Asymmetric Synthesis of the Indolizidine Alkaloids 207A, 209B, and 235B': 6-Substituted 2,3-Didehydropiperidine-2-carboxylate as a Versatile Chiral Building Block

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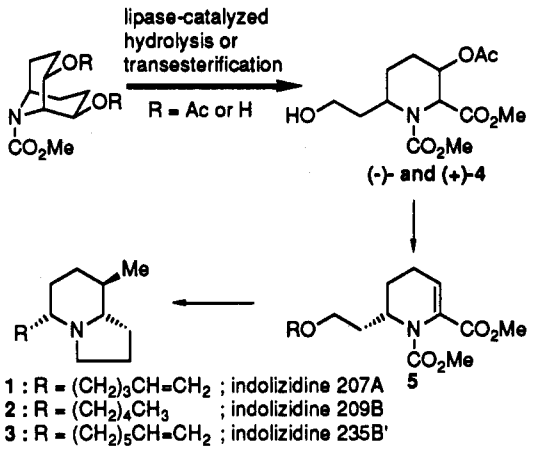
Summary: The asymmetric synthesis of 5-substituted 8-methylindolizidines 1–3 was achieved *via* the highly stereocontrolled Michael reaction of the title compound **5**.

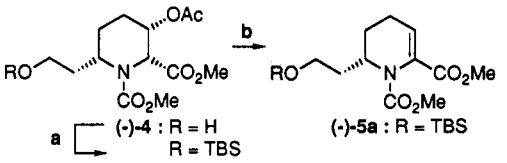
A number of alkaloids containing the 2,6(*cis* or *trans*)-disubstituted piperidine ring system are found in nature, and many of these alkaloids display significant biological activities.[1] As a consequence, new synthetic strategies[2] and useful chiral building blocks[3] have been developed for the efficient chiral synthesis of these alkaloids. Illustrative of our efforts in this field, we have recently reported the synthesis of both enantiomers of the homochiral piperidine **4**[4] and its application to the synthesis of 3-piperidinol alkaloids.[5] Herein, we describe the highly stereocontrolled syntheses of indolizidines **1**–**3**[6] starting from (−)-**4** (Scheme 1).

The compound 2,3-didehydropiperidine (−)-**5a** (R = TBS, $[\alpha]^{26}_D$ −54.8)[7] was first examined as a common chiral building block for the synthesis of alkaloids **1**–**3**, and the

Scheme 1

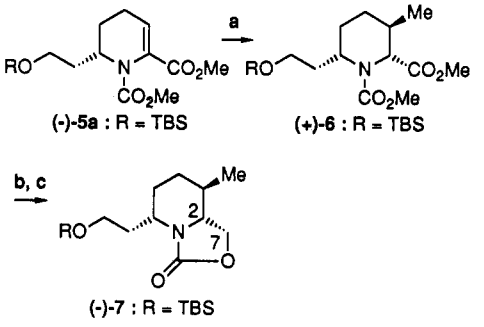


Scheme 2[a]



[a] (a) TBSCl, Et_3N, DMAP (95%); (b) NaH, DMF:benzene = 2:1, 50 °C (92%).

Scheme 3[a]



[a] (a) Me_2CuLi, −60 °C–rt (92%); (b) Super-Hydride (94%); (c) NaH, DMF:benzene = 2:1, 50 °C (93%).

transformation of (−)-**4** into (−)-**5a** was achieved in 87% yield (Scheme 2). The versatility of (−)-**5** was next examined. The Michael reaction of (−)-**5a** (R = TBS) with Me_2CuLi in THF was highly stereoselective and gave the adduct (+)-**6** ($[\alpha]^{26}_D$ +71.2) as a sole product in 92% yield. Reduction of (+)-**6** with Super-Hydride followed by treatment of the resulting alcohol (+)-**8** with base afforded the oxazolidinone (−)-**7** ($[\alpha]^{26}_D$ −10.9). Analysis of the coupling patterns of the methine proton at C_2 and the methylene protons at C_7 in the ^1H NMR spectrum of (−)-**7**[8] suggested that the stereochemistry of (+)-**6** could be assigned as shown in Scheme 3 by assuming that all the ring appendages lie in the equatorial orientation (Scheme 3).

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(6) Isolation: (a) (−)-Indolizidine 207A (**1**) and 235B' (**3**): Edwards, M. W.; Daly, J. W.; Myers, C. W. *J. Nat. Prod.* **1988**, *51*, 1188. (b) (−)-Indolizidine 209B (**2**): Daly, J. W.; Myers, C. W.; Whittaker, N. *Toxicon* **1987**, *25*, 1023. Nonchiral synthesis of **1**: (c) Reference 2g. Of **2**: (d) Comins, D. L.; Zeller, E. *Tetrahedron Lett.* **1991**, *32*, 5889. Of **3**: (e) Collins, I.; Fox, M. E.; Holmes, A. B.; Williams, S. F.; Baker, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 175. Chiral synthesis of (−)-**1**: (f) Reference 2l. Of (−)-**2**: (g) Reference 2g. (h) Aubé, J.; Rafferty, P. S.; Milligan, G. L. *Heterocycles* **1993**, *35*, 1141. (i) Satake, A.; Shimizu, I. *Tetrahedron: Asymmetry* **1993**, *4*, 1405. (j) Reference 2l. Of (+)-**2**: (k) Reference 2j.

(7) Satisfactory analytical and spectral data were obtained for all new compounds. Optical rotations were taken in chloroform unless otherwise stated.

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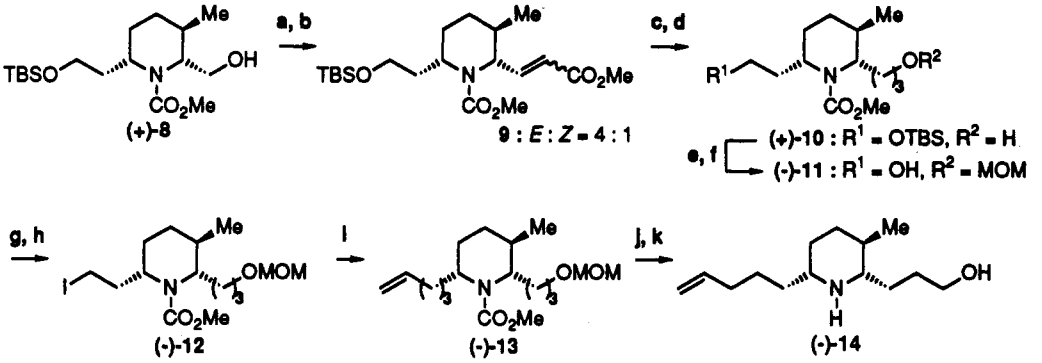
Scheme 4[a]



[a] (a) Swern oxidation; (b) NaH, $(EtO)_2P(O)CH_2CO_2Me$ (90% in two steps); (c) H_2, 5% Pd/C, MeOH; (d) Super-Hydride, rt (91% in two steps); (e) MOMCl, Hünig base (93%); (f) TBAF (95%); (g) MsCl, Et_3N, 0 °C; (h) NaI, acetone (85% in two steps); (i) $CH_2{=}CHCH_2MgCl$, CuI, −30 °C (74%); (j) ^{n}PrSLi, HMPA; (k) concd HCl, MeOH, reflux (65% in two steps).

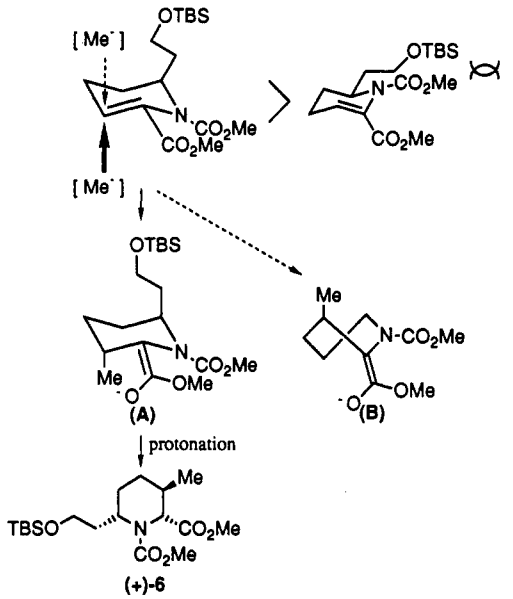


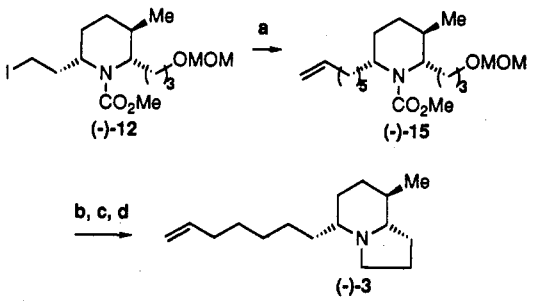
Figure 1.

The stereoselectivity of the above reaction results from the preferred α-axial attack, leading not to the boatlike B but to the chairlike transition state A[9] where the C_6 side chain occupies the quasiaxial orientation owing to $A^{(1,3)}$ strain[10,11] (Figure 1).

The synthesis of alkaloids **1**–**3** was accomplished as follows. The Swern oxidation of (+)-**8** ($[\alpha]^{26}_D$ +17.9) followed by the Wittig–Horner reaction of the resulting aldehyde afforded the α,β-unsaturated ester **9** in 90% overall yield as a 4:1 mixture of the *E* and *Z* isomers. Catalytic hydrogenation of **9** over 5% Pd on carbon at 4 atm and subsequent reduction of the resulting saturated ester with Super-Hydride provided the alcohol (+)-**10** ($[\alpha]^{26}_D$ +21.0) in 91% yield in two steps. Protection of the hydroxyl in (+)-**10** (93% yield, $[\alpha]^{26}_D$ +9.4) followed by deprotection at the C_6-side chain with TBAF gave the alcohol (−)-**11** ($[\alpha]^{26}_D$ −13.8) in 95% yield. The carbon-chain elongation of the ring appendage at C_6 was accomplished by a Grignard cross-coupling reaction involving the treatment of the iodide [(−)-**12**, $[\alpha]^{26}_D$ −22.0], derived from (−)-**11**, with allylmagnesium chloride and CuI at −30 °C, to afford the olefin (−)-**13** ($[\alpha]^{26}_D$ −10.9) in 74% yield with recovery of the starting iodide (13%).

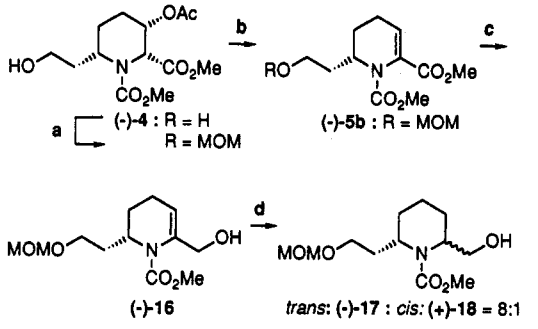
Finally, removal of the methoxycarbonyl in (−)-**13** with

Scheme 5[a]



[a] (a) $CH_2{=}CH(CH_2)_3MgCl$, CuI, −30 °C (82%); (b) ^{n}PrSLi, HMPA; (c) concd HCl, MeOH, reflux; (d) Ph_3P, CBr_4, Et_3N (63% in three steps).

Scheme 6[a]



[a] (a) MOMCl, Hünig base (92%); (b) NaH, DMF:benzene = 2:1, 50 °C (91%); (c) DIBAL, Et_2O, −78 to 0 °C (70%); (d) $NaBH_3CN$, TFA, −42 °C (*trans*, 65%, *cis*, 8%).

(8) The actual coupling constants are as follows: for C_3-H, ddd, J = 10.5, 7.5 4.5 Hz; for $C_{7\beta}$-H, dd, J = 8.5, 7.5 Hz; for $C_{7\alpha}$-H, dd, J = 8.5, 4.5 Hz.

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(11) This case is the first example of the stereocontrol due to the $A^{(1,3)}$ strain at the β position in the α-substituted 1-acyl-Δ^2-piperidine. For the related stereocontrol due to the $A^{(1,3)}$ strain at the α′ position in the α-substituted 1-acylpiperidinium ion, see: Natsume, M.; Sekine, Y.; Ogawa, M.; Soyagimi, H.; Kitagawa, Y. *Tetrahedron Lett.* **1979**, 3473. Comins, D. L.; Foley, M. A. *Tetrahedron Lett.* **1988**, *29*, 6711. Shono, T.; Matsumura, Y.; Onomura, O.; Sato, M. *J. Org. Chem.* **1988**, *53*, 4118. Hanson, G. J.; Russell, M. A. *Tetrahedron Lett.* **1989**, *30*, 5751. Hiemstra, H.; Speckamp, W. N. In *The Alkaloids*; Brossi, A., Ed.; Academic Press, Inc.: San Diego, 1988; Vol. 32, pp 271–339 and references cited therein. For related stereocontrol due to the $A^{(1,3)}$ strain at the α′ position in the α-substituted 1-acyl-4-piperidone, see: Comins, D. L.; Brown, J. D. *Tetrahedron Lett.* **1986**, *27*, 4549. Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445. Comins, D. L.; Dehgani, A. *Tetrahedron Lett.* **1991**, *32*, 5697. Comins, D. L.; Killpack, M. O. *J. Am. Chem. Soc.* **1992**, *114*, 10972. Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* **1993**, *115*, 8851 and references cited therein.

^{n}PrSLi in HMPA,[12] and subsequently the methoxymethyl with acid, furnished the amino alcohol (−)-14 [$[\alpha]^{26}_{D}$ −16.4 (lit.[21] $[\alpha]^{25}_{D}$ −16.5)] in 65% overall yield. The spectral data (IR, ^{1}H, ^{13}C NMR and mass) for the (−)-14 were in agreement with those reported.[21] The transformation of the amino alcohol (−)-14 into (−)-1 and (−)-2 has been reported by Kibayashi[21] (Scheme 4).

Similarly, the iodide (−)-12 was transformed to the olefin (−)-15 ($[\alpha]^{26}_{D}$ −6.5) in 82% yield. Deprotection of the ring nitrogen with ^{n}PrSLi and the C_2-appendage with acid followed by cyclization of the resulting amino alcohol was accomplished according to the Kibayashi protocol[21] to furnish (−)-3 [$[\alpha]^{26}_{D}$ −98.8 (MeOH) (lit.[6a] $[\alpha]^{25}_{D}$ −61 (MeOH)] in 63% overall yield. The spectral data (IR and ^{1}H NMR) for (−)-3 were identical with those of a natural sample[6a] (Scheme 5).

The formal synthesis of (−)-1 and (−)-2 and the first asymmetric total synthesis of (−)-3 were thus achieved, starting with (−)-5a (R = TBS) as a common chiral building block. Our synthesis confirmed the absolute configuration of (−)-3 as depicted in Scheme 5.

We also examined the transformation of (−)-5b (R = MOM, $[\alpha]^{26}_{D}$ −75.2) to the 2,6(*trans*)-disubstitutred piperidine (−)-17. The reduction of (−)-6 (R = MOM) with DIBAL gave the allyl alcohol (−)-16 ($[\alpha]^{26}_{D}$ −147.5) in 70% yield. Reduction of (−)-16 by application of Comins' conditions[13] afforded the *trans* piperidine [(−)-17, $[\alpha]^{26}_{D}$ −23.0] and the *cis* piperidine [(+)-18, $[\alpha]^{26}_{D}$ +11.3][14] in 65% and 8% isolated yields, respectively (Scheme 6). A 2,6(*trans*)-disubstituted piperidine is less accessible than the corresponding *cis* counterpart, so the carbon-chain elongation of the present *trans* system (−)-17 at the 2- or 6-position would arbitrarily be achieved by modification of the hydroxyl functionality to lead to the alkaloid of the *trans*(2,6)-piperidine system.

In summary, we have demonstrated the versatility of the title compound 5 for alkaloid synthesis by the asymmetric synthesis of indolizidines 1–3 and by its transformation into the less accessible 2,6(*trans*)-disubstituted piperidine 17.

Acknowledgment. We are grateful to Professor C. Kibayashi, Tokyo College of Pharmacy, for kindly providing us with ^{1}H and ^{13}C NMR spectra of (−)-14. We are also grateful to Doctor John W. Daly, National Institutes of Health, for kindly providing us with ^{1}H NMR spectra of (−)-3 and of its hydrochloride and an FTIR spectrum.

Supplementary Material Available: General experimental procedures and compound characterization data (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(13) Comins, D. L.; Weglarz, M. A. *J. Org. Chem.* **1991**, *56*, 2506.

(14) The *cis*-2,6-disubstituted piperidine (−)-18 ($[\alpha]^{26}_{D}$ −9.8) has been synthesized in the course of the synthesis of (−)-indolizidine 223AB starting with the asymmetric ring cleavage of the bicyclo[3.3.1]nonan-3-one at the "fork head": Momose, T.; Toshima, M.; Koike, Y.; Toyooka, N. Unpublished data. The spectral data (IR, ^{1}H, ^{13}C NMR and mass) for the *cis*-piperidine (+)-18 were identical with those for the *cis*-piperidine (−)-18.