3$)}. For spectroscopic data see ref. 5.

11,12-*Dinordriman*-8*β*-*ol* (**10**).—To a solution of the ketone (−)-**2** (0.5 g, 0.52 mmol) in dry THF (20 ml) at 0.1 M solution of diisobutylaluminium hydride in hexane (5 mL, 5 mmol) was added dropwise at room temperature. The reaction mixture was stirred for 2 h at room temperature. EtOAc (5 mL) and water (5 mL) were then successively added and the organic phase was separated. The aqueous layer was extracted with EtOAc. The combined organic phases were washed with brine, dried and concentrated. The residue was purified by column chromatography to afford the *β*-alcohol **10** (0.43 g, 80%), mp 89–91 °C (from hexane) (lit.,[5] 89–90 °C), $[\alpha]_D^{25}$ −18.8 (*c*, 0.32 in $CHCl_3$) [lit.,[5] −19.6 (*c*, 1.2 in $CHCl_3$)]. For spectral data, see ref. 5.

8*β*-*Acetoxy*-11,12-*dinordrimane* (−)-**2** (Polywood).—Acetylation of **10** (0.06 g, 0.31 mmol) under normal conditions with Ac_2O–pyridine gave the acetate (−)-**1** (0.07 g, 97%) as an oily product; $[\alpha]_D^{25}$ −15.60 (*c*, 0.52 in $CHCl_3$) (lit.,[5] $[\alpha]_D^{20}$ −16.47). The ^1H and ^{13}C NMR spectra were in accord with those kindly sent to us by Dr Näf (ref. 5).

We gratefully acknowledge the Consejo Nacional de Ciencia y Tecnología (Research Grant 1960451) for financial support. We also thank Dr F. Näf (Firmenich SA, Research Lab. Switzerland) for ^1H and ^{13}C NMR spectra of compounds (−)-**2** and (−)-**1** and Professor S. Alegría for helpful discussions.

Received, 22nd April 1997; Accepted, 29th September 1997
Paper E/7/02743E

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