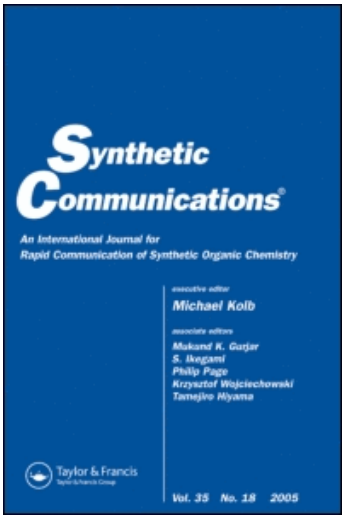

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Synthetic Studies on Ophiobolins[1]. Synthesis of 1β (H) -3,7α,11β-Trimethyl-*CIS*-Bicyclo [6.3.0] Undecan-4-One

Tushar Kanti Das[a]; Phanindra Chandra Dutta[a]
[a] Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta, India

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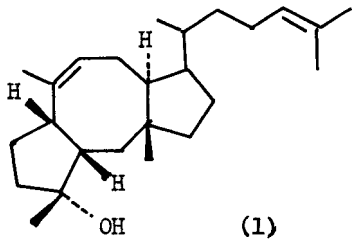
SYNTHETIC STUDIES ON OPHIOBOLINS[1]. SYNTHESIS OF 1β (H) -3,7∝,11β-TRIMETHYL-CIS-BICYCLO [6.3.0] UNDECAN-4-ONE

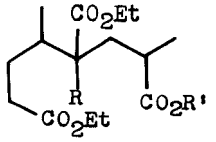
Tushar Kanti Das and Phanindra Chandra Dutta

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta - 700032, India

In our synthetic studies towards ophiobolin F (1)[2], we report here a stereospecific synthesis of 1β(H)-3,7∝,11β-trimethyl-cis-bicyclo [6.3.0]undecan-4-one (2) with defined stereochemistry at each of the four contiguous asymmetric centres and particularly with A/B cis ring juncture as present in (1). It may be mentioned here that no synthetic studies towards developing the characteristic ring systems present in ophiobolins have been reported so far.



(1)

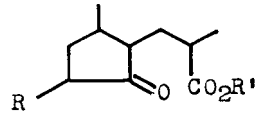


(3) R = CN, R' = Me

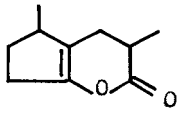
(4) R = H, R' = Et

The bicyclic ketone (10), an important synthon for

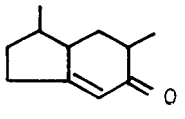
this purpose has been synthesised as follows. Diethyl 2-cyano-3-methyladipate (0.38 mole) was condensed with methyl methacrylate (1.2 mole) in t-butanol at 0° in presence of a catalytic amount of potassium-t-butoxide (4 g). The resulting cyano-triester (3) on acidic hydrolysis (conc. HCl, reflux 20 h) followed by esterification (EtOH, conc. H_2SO_4, reflux 15 h) furnished (4) and this was subjected to Dieckmann cyclisation [triester (0.26 mole), NaOEt (0.52 mole), C_6H_6 (250 ml), reflux 4 h]. The resulting product (5) on acidic hydrolysis (conc. HCl, reflux 15 h) followed by esterification afforded (6) in a satisfactory yield. (6) was hydrolysed under alkaline condition (10% aq-EtOH-KOH, reflux 5 h) and the crude keto-acid (7) was converted to the enol-lactone (8) by treatment with acetic anhydride in presence of a small amount of fused sodium acetate (reflux 4 h, oil-bath temperature 150°) under nitrogen. An ethereal solution of methylmagnesiumiodide (40% excess) was added slowly (2 h) under nitrogen with constant stirring to an ethereal solution of the enol lactone (8) at -78°. The resulting product on



(5) R = CO_2Et, R' = Et
(6) R = H, R' = Et
(7) R = R' = H



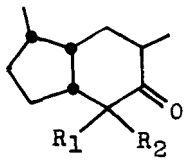
(8)



(9)

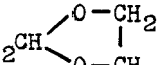
cyclisation (2% aq-MeOH-KOH, reflux 4 h) afforded the unsaturated ketone (9)(60%). This was catalytically hydrogenated (10% Pd-C, ethanol) at room temperature and under pressure (60 p.s.i.) to the desired saturated ketone (10)

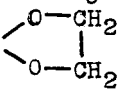
(g.l.c.~92%). As the double bond in (9) is unsubstituted, the catalytic hydrogenation should give mainly the thermodynamically favoured cis-fused[3] bicyclic ketone. The exo-orientation of the secondary methyl group in the cyclopentane ring with the adjacent ring hydrogen atom is consistent from model studies and is based on the greater steric stability of the side-chain in an exo-orientation in the cis-fused hydrindanone system. This is consistent with well-appreciated analogies[4].

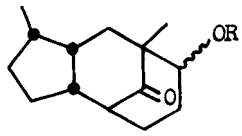


(10) $R_1 = R_2 = H$

(11) $R_1 = CO_2Me$, $R_2 = H$

(12) $R_1 = CO_2Me$, $R_2 = CH_2CH_2CH$ 

(13) $R_1 = H$, $R_2 = CH_2CH_2CH$ 



(14) R = H

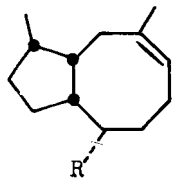
(15) R = Ts

(10) was carbomethoxylated in an excellent yield with dimethyl carbonate in presence of sodium hydride (reflux 2 h). The product (II) was alkylated with 1-bromo-3,3-ethylenedioxypropane in presence of sodium dust suspended in benzene and dimethylformamide (3:1, reflux 10 h) to afford (12) in a moderate yield. This was decarboxylated[5] by heating with lithium iodide (6 molar equivalent) in dimethylformamide (reflux 2 h) to furnish (13). Deketalisation with dilute acetic acid solution and subsequent intramolecular aldol condensation was achieved[6] by treatment with warm dilute hydrochloric acid in aqueous acetic acid solution. The yield

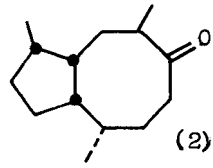
of the cyclisation step was only moderate as contrasted to simple cyclohexanone[6] systems. Because of the presence of the fused cyclopentane ring, the conformational mobility of the cyclohexane ring is somewhat restricted in this case and the yield of the cyclisation product is thereby lowered.

The epimeric mixture[7] of alcohols (14) was treated with toluene-p-sulphonyl chloride in pyridine at room temperature for thirtysix hours to afford the solid tosylates (15). The crude mixture of the epimeric tosylates was treated with sodium ethoxide[7] (0.9 molar equivalent) in ethanol at 60° for five minutes and afforded the desired C_5-C_8 ring fused cyclooctene ester (16) (g.l.c.~92%) together with recovery of a substantial amount of axial tosylate (m.p. 148°) which is present (~15%) in the mixture of tosylates. The cis stereochemistry at A/B ring-juncture in (16) and β-orientation of the secondary methyl group leading to all cis orientation in the contiguous three asymmetric centres will be maintained as these three centres have not been disturbed during these reactions. The alpha orientation of the secondary acid function in the eight membered ring has been assigned from mechanistic considerations associated with the fission of the bridge ring compound.

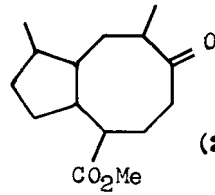
The unsaturated ester (16) was purified by hydrolysing (5% aq-MeOH-KOH, kept for 24 h at room temperature) to the crystalline acid (17) (m.p. 94-95°). Very mild alkaline conditions were used during fragmentation reaction and hydrolysis to avoid epimerisation of the ester function as this phenomenon is conspicuous in the cycloheptane[8] series. (17)



(16) R = CO_2Et
(17) R = CO_2H
(18) R = CO_2Me
(19) R = CH_2OH
(20) R = CH_2OTs
(21) R = CH_3
(22) R = $=CH_2$



(2)



(23)

was esterified with diazomethane to afford methyl ester (18) g.l.c., ~ 100%; n.m.r.*, δ: 5.3 (t, 1H, vinylic H), 1.75 (d, 3H, J = 1Hz, vinylic methyl), 3.55 (s, 3H, methoxyl), 1.0 (d, 3H, J = 6 Hz, C-11 methyl). An ethereal solution of (18) was reduced with lithium aluminium hydride (reflux 2 h) to afford the unsaturated primary alcohol (19) n.m.r., δ : 3.3 (d, 2H, J = 6 Hz, hydroxy methylene). The alcohol (19) was converted to the tosylate by treatment with toluene-p-sulphonyl chloride in pyridine at -10° and the crude pale yellow solid tosylate (20) was reduced with lithium aluminium hydride in ether (reflux 40 h). The product on sublimation, was found to contain three components (g.l.c.) in the ratio (8:1:1). In n.m.r., in addition to the desired olefinic proton at δ 5.3 (t, 1H) of the hydrocarbon (21), a small amount of the viny-

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* N.m.r. spectra were determined for solutions in carbon-tetrachloride on a Varian A-60D spectrometer. Column SE 30 on Varaportzo was employed for g.l.c.

lic impurity exhibited peaks at δ 4.5 (s) and 4.65 (s). Weak signals centred at δ 5.3 (d) is attributed to (19) arising from the (-O-S-) bond cleavage of the tosylate. Extensive column chromatography removed (19). In the mass spectrum of the chromatographed material, in addition to the molecular ion peak of the hydrocarbon (21) at 192, there was also present a peak at 190. The structure (22) was assigned to the vinylic impurity arising from elimination of tosylate function, from n.m.r. and mass spectral data. Diborane was passed into a solution of the mixture of (21) and (22) in tetrahydrofuran at 10-15° for three hours. The complex was treated with alkaline hydrogen peroxide solution for twelve hours. The resulting product in acetone was oxidised with Jones reagent at -5° to afford the eight membered ketone (2) in an excellent yield (g.l.c., single peak, ν_{max} 1710 cm^{-1}). The n.m.r. spectrum of (2) δ :0.9 (d, 3H, J=6 Hz, C-11 methyl), 0.96 (d, 3H, J = 6 Hz, C-7 methyl), 1.1 (d, 3H, J = 5.5 Hz, C-3 methyl) indicated that the diene (22) was removed completely as an acid formed during hydroboration and subsequent oxidation and characterised as methyl ester (23) n.m.r., δ :3.55 (s, 3H, methoxyl), 1.1 (d, 3H, J = 5.5 Hz, C-3 methyl), 0.9 (d, 3H, J = 6 Hz, C-11 methyl). The ketonic function in (2) is being utilised for the construction of the second five-membered ring along with the C_8-chain to complete the C_{25}-carbon frame-work.

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