Pergamon

Tetrahedron Letters, Vol. 37, No. 20, pp. 3541-3544, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00607-7

A Short Route for the Construction of the Tetracyclic Ring System of Silicine-Methuenine Alkaloids

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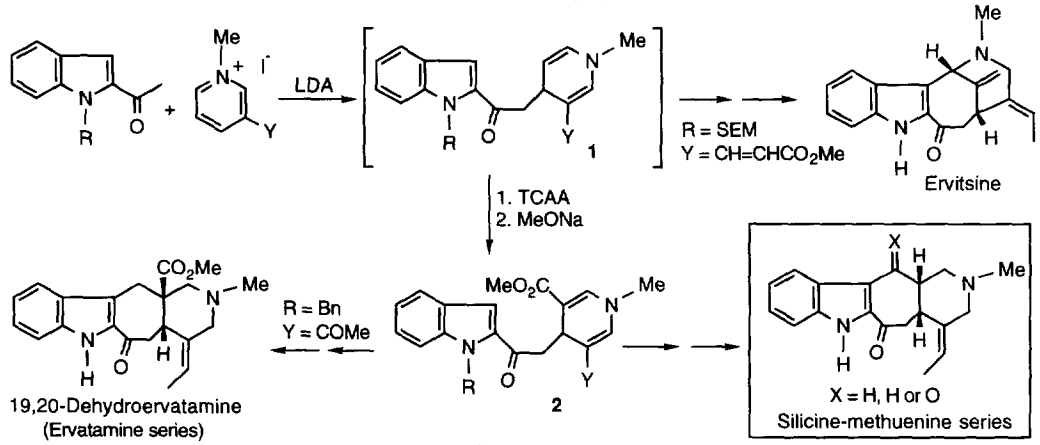
Abstract: A general synthetic entry to the tetracyclic ring system of silicine-methuenine alkaloids, involving the partial hydrogenation of dihydropyridines **2** followed by PPSE-induced cyclization of the resulting tetrahydropyridine esters **3**, is reported. Copyright © 1996 Published by Elsevier Science Ltd

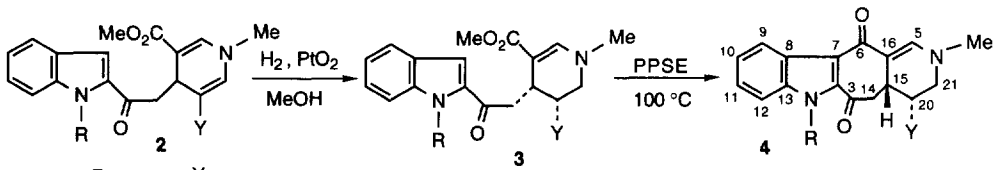
The nucleophilic addition of 2-acetylindole enolates to *N*-alkylpyridinium salts bearing an electron-withdrawing substituent at the 3-position leads to 4-[(2-indolylcarbonyl)methyl]-1,4-dihydropyridines **1**, which have proved to be useful intermediates in alkaloid synthesis. Straightforward biomimetic syntheses of ervitsine[1] and the alkaloids of the ervatamine group (19,20-dehydroervatamine, 20-epiervatamine),[2] the latter by way of a 3,5-diacyl-substituted 1,4-dihydropyridine **2**,[3] have been accomplished from dihydropyridines **1** (Scheme 1).

In this letter we further illustrate the potential and flexibility of the above methodology: dihydropyridines **2** also provide a direct access to the tetracyclic ring system of silicine-methuenine alkaloids.[4] In spite of their apparent structural simplicity, these alkaloids have received little synthetic attention, and 6-oxosilicine[5] is the only alkaloid of this group synthesized so far.[6]

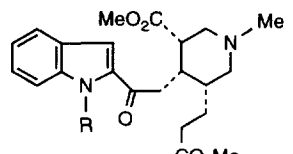


Scheme 1

The conversion of dihydropyridines **2** into the target tetracyclic systems required the partial hydrogenation of the dihydropyridine moiety and the closure of the seven-membered C ring. Both transformations have been satisfactorily accomplished starting from a variety of dihydropyridines **2**, bearing different substitution patterns at the β-position and at the indole nitrogen, as outlined in Scheme 2.



	R	Y
a	Me	CO_2Me
b	H	CO_2Me
c	Me	$CH=CHCO_2Me$ (for **2**); $(CH_2)_2CO_2Me$ (for **3** and **4**)
d	H	$CH=CHCO_2Me$ (for **2**); $(CH_2)_2CO_2Me$ (for **3** and **4**)
e	Me	COMe
f	Bn	COMe
g	Me	CH(OH)Me



5 **a**....R = Me
b....R = H

Scheme 2

Hydrogenation of dihydropyridines **2a-f**[2,3] in the presence of platinum led to the corresponding tetrahydropyridines **3a-f**, in which the substituents at the 3- and 4-positions are cis, as the exclusive or major products. The best yields were obtained in the 3,5-bis(methoxycarbonyl) series (series **a** and **b**).[7] As was expected, reduction of the acrylate moiety occurs from dihydropyridines **2c** and **2d** to chemoselectively give tetrahydropyridines **3c**[8] and **3d**. In these series, over-reduction to the corresponding piperidines **5** was also observed. On the other hand, hydrogenation of dihydropyridine **2e** predominantly gave the vinylogous urethanes **3e**[9] and **3g** in 55% overall yield, although the corresponding vinylogous amide was also formed to a considerable extent. All these results are shown in Table 1.

Table 1. Catalytic Hydrogenation of Dihydropyridines 2 and Cyclization of Tetrahydropyridines 3[a]

Dihydropyridine	Tetrahydropyridine % yield	Tetracycle % yield
2a	**3a**, 80	**4a**, 30
2b	**3b**, 60	**4b**, 40
2c	**3c**, 30[b,c]	**4c**, 40
2d	**3d**, 25[b]	**4d**, 25
2e	**3e**, 25+ **3g**, 30[d,e]	--
2f	**3f**, 45[f]	**4f**, 45[g]

[a] All yields are from material purified by column chromatography. All new compounds gave satisfactory spectral, analytical and/or HRMS data. [b] The corresponding piperidines **5** were formed in 15% yield. [c] The trans isomer was isolated in 15% yield. [d] This yield increased to 55% when reaction times were longer (48 h). [e] The isomeric vinylogous amide was isolated in 30% yield. [f] Reference 2. [g] Epimeric mixture at C-20.

Table 2. ^{13}C-NMR Chemical Shits of Tetrahydropyridines 3 and Tetracycles 4[a,b]

	C-3	C-5	C-6	C-14	C-15	C-16	C-20	C-21	NMe	Y
3a[c]	192.8	145.9	167.7[d]	44.2	29.7	97.0	41.2	44.6	42.7 32.0	51.8 172.6
3b	191.0	146.3	168.1[d]	43.6	30.0	96.9	41.0	44.4	42.7	50.7 168.1
3c	193.4	146.1	168.3[d]	43.1	30.6	98.0	35.9	49.1	42.7 32.1	25.4 31.8[e]
3d	192.5	146.4	168.6[d]	42.4	30.7	97.7	35.9	48.8	42.7	25.2 31.5[e]
3e	192.0	145.9	167.8[d]	43.6	28.9	97.8	48.5	44.5	42.8 32.1	30.2 209.2
3f	191.4	145.9	167.8[d]	43.4	28.4	97.7	48.3	44.5	42.7	30.0 209.2
3g[f]	195.3	146.7	167.9[d]	44.6	29.4	98.3	45.8	47.0	42.7 32.3	22.6 66.6
4a	194.2	147.1	183.5	48.0	28.9	107.8	41.4	45.3	43.3 32.6	52.3 171.5
4b[c]	192.8	146.4	183.8	46.4	29.4	108.7	42.1	45.2	43.1	52.3 171.6
4c	195.3	146.5	184.5	49.6	29.7	108.9	35.0	46.0	43.0 32.5	24.6 31.7[e]
4d	193.6	146.7	184.1	43.9	30.5	109.8	35.5	49.7	43.0	24.7 31.6[e]
4f[g]	193.7	146.7	183.9	48.6	28.5	106.5	51.0	45.7	43.3	29.1 206.1

[a] Biogenetic numbering as depicted in Scheme 2. [b] In ppm relative to TMS. Measured in $CDCl_3$ solution at 74.5 MHz. [c] Assignments were aided by HMQC. [d] For the OMe group (average value) 50.5. [e] For the CO_2Me group (average values) 51.5, 173.5. [f] In CD_3COCD_3 solution. [g] Major cis epimer.

The cis relationship between the tetrahydropyridine substituents in **3** is the result of the hydrogen uptake from the less hindered face of the dihydropyridine ring and, as could be determined from their ^{1}H-NMR spectra,[7-9] implies the equatorial disposition of the substituent at the 3-position and the pseudoaxial disposition of the (indolylcarbonyl)methyl group.

Closure of C ring was achieved by treatment of tetrahydropyridines **3** with trimethylsilyl polyphosphate (PPSE). The tetracyclic silicine-methuenine type systems **4**[10,11] were obtained in acceptable yields (Table 1). It is worth mentioning that in the 3,5-bis(methoxycarbonyl) series cyclization takes place chemoselectively on the α, β-unsaturated ester group.

Some significant ^{13}C-NMR chemical shifts of tetrahydropyridines **3** and tetracycles **4** are given in Table 2.

The results reported here establish a general synthetic entry to the tetracyclic ring system of silicine-methuenine alkaloids that may be applicable to the synthesis of alkaloids of this group.

Acknowledgment. Financial support from the DGICYT, Spain (project PB94-0214) is gratefully acknowledged. R.K. thanks the CICYT (Spain) for providing a postdoctoral fellowship. Thanks are also due to the "Comissionat per a Universitats i Recerca", Generalitat de Catalunya, for Grant SGR95-0428 and for a fellowship to B.V.

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7. **3a**: ^{1}H-NMR ($CDCl_3$, 500 MHz) 2.87 (masked, 1H, 3-H), 2.88 (dd, J = 14.5, 5.5 Hz, 1 H, CH_2CO), 2.99 (dd, J = 14.5, 7.5 Hz, 1 H, CH_2CO), 3.01 (s, 3H, NMe), 3.16 (ddd, J = 13.0, 4.5, 1.5 Hz, 1H, 2-H_{eq}), 3.43 (t, J = 13.0 Hz, 1H, 2-H_{ax}), 3.53 and 3.65 (2s, 3H, OMe), 3.83 (m, 1H, 4-H), 4.02 (s, 3 H, NMe), 7.10 (m, 1 H, indole 5-H), 7.35 (m, 4H, indole, 6-H), 7.68 (d, J = 8 Hz, 1 H, indole 4-H). Anal. calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.60; H, 6.41; N, 7.12.
8. **3c**: ^{1}H-NMR ($CDCl_3$, 300 MHz) 1.67 (m, 2H, CH_2), 1.93 (m, 1H, 3-H), 2.45 (m, 2H, CH_2CO_2Me), 2.74 (dd, J = 14.3, 3.0 Hz, 1H, CH_2CO), 2.95 (m, 3H, CH_2CO, 2-H), 3.00 (s, 3H, NMe), 3.40 (m, 1H, 4-H), 3.42 and 3.65 (2s, 3H, OMe), 4.05 (s, 3H, NMe), 7.15 (m, 1H, indole 5-H), 7.34 and 7.37 (2s, indole 3-H, 6-H), 7.35 (m, 2H, indole 6- and 7-H), 7.69 (dm, J = 8.0 Hz, 1H, indole 4-H). HRMS calcd for $C_{23}H_{28}N_2O_5$ 412.1998, found 412.2017.
9. **3e**: ^{1}H-NMR ($CDCl_3$, 300 MHz) 2.36 (s, 3H, MeCO), 2.90 (m, 4H, CH_2CO, 2-H, 3-H), 3.03 (s, 3H, NMe), 3.42 (t, J = 12.1 Hz, 1H, 2-Hax), 3.53 (s, 3H, OMe), 3.90 (m, 1H, 4-H), 4.02 (s, 3H, NMe), 7.12 (m, 1H, indole 5-H), 7.21 (s, 1H, 6-H), 7.38 (m, 3H, indole), 7.68 (dm, J = 8.0 Hz, 1 H, indole 4-H). Anal. calcd for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.47; H, 6.57; N, 7.61.
10. **4b**: ^{1}H-NMR ($CDCl_3$, 500 MHz, biogenetic numbering) 2.64 (dd, J = 17.5, 1.5 Hz, 1H, 14-H), 2.74 (dd, J = 17.5, 12.5 Hz, 1H, 14-H), 3.05 (m, 1H, 20-H), 3.16 (s, 3H, NMe), 3.36 (m, 2H, 21-H), 3.55 (dd, J = 12.5, 2.7 Hz, 1H, 15-H), 3.75 (s, 3H, OMe), 7.30 (m, 1H, 10-H), 7.40 (m, 2H, 11- and 12-H), 7.74 (s, 1H, 5-H), 8.55 (d, J = 8.0 Hz, 1H, 9-H), 9.50 (br, 1H, NH). Anal. calcd for $C_{19}H_{18}N_2O_4$: C, 67.45; H, 5.36; N, 8.28. Found: C, 67.56; H, 5.39; N, 8.08.
11. **4c**: ^{1}H-NMR ($CDCl_3$, 300 MHz, biogenetic numbering) 1.74 (m, 2H, 19-H), 2.04 (m, 1H, 20-H), 2.36 (m, 2H, 18-H), 2.55 (dd, J= 18.0, 12.7 Hz, 1H, 14-H), 2.87 (dd, J = 18.0, 2.2 Hz, 1H, 14-H), 3.02 (m, 3H, 15-H, 21-H), 3.10 (s, 3H, NMe), 3.65 (s, 3H, OMe), 3.99 (s, 3H, NMe), 7.28 (m, 1H, 10-H), 7.41 (m, 2H, 11-H, 12-H), 7.12 (s, 1H, 5-H), 8.50 (d, J = 8.0 Hz, 1H, 9-H). HRMS calcd for $C_{22}H_{24}N_2O_4$ 380.1736, found 380.1745.

(*Received in UK* 22 *February* 1996; *revised* 26 *March* 1996; *accepted* 29 *March* 1996)