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A NOVEL AND REVERSIBLE REARRANGEMENT OF A SECO-LANOSTEROL DERIVATIVE

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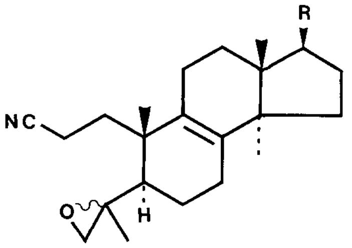
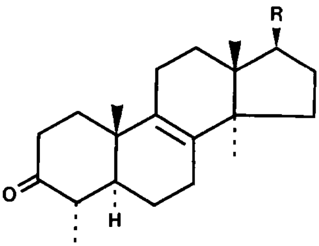
Abstract: Treatment of 3-nitrilo-3,4-seco-5α-lanost-8-en-30-al (3) with boron trifluoride - phosphoric acid complex induces an unprecedented rearrangement involving a 14α→8α methyl migration.

Seco-epoxy nitriles such as (1) are the key intermediates in an efficient method for the conversion of 4,4-dimethyltriterpenoids into 4α-monomethyl compounds.[1] In our hands, synthesis of the ketone (2) from (1) under the literature conditions, namely, treatment with boron trifluoride diethyletherate in refluxing toluene, gave a product which was contaminated by the corresponding 7-ene isomer. There is ample precedent for the acid-catalysed equilibration of 7- and 8-enes in the lanosterol series.[2] An investigation of alternative Lewis acids revealed that tin (IV) chloride was a superior reagent for this particular reaction. Treatment of the epimeric mixture of epoxy nitriles (1)[1] with an excess of tin (IV) chloride in refluxing toluene for 4 h reproducibly afforded the pure, crystalline ketone (2), m.p. (from methanol) 108-110°C in 85 % yield.



(1)



(2)

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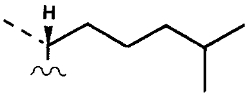
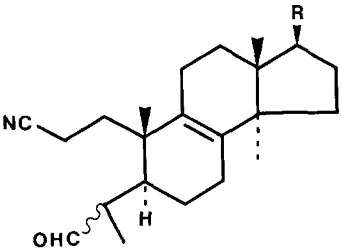
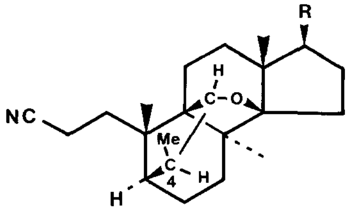


When the epimeric mixture of epoxy nitriles (1) was treated with an excess of boron trifluoride phosphoric acid complex in toluene at room temperature, rapid formation of the epimeric nitrile aldehydes (3) (ratio 2:1 by ^{1}H n.m.r. spectroscopy) was followed by further conversion (4 h) into a single, isomeric product (4), m.p. (from methanol) 113-114°C, $[\alpha]_D + 30^{\circ}$ (c 1.1 in chloroform), in 60 % yield.

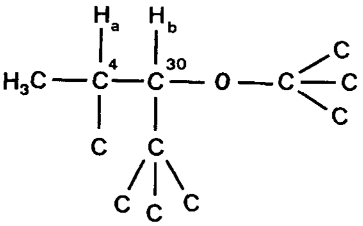


(3)



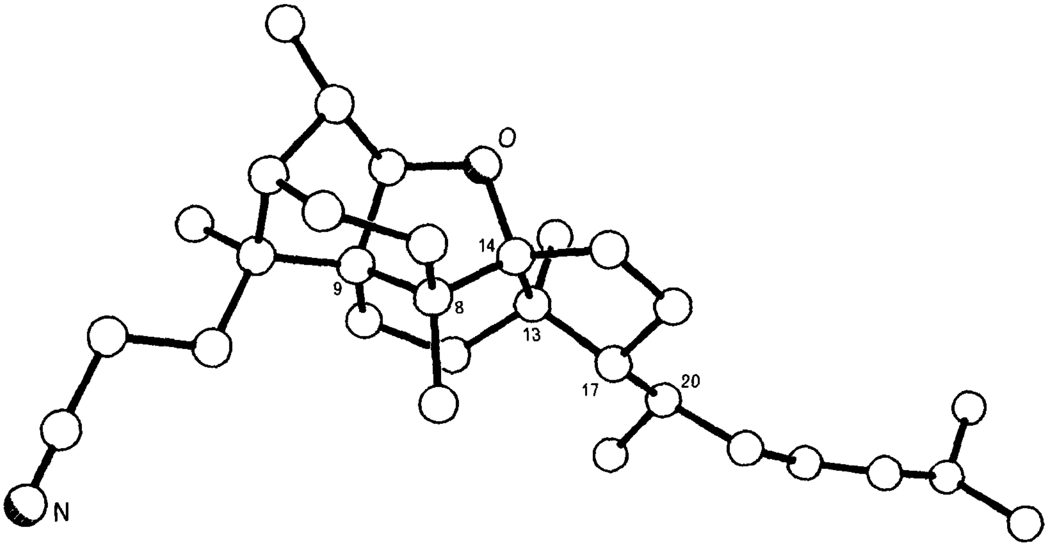
(4)

The off-resonance ^{13}C n.m.r. spectrum of compound (4) exhibited only three signals downfield from deuteriochloroform, δ 96.4 (d), 102.4 (s), and 120.5 (s, -CN) ppm.[3] The product clearly did not contain a carbon-carbon double bond. The ^{1}H n.m.r. spectrum of (4) included signals at δ 3.66 (1H, d, J 1.9 Hz) and 1.17 (3H, d, J 8 Hz) ppm. This data together with the results from decoupling experiments established the part structure (5), indicating that both termini of the aldehyde carbonyl group had become bonded to quaternary centres. The small coupling constant between H_a and H_b in (5) (1.9 Hz) further suggested that this fragment was part of a rigid, cyclic ether.[4]



(5)

The structure and stereochemistry of the ether (4) were finalised by single crystal X-ray structural analysis (Figure).



FIGURE

Crystals of the ether (4), $C_{30}H_{49}NO$, are orthorhombic $\underline{a}$ = 8.344(1), $\underline{b}$ = 17.476(2), $\underline{c}$ = 18.545(3) Å, $\underline{U}$ = 2704 Å^3, space-group $\underline{P}\ 2_1 2_1 2_1$, $\underline{Z}$ = 4, $\underline{D}_c$ = 1.08 g cm^{-3}. Of the 2059 independent reflections ($\theta \leqslant 58^\circ$) measured on a diffractometer using Cu-$\underline{K}_\alpha$ radiation 420 had $|\underline{F}_o| < 3\sigma(|\underline{F}_o|)$ and were classified as unobserved. The structure was solved by direct methods and refined anisotropically to $\underline{R}$ = 0.060. Thermal motion in the structure is high and is particularly pronounced in the C(17) side-chain. Rings B and C adopt chair and boat conformations respectively. There are some notable departures from tetrahedral geometry; the C(13)C(17)C(20) angle is 120.7(4)° and in the strained tetrahydrofuran ring the angles at C(9), C(8) and C(14) are 97.4(3), 97.9(3) and 100.5(3)° respectively. The nitrile group is linear with C-C and C≡N distances of 1.445(8) and 1.122(8) Å respectively.

We have not detected any product corresponding to (4) but epimeric at C-4, despite the fact that the epoxide (1) and the aldehyde (3) are both clearly epimeric mixtures. The preferential cyclisation of one epimer of the aldehyde (3) must reflect steric congestion involving the 31-methyl group, the 7β-hydrogen, and the (complexed) oxygen atom in the transition state that would lead to the alternative product.

1,2-Methyl migrations are a fundamental feature of the rearrangements involved in the biosynthesis of triterpenoids,[5] and form an important aspect of the chemistry of certain families of triterpenoids.[6] The formation of the ether (4) is the first example of an *in vitro* reaction involving the 1,2-migration of the 32-methyl group of a lanosterol derivative It reflects the special (intramolecular) ability of the aldehyde (3) to deliver an electrophile to the normally sterically disfavoured 9β position. Interestingly, this novel 1,2-methyl rearrangement is reversible. Treatment of the ether (4) with boron tribromide in dichloromethane gave an epimeric mixture of the aldehydes (3), further characterised by conversion by tin (IV) chloride into the crystalline ketone (2).

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References

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2. J.F. Cavalla, J.F. McGhie, and M.K. Pradhan, *J.Chem.Soc.*, 1951, 3142.
3. Full spectrum - δ ($CDCl_3$) 12.1 (t), 18.7 (q), 19.4 (q), 21.7 (q), 21.8 (q), 22.5 (q), 22.8 (q), 23.9 (q + t), 25.1 (t), 25.8 (t), 26.8 (t), 28.0 (d), 28.1 (t), 30.4 (t), 31.4 (t), 32.9 (t), 34.8 (d), 35.8 (t), 39.5 (t), 43.6 (d), 44.9 (s), 46.6 (s), 48.4 (d), 48.6 (s), 57.6 (d), 58.0 (s), 96.4 (d), 102.4 (s) and 120.5 (s) ppm.
4. For a related reaction, see J.W. Blunt, E.J. Ditzel, M.P. Hartshorn, Lu Hieng Sieng, M.H.G. Munro, and W.T. Robinson, *Tetrahedron Letters*, 1981, 1923.
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6. For example, the euphol-isoeuphenol rearrangement: D.H.R. Barton, J.F. McGhie, M.K. Pradhan, and S.A. Knight, *J.Chem.Soc.*, 1955, 876; the friedo-oleanane rearrangement: G. Brownlie, F.S. Spring, R. Stevenson, and W.S. Strachan, *J.Chem.Soc.*, 1956, 2419.

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