

AN ASYMMETRIC SYNTHESIS OF THE ANT VENOM ALKALOID (3*S*,5*S*,8*aR*)-3-BUTYL-5-(4-PENTENYL)INDOLIZIDINE VIA THE SHARPLESS ASYMMETRIC DIHYDROXYLATION[#]

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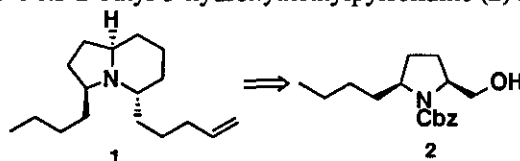
Abstract- The first asymmetric synthesis of the ant venom alkaloid (3*S*,5*S*,8*aR*)-3-butyl-5-(4-pentenyl)indolizidine (**1**) has been performed by starting with the Sharpless asymmetric dihydroxylation of *N*-alkenylcarbamate (**3**) followed by reductive annulation (5-exo-tetrahedral).

Indolizidine alkaloids offer attractive targets for synthesis because of their unique structures and intriguing biological activities.¹ Recently, a novel 3,5-dialkylated indolizidine (**1**) was isolated from the ant venom of *Monomorium smithii*.² Its absolute configuration and potential biological activities, however, remain unknown owing to its short supply from natural sources. So far, the synthesis of **1** has been reported only once in its racemic form,² and its chiral synthesis has never been performed. Our interest in this field is directed towards the synthetic utilization of the Sharpless asymmetric dihydroxylation (AD) reaction,³ as employed for the enantioselective construction of oxygen⁴ and nitrogen⁵ heterocycles leading to natural products. In this communication, we impart the first asymmetric synthesis of **1** via construction of *cis*-2,5-disubstituted pyrrolidine by capitalizing on AD reaction as a crucial step of a homochiral 4-pentenylcarbamate available from L-norleucine.

Recent investigations in this laboratory have disclosed that the kinetically controlled amidomercuration of α -

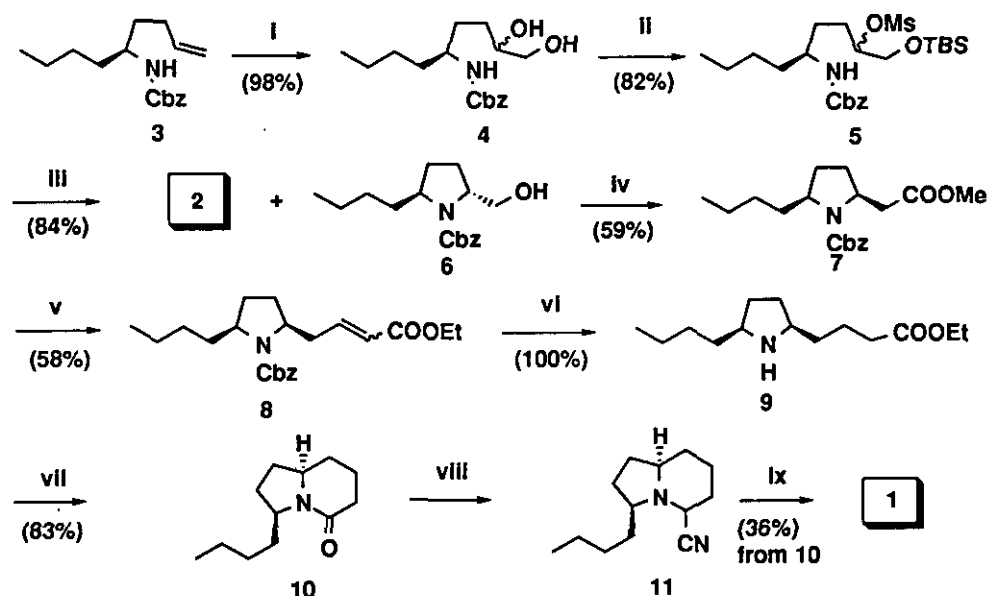
[#] This paper is dedicated to the memory of the late Professor Yoshio Ban.

amino acids-derived α -alkylated 4-pentenylcarbamates resulted in stereoselective cyclization (5-*exo-trig*) and provided the *trans*-2-alkyl-5-(hydroxymethyl)pyrrolidine. The latter has been converted to several biologically active nitrogen-containing compounds such as (+)-pyrrolidine 197B,^{6a} (+)-xenovenine,^{6b} and (+)-indolizidine 195B.^{6c} This time we needed the *cis*-2-butyl-5-hydroxymethylpyrrolidine (**2**) for the preparation of **1**.



Unfortunately, examination of the various amidomercuration under thermodynamically controlled conditions resulted in *trans*-selectivity preferentially. Accordingly, our regard was focused on the Sharpless AD reaction as a step enforcing the introduction of a stereogenic center and subsequent stereoselective construction of the *cis*-pyrrolidine (**2**) by 5-*exo-tet* cyclization. Our synthesis of **1** began with the Sharpless AD reaction of (*S*)-*N*-benzyloxycarbonyl-1-butyl-4-pentenylamine (**3**), readily accessible from L-norleucine.^{6a} Treatment of **3** with AD-mix- β (Aldrich No. 39,276-6) at 0 °C in *tert*-butyl alcohol/water (1:1) for 24 h afforded a diastereomeric mixture of the diols (**4**). Selective protection of the primary hydroxyl in **4** with *tert*-butyldimethylsilyl followed by mesylation of the secondary hydroxyl provided the mesylate (**5**). Exposure of **5** to an atmosphere of hydrogen in the presence of Pd(OH)₂ as a catalyst in methanol caused concurrent debenzyloxycarbonylation and annulation (5-*exo-tet*) to give the pyrrolidine salt, which was converted by a two-step sequence (i, de-*tert*-butyldimethylsilylation; ii, *N*-benzyloxycarbonylation) to a separable 4:1 mixture of the 2,5-*cis*-disubstituted pyrrolidine (**2**) and its *trans* isomer (**6**).

With the requisite **2** in hand, the elongation of its appendage was initiated. The Jones oxidation of **2** gave the acid, which on the subsequent Arndt-Eistert homologation provided the ester (**7**). Next, application of a three-step sequence (i, reduction; ii, the Swern oxidation; iii, the Horner-Emmons reaction) to **7** gave the α,β -unsaturated ester (**8**). Both debenzyloxycarbonylation and olefin reduction were effected by catalytic hydrogenation over Pd(OH)₂ of **8** to give **9**, but failed in further annulation into indolizidinone. The intramolecular lactamization of **9** was performed by the Weinreb's procedure⁷ utilizing trimethylaluminum to give the synthetic intermediate (**10**). The spectral data for **10** were completely identical with those reported.² According to the Jones's method² described for the synthesis of ($\pm$)-**1** from ($\pm$)-**10**, **10** was converted *via* the amino nitrile to the desired (+)-(3*S*,5*S*,8*aR*)-3-butyl-5-(4-pentenyl)indolizidine (**1**)⁸ (bp 65-70 °C/1 mmHg) [α]_D²⁶ +71.4° (c 0.645, CHCl₃), whose spectral data were in accordance with those reported.^{2,9}



i, AD-mix- β ; ii, 1) TBSCl/imidazole/DMF; 2) MsCl/Et₃N; iii, 1) H₂/Pd(OH)₂; 2) 1% HCl; 3) CbzCl/NaOH; iv, 1) CrO₃/H⁺/acetone; 2) CH₂N₂; 3) AgCOOPh/MeOH; v, 1) LiBH(Et)₃; 2) (COCl)₂/DMSO/Et₃N; 3) (EtO)₂P(O)CH₂COOEt/NaH; vi, H₂/Pd(OH)₂; vii, Me₃Al; viii, 1) DIBALH; 2) 60% HClO₄; 3) KCN; ix, 1-pentenylmagnesium bromide

In conclusion, we have demonstrated the new construction of 2,5-*cis*-disubstituted pyrrolidine ring using the Sharpless asymmetric dihydroxylation as a key reaction and the first asymmetric synthesis of the ant venom alkaloid (1). Accordingly, this method provides a promising avenue to the voluntarily stereoselective synthesis of homochiral α,α' -disubstituted pyrrolidine and piperidine rings, which could be led the related biologically active compounds.

ACKNOWLEDGMENT

We are grateful to Professor K. B. Sharpless, The Scripps Research Institute, for providing us a manuscript copy of ref. 3a before its publication.

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- 8 ^1H Nmr (CDCl_3) δ 0.91 (3 H, t, $J=7$ Hz), 0.96-2.2 (12 H, m), 2.4-2.7 (2 H, br d), 3.0-3.2 (1H, m), 4.98(1H, br d, $J=10$ Hz), 5.03 (1H, br d, $J=17$ Hz), 5.7-5.9 (1 H, m); ^{13}C nmr (CDCl_3) δ 14.11, 19.32, 20.04, 23.10, 26.93, 27.73, 28.31, 28.77, 29.46, 32.43, 32.54, 34.07, 52.64, 56.27, 58.54, 114.44, 138.92.
- 9 The optical rotation of natural product (**1**) is not reported in ref.2.

Received, 6th January, 1995