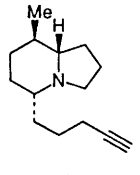
The Total Synthesis of (−)-Indolizidines 205A and 235B[1]

Yuji Shishido and Chihiro Kibayashi*

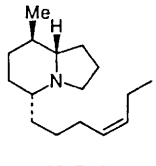
Tokyo College of Pharmacy, Horinouchi, Hachioji, Tokyo 192-03, Japan

The total synthesis of (−)-indolizidines **205A** and **235B**, alkaloids from the arrow poison-frog, *via* a common chiral oxazino-lactam, prepared by an asymmetric intramolecular Diels–Alder reaction of an *N*-acylnitroso intermediate, is described.

Indolizidines **205A**[2] **1** and **235B 2**, a new sub-group of the 5-substituted 8-methylindolizidine from the Panamanian arrow poison-frog *Dendrobates pumilio*, have recently been described by Tokuyama, Daly and coworkers.[3] The assigned relative stereochemistry of these indolizidines has been confirmed recently by the synthesis of their racemates carried out by Holmes *et al.*[4] On continuation of our studies on developing synthetic entries into optically active dendrobatid alkaloids,[5] we report herein the first chiral synthesis of (−)-indolizidines **205A** and **235B** from a common chiral intermediate. The key step of this approach is an asymmetric nitroso Diels–Alder reaction.



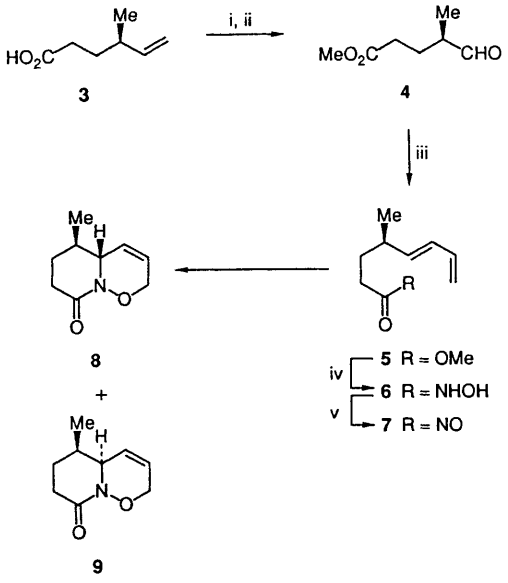
205A 1



235B 2

Based upon our earlier work[6] we envisaged examining a [4 + 2] intramolecular cycloaddtion reaction using a chiral *N*-acylnitroso intermediate (Scheme 1). Toward this end (*R*)-4-methylhex-5-enoic acid **3**, prepared from (*R*)-citronellol according to known procedures,[7] was converted to the aldehyde **4**† *via* esterification (CH_2N) followed by ozonolysis in 67% overall yield. Wittig condensation (CH_2=CHCH=PPh_3) of **4** afforded the diene **5** (41% yield) including the (5*Z*)-isomer; the *E*/*Z* mixture was converted to the single (5*E*)-isomer **5** by photoisomerization. Compound **5** was converted to the hydroxamic acid **6** in 79% overall yield by a sequential procedure involving alkaline hydrolysis, chlorination of the resulting carboxylic acid and treatment with hydroxylamine. Oxidation of **6** with tetrapropylammonium periodate at 0 °C generated the *N*-acylnitroso compound **7** *in situ*, which

† All new compounds reported exhibited spectroscopic data consistent with their proposed structures, and were characterised by elemental analysis and/or high resolution mass spectra.

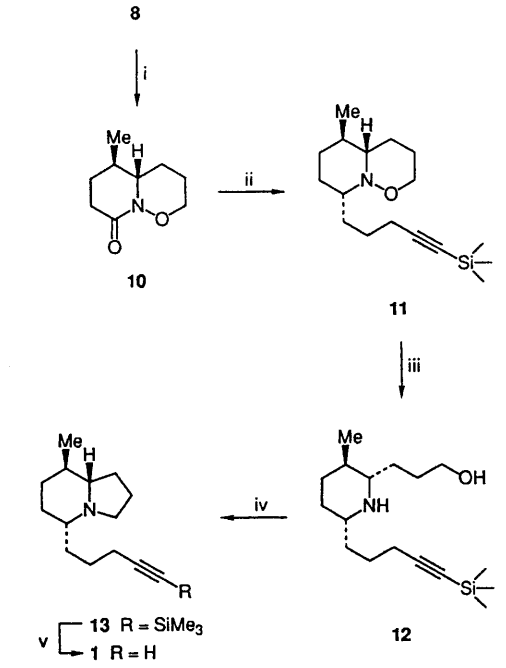


Scheme 1 *Reagents and conditions*: i, CH_2N_2, Et_2O; ii, O_3, $NaHCO_3$, MeOH, −65 °C, then Me_2S, room temp.; iii, $CH_2{=}CHCH_2PPh_3Br$, Bu^nLi, Et_2O, 0 °C → room temp., then *hv*, I_2, tetrahydrofuran (THF); iv, (*a*) KOH, H_2O–EtOH; (*b*) $(COCl)_2$, CH_2Cl_2, then $NH_2OH{\cdot}HCl$, aq. Na_2CO_3, $CHCl_3$; v, $(Pr^n)_4NIO_4$, $CHCl_3$, 0 °C

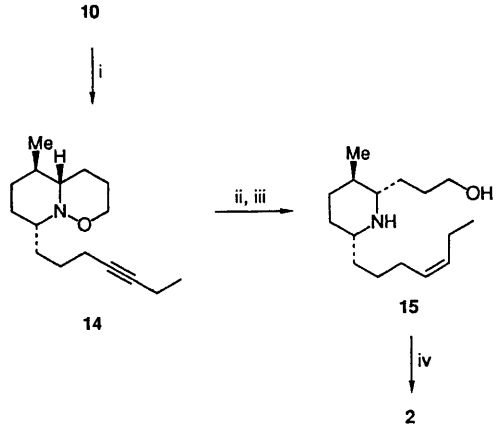
smoothly underwent [4 + 2] cycloaddition to yield a 1.8:1 mixture (88% yield) of the bicyclic *trans*- and *cis*-oxazinolactams **8** and **9** in favour of desired **8**, which was separated by chromatography and recrystallization. The relative stereochemistry of **8** was assigned by ^1H NMR analysis‡ of its dihydro derivative **10**, obtained by hydrogenation (Scheme 2).

The introduction of the alkyl side chain was accomplished with full stereochemical control by using **10**. Thus, compound **10** was subjected to Grignard reaction [$Me_3SiC{\equiv}C(CH_2)_3MgBr$] followed by $NaBH_4$ reduction under the acidic conditions (AcOH) as shown in Scheme 2. This was performed in one pot and resulted in **11**‡ as a single isomer in 65% overall yield from **10**. Reductive cleavage of the N–O bond by treatment with zinc and aqueous acetic acid gave **12** in 90% yield. Intramolecular cyclization proceeded smoothly by exposure of **12** to PPh_3 and CBr_4 in CH_2Cl_2 (0 °C, 30 min) followed by treatment with Et_3N, affording **13** in 73% yield. Subsequent desilylation (aq. KOH–MeOH) of **13** provided (−)-indolizidine **205A 1** in 77% yield. Synthetic **1** exhibited ^1H and ^{13}C NMR spectra identical with those of natural **205A**[3] and those reported[4a] for the synthetic racemate of **205A**, and had $[\alpha]_D^{20}$ −74.2° (*c* 0.82, MeOH) {lit.[3] $[\alpha]_D$ −35°(*c* 0.24, MeOH)}. These results establish the absolute configuration of the natural enantiomer of **205A** as 5*R*,8*R*,8a*S* **1**.

With the key intermediate **10** prepared, we next envisaged application of the above methodology to the synthesis of **235B**



Scheme 2 *Reagents and conditions*: i, H_2, Pd–C, MeOH; ii, $Me_3SiC{\equiv}C(CH_2)_3MgBr$, Et_2O, then $NaBH_4$, AcOH; iii, Zn, aq. AcOH, THF; iv, PPh_3, CBr_4, CH_2Cl_2, then Et_3N; v, aq. KOH, MeOH

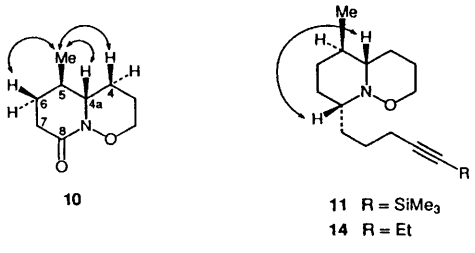


Scheme 3 *Reagents and conditions*: i, $CH_3CH_2C{\equiv}C(CH_2)_3MgBr$, THF, then $NaBH_4$, AcOH; ii, H_2, Lindlar catalyst, quinoline, MeOH; iii, Zn, aq. AcOH, THF; iv, PPh_3, CBr_4, CH_2Cl_2, then Et_3N

2 as outlined in Scheme 3. Thus, **10** was converted to **14** (70%)‡ as a single isomer in one pot by tandem treatment with the Grignard reagent [$MeCH_2C{\equiv}C(CH_2)_3MgBr$] and $NaBH_4$ in AcOH. Lindlar hydrogenation followed by reductive N–O bond cleavage (Zn, aq. AcOH) afforded **15** in 87% overall yield, which was converted to (−)-indolizidine **235B 2** in 70% yield by treatment with PPh_3–CBr_4 followed by Et_3N. Synthetic **2** showed ^1H and ^{13}C NMR spectra in full accordance with those of natural **235B**[3] and those reported[5b] for the synthetic racemate of **235B**, however, the observed optical rotation for our synthetic material {$[\alpha]_D^{28}$ −85.4° (*c* 0.79, MeOH)} was found to be quite different from that reported[3] for the natural sample of **235B** {$[\alpha]_D$ +11.3° (*c* 1.0, MeOH)}.

As described above in this paper, indolizidine **205A 1** possessing the natural configuration (5*R*,8*R*,8a*S*) is laevorotatory. In addition, congeneric indolizidine **235B′**, recently isolated from *D. speciousus*, is also found to be laevorotatory {$[\alpha]_D^{25}$ −61° (*c* 0.5, MeOH)}.[8] Recently, indolizidine **209B** with the 5*R*,8*R*,8a*S* configuration has been synthesized by Holmes *et al.*[4a] and found to be laevorotatory {$[\alpha]_D^{20}$ −94.3° (*c* 1.85, MeOH)}. All these facts strongly suggest that, in

‡ The relative configurations of the alkyl substitutents at 4a and 5 positions for **10** and at 4a and 8 positions for **11** and **14** were established by NOE measurements in their 500 MHz ^1H NMR spectra. The NOE interactions are depicted as below. The *trans* stereochemistry of **10** was also confirmed by the coupling constants (8.2 Hz) with axial H-4a and H-5.



general, the naturally occurring 5-substituted 8-methylindolizidine congeners including **235B** should have the 5*R*,8*R*,8a*S* configuration and be laevorotatory.[9] The apparent discrepancy in the optical rotation data observed for our synthetic **2** and that reported[3] for the natural sample seems rather surprising, and it appears that the further investigation is needed of the natural material of indolizidine **235B**.

In conclusion, our synthesis based on the asymmetric nitroso Diels–Alder reaction demonstrates a versatile protocol for the chiral entry to the 5-substituted 8-methylindolizidine class of dendrobatid alkaloids which should be applicable to other natural congeners.

We are grateful Dr J. W. Daly (National Institutes of Health) for valuable information on natural 5-substituted 8-methylindolizidines and to Dr A. B. Holmes (University of Cambridge) for spectra of synthetic 5-substituted 8-methylindolizidines. This work was supported in part by a Grant-in-Aid for Scientific Research (No. 01571167) from the Ministry of Education, Science and Culture, Japan (to C. K.).

Received, 15th February 1991; Com. 1/00735A

References

1 This work was presented at the 109th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April, 1989; Abstracts of Papers, part 2, p. 25; and at the 15th Symposium on Progress in Organic Reactions and Syntheses, Kobe, December, 1989; Abstracts of Papers, p. 79.

2 For identification of dendrobatid alkaloids, bold face numerical designations based on molecular weight with additional identifying letter(s) have been proposed by Daly (J. W. Daly, G. B. Brown, M. Mensah-Dwumah and C. W. Myers, *Toxicon*, 1978, **16**, 163; J. W. Daly, in *Progress in the Chemistry of Organic Natural Products*, eds. W. Herz, H. Grisebach and G. W. Kirby, Springer-Verlag, Vienna, 1982, vol. 41, pp. 205–340).

3 T. Tokuyama, N. Nishimori, A. Shimada, M. W. Edwards and J. W. Daly, *Tetrahedron*, 1987, **43**, 643.

4 (*a*) A. L. Smith, S. F. Williams, A. B. Holmes, L. R. Hughes, Z. Lidert and C. Swithenbank, *J. Am. Chem. Soc.*, 1988, **110**, 8696; A. B. Holmes, A. L. Smith, S. F. Williams, L. R. Hughes, Z. Lidert and C. Swithenbank, *J. Org. Chem.*, 1991, **56**, 1393; (*b*) I. Collins, M. E. Fox, A. B. Holmes and S. F. Williams, *J. Chem. Perkin Trans. 1*, 1991, 175.

5 (*a*) N. Yamazaki and C. Kibayashi, *J. Am. Chem. Soc.*, 1989, **111**, 1396; (*b*) N. Machinaga and C. Kibayashi, *Tetrahedron Lett.*, 1990, **31**, 3637; (*c*) N. Machinaga and C. Kibayashi, *J. Org. Chem.*, 1991, **56**, 1386; (*d*) N. Machinaga and C. Kibayashi, *J. Chem. Soc., Chem. Commun.*, 1991, 405.

6 (*a*) H. Iida, Y. Watanabe and C. Kibayashi, *J. Am. Chem. Soc.*, 1985, **107**, 5534; (*b*) Y. Watanabe, H. Iida and C. Kibayashi, *J. Org. Chem.*, 1989, **54**, 4088.

7 G. J. Cernigliaro and P. J. Kocienski, *J. Org. Chem.*, 1977, **42**, 3622; D. R. Williams, B. A. Barner, K. Nishitani and J. P. Phillips, *J. Am. Chem. Soc.*, 1982, **104**, 4708.

8 M. W. Edwards, J. W. Daly and C. W. Myers, *J. Nat. Prod.*, 1988, **51**, 1188.

9 Laevorotatory enantionmers of other natural 5-substituted 8-methylindolizidines **207A** and **209B** both possessing the 5*R*,8*R*,8a*S* configuration have been synthesized in this laboratory, which will be reported in due course.