Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 12, pp. 1963–1966, 1997

Printed in Great Britain
PII: S0957-4166(97)00210-3
0957-4166/97 $17.00 + 0.00

Stereocontrolled elaboration of quaternary carbon centers involving the asymmetric Michael-type alkylation of chiral imines: an efficient enantioselective access to (+)-vincamine

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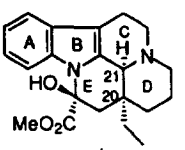
Abstract: Michael adduct (*S*)-**5b**, resulting from the condensation of chiral imine **4** with methyl acrylate, was transformed in two steps into lactone (*S*)-**8b**. Tryptamine-induced ring-opening of this lactone gave **9**, which was finally converted in three steps into the key tricyclic derivative (*S*)-**11b**, a known precursor of (+)-vincamine **1**. © 1997 Published by Elsevier Science Ltd

(+)-Vincamine **1** is the major alkaloid encountered in periwinkle (*Vinca minor* L., *Apocynaceae*).[1] In man, the best established pharmacological property of **1**, and semisynthetic derivatives, such as ethyl apovincaminate **2** (vinpocetine, Cavinton®),[2] is the cerebroprotective activity, caused by a dilation of cerebral arteries, improving the global cerebral blood flow. Recent investigations have shown that pharmacon **2** exhibits also a protective effect against brain damage caused by ischemia,[3] a gastroprotective action,[4] and a remarkable promising activity in removing tumoral calcinosis.[5]



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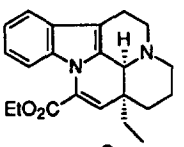

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Severeral strategies for the synthesis of (+)-vincamine **1** (the "biogenetic" numbering system was used here)[6] and analogs have been developed.[1] The common feature in these approaches was to establish first the tetracyclic [ABCD]-type octahydro[2,3-a]quinolizine system of these alkaloids bearing two controlled stereogenic centers, namely the quaternary carbon center at C-20 and the adjacent methine at C-21 (exemplified by **12**, *vide infra*), and to achieve the synthesis by creating the fifth ring E.

The present basic strategy illustrated a general methodology for the stereocontrolled elaboration of a quaternary carbon center,[7] as key step in the construction of the tricyclic [ABD]-type cornerstone (*S*)-**11b**, precursor of **12**. Thus, the first stage in the synthesis of our goal **1** was the construction of the disubstituted cyclopentanone **5a**, bearing a stereocontrolled quaternary carbon center (future C-20 center of **1**), by using the asymmetric Michael reaction involving chiral imines we reported a decade ago.[8] Accordingly, imine **4**, prepared from 2-ethylcyclopentanone **3** and *R*-(+)-1-phenylethylamine of 97% ee (powdered 4 Å molecular sieves, cyclohexane, 20°C, 72 h), was added to methyl acrylate (neat, 24 h at 40°C) to lead, after hydrolytic work-up (10% aqueous AcOH, 20°C, 2 h), to ketoester (*S*)-**5a** (83% overall yield, 90% ee).[9]

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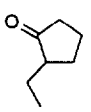

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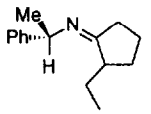

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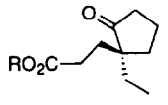
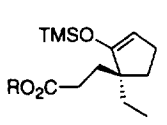


5

a : R = Me b : R = *i*-Pr

Strategically, we envisaged the construction of the tricyclic key intermediate **11a** by tryptamine-induced ring-opening of the lactone **8a**, derived from adduct **5a**, followed by cyclization into the desired lactam. To attain this end, **5a** was first converted into silyl enol ether (*S*)-**6a**[10] (NaI, TMSCl, Et_3N, 30 min at 20°C in MeCN, 95% yield), which was then transformed into hydroxy acid (*S*)-**7a** (*i*: O_3, CH_2Cl_2/MeOH, −78°C; *ii*: $NaBH_4$), next cyclized into lactone (*S*)-**8a** (cat. 12 *N* HCl, CH_2Cl_2, 3 h at 20°C, 80% overall yield). However, all attempts at ring-opening of **8a**, by means of tryptamine, were thwarted by the competitive attack to the ester group of the propanoate appendage. We therefore decided to replace the methyl ester group of **8a** by an isopropyl moiety, less sensitive to nucleophilic attack. For that purpose adduct **5a** was transesterified into (*S*)-**5b** (cat. *i*-PrONa, *i*-PrOH, 15 min at 20°C, 80% yield). The latter compound was then transformed into lactone (*S*)-**8b**[11] with a 75% yield, according to the same protocol used for converting **5a** into **8a**.



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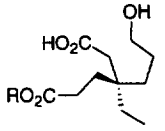

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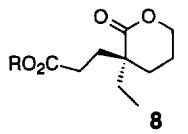
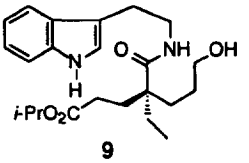


8

a : R = Me b : R = *i*-Pr a : R = Me b : R = *i*-Pr a : R = Me b : R = *i*-Pr

*To our delight ring-opening of lactone **8b** now proceeded in a completely chemoselective fashion* (DMF, 2 h at 100°C), furnishing compound (*S*)-**9** with a 80% yield.[11]

We next examined the conversion of amido alcohol **9** into our goal **11b**. With this aim in view, compound **9** was first transformed into bromide (*R*)-**10** (CBr_4/PPh_3, CH_2Cl_2, 2 h at 20°C, 80% yield).[12] Cyclization of **10** was next attempted. After extensive experimentation,[13] we discovered that treatment of **10** with KH in the presence of 18-crown-6 (THF, 10 min at 20°C) furnished quantitatively the desired tricyclic lactam (*S*)-**11a**. The latter compound, upon transesterification (cat. MeONa, MeOH, 1 h at 20°C, quantitative), finally gave our goal (*S*)-**11b**.[14]



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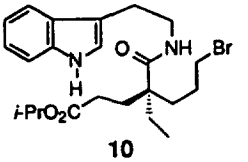

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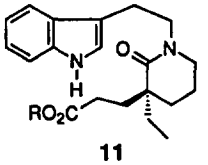

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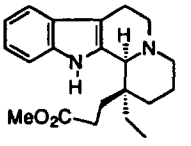

12

a : R = *i*-Pr b : R = Me

Physical and spectroscopic data of compound **11b** proved to be identical in all respects with those reported in the literature.[15] Moreover, seeing that Bischler–Napieralski cyclization of **11b**, prepared by another route,[15] followed by reduction, led to the tetracyclic derivative **12**, a known, direct precursor of (+)-vincamine **1**, the present approach constitutes a formal, efficient enantioselective synthesis of

this alkaloid. Further extensions of the present methodology are currently under investigation in our laboratories.

Acknowledgements

The authors would like to thank FINEP/PADCT (financial support), CAPES (fellowship to JCFA), UFRJ (fellowship to ABCS), E. Miguez and F. Santos (NMR spectra), C. Migues (mass spectra), and Prof. Octavio A. C. Antunes (IQ-UFRJ) and Dr. Didier Desmaële (Paris XI) for helpful discussions.

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14. **5b**: oil; $[\alpha]_D^{20}$ +9.5 (c 2, EtOH); IR (cm^{-1}) 2971, 1734; ^1H NMR (200 MHz, $CDCl_3$) δ 0.84 (t, J=7.6 Hz, 3H) 1.23 (d, J=6.3 Hz, 6H) 1.39–1.54 (m, 2H) 1.62–2.00 (m, 6H) 2.10–2.40 (m, 4H) 4.99 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.0 (CH_3) 18.2 (CH_2) 21.5 (CH_3) 26.6 (CH_2) 28.6 (CH_2) 29.2 (CH_2) 32.9 (CH_2) 37.9 (CH_2) 50.7 (C) 67.29 (CH) 172.6 (C) 222.0 (C); MS m/z (%) 226 (M^+, 19) 167 (86) 111 (100); HRMS, calculated for C_{13} $H_{22}O_3$: 226.156895, found: 226.15649. **6b** : oil; IR (cm^{-1}) 1730, 1645; ^1H NMR (200 MHz, C_6D_6) δ 0.12 (s, 9H) 0.84 (t, J=7.35 Hz, 3H) 1.03 (d, J=6.30 Hz, 3H) 1.04 (d, J=6.30 Hz, 3H) 1.27–1.49 (m, 2H) 1.56 (m, 2H) 1.84–1.95 (m, 2H) 2.06 (m, 2H) 2.36 (m, 2H) 4.51 (m, 1H) 5.02 (m, 1H). **8b** : oil; IR (cm^{-1}) 1720; ^1H NMR (200 MHz, $CDCl_3$) δ 0.92 (t, J=7.5 Hz, 3H) 1.22 (d, J=6.3 Hz, 6H) 1.45–2.00 (m, 8H) 2.34 (m, 2H) 4.32 (m, 2H) 4.99 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.2 (CH_3) 20.7 (CH_2) 21.4 (2 CH_3) 29.0 (CH_2) 29.5 (CH_2) 31.1 (CH_2) 33.0 (CH_2) 45.1 (C) 67.5 (CH) 69.8 (CH_2) 172.3 (C) 174.8 (C); MS m/z (%) 214 (9) 183 (80) 128 (100). **9**: oil; $[\alpha]_D^{20}$ −1.1 (c 4.5, EtOH); IR (cm^{-1}) 3340, 2940, 1720, 1640; ^1H NMR (200 MHz, $CDCl_3$) δ 0.76 (t, J=7.40 Hz, 3H) 1.22 (d, J=6.22, 6H) 1.25–1.85 (m, 9H) 2.13 (m, 2H) 2.98 (t, J=6.60, 2H) 3.47 (t, J=6.0 Hz, 2H) 3.63 (dd, J=12.5 Hz, J=6.0 Hz, 2H) 4.97 (m, J=6.2 Hz, 1H) 5.86 (NH) 7.04–7.28 (m, 3H) 7.38 (d, J=7.50 Hz, 1H) 7.63

(d, J=7.40 Hz, 1H) 8.17 (NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.0 (CH_3) 21.6 (CH_3) 26.8 (CH_2) 29.0 (CH_2) 29.3 (CH_2) 30.0 (CH_2) 39.6 (CH_2) 47.7 (C) 62.3 (CH_2) 67.7 (CH) 111.2 (CH) 112.2 (C) 118.4 (CH) 119.00 (CH) 121.7 (CH) 122.2 (CH) 127.0 (C) 136.3 (C) 173.1 (C) 176.0 (C); MS m/z (%) 402 (M^+, 4) 254 (15) 143 (100). **10**: oil; $[\alpha]_D^{20}$ +3.8 (c 2.1, EtOH); IR (cm^{-1}) 3290, 2971, 1733, 1612,; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.76 (t, J=7.2 Hz, 3H) 1.22 (d, J=6.2 Hz, 6H) 1.46 (q, J=7.2 Hz, 2H) 1.50–1.70 (m, 4H) 1.54–1.82 (m, 2H) 2.04–2.18 (m, 2H) 2.98 (t, J=6.6 Hz, 2H) 3.28 (t, J=6.0 Hz, 2H) 3.62 (m, 2H) 4.97 (m, 1H) 5.79 (NH) 7.04–7.06 (m, 1H) 7.09–7.25 (m, 2H) 7.38 (m, 1H) 7.62 (m, 1H) 8.23 (NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 7.9 (CH_3) 21.6 (2 CH_3) 25.2 (CH_2) 26.7 (CH_2) 27.1 (CH_2) 29.0 (CH_2) 29.3 (CH_2) 32.7 (CH_2) 33.9 (CH_2) 39.5 (CH_2) 47.7 (C) 67.7 (CH) 111.2 (CH) 112.6 (C) 118.5 (CH) 119.3 (CH) 122.0 (2 CH) 127.1 (C) 136.3 (C) 172.8 (C) 175.2 (C). **11a** : oil; $[\alpha]_D^{20}$ +10.3 (c 1.55, EtOH); IR (cm^{-1}) 3268 2936 1729 1614; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.86 (t, J=7.5, 3H) 1.23 (d, J=6.2, 6H) 1.40–2.10 (m, 8H) 2.16–2.42 (m, 2H) 3.00 (m, 2H) 3.20 (m, 2H) 3.65 (m, 2H) 5.00 (m, J=6.2 Hz, 1H) 7.01–7.05 (m, 1H) 7.06–7.23 (m, 2H) 7.33–7.40 (m, 1H) 7.61–7.71 (m, 1H) 8.48 (NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.4 (CH_3) 19.6 (CH_2) 21.6 (CH_3) 22.9 (2 CH_2)) 29.3 (CH_2) 30.8 (CH_2) 33.1 (CH_2) 44.1 (CH) 48.4 (CH_2) 48.7 (CH_2) 67.4 (CH) 111.1 (CH) 112.8 (C) 118.5 (CH) 119.0 (CH) 121.6 (CH) 122.1 (CH) 127.3 (C) 136.2 (C)173.3 (C) 173.6 (C); MS m/z (%) 384 (M^+, 6) 325 (9) 143 (100).

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(Received in UK 14 April 1997)