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SYNTHESIS OF CYCLIC ETHER

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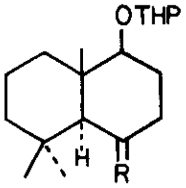
Abstract - A stereospecific synthesis of the 6β,20-epoxy-12-hydroxyabieta-8,11,13-triene (14) is described.

The cleavage of the cyclic ethers has been found extremely useful in the synthesis of carboxylic acid, and thus has provided route to suitable synthon for the synthesis of natural products[1,2]. In light of these observations it was felt that the synthesis of the cyclic ether (14) and its rupture should provide a reasonable access to some natural products related to terpenes such as rosmanol[3] and galdosol[4]. In addition the cyclic ether (14) seems to be an important synthon for entry into pisiferic acid, a bioactive diterpene[5]. To this end we have undertaken the synthesis of the cyclic ether (14) whose details are described in the present communication.

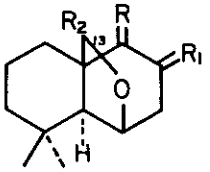
The starting material chosen for the present synthesis was the previously reported[6] alcohol (1). Oxidation of the alcohol (1) with the reagent of Sarett[7] yielded the ketone (2) (74%), mp 89-91°C (ether), m/z 210 ($M^+-C_5H_8O$) and ν_{max} (KBr) 1700 (CO) cm^{-1}, which on attempted isomerization with base was recovered unchanged. Ketone (2) on reduction with lithium aluminium hydride in tetrahydrofuran afforded the alcohol (3) (56%), mp 112-113°C (hexane-ether), m/z 194 ($M^+-C_5H_8O-H_2O$), ν_{max} (KBr) 3450 (OH) cm^{-1} and δ ($CDCl_3$) 3.28-4.26 (m, 4H) (H on C-6', C-9 and C-6) and 4.68 (m, 1H, C-2') ppm. It was very difficult to ascertain the peak width ($W_{1/2}$) of the C-6 proton signal of the alcohol (3) because it was obscured by the protons of C-6', C-6 and C-9 and therefore the configuration of the C-6 hydroxyl group of alcohol (3) could not be determined at this stage. However from the reported works from our laboratory[8] and on the basis of the nmr spectroscopic data of the alcohols (1) and (3) there was every reason to assume the axial nature of the C-6 hydroxyl group of the alcohol (3). This stereochemical assignment was confirmed by



(1) $R = <^{\mathrm{OH}}_{\mathrm{H}}$

(2) $R = O$

(3) $R = <^{\mathrm{OH}}_{\mathrm{H}}$

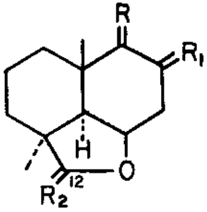


(4) $R = <^{\mathrm{OTHP}}_{\mathrm{H}}$, $R_1 = R_2 =$ H,H

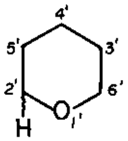
(6) $R = O$, $R_1 = R_2 =$ H,H

(7) $R = R_2 = O$, $R_1 =$ H,H

(10) $R = O$, $R_1 = CHOH$, $R_2 =$ H,H



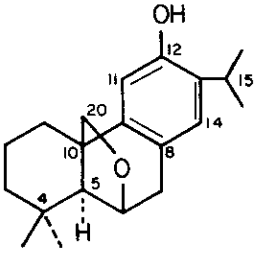
THP =



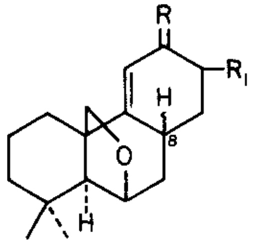
(5) $R = <^{\mathrm{OTHP}}_{\mathrm{H}}$, $R_1 = R_2 =$ H,H

(8) $R = O$, $R_1 = R_2 =$ H,H

(9) $R = R_2 = O$; $R_1 =$ H,H



(14)



(11) $R = O$, $R_1 = H$

(12) $R = O$, $R_1 = COOC_2H_5$

(13) $R = O$, $R_1 = (OH)C<^{\mathrm{CH_3}}_{\mathrm{CH_3}}$

the latter events.

Irradiation[8] of cyclohexane solution of the alcohol (3) with lead tetraacetate and iodine afforded as expected a mixture of the cyclic ethers which on cromatographic purification over silica gel gave the cyclic ether (4) (45%), mp 69-70°C (hexane), m/z 210 (M^+-C_5H_8O) and δ ($CDCl_3$) 0.86 (s, 3H), 0.96 (s, 3H) (C_4-Me), 3.38-4.26 (m, 6H) (H on C-6', C-6, C-9 and C-13) and 4.72 (m, 1H, C-2') ppm and the oily bicyclic ether (5) (20%), m/z 210 (M^+-C_5H_8O), δ ($CDCl_3$) 1.01 (s, 3H), 1.08 (s, 3H) (C_4-Me and C_{10}-Me), 3.42-4.32 (m, 6H) (H on C-6', C-6, C-9 and C-12) and 4.78 (m, 1H, C-2') ppm. The structural and stereochemical assignment of these cyclic ethers were tentatively made from our previous work[8]. The spectroscopic evidence did not unequivocally differentiate (4) from (5). So to this end we sought chemical reactions to establish their identity.

Treatment of the cyclic ether (4) in acetone with Jones reagent[9] at 0°C yielded the ketone (6) (62%), mp 81-84°C (ether-hexane), m/z 208 (M^+), ν_{max} (KBr) 1710 (CO) cm^{-1} which on oxidation with chromium trioxide in acetic acid at 20°C for 2 h afforded the lactone (7) (52%), mp 80-81°C (ether-hexane), m/z 222 (M^+) ν_{max} (KBr) 1765 (γ-lactone) and 1710 (CO) cm^{-1}; δ ($CDCl_3$) 0.91 (s, 3H) 1.03 (s, 3H) (C_4-Me), 1.85 (d, 1H, J=6 Hz, C_5-H) and 4.85 (m, 1H oxymethine) ppm. Similarly treatment of the cyclic ether (5) with Jones reagent[9] yielded the oily ketone (8) (71%), m/z 208 (M^+), ν_{max} (film) 1712 (CO) cm^{-1} and this on oxidation with chromium trioxide in acetic acid at 20°C for 2 h afforded the γ-lactone (9) (48%), mp 119-121°C (ether-pentane), whose mixed melting point with an authentic specimen (lit.[10] mp 121-122°C) remained underpressed and thus the structure of the γ-lactone (9) was confirmed. The confirmation of the structure of the γ-lactone (9) also established the structure of the cyclic ether (5). The structural and stereochemical assignment of the cyclic ether (5) and the lactone (9) also indirectly settled the structure of the cyclic ether (4) and the γ-lactone (8).

It was observed that increase of reaction time and temperature of the oxidation of the cyclic ethers (4) and (5) led mainly undesired products.

Our next goal was to annulate the cylic ether (6) to the tricyclic ketone (11) which we accomplished by Robinson annelation. The cyclic ether (6), on being treated with ethyl formate, gave hydroxymethylene derivative (10) (67%), m/z 236

(M^+), ν_{max} (film) 3445 (OH), 1670 (CO) and 1595 (C=C) cm^{-1}. The adduct, formed by treatment of the hydroxymethylene derivative (10) with 1-diethylaminobutanone-3-methiodide, was heated under reflux with sodium methoxide in methanol to yield the cyclic ketone (11) (70%), mp 108-110°C (ether-hexane), m/z 260 (M^+), ν_{max} (KBr) 1655 (CO) and 1601 (C=C) cm^{-1}. The nmr spectrum indicated that the cylic ketone (11) was a mixture of 8α and 8β epimers. As our aim was to aromatize the ring C, no attempt was made to separate the isomers.

Treatment of the ketone (11) with sodium hydride and diethyl carbonate in 1,2-dimethoxyethane furnished principally the keto-ester (12), m/z 332 (M^+) and 286 (M^+-C_2H_5OH); ν_{max} (film) 1745 (ester CO) and 1660 (ketonic CO) cm^{-1}. Reaction of the keto-ester (12) with methyl lithium in diethyl ether produced the oily ketol (13) (45%), m/z 300 (M^+-H_2O), ν_{max} (film) 3355 (OH) and 1655 (CO) cm^{-1}. The ketol (13) on being heated under reflux with methanolic hydrochloric acid (10%) was converted to the cyclic ether (14) (46%), mp 102-105°C (ether), m/z 300 (M^+), ν_{max} (KBr) 3360 (OH) cm^{-1}, δ ($CDCl_3$) 0.96 (s, 6H), (C_4-CH_3), 1.26 (d, 6H, J=6 Hz, C_{15}-CH_3), 1.62 (d, 1H, J=6 Hz, C_5-H),3.82 (q, 2H, J=6 Hz, C_{20}-2H), 6.62 (s, 1H) and 6.84 (s, 1H) (aromatic protons).

In conclusion the cyclic ether (14) is considered to be an attractive precursor which can undergo typical reactions at ether and hydroxyl function thereby yielding valuable intermediates for the synthesis of natural products[11].

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