SYNTHESIS OF (±)-1β-METHOXY-9β,7β-EPOXY-5α-METHYL-TRANS-DECALIN[1]

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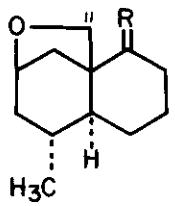
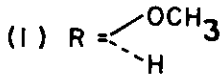
Abstract - The ketal-ketone (14), prepared from dione (3), was converted to the olefin (16) which on reduction and methylation yielded the ketone (18). The alcohol (19), obtained by reduction with sodium and n-propanol, on oxidation with lead tetraacetate in benzene afforded the cyclic ether (1) which on treatment with trichloromethylsilane and sodium iodide followed by oxidation with Jones reagent produced the keto-ether (2). The α,β-unsaturated ketone (21), prepared from keto-ether (2), was subjected to cyanation, hydrolysis, esterification and deoxygenation respectively to obtain ester (23) whose conversion to lactone (24) followed by reduction, oxidation and esterification afforded the keto-ester (25). The olefinic material obtained from the keto-ester (25) was treated with silver chromate and iodine to obtain α-keto halogenated product and this on treatment with diphosphorous tetraiodide yielded the keto-ester (26).

In connection with our planned synthesis of natural products we required a convenient preparation of the cyclic ether (1) which represents a potential synthon for the synthetic entry to phytoallexin natural products like glutinosone[2] (27). The present communication describes a concise route to this important molecule.

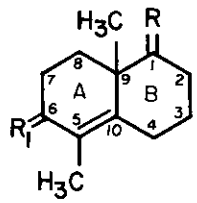
The dione (3), prepared by the published procedure[3], was chosen as reference material for the present investigation. In order to experiment some reactions on the double bond and the carbonyl group of ring A of the dione (3), it was felt necessary to block the carbonyl group of ring B. It was found unsatisfactory to continue the synthetic objective by protecting the carbonyl group by ketal moiety and thus an alternative protecting group was sought. Selective reduction of the dione (3) with sodium borohydride in ethanol yielded the known[4] alcohol (4) which was

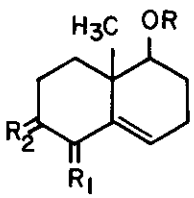
treated with benzyl chloride and sodium hydride with the hope of obtaining the benzyl derivative (5) which can show acceptable stability towards a variety of acidic and basic reagents. The result was disappointing because instead of getting the desired product (5), two products (6) and (7), as analyzed by spectroscopic data, in yields 63% and 18% respectively, were produced. This result perfectly agree with the result of Heathcock and Raticliffe[5] who reported that it was not possible to alkylate the hydroxyl group of the α,β-unsaturated bicyclic ketone without blocking the carbonyl group. The stereochemical assignment of the benzyl group at C-5 of (6) and (7) was assigned on the basis of published work.[6] The alkylated products (6) and (7) were of little interest for our synthetic objective and thus no conclusive evidence was sought to confirm the above mentioned assignment of the benzyl group. As the desired product (5) was not obtained, an alternative protecting group was sought. Benzoylation of the alcohol (4) with benzoyl chloride and pyridine yielded the benzoylated product (8) which was subjected to ketalization by heating for 40 hr with ethylene glycol in benzene and catalytic amount of p-toluenesulfonic acid. The resulting product on chromatographic purification yielded the ketal (9) in 77%, mp 140-142°C (hexane), m/z 342 (M^+), 220 (M^+-C_6H_5COOH) and 205 (M^+-C_6H_5COOH-CH_3), ν_{max} (KBr) 1712 cm^{-1} (CO), δ ($CDCl_3$) 1.17 (s, 3H, 9-CH_3), 1.69 (s, 3H, 5-CH_3) and 4.01 (m, 4H, 6-ketal) and ketal (10) in 32% yield, mp 103-105°C (hexane), m/z 342 (M^+), ν_{max} (KBr) 1715 cm^{-1} (CO), δ ($CDCl_3$) 1.15 (s, 3H, 9-CH_3), 1.22 (d, 3H, J=6 Hz, 5-CH_3), 4.06 (m, 4H, 6-ketal) and 5.65 (m, 1H, vinyl proton). For our synthetic objectives, the separation of two ketals (9) and (10) was not necessary. However the obtention of the ketals (9) and (10) in unequal proportion differed the observation of Becker and collaborators[7] who reported the ketalization of the bicyclic system in which enone group is substituted in the α and β position yields two isomers in 1:1 ratio. The alcoholic material obtained by reduction of the mixture of the ketals (9) and (10) with lithium aluminium hydride was methylated with methyl iodide and sodium hydride. The resulting material on heating with aqueous acetic acid afforded the ketone (11) in 75% yield. Reduction of the ketone (11) with sodium and n-propanol[8] yielded the alcohol (12) in 50%. The trans ring juncture of rings A and B of the alcohol (12) was assigned on the basis of analogy[8] and the latter events also confirmed it. There was every reason, on the basis of published report[8], to assume the β-orientation of the hydroxyl and α-orientation of the 5-methyl group. However, this point not being crucial, was



(1) R = 

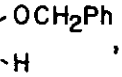
(2) R = O





(3) R = R_1 = O

(4) R =  , R_1 = O

(5) R =  , R_1 = O

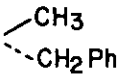
(8) R =  , R_1 = O

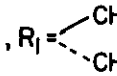
(9) R =  , R_1 =

(11) R =  , R_1 = O

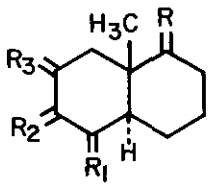
(14) R =  , R_1 = O

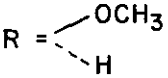
(17) R =  , R_1 = H, H

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

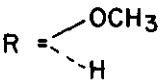
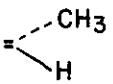
(7) R = CH_2Ph, R_1 =  , R_2 = O

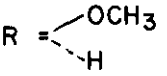
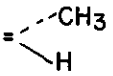
(10) R = Bz, R_1 = ~~ CH_3, H, R_2 =

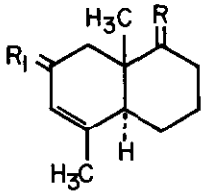


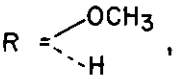
(12) R =  , R_1 = ~~CH_3, H , R_2 = ~~OH, H , R_3 = H, H

(15) R =  , R_1 = ~~CH_3, H, R_2 = ~~OH, H , R_3 = H, H

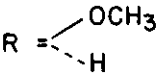
(19) R =  , R_1 =  , R_2 = H, H , R_3 = 

(20) R =  , R_1 =  , R_2 = H, H , R_3 = O



(13) R =  , R_1 = H, H

(16) R = O , R_1 = H, H

(18) R =  , R_1 = O

not verified. Tosylation of the alcohol (12) followed by heating the resulting tosylate with lithium bromide and lithium carbonate in dimethylformamide[9] yielded the olefin (13) in 80% yield, m/z 194 (M^+), δ ($CDCl_3$) 1.02 (s, 3H, 9-CH_3), 1.62 (s, 3H, 5-CH_3 and 5.45 (m, 1H, vinyl proton). Later on accidently a simple method

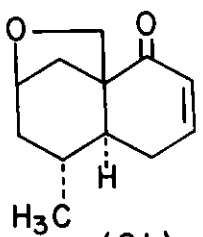
was developed for the synthesis of the olefin (13) which is described as follows. The ketal-ketone (14) on reduction with sodium and n-propanol afforded the alcohol (15) in 42% yield. Tosylation of the alcohol (15) followed by heating the tosylate with lithium bromide and lithium carbonate in dimethylformamide produced the olefinic ketone (16) in 80% yield, bp 82-85°C (0.05 mm) (bath), m/z 178 (M^+), ν_{max} (film) 1720 cm^{-1} (CO), δ ($CDCl_3$) 1.08 (s, 3H, 9-CH_3), 1.65 (s, 3H, 5-CH_3) and 5.68 (m, 1H, vinyl proton) and these spectroscopic data were almost identical with the data reported.[10] It is worthwhile to mention that the olefinic ketone (16) was utilized by Garver and van Tamelen[10] in the total synthesis of (±)-triptolide, a promosing anticancer natural product. Thus our alternative synthesis of the olefinic ketone (16) constitutes a formal total synthesis of (±)-triptolide. No authentic specimen was available for direct comparison. Reduction of the olefinic ketone (16) with sodium borohydride in methanol yielded an alcoholic material which was methylated with methyl iodide and sodium hydride. The resulting material on purification afforded the oily olefin (13) in 74% yield.

Allylic oxidation[11] of the olefin (13) with chromic acid and pyridine gave the α,β-unsaturated ketone (18) in 48% yield, mp 140-142°C (hexane), m/z 208 (M^+), ν_{max} (KBr) 1680 cm^{-1} (C=C-C=O), δ ($CDCl_3$) 1.08 (s, 3H, 9-CH_3), 3.68 (s, 3H, OCH_3) and 5.45 (s, 1H, vinyl proton). In addition of the ketone (18), the ketone (11) was obtained in 30% yield whose formation clearly indicated the initial formation of the olefin (17) during oxidation which was finally converted to (11). In order to realize the desired objective, the ketone (18) was subjected to reduction with sodium and n-propanol to obtain the alcohol (19) in 42% yield whose stereochemical assignment was confirmed by the following experiments.

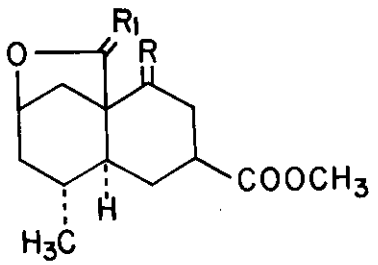
The alcohol (19), on treatment with cerium ammonium nitrate in aqueous acetonitrile[12], yielded the cyclic ether (1) in 25% yield, m/z 210 (M^+), δ ($CDCl_3$) 1.25 (d, 3H, d=6 Hz, 5-CH_3), 3.65 (s, 3H, OCH_3) and 4.25 (m. 2H, C-11) and the ketone (20) in 30% yield, m/z 210 (M^+), ν_{max} 1720 cm^{-1} (CO) and δ ($CDCl_3$) 1.09 (s, 3H, 9-CH_3), 1.24 (d, 3H, J=6 Hz, 5-CH_3) and 3.65 (s, 3H, OCH_3). The yield of the cyclic ether (1) was substantially increased to 30% on irradiation with 250-W incandescent lamp of a solution of the alcohol (19) in benzene containing lead tetraacetate and calcium carbonate. This experiment afforded the ketone (20) in 15%.

In order to accomplish the transformation of the cyclic ether (1) to the natural product glutinosone (27), the conversion of the cyclic ether (1) to the already

reported[3] cyclic ether (2) was required, and this operation proved very frustrating owing to the inertness of the methoxy group towards many reagents. After a series of trials the experimental procedure which proved somewhat satisfactory consisted in the treatment of the cyclic ether (1) with trichloromethyl silane and sodium iodide in acetonitrile[13]. The resulting material without purification was oxidized with Jones reagent[14] at 0°C to obtain the already reported[3] cyclic ether (2) in 30% yield whose spectroscopic data nicely matched with the published data.[3]



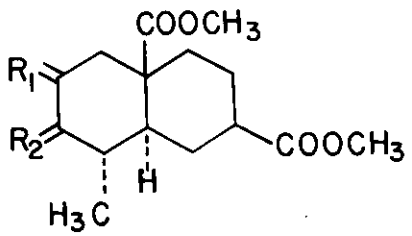
(21)



(22) R = O, R_1 = H, H

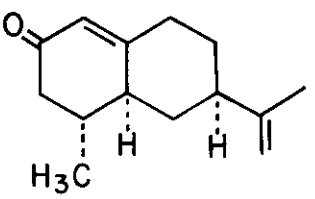
(23) R = R_1 = H, H

(24) R = H, H, R_1 = O



(25) R_1 = O, R_2 = H, H

(26) R_2 = O R_1 = H, H



(27)

Bromination of the cyclic ether (2) with bromine and glacial acetic acid followed by dehydration of the resulting material with lithium carbonate, lithium bromide and dimethyl formamide produced the oily α,β-unsaturated ketone (21) m/z 192 (M^+) ν_{max} 1645 cm^{-1} (CO), δ ($CDCl_3$) 5.74 (1H, d, J=2 Hz) and 5.96 (1H, d, J=2 Hz) (olefinic protons) which was subjected to cyanation reaction[15] by heating with potassium cyanide in dimethylformamide and ammonium chloride. The resulting material obtained on alkaline hydrolysis (40% methanolic potassium hydroxide) on esterification with diazomethane afforded the oily ester (22) in 32% yield, m/z 207 (M^+-COOH), ν_{max} 1720 and 1740 cm^{-1} (CO), δ 3.65 (s, 3H, OCH_3). The stereochemical assignment of the carboxylate group was assigned on the basis of analogy.[16] Elimination of the carbonyl group of the ester (22) by the method of Clemmensen[17] yielded the ester (23) in 52% yield, m/z 236 (M^+) and 191 (M^+-COOH). The crude ester (23) on oxidation with chromium trioxide and acetic acid yielded the lactone (24) in 48% yield, m/z 250 (M^+) and 205 (M^+-COOH), ν_{max} 1765 cm^{-1} (γ-lactone) which was subjected to reduction with lithium aluminium hydride to obtain an alcoholic material, as evidenced by the i.r. spectroscopy, and this on oxidation with Jones reagent at room temperature for 12 hr, yielded an acidic material which on esterification with diazomethane produced the keto-ester (25) in 10% yield, a thick liquid, with a tendency to crystallize, ν_{max} 1720 and 1735 cm^{-1} (CO), m/z 282 (M^+). As our objective was to accomplish the transposition of the carbonyl group of the keto-ester (25) and in addition as the amount available of the keto-ester (25) was not satisfactory, no attempt was made to purify, crystalize and characterize it. A number of methods are available to realize the transformation of the keto-ester (25) to the keto-ester (26) but owing to the nonavailability of the keto-ester (25) in sufficient amount and the susceptibility of the carboxylate group towards many reagents, a simple method was sought. The reduction of the keto-ester (25) with sodium borohydride in ethanol at 0°C yielded an alcoholic material which on dehydration with phosphorous oxychloride and pyridine produced an olefinic material as evidenced by spectroscopy. The olefinic material, not homogeneous in t.l.c., was treated with silver chromate and iodine dichloromethane.[18] The resulting crude deep brown colored material which exhibited strong carbonyl group in the IR spectrum and the presence of halogen (flame test), contained a mixture of four products, as evidenced by t.l.c., on treatment with diphosphorous tetraiodide[19] and dichloromethane yielded the keto-ester (26) in 4% yield, mp 103-105°C (ether) |lit.[10] mp 105-106°C|, m/z 282 (M^+) and 221 (M^+-

COOH-CH_3), ν_{max} 1720 and 1735 cm^{-1} (CO), δ 1.05 (3H, d, J=6 Hz, 4-CH_3), 3.72 (each 3H, s, 2COOCH_3). These spectroscopic data were found almost identical with the published data.[20] Lack of authentic specimen did not permit us to make a direct comparison.

As the keto-este (26) has been utilized[20] for the synthesis of glutinosone (27), the synthesis of the former constitutes an alternative approach for the synthesis of glutinosone (27). It is worthwhile to mention that the synthesis of the cyclic ether (1) was undertaken not only for the synthesis of glutinosone (27) but to extend its utility in the synthesis of other natural products. This programm is under active investigation.

ACKNOWLEDGEMENTS

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