A synthetic route to the alkaloids of the ervatamine group. First total synthesis of (±)-6-oxo-16-episilicine

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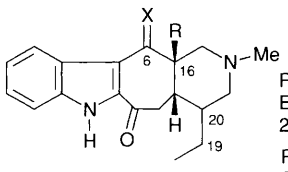
A general route to silicine-methuenine alkaloids, exemplified by the synthesis of 6-oxo-16-episilicine, involving the nucleophilic addition of an acetylindole enolate to the pyridinium salt 2, methoxycarbonylation of the resulting 1,4-dihydropyridine, controlled catalytic hydrogenation, cyclization on the indole 3-position and further functional group manipulations, is reported.

1,4-Dihydropyridines resulting from the addition of indole-containing enolates (in particular, those derived from indoleacetic esters and acetylindoles) to 1-alkyl-3-acylpyridinium salts have proved to be exceptionally versatile intermediates for alkaloid synthesis, providing straightforward access to a number of indole alkaloids belonging to different structural types.[1] These dihydropyridines have usually been elaborated into polycyclic alkaloid systems either by acid-[1] or electrophile-promoted[2] cyclization, *via* a dihydropyridinium cation. Alternatively, they have been further functionalized to give 4-substituted 3,5-diacyl-1,4-dihydropyridines,[3] from which we have recently reported both a biomimetic synthesis[4] of several alkaloids of the ervatamine group[5] bearing the characteristic methoxycarbonyl substituent at C-16 (biogenetic numbering)[6] and the construction of the tetracyclic ring system of silicine-methuenine alkaloids,[7] which do not incorporate this substituent. In spite of their apparent structural simplicity, only one C-16 unsubstituted alkaloid of the ervatamine group, 6-oxosilicine, has been synthesized so far.[8]

We report here the synthesis of 6-oxo-16-episilicine, an alkaloid reported as a component of *Hazunta modesta*,[9] using a 1,4-dihydropyridine **4** bearing two different electron-withdrawing groups at the β-positions as the key intermediate. Our synthetic plan involves the chemoselective differentiation of the dihydropyridine double bonds by catalytic hydrogenation and the closure of the seven-membered C ring, taking advantage of the C-5 methoxycarbonyl substituent of the resulting tetrahydropyridine. On the other hand, the acrylate moiety of the starting pyridinium salt not only increases the electrophilicity of the pyridinium ring, facilitating the nucleophilic addition in the first step of the synthesis, but was also envisaged as the precursor of the C-20 two-carbon substituent (ethylidene† or ethyl) of silicine-methuenine alkaloids.

The synthetic sequence is outlined in Scheme 1. Thus, the reaction of the enolate derived from 2-acetyl-1-benzylindole **1** with 3-[2-(methoxycarbonyl)vinyl]pyridinium salt **2**, followed by *in situ* trapping of the initially formed mixture of dihydropyridines with trichloroacetic acid anhydride gave (60% yield)‡ a nearly equimolecular mixture of 1,4-dihydropyridine **3** and the regioisomeric 3,5-disubstituted 1,2-dihydropyridine, which were easily separated by column chromatography. A subsequent haloform-type reaction from **3**, with sodium methoxide in methanol, afforded dihydropyridine **4** in 85% yield. The doubly vinylogous urethane moiety of **4** was reduced by catalytic hydrogenation, using ethyl acetate as the solvent, to give the *cis*-tetrahydropyridine **5**§ in 50% yield. Minor amounts of the corresponding *trans*-isomer (10%) and piperidine (20%) were also isolated. Closure of the C ring was achieved by treatment of tetrahydropyridine **5** with trimethylsilyl polyphosphate (PPSE) to give tetracycle **6** in 35% yield.

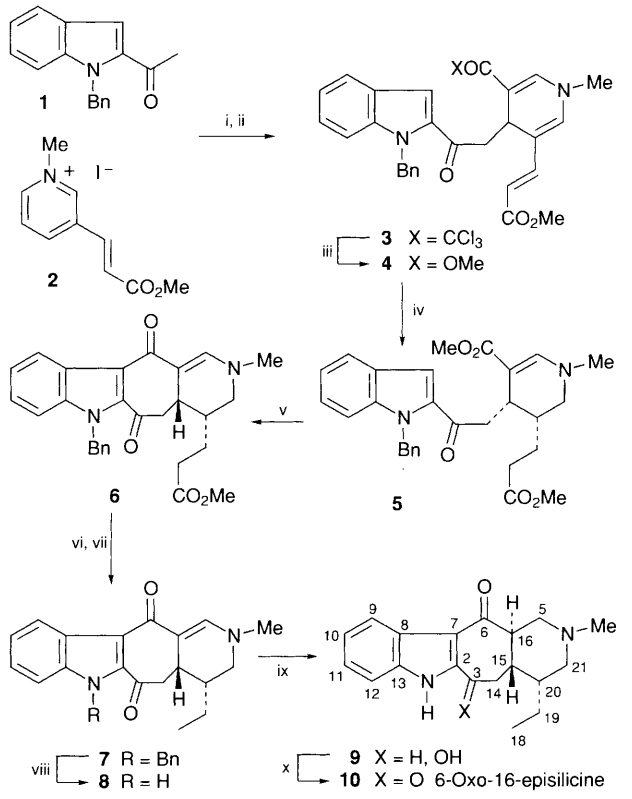
The elaboration of the C-20 ethyl substituent was effected by Barton decarboxylation,[11] which makes use of the easy homolytic decomposition of thiohydroxamic esters. Thus,



R = CO_2Me:
Ervatamine (X = H, H; β-Et)
20-Epiervatamine (X = H, H; α-Et)

R = H:
Silicine (X = H, H; α-Et)
20-Episilicine (X = H, H; β-Et)
16-Episilicine (X = H, H; α-Et; 16-epi)
Methuenine (X = H, H; 19,20-didehydro)
6-Oxosilicine (X = O; α-Et)
6-Oxo-16-episilicine (X = O; α-Et; 16-epi)

Fig. 1



Scheme 1 *Reagents and conditions*: i, LDA–THF, −30 °C, 1.5 h; ii, $(CCl_3CO)_2O$, 0 °C, 3.5 h; iii, MeONa, MeOH, room temp., 3 min; iv, H_2, PtO_2, AcOEt, 2 h; v, PPSE, 110 °C, 1.5 h; vi, LiOH, 5:1 MeOH–H_2O, reflux, 2.5 h, then 1 mol dm^{-3} HCl; vii, 2,2′-dithiobis(pyridine-*N*-oxide), Bu_3P, CH_2Cl_2, room temp., then Bu^{t}SH, *hv*, 5–20 °C, 2 h; viii, $AlCl_3$, C_6H_6, room temp., 2 h; ix, $NaCNBH_3$, MeOH, AcOH, room temp., 3.5 h, then MnO_2, $CHCl_3$, room temp., 1 h

hydrolysis of the propionate ester portion of **6**, followed by treatment of the resulting acid with 2,2′-dithiobis(pyridine-*N*-oxide) and tributylphosphine,[12] with subsequent photolysis in the presence of 2-methyl-2-propanethiol as the hydrogen donor, gave tetracycle **7** in 75% overall yield from **6**. The synthesis was completed by deprotection of the indole ring of **7** with aluminium chloride in benzene (78%) followed by stereoselective reduction of the 5,16 double bond of **8** with sodium cyanoborohydride. As the reduction of the 2-acylindole carbonyl group occurred to some extent under these conditions, the crude mixture of tetracycles **9** and **10** was directly treated with manganese dioxide. In this way, (±)-6-oxo-16-episilicine **10** was obtained in 75% overall yield from **8**. The nature of the *trans* fusion of the C/D rings in **10** was established by inspection of the ^{1}H and ^{13}C NMR data, hitherto unreported, with the aid of 2D NMR techniques.¶

Comparison of the ^{13}C NMR chemical shifts with those reported for 6-oxosilicine[13] was also of diagnostic value.

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Footnotes

† The usefulness of the acrylate moiety in the elaboration of the C-20 ethylidene substituent present in indole alkaloids is well-established (ref. 10).

‡ All yields are from material purified by column chromatography. Satisfactory spectral, analytical and/or HRMS data were obtained for all new compounds.

§ *Selected data* for **5**: δ_H(300 MHz, $CDCl_3$) 1.57 (m, 2 H, CH_2), 1.89 (m, 1 H, py 3-H), 2.31 (m, 2 H, CH_2), 2.78 (dd, *J* 14.6 and 5.3 Hz, 1 H, CH_2CO), 2.94 (m, 3 H, py 2-H, CH_2CO), 2.95 (s, 3 H, NMe), 3.40 (m, 1 H, py 4-H), 3.48 and 3.62 (2s, 6 H, OMe); δ_C(75 MHz, $CDCl_3$) 25.3 (CH_2), 30.4 (py C-4), 31.5 (CH_2), 35.7 (py C- 3), 42.6 (NMe), 43.0 (CH_2CO), 48.2 (py C-2), 97.9 (py C-5), 146.1 (py C-6).

¶ ^{1}H–^{1}H COSY, HMQC and NOESY: δ_H(500 MHz, $CDCl_3$) 0.96 (t, *J* 7.5 Hz, 3 H, 18-H), 1.34 (m, 1 H, 19-H), 1.63 (m, 1 H, 20-H), 1.73 (m, 1 H, 19-H), 1.85 (t, *J* 11.5 Hz, 1 H, 5-H_{ax}), 1.88 (br d, *J* 13 Hz, 1 H, 21-H_{ax}), 2.26 (td, *J* 11 and 4 Hz, 1 H, 15-H_{ax}), 2.29 (s, 3 H, NMe), 2.78 (d, *J* 16 Hz, 1 H, 14-H), 2.94 (dt, *J* 13 and 1.7 Hz, 1H, 21-H_{eq}), 2.97 (td, *J* 11.5 and 4 Hz, 1 H, 16-H_{ax}), 2.99 (dd, *J* 16 and 11 Hz, 1 H, 14-H), 3.55 (ddd, *J* 11.5, 4 and 1.4 Hz, 1 H, 5-H_{eq}), 7.32 (m, 1 H, 10-H), 7.45 (m, 2 H, 11-H and 12-H), 8.37 (d, *J* 8.1 Hz, 1 H, 9-H); δ_C(75 MHz, $CDCl_3$) 12.7 (C-18), 18.3 (C-19), 36.7 (C-15), 42.4 (C-20), 46.4 (NMe), 47.3 (C-14), 51.8 (C-16), 57.5 (C-21), 59.5 (C-5), 111.9 (C-12), 118.2 (C-7), 123.8 (C-10), 124.6 (C-9), 127.4 (C-11), 128.6 (C-8), 134.3 (C-2), 135.8 (C-13), 192.8, 197.7 (C-3, C-6).

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