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A SYNTHETIC APPROACH TO NOREUDESMANOID PHYTOALEXINS[1]

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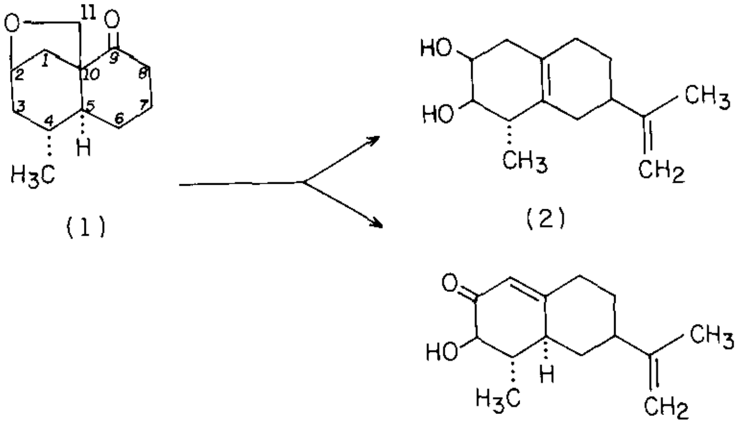
Abstract - A stereoselective synthesis of 2β, 10β-oxymethylene-4α-methyl-9-oxo-trans-decalin (1) is reported starting from the known dienone (4).

Extensive efforst towards the investigations of the phytoalexin natural products have been stimulated over the past few years by their significant role in the control of plant disease[2]. As part of a general project aimed at the total synthesis of terpenes[3], an attempt was made to synthesize the cyclic ether (1), which provides *functionality* well suited for elaborating the synthesis of rishitin[4] (2) and glutinosone[5] (3) which are phytoalexin natural products of terpenoid structure. The present communication[6] describes the pathways developed to find a route to the cyclic ether (1).

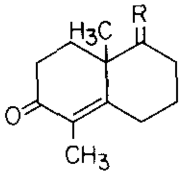


(1)

(2)

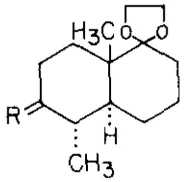
(3)

The already reported[7] dienone (4), chosen as starting material, was prepared by a slight modification of the method of Zoretic[8] which consists in the condensation of 2-methyl-1,3-cyclohexadione and 1-chloro-3-pentanone (both commercially available) under Dean-Stark conditions in benzene and a catalytic amount of p-toluene-sulphonic acid. The dienone (4), obtained in 60% yield, was transformed to the known ketal-ketone[9] (5) in a straightforward manner. The conversion of the ketal-ketone (5) to the saturated ketal-ketone (6), m/z 238 (M^+), ν_{max} (film) 1715 cm^{-1} (CO) and δ (CCl_4) 0.93 (3H, d, J=6 Hz, 4-CH_3), 1.22 (3H, s, 10-CH_3) and 3.87 (4H, s, $-OCH_2CH_2O-$) was accomplished by metal ammonia reduction and the conditions for the optimum yield (78%) consisted in the addition of a solution of the compound (5) (14 mmol) and t-butanol (10.6 mmol) in tetrahydrofuran to a solution of lithium (52 mmol) in dry distilled liquid ammonia. The configurational assignment of 4-CH_3 and 5-H was made upon analogy[10]. In addition to the product (6), the metal ammonia reduction of the compound (5) yielded the alcohol (7, 4.7%), mp 93-95°C (ether), m/z 240 (M^+) and 222 (M^+-H_2O), ν_{max} (KBr) 3400 cm^{-1} (OH). Treatment of the alcohol (7) with acetyl chloride in ether containing pyridine afforded the acetate (8, 86%), mp 73.5-74.5°C (hexane), m/z 282 (M^+) and 223 (M^+-OAc), δ (CCl_4) 0.82 (3H, d, J=5 Hz, 4-CH_3), 1.02 (3H, s, 10-CH_3), 2.04 (3H, s, $COCH_3$) and 3.90 (4H, m. $-OCH_2CH_2O-$). No attempt was made however to determine the configuration of the hydroxyl group of the alcohol (7) and the acetyl group of (8).



(4) R = O

(5) R = $\left[\begin{smallmatrix}O\\O\end{smallmatrix}\right.$

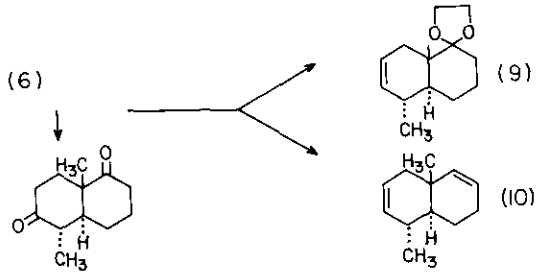


(6) R = O

(7) R = ∿∿OH,H

(8) R = ∿∿OAc,H

In order to introduce a double bond at the 2,3 position of the compound (6), it was made to react with p-toluenesulphonyl hydrazide in benzene using a catalytic amount of boron trifluoride etherate. The crude tosylhydrazone derivative, on treatment with lithium di-isopropylamide in tetrahydrofuran[11] at -78°C, yielded an oily olefin (40%), whose structural assignment (9) followed unambiguously from its spectra, m/z 222 (M^+), δ (CCl_4) 0.93 (3H, s, 10-CH_3), 0.97 (3H, d, J=6 Hz, 4-CH_3), 3.87 (4H, m, $-OCH_2CH_2O-$) and 5.40 (2H, m, vinyl protons). One of the byproducts obtained in 34% yield during this reaction gave a molecular ion peak (m/z) at 162 (M^+) in the mass spectrum and thus was assigned the diolefin (10) structure. We believe that the diketone (11), generated by the deprotection of the ketal group of the compound (6) by boric acid, which results from even a slight contact of moisture with boron trifluoride etherate, reacted with p-toluenesulphonyl hydrazide to form the ditosylhydrazone derivative, and this then underwent reductive elimination by lithium di-isopropylamide to give de diolefin (10) which could not be characterized fully owing to our failure in eliminating the minor impurities present in it. In order to improve the yield of the olefin (9) and minimize the proportion of the side product diolefin (10), an alternative approach was sought which consisted in stirring the compound (6) in methanol with p-toluenesulfonyl hydrazide without using any catalyst. The crude tosylhydrazone on reduction with lithium di-isopropylamide in tetrahydrofuran or with methyllithium in ether-tetrahydrofuran yielded the olefin (9) in 86% yield.

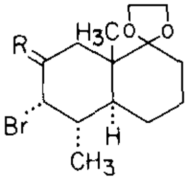


The following steps involved the transformation of the olefin (9) to its bromohydrin derivative (12) which was accomplished by treating the former with N-bromosuccinimide in aqueous dimethyl sulfoxide[12]. The crude bromohydrin derivative (12), m/z 239 (M^+-Br), 221 (M^+-Br-H_2O); ν_{max} (film) 3425 cm^{-1} (OH); δ (CCl_4) 0.97 (3H, s, 10-CH_3), 1.22 (3H, d, J=6 Hz, 4-CH_3), 2.52 (broad s, 1H, exchangeable by D_2O), 3.95 (4H, m, -OCH_2CH_2O-), 4.10 (m, 1H) and 4.30 (m, 1H) (CHOH and CHBr); C_{13}-NMR: δ ($CDCl_3$) 112.8 (C-9), 72.3 (C-2), 42.9 (C-10) and 40.6 (C-3), was sufficiently pure, as evidenced from its t.l.c. and spectral data, for the next step. This finding delighted us because owing to the labile nature of most of the bromohydrins we anticipated its damage during the chromatographic purification. The structural assignment of the newly generated hydroxyl and bromine groups was assigned on the basis of literature data[13] and examination of molecular models which indicate the preferential attack of the bromine from the α-side of the molecule to form α-bromonium ion and this then undergoes antiparallel[14] attack by the dimethyl sulfoxide to produce the trans-diaxial bromohydrin (12).

Irradiation[15] of a cyclohexane solution of the bromohydrin (12) with a tungsten lamp in the presence of lead tetraacetate and iodine led to the formation of the oily bromoketone (13) (9%), m/z 237 (M^+-Br), ν_{max} (film) 1720 cm^{-1} (CO), bromolactone (14) (14%), mp 139-140°C (hexane), m/z 251 (M^+-Br), ν_{max} (KBr) 1785 cm^{-1} (γ-lactone), δ (CCl_4) 1.21 (3H, d, J=7.5 Hz, 4-CH_3), 3.91 (4H, m, -OCH_2CH_2O-) 4.31

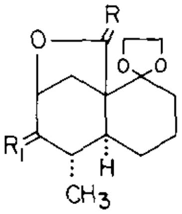
(1H, m) and 4.72 (1H, m) (CHO and CHBr), a large amount of iodocyclohexanone and other unidentified products.

In view of the low yield of the bromolactone (14) which was supposed to be converted to the bromoether (15) for our synthetic objective, an alternative method of photolysis was experimented,



(12) R = $<^{OH}_{H}$

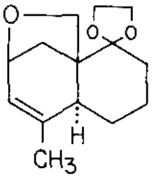
(13) R = O



(14) R = O; R_1 = $<^{Br}_{H}$

(15) R = H,H; R = $<^{Br}_{H}$

(16) R = R_1 = H,H



(17)

which consisted in the irradiation of a solution of the bromohydrin (12) in refluxing benzene with a tungsten lamp for 2.5h. This modified procedure yielded the bromoketone (13) (15%) whose identity was confirmed by comparing its spectral data with an authentic sample previously mentioned and bromoether (15) (63%), mp 57.5-58.5°C (hexane), m/z 318 (M^+, ^{81}Br) and 316 (M^+, ^{79}Br), 289 and 287 (M^+-CHO) and 237 (M^+-Br), δ (CCl_4) 1.01 (3H, d, J=6 Hz, 4-CH_3), 3.91 (4H, m, -OCH_2CH_2O-), 4.11 (1H, m) and 4.31 (1H, m) (CHO and CHBr).

To complete the synthesis of the target molecule, all that required was debromination of the bromoether (15) followed by deprotection of the ketal function. This process proved to be surprisingly problematic than expected probably owing to the inert nature of 3-Br atom of the bromoether (15) and thus merits some brief discussions. On stirring the bromoether (15) with tri-n-butyltin hydride[16] (1.2 equivalent) in tetrahydrofuran at room temperature for 9h, the bromoether (15) was recovered unchanged. The reaction was repeated by heating for 1.5h the bromoether (15) and tri-n-butyltin hydride in benzene in presence of azobisisobutyronitrile as initiator. The starting material was partially recovered along with various decomposition products as evidenced in t.l.c. Finally a successful result was obtained by heating the bromoether (15) and tri-n-butyltin hydride in methanol which yielded the desired ketal (16) in 56% yield, m/z 238 (M^+) which on hydrolysis with dilute hydrochloric acid yielded the cyclic ether (1) in a satisfactory yield, m/z 194 (M^+), ν_{max} (film) 1705 cm^{-1} (CO), $\delta(CCl_4)$ 0.98 (d, 3H, J=6 Hz), 3.41 (d, 1H, J=7.5 Hz) and 4.21 (d, 3H, J=7.5 Hz). The same cyclic ether (1) was obtained by stirring the bromoether (15) with tri-n-butyltin hydride in tetrahydrofuran for 70h at room temperature followed by heating the resulting product, in acetone and dilute hydrochloric acid. It is worthwhile mentioning that the debromination procedure though served admirably, was not very encouraging owing to the laborious and tedious operation involved in the process of separation of the cyclic ether (1) from the organotin impurities which resulted during the reaction. In order to overcome this drawback, the bromoether (15) was treated with sodium borohydride in anhydrous dimethyl sulfoxide and was heated under reflux for 3h. The resulting product, obtained in 60% yield was found to be a mixture of ketal (16) and olefinic ketal (17) in a 1:1 proportion as proved on the basis of the spectral data (n.m.r. and mass). Although it might prove possible to separate the ketals (16) and (17), this was not attempted due to the poor yields obtained.

In conclusion, a stereoselective synthesis of the cyclic ether (1) has been achieved in moderate yield. The reaction condition of some of the experiments could be altered in order to improve the yield of the target molecule, the cyclic ether (1). Such a project is under investigation together with the accumulation of sufficient material for an assault on the natural products - Glutinosone and Rishitin.

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REFERENCES AND NOTES

1. This work has been dedicated with warm regards and affection to Dr. Gabriel Chuchani, founder of the Department of Chemistry of our Institute (IVIC), on the occasion of his 60th birthday.
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