Ring Expansion: Synthesis of the Velbanamine Piperidine Core

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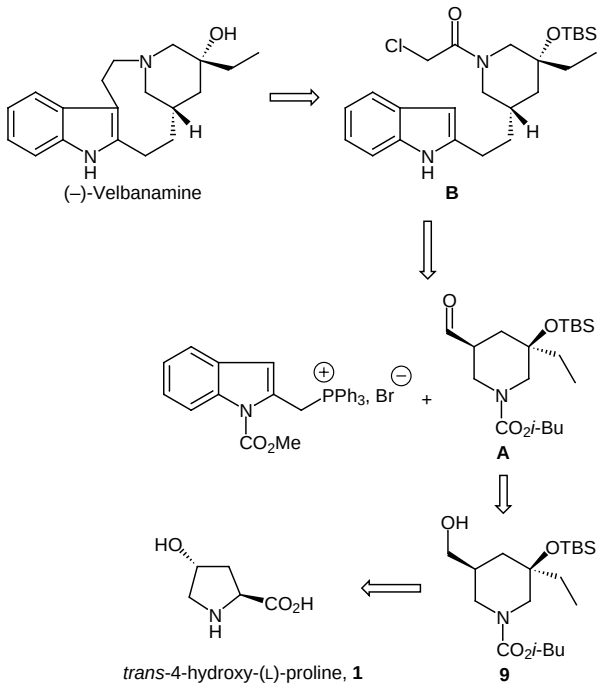
Abstract: A ring expansion reaction applied to a substituted prolinol has been used in order to obtain the piperidine core of (-)-velbanamine, an alkaloid extracted from *Tabernaemontana eglandulosa*.

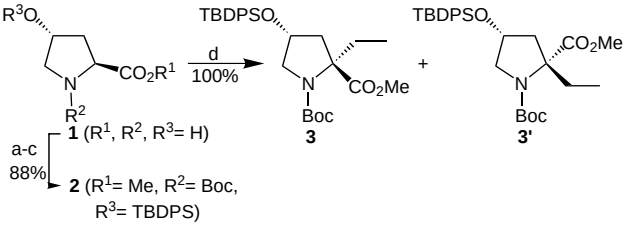
Key words: (-)-velbanamine, alkaloid, ring expansion, piperidines, *trans*-4-hydroxy-(L)-proline

Of the numerous alkaloids isolated from the pantropical plant *Catharanthus roseus*, vinblastine and vincristine have antitumor activity and are used in the treatment of Hodgkin's disease and leukemia.[1] Reductive cleavage of both alkaloids gave the indole derivative (+)-velbanamine.[2] On the other hand, (–)-velbanamine was extracted from leaves and twigs of *Tabernaemontana eglandulosa* in 1984.[3] Five racemic syntheses of velbanamine and two chiral non-racemic syntheses of (+)-velbanamine and (–)-velbanamine have been achieved previously.[4–6] For our part, we have envisaged the synthesis of (–)-velbanamine by photochemical cyclization[7] of α-chloroacetamide **B** to built up the 9-membered ring, and enantioselective ring expansion of prolinol to piperidin-3-ol[8] to afford the 3,3,5-trisubstituted piperidine ring present in (–)-velbanamine. The precursor of the α-chloroacetamide **B** could be obtained by condensation of the phosphonium methyl indole bromide[9] with piperidinoaldehyde **A**. Here, we would like to report the synthesis of alcohol **9** from *trans*-4-hydroxy-(L)-proline, which is the precursor of aldehyde **A** (Scheme 1).



Scheme 1 Retrosynthetic Scheme

The enantiomerically pure commercially available *trans*-4-hydroxy-(L)-proline **1** was transformed, in quantitative yield, to the corresponding methylester carbamate by treatment with $SOCl_2$ in the presence of methanol, followed by the nitrogen protection as a *tert*-butyl carbamate. After protection of the hydroxy group at C-4 (TBDPSCl, imidazole, DMF, r.t., 88%), the corresponding silyl-ether **2**[10] was treated with LDA at –78 °C and the enolate was quenched with ethyl iodide (7.5 equiv) in the presence of HMPA (7.0 equiv)[10] to afford two inseparable alkylated compounds **3** and **3'** in a 78:22 ratio and in quantitative yield (Scheme 2).



Scheme 2 (a) $SOCl_2$ (1.2 equiv), MeOH, 0 °C to r.t., 1 day; (b) Boc_2O (1.1 equiv), Et_3N (2.2 equiv), dioxane–H_2O, 2:1, r.t., 1 day; (c) TBDPSCl (1.0 equiv), imidazole (2.5 equiv), DMF, r.t., 2 days; (d) LDA (2.0 equiv), THF, –78 °C, 1 h then HMPA (7.0 equiv), EtI (7.5 equiv), –78 °C, 20 min.

To determine the relative stereochemistry between the hydroxy group at C-4 and the ester group at C-2, the minor isomer **3'** was transformed to the corresponding hydroxy acid, as the *cis* isomer should cyclize to produce the corresponding lactone. After deprotection of the hydroxy groups at C-4 in **3** and **3'**, using TBAF (MS 4 Å, THF, r.t.), the hydroxyesters **10** and **10'** were isolated in 87% yield and separated by chromatography. Compound **10'** was treated with LiOH and transformed to the hydroxy acid **11** (89%) which, after treatment with diphenylphosphorylazide (DPPA) in the presence of Et_3N in DMF,[10] led to lactone **12**[11] in 44% yield (Scheme 3).

As the minor diastereomer **3'** clearly has the *cis* relationship between the hydroxy group at C-4 and the ester at

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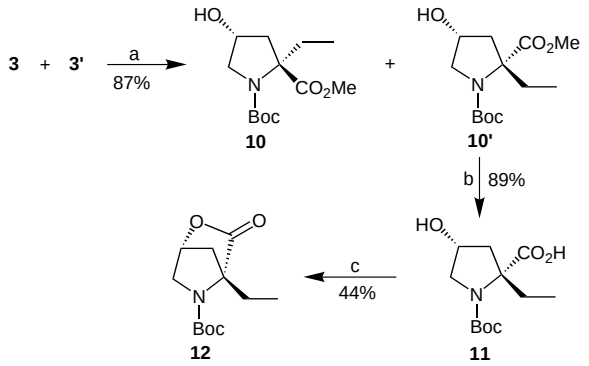
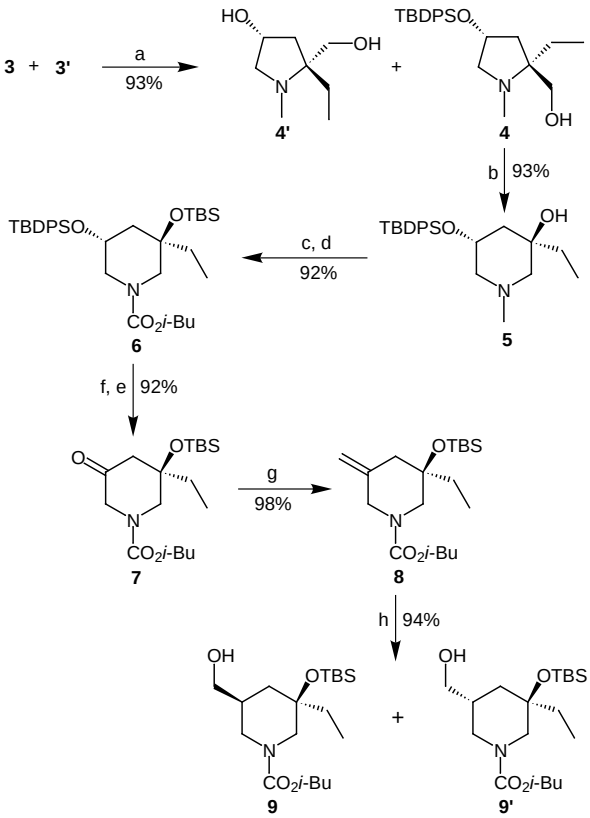


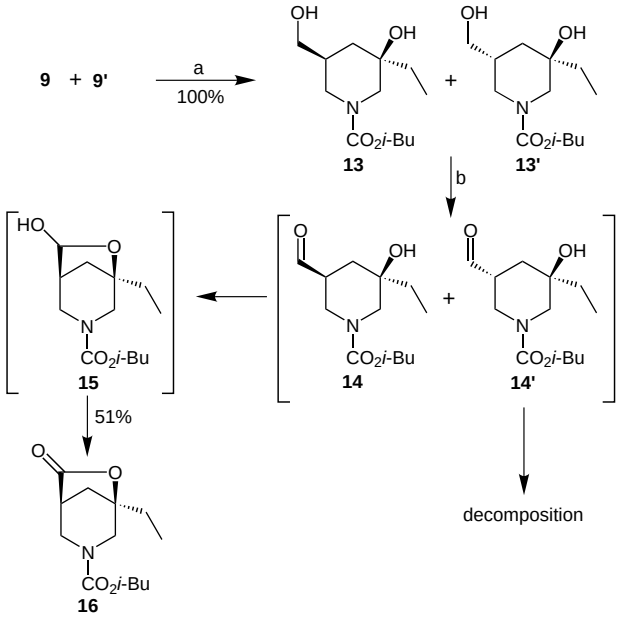
Scheme 3 (a) TBAF (2.0 equiv), powdered MS 4 Å, THF, r.t., 2.5 days; (b) LiOH (2.8 equiv), THF–H_2O, 1:1, 0 °C to r.t., 17 h; (c) DPPA (1.2 equiv), Et_3N (2.3 equiv), DMF, 0 °C to r.t., 5 h.

C-2, the major isomer **3** has the desired *trans* relative stereochemistry required for our synthesis. The mixture of compounds **3** and **3'** was reduced with $LiAlH_4$ in refluxing THF to afford the corresponding prolinols **4**[12] and **4'** (ratio **4**/**4'** = 78/22) in 93% yield, which could be separated by flash chromatography. It is worth noting that the silylether group of the *cis* diastereomer was deprotected under these conditions.[13] Ring expansion conditions[8g] applied to **4**, using trifluoroacetic anhydride (TFAA) in THF at r.t. followed by addition of Et_3N and NaOH, led to piperidinol **5**[14] in 93% yield and with a diastereomeric excess of >98%. After protection of the tertiary alcohol at C-3 (TBSOTf, 2,6-lutidine, CH_2Cl_2, r.t.) followed by the *N*-demethylation and carboxylation of the piperidine using isobutyl chloroformate in presence of K_2CO_3 in refluxing toluene,[15] the 3,3,5-trisubstituted piperidine **6** was isolated in 92% yield. Selective deprotection of the C-5 silylether was achieved with TBAF (1.0 equiv) and PCC oxidation afforded the aminoketone **7** in 92% yield. Transformation of **7** to the desired alcohol **9** was achieved in two steps *via* the methylene piperidine **8**. Treatment of ketone **7** with Cp_2TiMe_2, in THF in the dark[16] afforded the methylene piperidine **8** (98%), which was then transformed to the primary alcohols **9** and **9'** in 94% yield and in a ratio of 61:39 with BH_3·THF/NaOH, H_2O_2. Remarkably, the ratio in **9**/**9'** was not improved when a hindered borane such as *t*-hexylborane was used (Scheme 4).

To determine the relative stereochemistry between the hydroxy at C-3 and the hydroxymethyl at C-5 in compounds **9**/**9'**, the alcohol at C-3 was deprotected (TBAF, THF, reflux, 100% yield) and the diol was oxidized (TPAP, NMO, MS 4 Å, CH_2Cl_2/CH_3CN). Under these conditions, lactone **16** was the only compound isolated. The monitoring of this reaction by GC/MS shows us that lactone **16** was obtained via the hydroxyaldehyde-lactol **14**-**15**. The minor compound **13'** was transformed to hydroxyaldehyde **14'**,[17] which decomposed very rapidly under these conditions (Scheme 5).



Scheme 4 (a) $LiAlH_4$ (4.8 equiv), THF, 0 °C to reflux, 2 h; (b) TFAA (1.2 equiv), THF, 0 °C, 1.2 h then Et_3N (4.0 equiv), 0 °C to r.t., 2 days then 3.75 N NaOH (20.0 equiv), r.t., 2 h; (c) TBSOTf (1.2 equiv), 2,6-lutidine (3.0 equiv), CH_2Cl_2, r.t., 1 h; (d) $ClCO_2i$-Bu (1.0 equiv), K_2CO_3 (0.6 equiv), toluene, reflux, 3 h; (e) TBAF (1.0 equiv), powdered MS 4 Å , THF, r.t., 3.5 h; (f) PCC (2.5 equiv), powdered MS 4 Å , CH_2Cl_2, r.t., 2.5 h; (g) Cp_2TiMe_2 (3.2 equiv), THF, dark, reflux, 4 h; (h) BH_3·THF (1.1 equiv), THF, 0 °C, 50 min then 3.75 N NaOH (4.0 equiv), 30 % H_2O_2 (8.0 equiv), 0 °C to r.t., 1.5 h.



Scheme 5 (a) TBAF (5.0 equiv), THF, reflux, 17 h; (b) TPAP (0.04 equiv), NMO (3.0 equiv), powdered MS 4 Å , CH_2Cl_2/CH_3CN = 10/1, r.t., 1.5 h.

By employing a ring expansion of the 2,2,4-trisubstituted prolinol **4**, we were able to obtain the 3,3,5-trisubstituted piperidine **5** with excellent diastereoselectivity. This latter compound can be transformed in four additional steps to piperidine **9**, which will be utilized in the synthesis of (–)-velbanamine.

References and Notes

(1) Noble, R. N. *Can. Cancer Conf.* **1961**, *4*, 333.
(2) Neuss, N. *Bull. Soc. Chim. Fr.* **1962**, 1509.
(3) Van Beck, T. A.; Verpoorte, R.; Baerheim Svendsen, A. *Tetrahedron* **1984**, *40*, 737.
(4) Racemic syntheses: (a) Büchi, G.; Kulsa, P.; Rosati, R. L. *J. Am. Chem. Soc.* **1968**, *90*, 2448. (b) Büchi, G.; Kulsa, P.; Ogasawara, K.; Rosati, R. L. *J. Am. Chem. Soc.* **1970**, *92*, 999. (c) Narisada, M.; Watanabe, F.; Nagata, W. *Tetrahedron Lett.* **1971**, *12*, 3681. (d) Takano, S.; Hirama, M.; Ogasawara, K. *J. Org. Chem.* **1980**, *45*, 3729.
(5) Chiral syntheses for (-)-velbanamine: Takano, S.; Yonaga, M.; Chiba, K.; Ogasawara, K. *Tetrahedron Lett.* **1980**, *21*, 3697.
(6) Chiral syntheses for (+)-velbanamine: (a) Kutney, J. P.; Bylsma, F. *J. Am. Chem. Soc.* **1970**, *92*, 6090. (b) Kutney, J. P.; Bylsma, F. *Helv. Chim. Acta* **1975**, *58*, 1672. (c) Takano, S.; Uchida, W.; Hatakeyama, S.; Ogasawara, K. *Chem. Lett.* **1982**, 733.
(7) For the synthesis of a 9-membered ring by photochemical cyclization see: Amat, M.; Coll, M.-D.; Bosch, J.; Espinosa, E.; Molins, E. *Tetrahedron: Asymmetry* **1997**, *8*, 935.
(8) (a) Cossy, J.; Dumas, C.; Michel, P.; Gomez Pardo, D. *Tetrahedron Lett.* **1995**, *36*, 549. (b) Cossy, J.; Dumas, C.; Gomez Pardo, D. *Synlett* **1997**, 905. (c) Cossy, J.; Dumas, C.; Gomez Pardo, D. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1343. (d) Wilken, J.; Kossenjans, M.; Saak, W.; Haase, D.; Pohl, S.; Martens, J. *Liebigs Ann.* **1997**, 573. (e) Langlois, N.; Calvez, O. *Synth. Commun.* **1998**, *28*, 4471. (f) Davis, P. W.; Osgood, S. A.; Hébert, N.; Sprankle, K. G.; Swayze, E. E. *Biotechnol. Bioeng.* **1999**, *61*, 143. (g) Cossy, J.; Dumas, C.; Gomez Pardo, D. *Eur. J. Org. Chem.* **1999**, 1693. (h) Michel, P.; Rassat, A. *J. Org. Chem.* **2000**, *65*, 2572.
(9) Nagarathnam, D. *Synthesis* **1992**, 743.
(10) Nagumo, S.; Mizukami, M.; Akutsu, N.; Nishida, A.; Kawahara, N. *Tetrahedron Lett.* **1999**, *40*, 3209.
(11) **12**: $[\alpha]^{20}_D$ = –98.9 (*c* 1.8, $CHCl_3$). Mp: 63 °C. IR (KBr): 1781, 1697, 1366, 1331 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.92 (m, 1 H), 3.59 (d, 1 H, *J* = 11.8 Hz), 3.54 (d, 1 H, *J* = 11.8 Hz), 2.50 (m, 1 H), 2.16-1.94 (3 H), 1.44 (s, 9 H), 1.00 (t, 3 H, *J* = 7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1 (s), 154.8 (s), 81.2 (s), 74.9 (d), 68.3 (s), 53.3 (t), 42.9 (t), 28.2 (q,), 20.1 (t), 9.0 (q). EI MS *m/z* (relative intensity): 241 (M^+, 0.06), 197 (15), 168 (11), 141 (62), 112 (15), 97 (22), 96 (25), 84 (13), 68 (10), 57 (100), 56 (13), 55 (11). Elemental analysis: calcd. for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.80. Found: C, 59.92; H, 8.04; N, 5.55.
(12) **4:** $[\alpha]^{20}_D$ = +2.4 (*c* 1.36, $CHCl_3$). IR(neat): 3416, 1472, 1428, 1111 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.75–7.54 (4 H), 7.48–7.30 (6 H), 4.32 (m, 1 H), 3.26 (d, 1 H, *J* = 10.3 Hz), 3.14 (d, 1 H, *J* = 10.3 Hz), 3.12 (br s, 1 H), 3.11 (dd, 1 H, *J* = 9.2 and 6.6 Hz), 2.68 (m, 1 H), 2.18 (s, 3 H), 2.03 (dd, 1 H, *J* = 13.6 and 8.5 Hz), 1.81 (dd, 1 H, *J* = 13.6 and 4.4 Hz), 1.71 (dq, 1 H, *J* = 13.2 and 7.7 Hz), 1.42 (m, 1 H), 1.07 (s, 9 H), 0.91 (t, 3 H, *J* = 7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6 (d), 134.1 (s), 134.0 (s), 129.6 (d), 127.6 (d), 127.5 (d), 70.3 (d), 65.7 (s), 62.9 (t), 62.7 (t), 40.8 (t), 32.8 (q), 26.8 (q), 23.3 (t), 19.0 (s), 8.7 (q). EI MS *m/z* (relative intensity): 397 (M^+, 0.1), 368 (11), 367 (32), 366 (100), 254 (4), 199 (10), 183 (5), 154 (10), 135 (4), 110 (20), 82 (6). MS (CI^+, CH_4) *m/z* (relative intensity): 398 ($M+H^+$, 100), 396 (28), 380 (17), 366(16), 320(17), 179(19), 154(47). HRMS (CI^+, CH_4): calcd. for $C_{24}H_{35}NO_2Si$ ($M+H^+$): 398.2515. Found: 398.2519.
(13) de Vries, E. F. J.; Brussee, J.; van der Gen, A. *J. Org. Chem.* **1994**, *59*, 7133.
(14) **5:** $[\alpha]^{20}_D$ = +18.2 (c 1, $CHCl_3$). IR(neat): 3442, 1461, 1428, 1136, 1111 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.81–7.61 (4 H), 7.52–7.31 (6 H), 4.08 (dddd, 1 H, *J* = 10.2, 10.2, 5.1 and 5.1 Hz), 2.81 (ddm, 1 H, *J* = 10.5 and 5.0 Hz), 2.71 (m, 1 H), 2.45 (dm, 1 H, *J* = 11.4 Hz), 2.21 (s, 3 H), 1.97 (dm, 1 H, *J* = 12.7 Hz), 1.90-1.80 (2 H), 1.47 (m, 2 H), 1.26 (dd, 1 H, *J* = 12.7 and 10.8 Hz), 1.11 (s, 9 H), 0.91 (t, 3 H, *J* = 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7 (d), 135.6 (d), 134.3 (s), 134.1 (s), 129.6 (d), 129.5 (d), 127.5 (d), 71.0 (s), 67.0 (d), 64.5 (t), 62.8 (t), 45.7 (q), 43.6 (t), 32.3 (t), 26.9 (q), 19.1 (s), 7.1 (q). EI MS *m/z* (relative intensity): 397 (M^+, 7), 379 (24), 340 (79), 263 (22), 262 (100), 261 (12), 225 (10), 199 (23), 197 (12), 183 (25), 181 (13), 142 (12), 135 (14), 124 (19), 84 (12), 58 (38). MS (CI^+, CH_4) *m/z* (relative intensity): 398 ($M+H^+$, 100), 380 (19), 340 (7), 321 (9), 320 (39), 302 (5), 179 (2), 142 (8). HRMS (CI^+, CH_4): calcd. for $C_{24}H_{36}NO_2Si$ ($M+H^+$): 398.2515. Found: 398.2521.
(15) Kratzel, M.; Weigl, A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1009.
(16) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392.
(17) The minor diastereomer **14'** was only detected by GC/MS.