α-Hydroxy Ketone Rearrangement as a Key Step *en route* to the Calebassinine Skeleton

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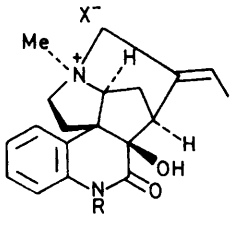
The first stereocontrolled synthesis of the unique calebassinine-1 skeleton has been developed utilising base-catalysed α-hydroxy ketone rearrangement as a key step.

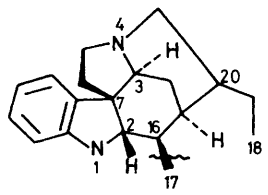
The structure of calebassinine-1, isolated from the calabash curare of *Strychnos solimoesana* and conclusively established (by *X*-ray crystallography) as (**1**),[1] is of some interest since it represents the only naturally occurring molecule known to date which contains the 7(2→16) *abeo*-17-norcuran skeleton. Our previous use of the α-hydroxy ketone rearrangement, equation (1) in a synthesis of the *Melodinus* ring system[2] led us to consider a related strategy for (**1**). Specifically, tandem retroaldol fragmentation–recyclisation of the species (**3**) would be expected to proceed in the desired stereochemical sense since this is favoured in (**3**) by the bonding and heteroatom disposition. We now report the first synthesis of (**4**) from strychnine (**5**) with retention of stereochemistry; this requires (i) disconnection of the C(16)–C(17) bond, (ii) upward and downward adjustments of oxidation states, respectively, at C(2)–C(16) and C(18) sites, and (iii) skeletal rearrangement of (**3**).

The Wieland–Gumlich aldehyde (**6**), prepared from (**5**) by a standard method,[3] was chosen as a convenient starting material. However, using protecting groups or compound (**6**) with the N(1) position unprotected proved to be incompatible with the synthetic plan or with the survival of the vital α-amino-α-hydroxyketo group in (**3**); we therefore opted for blocking N(1) as the N-methyl derivative (**7**), m.p. 199—201 °C [$NaBH_3CN$, 40% aq. formaldehyde, acetic buffer (pH 3.7), room temp.]. Exposure of (**7**) to hydroxylamine-*O*-sulphonic acid in water[4] at room temp. led to the 16β-nitrile (**8**), m.p. 207—208 °C, which after protection of the hydroxy group [Bu^tMe_2SiCl, Hünig's base, dimethylformamide (DMF)] was subjected to oxidative decyanation[5] [lithium di-isopropylamide (LDA), tetrahydrofuran (THF), −78 °C, then dioxygen] followed by reductive quenching (1 M $SnCl_2$, 1 M HCl, 0 °C) to afford (**9**)† in 45% overall yield from (**5**). Regioselective hydroxylation at C(2) of (**9**) by metal oxidants[2] proved troublesome owing to the difficulty of isolating the resultant α-amino-α-hydroxyketone (**10**) and the ease with which (**10**) (or its equivalent iminium ion) underwent retro-Mannich reaction followed by recondensation to give indole-containing product(s).[6] This problem was overcome by

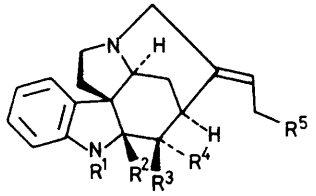
† Satisfactory elemental analyses and/or spectroscopic data (^1H and ^{13}C n.m.r., mass, and i.r.) were obtained for compounds (**4**), (**9**), (**11**), (**14**), and (**16**).



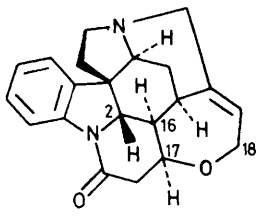
(1) R = H
(4) R = Me



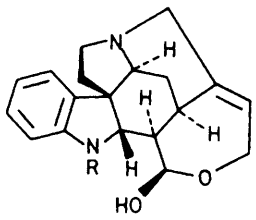
(2) Curan skeleton



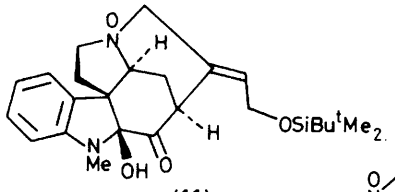
(3) R^1 = H, R^2 = OH, R^3R^4 = O, R^5 = H
(8) R^1 = Me, R^2 = H, R^3 = CN, R^4 = H, R^5 = OH
(9) R^1 = Me, R^2 = H, R^3R^4 = O, R^5 = $OSiBu^tMe_2$
(10) R^1 = Me, R^2 = OH, R^3R^4 = O, R^5 = $OSiBu^tMe_2$



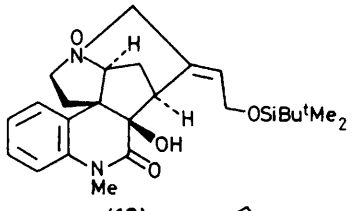
(5)



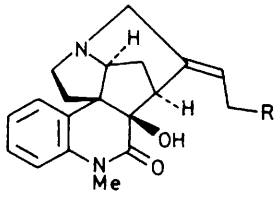
(6) R = H
(7) R = Me



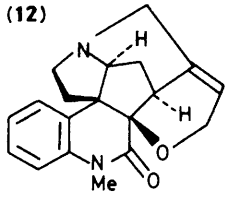
(11)



(12)

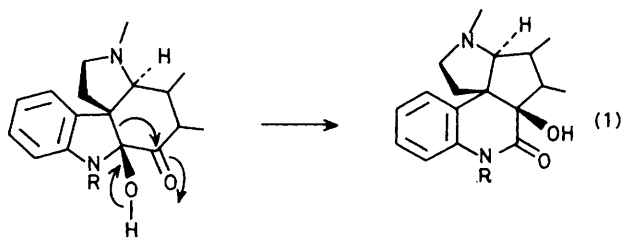


(13) R = $OSiBu^tMe_2$
(14) R = OH
(15) R = SPh
(16) R = H



(17)

blocking temporarily the N(4) position as the *N*-oxide before attempting hydroxylation at C(2). During the course of defining the conditions for *N*-oxidation we found that reaction of (**9**) with *m*-chloroperbenzoic acid (*m*-CPBA) (2.1 equiv.) in chloroform at room temp. (30 min) proceeded regio- and



(1)

stereo-selectively‡ to provide 2-hydroxy-*N*(4)-oxide (**11**) in nearly quantitative yield. Treatment of (**11**) with potassium hydride in dimethoxyethane (DME) in the presence of 18-crown-6 at room temp. (1 h) furnished the anionic rearrangement product (**12**) as the sole product (89%).

The sequential removal of the *N*-oxide function [to give (**13**)] (H_2,Pd/C,EtOAc) and the t-butyldimethylsilyl ether protecting group (HF_x·pyridine, THF) produced (**14**).† This was, in turn, smoothly converted into the sulphide (**15**) (Bu_3P, Ph_2S_2, THF, 40 °C) and subsequently reduced with nickel boride ($NiCl_2·6H_2O$, $NaBH_4$, MeOH, 0 °C) providing a 16:3:1 mixture of (*Z*)-(**16**)† and (*E*)-ethylidene products, and dihydro-(**16**), respectively, in 85% overall yield from (**12**). In order to avoid the undesirable and cumbersome separation step incurred by the formation of the last two compounds, t-butyldimethylsilyl ether (**13**) was directly subjected to stereoselective replacement of the Bu^tMe_2SiO group by hydride *via* a Pd^0 complex, according to Hutchins' method.[7] Thus, when (**13**) was exposed to $LiEt_3BH$ (2 equiv.) in the presence of PPh_3 (1 equiv.) and $Pd(PPh_3)_4$ (0.1 equiv.) in refluxing THF (65 h), a 6:4 mixture of (**16**) and the dihydropyran (**17**) was isolated (91%) but with no evidence of (*E*)-alkene or over-reduction products. Finally, quaternisation of (**16**) with MeI in acetone gave the corresponding N(4)-methiodide in quantitative yield. This was shown by t.l.c., fast atom bombardment mass spectrometry, and 300 MHz ^1H n.m.r. data to be identical with (**4**), obtained by methylation (MeI, NaH, DMF, room temp.) of a sample of calebassinine-1 (**1**; X = picrate), generously supplied by Professor Hesse.

Following Hesse's biogenetical proposal,[1] calebassinine-1 may well arise from a suitable *Strychnos* precursor by heterolytic cleavage of a 2-hydroperoxide, however our synthesis suggests a possible α-hydroxy ketone rearrangement as an alternative pathway to this unique alkaloid skeleton.

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‡ The alternative α-hydroxylation would result in an energetically unacceptable *trans* fusion of the B/C ring system. This unusual hydroxylation is believed to proceed through the Δ^2-enol of (**9**) (or its *N*-oxide) that undergoes epoxidation followed by rearrangement to give (**11**).