Formation of 9,25-Cyclofernane by Reductive Homoallylic Cyclization of Fern-9(11)-en-25-ol Mesylate

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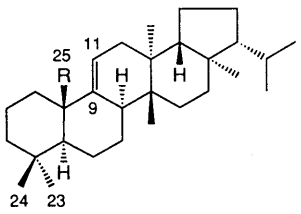
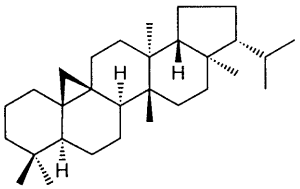
Treatment of fern-9(11)-en-25-ol mesylate (2) with $LiAlH_4$ in refluxing tetrahydrofuran afforded 9,25-cyclofernane (4), a new cyclopropane ring-containing triterpene, in a moderate yield.

Keywords 9,25-cyclofernane; cyclopropane triterpene; reductive cyclization; homoallylic mesylate; lithium aluminum hydride

We have recently reported the isolation of fern-9(11)-en-25-oic acid (**1**) from the fern *Adiantum venustum*.[1] Fernane triterpenes which have an oxygen functionality at the C-25 position are very rare.[2] We therefore attempted to confirm the structure of **1** by leading it to the well-known compound fern-9(11)-ene,[2,3] through a standard sequence of reactions involving $LiAlH_4$ reduction of the corresponding C-25 mesylate **2**. However, the major product of the $LiAlH_4$ reduction was not fern-9(11)-ene, but a 9,25-cyclized compound. In this paper we describe this unique reductive cyclization of the homo-allylic mesylate system in the fernane triterpene skeleton.



1 : R = COOH
2 : R = CH_2OMs
3 : R = CH_2OH



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Reduction of the methyl ester of the acid **1**[1] with excess $LiAlH_4$ in refluxing tetrahydrofuran (THF) afforded the C-25 alcohol **3**, mp 187—189 °C, in 60% yield. Treatment of **3** with methanesulfonyl chloride in pyridine afforded the mesylate **2** as an oil, which was characterized by ^{1}H-NMR spectroscopy, δ 2.96 (3H, s, $MeSO_2$), 4.04 (1H, d, J=9.5 Hz, 25-H_a), 4.50 (1H, d, J=9.5 Hz, 25-H_b).

A mixture of the mesylate and excess $LiAlH_4$ in dry THF was refluxed for 10 h. Usual work-up afforded a crude product, which was separated by silica gel chromatography to give the non-polar hydrocarbon fraction (75% from (**3**)) and the C-25 alcohol **3** (24% from **3**). GC-MS analysis of the hydrocarbon fraction revealed the presence of four compounds in this fraction, with the least mobile compound **4** being the major product (57%). Further separation of the fraction by PTLC followed by recrystallization furnished compound **4**, mp 198—199 °C, MS m/z: 410 (M^+), in 37% yield from **3**.

The ^{1}H-NMR spectrum of **4** showed the presence of seven methyl groups [five singlets at δ 0.76, 0.79, 0.82, 0.93, 0.97 and two doublets at δ 0.83 (J=7.1 Hz), 0.88 (J=7.0 Hz)]. In addition, the signal at δ 0.00 (1H, d, J=4.7 Hz) is reminiscent of a cyclopropane ring proton. This signal was correlated with the proton at δ 0.84 (1H, d, J=4.7 Hz) by decoupling and nuclear Overhauser effect (NOE) experiments. Further, the C–H correlation spectroscopy (COSY) spectrum of **4** revealed that these two protons were attached to a methylene carbon, of which the signal appeared at δ 20.4. Furthermore, J-resolved C–H two-dimensional experiments on **4** furnished evidence for the cyclopropane nature of the methylene carbon, which showed a $^1J_{C-H}$ value of 155 Hz.[4] The ^{13}C-NMR assignments (Table I) of **4**, assisted by insentive nuclei enhanced by polarization transfer (INEPT) experiments, revealed that two methylene and one quaternary aliphatic carbons newly appeared with concomitant disappearance of the oxymethylene (C-25) and olefinic (C-9 and C-11) carbons of the starting mesylate **2**. Hence, the structure of the major product obtained by the $LiAlH_4$ reduction was determined to be 9,25-cyclofernane (**4**).

Only a few examples of reductive cyclization of homoallylic mesylates have been reported.[5—7] It appears that the cyclopropane formation becomes a major reaction path only when certain structural requirements are met, though these remain to be fully elucidated (*e.g.*, the importance

TABLE I. ^{13}C-NMR Data for 9,25-Cyclofernene (**4**) ($CDCl_3$, 125 MHz)

C	$\delta^{a)}$	C	$\delta^{a)}$
1	30.9[b] (t)	16	35.9 (t)
2	21.4 (t)	17	42.8 (s)
3	42.7 (t)	18	52.5 (d)
4	34.7 (s)	19	20.1 (t)
5	41.3 (d)	20	28.3 (t)
6	18.8 (t)	21	59.8 (d)
7	18.2 (t)	22	30.8 (d)
8	34.9 (d)	23	30.3 (q)
9	19.8[c] (s)	24	19.9 (q)
10	21.9[c] (s)	25	20.4 (t)
11	26.5 (t)	26	14.7[d] (q)
12	32.4[b] (t)	27	14.9[d] (q)
13	40.8 (s)	28	14.9[d] (q)
14	38.1 (s)	29	22.1 (q)
15	28.9 (t)	30	23.0 (q)

a) The multiplicity was determined by INEPT experiments. *b*—*d*) Assignments may be interchanged.

of the C-24 methyl group). An ionic mechanism has been proposed for these cyclizations.[5-7] However, we would like to point out the feasibility of a radical mechanism. These mechanisms could be distinguished by comparison of the tributyltin hydride reduction of a thiocarbonate derivative.

9(25)-Cyclofernane has been synthesized for the first time. Although the cycloartane and related triterpenes are often encountered in plants, no report has appeared on natural products bearing the 9,25-cyclofernane skeleton.

Experimental

Melting points were measured on a Yazawa BY-1 hot-stage microscope and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL GSX-500 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. GC-MS analysis was performed with a Shimadzu DF 9020 spectrometer equipped with a capillary column (Shimadzu HiCap CBP-1-S25-050, 15 m, column temperature 270 °C).

9,25-Cyclofernane The methyl ester **1** (40 mg) was added to a stirred suspension of $LiAlH_4$ (40 mg) in dry THF (8 ml) and the mixture was refluxed for 5 h under a nitrogen atmosphere. After addition of moist ether and then 2 N HCl, the mixture was extracted with AcOEt. The organic layer was dried over Na_2SO_4 and concentrated. The residue was chromatographed on silica gel with hexane–benzene (1 : 1) to give the alcohol **3** (23 mg) as white crystals, mp 187—189 °C. ^{1}H-NMR δ: 3.29 (1H, d, J=10.6 Hz, 25-H_a), 3.76 (1H, t, J=10.6 Hz, 25-H_b, this signal became a doublet upon addition of D_2O).

Methanesulfonyl chloride (15 μl) was added to the alcohol **3** (20 mg) in pyridine (1 ml) at 0 °C and the mixture was stirred for 30 min. Extractive work-up (AcOEt) afforded a crude mesylate (21 mg) as an oil (no purification was attempted). TLC analysis of the sample indicated that the starting **3** was converted into the mesylate **2** in good yield.

The mesylate **2** (21 mg) was dissolved in dry THF (3 ml) and $LiAlH_4$ (30 mg) was added to the solution at room temperature under a nitrogen atmosphere. The mixture was refluxed for 10 h, then cooled to room temperature and carefully diluted with moist ether. Extractive work-up (ether) afforded a crude product. This was chromatographed on silica gel to give the hydrocarbon fraction (14 mg, eluted with hexane) and the alcohol **3** (6 mg, eluted with hexane–benzene, 1 : 1). GC-MS analysis of the hydrocarbon fraction using an OV-17 capillary column showed four peaks: 1st peak (4.4 min), 12%, MS m/z: 408 (M^+); 2nd peak (4.9 min), 7%, MS m/z: 410 (M^+); 3rd peak (5.4 min), 24%, MS m/z: 408 (M^+); 4th peak (6.0 min), 57%, MS m/z (relative intensity %): 410 (M^+, 13), 395 (16), 286 (36), 271 (14), 243 (36), 205 (49), 163 (34), 149 (33), 137 (39), 121 (45), 107 (63), 109 (62), 95 (98), 81 (89), 698 (100), 55 (85).

The hydrocarbon fraction was separated into "the less polar fraction" (9 mg) and "the more polar fraction" (5 mg) by PTLC (Merck 0.25 mm thickness plates, petroleum ether as the developing solvent). GC-MS analysis of the separated fractions indicated that the "less polar fraction" contained the materials corresponding to the 2nd and 4th peaks on GC, while "the polar fraction" contained the materials in the other two peaks. Crystallization of the "less polar fraction" from MeOH yielded compound **4** (7.1 mg) as white crystals, mp 198—199 °C. MS m/z: 410.3901 (Calcd for $C_{30}H_{50}$: 410.3913).

The compound corresponding to the second peak in the above GC-MS analysis was identified as fern-9(11)-ene by direct comparison with an authentic sample. This unambiguously established the structure of **1**.

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