Tetrahedron Letters No. 35, pp 3249 - 3252. 0040-4039/79/0822-3249$02.00/0
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SYNTHETIC STUDIES ON ALKALOIDS.[1] PART 2. STEREOSPECIFIC SYNTHESIS OF 1β-METHYL-13α-ACETOXY-8,11-DIOXOTETRACYCLO[7:2:2:$0^{5,11}$:$0^{5,12}$]TRIDEC-$\Delta^{6,7}$-ENE; MODEL REACTIONS ON THE CONSTRUCTION OF ACONITINE SKELETON

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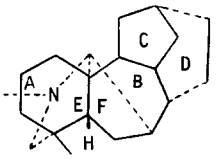
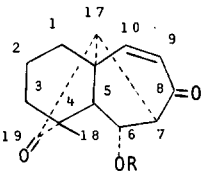
The title compound (2), an advanced relay towards the well-appreciated aconitine skeleton (1) of the C_{19}-norditerpene alkaloids, has been synthesised *via* regiospecific intramolecular oxocarbenedo C-H σ-bond insertion as the key step and this intermediate has the full potential for further elaboration to the intact skeleton.

The complex hexacyclic ring system represented by the aconitine skeleton (1) of the C_{19}-norditerpene alkaloids,[2] known for many pharmacological and physiological properties, presents a conspicuous challenge for any synthetic access to this framework. Wiesner et. al. have placed on record[3] the first formal synthesis of this novel skeleton which involves the biogenetic type rearrangement of a denudatine skeleton as the key step. In a previous model study, we demonstrated the incorporation of the C_{19}-C_{17} and C_7-C_{17} bridges in such a ring system through regiospecific intramolecular C-H σ-bond insertion[1] (SCHEME -1). Attempts to construct this tricyclic skeleton *via* intramolecular solvolytic cyclization of a keto carbene from a more readily available aromatic precursor[1] (SCHEME -2) was found unrewarding in view of the very poor yield and competitive side reactions. We now wish to describe the construction of the rings A, B, E and F of (1) and to this end, a regio- and stereospecific synthesis of the title compound (2) is recorded here. The α,β-enone system in (2) could be utilised through standard chemical reactions to build up the remaining C and D rings of (1).

Condensation[4] of methoxyacetyl chloride with the piperidine enamine of propionaldehyde afforded (78%) the keto aldehyde (3),[5] b.p. 97-99° (7 mmHg), ν_{max} 1730, 1715 cm^{-1}. Jones oxidation of (3) to the corresponding acid followed by esterification with ethereal CH_2N_2 solution gave (93%) the keto ester (4), b.p. 103° (5 mmHg). Addition of the Grignard reagent, prepared

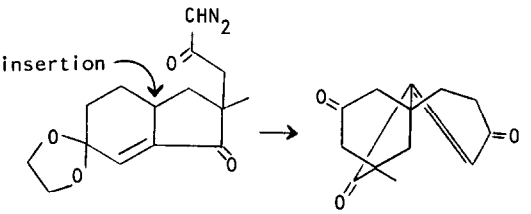


(1)

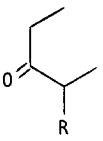


(2) R = Ac

(19) R = H,
C-6 epimeric mixture

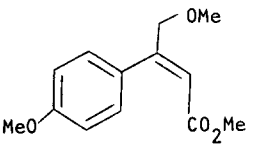


SCHEME -1



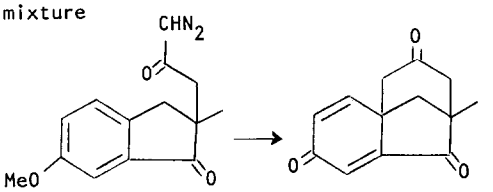
(3) R = CHO

(4) R = CO_2Me

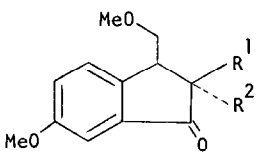


(5)

(6) 2,3-dihydro



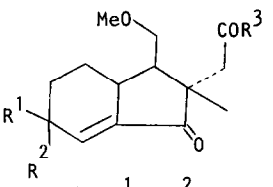
SCHEME -2



(7) $R^1 = R^2 = H$

(8) $R^1 = H$, $R^2 = CH_2CO_2Et$

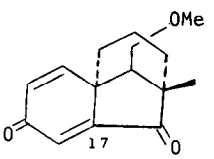
(9) $R^1 = CH_3$, $R^2 = CH_2CO_2Et$



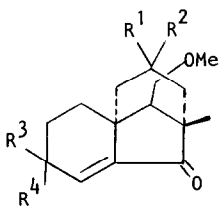
(10) $R^1 = R^2$ = ethylenedioxy,
R^3 = OMe

(11) $R^1 = R^2$ = ethylenedioxy,
R^3 = OH

(12) $R^1 = R^2$ = ethylenedioxy,
$R^3 = CHN_2$

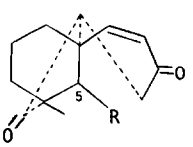


(15)



(13) $R^1 = R^2 = O$,
$R^3 = R^4$ = ethylenedioxy

(14) $R^1 = R^2 = H$,
$R^3 = R^4 = O$



(16) R = CH_2OMe

(17) R = CH_2OH

(18) R = CHO

from p-bromoanisole and magnesium, to (4) and subsequent dehydration of the crude Grignard product with $POCl_3$ and pyridine yielded (75%) the ester (5), b.p. 117° (0.1 mmHg), ν_{max} 1718, 1600 cm^{-1}, λ_{max} 257, 293 nm, δ (CCl_4) 6.9 and 6.2 (1H, s). This was evidently (n.m.r. and t.l.c.) present in a mixture of cis and trans isomers. Catalytic hydrogenation of (5) over Pd/C (10%) gave (6), b.p. 123° (0.2 mmHg), ν_{max} 1735, 1600 cm^{-1}, which was saponified to the corresponding acid. Conversion of this acid into the acid chloride ($SOCl_2$ and pyridine) and subsequent intramolecular cyclization[6] in the presence of $AlCl_3$ in CH_2Cl_2 afforded (81%) the homogeneous indanone (7), b.p. 146° (0.1 mmHg), ν_{max} 1695, 1600 cm^{-1}, δ (CCl_4) 3.93 (3H, s), 3.81 (3H, s), 3.70 (2H, d, J 6 Hz), 3.08 (1H, m), 2.60 (2H, d, J 6 Hz). Alkylation of (7) with molar equivalent of ethyl bromoacetate in the presence of NaH and DME gave (63%) the monoalkylated product (8), m.p. 65°, ν_{max} 1735, 1695, 1600 cm^{-1}, and a small amount (7%) of the dialkylated product. Methylation of (8) with MeI in the presence of NaH afforded (91%) the desired indanone (9), m.p. 72°, δ ($CDCl_3$) 4.23 (2H, q, J 6 Hz), 3.93 (3H, s), 3.81 (3H, s), 3.72 (2H, d, J 6 Hz), 3.05 (1H, t, J 6 Hz), 2.22 (2H, s), 1.31 (3H, t, J 6 Hz), 1.28 (3H, s). A series of standard reactions were performed[1] to form (10). Saponification of (9) to the corresponding acid and subsequent careful reduction of this acid with calculated equivalent of lithium in liquid NH_3 in the presence of THF and t-butyl alcohol and cleavage of the resulting enol ether with aqueous HCl gave the endione which was selectively ketalised by ethylene glycol and p-TsOH to afford the oily ketal. This was esterified with ethereal CH_2N_2 to give (61% overall) the ketal ester (10), m.p. 61°, δ ($CDCl_3$) 6.78 (1H, s), 3.90 (4H, t, J 1 Hz), 3.71 (3H, s), 3.62 (2H, d, J 6 Hz), 3.55 (3H, s), 1.18 (3H, s). Alkaline hydrolysis of (10) afforded (83%) the ketal acid (11), m.p. 82.5°, ν_{max} 1726, 1695, 1620 cm^{-1}, which was converted (via sodio-salt and oxalyl chloride) into the corresponding acid chloride. Treatment of this acid chloride with ethereal CH_2N_2 gave (61%) after purification (short-packed alumina column) the α-diazomethyl ketone (12), m.p. 75°, ν_{max} 2110, 1695, 1620 cm^{-1}. Decomposition of a solution of (12) in THF and cyclohexane (2:8) in the presence of activated CuO catalyst and under illumination (500W tungsten lamp) followed by isolation through chromatography of the resulting product gave (49%) the tricyclic ketone (13), m.p. 43°, as a result of regiospecific C-H insertion. The olefinic proton in the n.m.r. was intact. The predominance of C-H insertion over addition to the double bond is justified because the molecule resulting from the latter process will be highly strained. Preferential Wolff-Kishner reduction of (13) and subsequent ketalisation of the product afforded (71%) the endione (14), m.p. 59°, ν_{max} 1695, 1680, 1620 cm^{-1}, δ ($CDCl_3$) 6.67 (1H, s), M^+ 248. When refluxed with DDQ in dioxan,

(14) gave[7] (73%) the diendione (15), m.p. 46°, λ_{max} 246 nm, ν_{max} 1690, 1650, 1620 cm^{-1}, δ ($CDCl_3$) 6.88 (1H, d, J 9 Hz), 5.96 (2H, d and s, J 9 Hz), M^+ 250. Preferential reduction of the endione double bond was satisfactory by using[8] the Zn/EtOH system to obtain (16), m.p. 70°, 96% homogeneous in g.l.c., δ ($CDCl_3$) 6.83 (1H, d, J 9 Hz), 5.98 (1H, d, J 9 Hz), 3.71 (3H, s), 3.62 (2H, d, J 6 Hz), 1.07 (3H, s). The above reduction resulted in the exclusive formation of the more stable[9] isomer (16) because the stereochemical purity (g.l.c.) of this diketone, with a vinylogous hydrogen at C-5 (aconitine nomenclature), remained unperturbed under rigorous condition of base catalysed equilibration. Demethylation[10] of (16) with BBr_3 in CH_2Cl_2 gave (86%) the alcohol (17), m.p. 98.5°, which was oxidised to the corresponding aldehyde (18), m.p. 82°, ν_{max} 1735, 1680, 1620 cm^{-1}, δ ($CDCl_3$) 9.7 (1H, t, J 5 Hz), by treatment with CrO_3-pyridine complex. Internal aldol condensation[11] of (18) in the presence of aqueous acid afforded (53%) the epimeric ketol mixture (19), a viscous liquid, which was difficult to separate through chromatography or fractional crystallisation. The α,β-enone system of (19) was intact in n.m.r. and i.r. indicating that the cyclization has taken place in the desired position. The ketols (19) were converted into their corresponding acetates and subsequent chromatographic purification gave (81%) the desired isomer (2), m.p. 117°, ^{13}C-n.m.r./δ ($CDCl_3$) 222.2 (C-19), 201.1 (C-8), 159.8 (C-10), 133.7 (C-9), 82.2 (C-6), 61.8 (C-7), 52.8 (C-4), 49.8 (C-17), 48.2 (C-11), 38.2 (C-5), 33.1 (C-3), 27.7 (C-1), 26.2 (C-2), 20.9 (C-18), M^+ 274. The carbon magnetic resonances are in close accord with such a ring system as present in the alkaloids. Studies are under way to build up the remaining C and D rings of skeleton (1).

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(Received in USA 16 March 1979)