A Synthetic Approach to Gelsemicine

Neil K. Hamer

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

A short stereoselective synthesis, from the cycloadduct of 3,3-dimethoxycyclopropene and 4-methyl-2*H*-pyran-2-one, of the tricyclic aza-oxa-undecane ring present in gelsemicine is reported.

There has been considerable recent interest in synthetic approaches to gelsemium alkaloids[1] but, although a successful route to koumine[2] has lately been reported, synthesis of other structural types has not yet met with success. Here we describe a short stereoselective route to the bridged tricyclic aza-oxa-undecane ring system in gelsemicine (**1**) by a strategy which has potential for the introduction of the oxindole moiety and the C ethyl group. A preliminary report[3] of the synthesis of a related compound with this ring system appeared some years ago.

Thermal [3 + 4] cycloaddition[4] of 3,3-dimethoxycyclopropene[5] to excess 4-methyl-2*H*-pyran-2-one[6] gave the oxabicyclo[3.2.2]nonadienone (**2**) (78%) which underwent hydrogenation (Rh on alumina) with high stereoselectivity to give (**3a**) (92%). The configuration of (**3a**) was established by a crystal structure determination[7]† on the ketone (**3b**) resulting from mild acid hydrolysis (0.05 M HCl/aq. MeCN). This high stereoselectivity (also found using Wilkinson's catalyst which, however, gave a slower and less clean reaction) is probably a consequence of more rapid hydrogenation of the disubstituted double bond leading to enhanced steric differentiation of the faces of the trisubstituted alkene.

Attempts to reduce the lactone (**3a**) to the saturated ether (**4a**) using $HSiCl_3/Bu^tOOBu^t/h\nu$[3,8] or by initial thionation[9] of the ester carbonyl followed by Raney nickel reduction were unsuccessful. However, reduction with $LiAlH_4$ followed by cyclisation of the resulting diol (TsCl/NaH; Ts = SO_2-C_6H_4Me-*p*), gave the required (**4a**) (54% over two steps) which was quantitatively hydrolysed (HCl/aq. MeOH) to (**4b**).‡

Reductive amination ($MeNH_2/NaBH_3CN$)[10] of (**4b**) gave a mixture (4 : 1) (84%) of two secondary amines. The ^1H NMR

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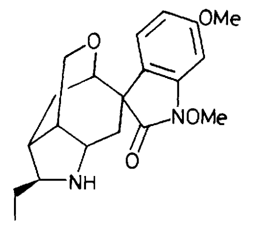
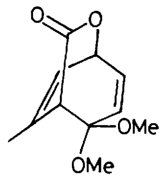
† *Crystal data* for $C_9H_{12}O_3$: M = 168.19, monoclinic, space group $P2_1/n$, a = 10.219(3), b = 8.014(2), c = 10.274(2) Å, β = 93.63(2)°, U = 839.7 Å^3, Z = 4, D_c = 1.33 g cm^{-3}, $F(000)$ = 360, graphite monochromated Cu-K_α radiation (λ = 1.54178 Å), μ(Cu-K_α) = 7.83 cm^{-1}. 2365 data measured on a Nicolet R3 mμ diffractometer to $2\theta_{max.}$ = 116°. 1024 unique reflections with $F > 4\sigma(F)$. Structure solved by centrosymmetric direct methods and refined by blocked cascade least squares (all non-hydrogen atoms anisotropic, H in AFIXed positions) to R = 0.046 and R_w = 0.052. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

‡ *Spectroscopic data* for (**4b**): ^1H NMR ($CDCl_3$) at 250 and 400 MHz supplemented by COSY and NOE experiments permitted the following assignments (s denoting protons *syn* to the 8-methyl group): δ 4.26 (ddd, 1H, J 7.7, 5.4, 2.4 Hz, 5-H), 3.90 (dd, 1H, J 11, 1.7 Hz, 7-Hs), 3.86 (dd, 1H, J 11, 5.4 Hz, 7-H), 2.58 (ddd, 1H, J 17.3, 7.1, 4 Hz, 3-Hs), 2.41 (m, 2H, 1-H, 9-H), 2.36 (m, 1H, J ~17, 8 Hz + small couplings, 3-H), 2.09 (m, 1H, 8-H) 2.05 (m, 1H, collapsed to a br. d, J 15 Hz after ^2H exchange of 3 protons, 4-Hs), 1.75 (dddd, 1H, J 15, 8.2, 5.4, 4.1 Hz, 4-H) 1.24 (dd, 1H, J 14, 7.9 Hz, 9-Hs), 1.01 (d, 3H, J 7.2 Hz, Me).



(1)



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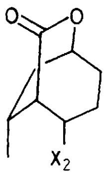
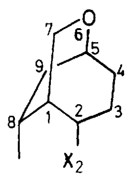


(3)

a; X = OMe
b; X_2=O



(4)

a; X = OMe
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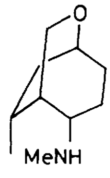
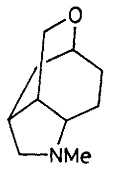
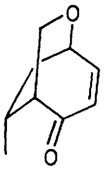


(5)



(6)



(7)

spectrum of the major isomer showed a substantial NOE between the N–CH proton and one of the $O–CH_2$ protons; this is therefore (**5**). After chromatographic separation of this isomer, *N*-chlorination (NaOCl), followed by the Hofmann–Löffler–Freytag reaction ($h\nu/CF_3CO_2H$ then KOH/MeOH),[11] gave clean cyclisation (82%) to (**6**) whose ^1H NMR spectrum was similar to that of (**5**), apart from replacement of the Me doublet by new signals from the $N–CH_2$ group (δ 2.65, 2.76) as part of an ABX system.

With a view to future elaboration of the spiro-oxindole unit in (**1**), (**4b**) was dehydrogenated to (**7**) by reaction of the trimethylsilyl enol ether with $Pd(OAc)_2$/benzoquinone.[12] Modification of the synthesis to permit introduction of the C-ethyl group of (**1**), either into the starting pyranone[13] or, probably with greater stereoselectivity, by nucleophilic addition to an appropriate imine should not be difficult.

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