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SYNTHESIS OF BICYCLIC INTERMEDIATES FOR DITERPENOID ALKALOIDS

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Abstract- Synthesis of ester 9 from olefin 1 is described. Transformation of 9 to lactams 20 and 21 has been realized.

The complex ring structures of diterpenoid alkaloids posed a synthetic challenge to the organic chemists for a long time. Extensive efforts in the last two decades towards the synthetic aspects in this field has led to the total synthesis of atisine, garryine, potential intermediates and related model compounds.[1] The major obstacle in the synthesis of Garrya and Atisine group of diterpenoid alkaloids lies in the construction of heterobridged trans-decalin characteristic of these bases. In relation with our synthetic studies on diterpenoid alkaloids[2] it was planned a few years ago[3] to synthesise the angularly carboxylated ester 9 and then to realise its transformation to acid 16 which by suitable photolysis would allow the entry into the tricyclic amine systems 20 and its derivative 21, characteristic structural units of many diterpenoid alkaloids. The research was delayed for several reasons and in the meantime an excellent approach to the synthesis of 20 and 21 was published by Meyer and associates.[4] Thus it was thought worthwhile to publish our result which are discussed in the present report.

Olefin 1, prepared by the published procedure[5], on hydroboration[6] afforded the crystalline alcohol 2 in 80% yield, mp. 62-64° (hexane), IR (KBr) 3500 cm^{-1}, m/e 196 (M^+) and δ 3.88 (m, 1H, $W_{1/2}$ = 14 Hz) characteristic[7] of the axial proton at C-6. Oxidation[8] of 2 with CrO_3/hexamethylphosphoric triamide afforded the oily ketone 3, bp. 98-105°/0.2 mm (bath) in 95% yield and this was recovered unchanged on treatment with acid and base and therefore indicating the more stable trans-fusion of the ring A/B of ketone 3. A byproduct of the hydroboration process that resulted in 4% yield was identified as the hydrocarbon 4, bp. 106-112°/17 mm (bath), m/e 180 (M^+) and was found identical by comparing its IR spectrum with the authentic specimen.[9]

Protonolysis[10] of the B-H moiety of olefin 1, effected by boric acid, probably formed by the presence of a trace of water, produced the hydrocarbon 4. Reduction of ketone 3 with $LiAlH_4$ afforded 82% yield of the crystalline alcohol 7, mp. 48-50° (hexane), IR (KBr) 3480 cm^{-1} and δ 4.38 (m, 1H, $W_{1/2}$= 6Hz) which is the characteristic[7] of the equatorial proton at C-6. Irradiation[11,12] of the cyclohexane solution of 3 with a tungsten lamp in the presence of $Pb(OAc)_4/I_2$ afforded cyclic ether 5, bp. 110-115°/20 mm (bath) in 36% yield, m/e 194 (M^+) and δ 0.93 (3H, s), 1.05 (3H, s), 3.80 (m, 2H at C-12), ketone 3 in 60% yield and a small amount of an oily material which was not investigated. Oxidation of 5 with CrO_3/AcOH afforded the crystalline acid 8 in 70% yield, mp. 130-132° (ether), m/e 224 (M^+) and 179 (M^+-COOH) and this on esterification with trimethyloxonium tetrafluoborate[13] afforded the oily ester 9 in 85% yield, bp. 85-92/0.25 mm (bath), m/e 238 (M^+) and 193 (M^+-COOH) and δ 0.96 (3H, s) 1.45 (3H, s) and 3.75 (3H, s, OCH_3). The chemical transformation[14] of 9 to the already known acid[16] confirmed the structure of 9 and the cyclic ether 5.

Kinetic enolate of 9, generated by lithium diisopropylamide in 1,2-dimethoxyethane, reacted with trimethylsilyl chloride to furnish as expected[17] the less highly substituted enol ether 10 in predominant amount along with a little amount of highly substituted enol ether 11. Epoxidation[18] of the crude enol ethers in CH_2Cl_2 with m-chloroperbenzoic acid afforded a mixture of products which on hydrolysis with HCl in ether followed by chromatographic purification over silica gel afforded the oily hydroxy ketone 12 in 50 % yield, IR (film) 1705 (unresolved ester and ketonic carbonyl) and 3450 (OH) cm^{-1}; m/e 191 (M^+-COOH-H_2O). Treatment of 12 with MeI and NaH in tetrahydrofuran furnished 13 a mobile oil, in quantitative yield which on Clemmensen reduction produced 14 in 75% yield, bp. 162-166°/12 mm (bath), m/e 254 (M^+) and 209 (M^+-COOH). It is worthwhile to mention that probably owing to the steric obstacle attempts to removal of C-6 carbonyl group of 12 by mild reducing agents could not be achieved and on the other hand attempts to eliminate the mentioned carbonyl group of 12 by applying drastic methods of reduction like of Clemmensen and Huang-Minlon modification of Wolff-Kishner gave products whose identification was not possible. On demethylation of 14 with boron triamide[19] at 5° followed by oxidation with Jones reagent produced 15, a semi-solid material, in 65% yield. Heating the ester 15 under reflux with quinoline and acetic acid[15] yielded 16 in 78% yield, crude mp. 94-99° which on esterification[13] with triethyloxonium tetrafluoborate produced 17 in 80% yield, 45-47° (Pet.ether) and this on admixed with the authentic[16] specimen (mp. 45-46.5°) did not exhibit any depression in mp. The IR spectra of 17 and the authentic specimen were indistinguishable and thus the structure of the acid 16 and ester 17 remained established.

Ketalization of 15 under the standard condition afforded the oily ketal 18 which was subjected to neutral hydrolysis[20] by heating under reflux for 85 hrs with a mixture of chlorotrimethylsilane, and sodium iodide in acetonitrile. An excellent yield of an acidic material contaminated with very little amount of ketal 18 as observed by tlc, was obtained which on treatment with acid free oxalyl chloride afforded the respective acid chloride and this was converted to azide 19 by adding a mixture of pyridine, and hydrazoic acid in toluene.[21] After elimination of toluene at 0° under reduced pressure the azide was immediately taken in dry thiophene-free benzene which in the IR spectrum showed absorption at 1705 and 2155 cm^{-1} characteristic of $-CON_3$ group. Azide 19 in benzene solution was irradiated[22,23] using a *Hanovia ultraviolet lamp* 450 w at room temperature in a 1-cm quartz cell. A steadv evolution of nitrogen was observed and the reaction was complete within 5 hrs. The resulting dark solution was concentrated and deketalized by heating with p-toluenesulphonic acid for 10 hrs. The resulting products on chromatographic purification over silicagel afforded the desired lactam 20 in 7.8% yield, mp. 157-159° (CH_2Cl_2-n-hexane) which mixed with an authentic specimen[4] (mp. 158-5-160.5°) did not exhibit any depression in mp.

Lactam 20 on heating with excess $LiAlH_4$ in dioxane for 6 days followed by oxidation with pyridinium chlorchromate[24] afforded a pale yellow oily carbonyl compound which in the IR spectrum showed bands at 1708 and 3365 cm^{-1}. The crude oily compound on treatment with mesityl chloride and pyridine yielded 21 (55% based from the starting lactam 20), mp. 181-183° (CH_2Cl_2-hexane) and its mixed mp. with authentic specimen[4] (mp. 183.5-184.5°) remained undepressed. The IR spectra of 21 1705, 1318 and 1152 cm^{-1} was indistinguishable from the IR spectra of the authentic specimen.

In conclusion the synthesis of 9 and its transformation to 20 and 21 constitutes an additional approach for the preparation of potential intermediates for diterpenoid alkaloid synthesis.

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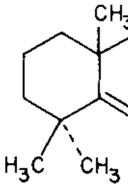

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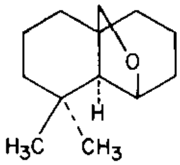

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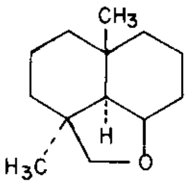

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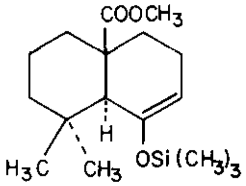

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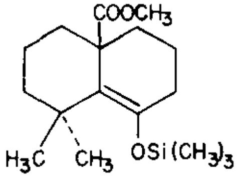

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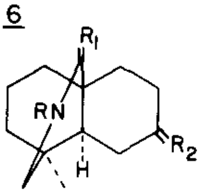
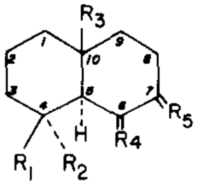


20 $R = H$, $R_1 = R_2 = O$

21 $R = Ms$, $R_1 = H, R_2 = O$



2 $R_1 = R_2 = R_3 = CH_3; R_4 = \overset{\cdots OH}{\underset{H}{<}}$; $R_5 = H,H$

3 $R_1 = R_2 = R_3 = CH_3; R_4 = O$; $R_5 = H,H$

4 $R_1 = R_2 = R_3 = CH_3; R_4 = R_5 = H,H$

7 $R_1 = R_2 = R_3 = CH_3; R_4 = \overset{OH}{\underset{\cdots H}{<}}$; $R_5 = H,H$

8 $R_1 = R_2 = CH_3$; $R_3 = COOH$; $R_4 = O$; $R_5 = H,H$

9 $R_1 = R_2 = CH_3$; $R_3 = COOCH_3$; $R_4 = O$; $R_5 = H,H$

12 $R_1 = R_2 = CH_3$; $R_3 = COOCH_3$; $R_4 = O$; $R_5 = \cdots OH$

13 $R_1 = R_2 = CH_3$; $R_3 = COOCH_3$; $R_4 = O$; $R_5 = \cdots OCH_3$

14 $R_1 = R_2 = CH_3$; $R_3 = COOCH_3$, $R_4 = H,H$; $R_5 = \cdots OCH_3$

15 $R_1 = R_2 = CH_3$; $R_3 = COOCH_3$; $R_4 = H,H$; $R_5 = O$

16 $R_1 = R_2 = CH_3$; $R_3 = COOH$; $R_4 = H,H$; $R_5 = O$

17 $R_1 = R_2 = CH_3$; $R_3 = COOC_2H_5$, $R_4 = H,H$, $R_5 = O$

18 $R_1 = R_2 = CH_3$; $R_3 = COOCH_3$, $R_4 = H,H$, $R_5 = {}^{O}_{O}\rfloor$

19 $R_1 = R_2 = CH_3$; $R_3 = CON_3$, $R_4 = H,H$, $R_5 = {}^{O}_{O}\rfloor$

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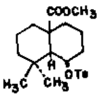

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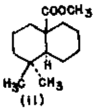
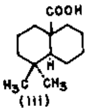


(ii)



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