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A concise asymmetric synthesis of 5,8-disubstituted indolizidine alkaloids. Total synthesis of (−)-indolizidine 209B

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Abstract—A general access to 5,8-disubstituted indolizidine alkaloids has been developed, where the asymmetric addition of an optically active allenyltitanium to benzyl[4-(*tert*-butyldimethylsilyloxy)butylidene]amine (**2**) is the key reaction. As a typical example, (−)-indolizidine **209B** was efficiently synthesized in 40% overall yield in a five-step reaction starting from readily available (*S*)-1-methyl-3-trimethylsilylprop-2-ynyl phosphate (**1**). © 2002 Elsevier Science Ltd. All rights reserved.

5,8-Disubstituted indolizidine alkaloids, such as (−)-**209B**, (−)-**235B** and (−)-**205A** (Fig. 1), have been isolated from the skin of poison frogs of the Dendrobatidae family. Due to the extreme scarcity of these alkaloids from natural sources and their potent biological activities in neuroscience,[1] considerable attention has been paid to the chemical synthesis of these indolizidines.[2] In line with our continuing interest in synthesizing dendrobatid alkaloids,[3] we report herein a new and concise enantioselective synthesis of 5,8-disubstituted indolizidine alkaloids.

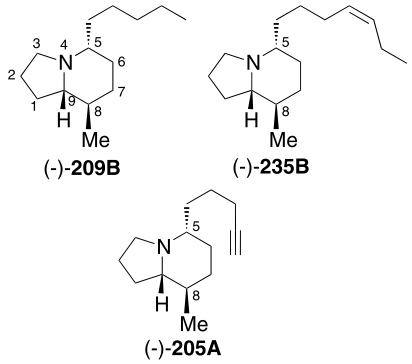

Figure 1.

Recently, we have reported a facile generation of optically active allenyltitaniums from readily accessible optically active secondary propargyl phosphates and a Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl reagent, which proceeds with >97% chirality transfer.[4,5] We expected that the reaction of the optically active allenyltitanium with an imine could construct the key consecutive chiral centers at the 8- and 9-positions of the indolizidine structure with correct relative and absolute stereochemistries,[6] thus providing a new efficient entry to 5,8-disubstituted indolizidines.

The allenyltitanium, prepared from (*S*)-1-methyl-3-trimethylsilylprop-2-ynyl phosphate (**1**) with 97.8% e.e.[7] and Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl, reacted smoothly with benzyl[4-(*tert*-butyldimethylsilyloxy)butylidene]amine (**2**) to afford the desired product *anti*-**3** and its diastereomer *syn*-**3** in 87% total yield with a ratio of 9:1 (Scheme 1).[8,9] The enantiomeric excess (e.e.) of the major diastereomer *anti*-**3** was determined to be >95% by ^{1}H NMR analysis after derivatization to the corresponding (*R*)- and (*S*)-2-methoxy-2-trifluoromethyl-2-phenylacetyl (MTPA) ester **8** by conventional reactions shown in Scheme 2.[10]

The inseparable diastereomeric mixture of **3** thus produced was desilylated with tetrabutylammonium fluoride to give compound **4** in 89% yield, which in turn was cyclized to pyrrolidine **5** in 91% yield by treatment with 1.5 equiv. of PPh_3 and 2 equiv. of imidazole in CCl_4. The diastereomeric ratio of **5** was found to be 89:11 by GC analysis. Compound **5** was then reacted successively with *n*-BuLi and *N*-methoxy-*N*-methylhexanoamide to afford relatively unstable ynone **6**. Upon

Keywords: indolizidine alkaloid; asymmetric addition; chiral allenyltitanium; imine.

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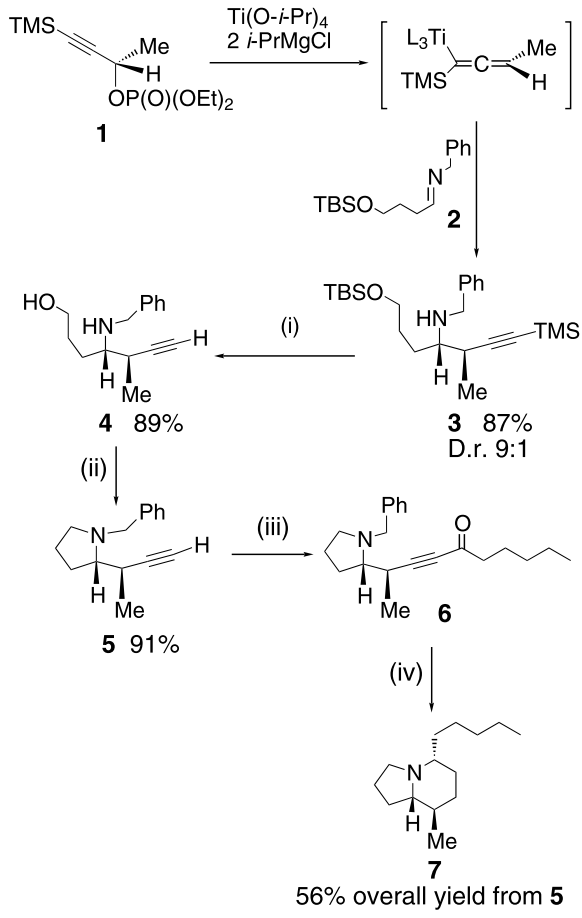
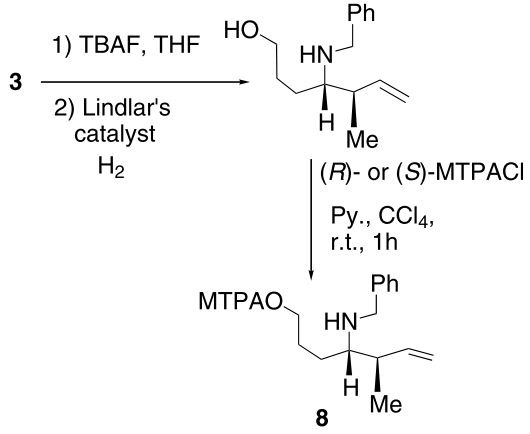


Scheme 1. *Reagents and conditions*: (i) TBAF, THF; (ii) PPh_3 (1.5 equiv.), imidazole (2 equiv.), CCl_4, reflux, 12 h; (iii) *n*-BuLi (1.1 equiv.), −78°C (2 h), then *N*-methoxy-*N*-methylhexanoamide (1.5 equiv.), −78 to 0°C; (iv) Pd/C (10%), H_2, MeOH, 12 h.



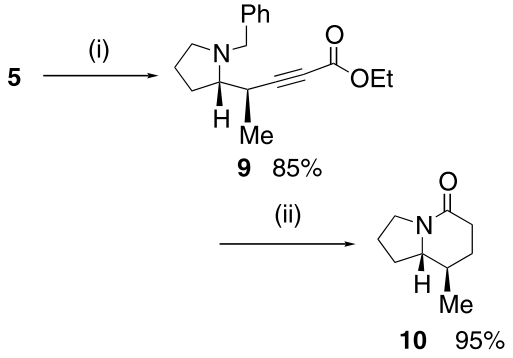
Scheme 2.

purification through a short column (silica gel), **6** was immediately subjected to hydrogenation over Pd/C in methanol. From the reaction mixture, (−)-indolizidine **209B** (**7**)[11] and its diastereomer (8-*epi*-**7** or *ent*-8-*epi*-**7**)[12] were isolated by column chromatography [silica gel, triethylamine: hexane (1:50) then triethylamine:ether:hexane (1:5:50)] in 56 and 6% yield, respectively. It should be noted that their corresponding 5-epimers were not detected, which indicates that the reaction proceeds with complete diastereoselectivity.[13] Thus, total synthesis of (−)-indolizidine **209B** was efficiently achieved in 40% overall yield in a five-step reaction starting from the readily accessible optically active secondary propargyl phosphate **1**.

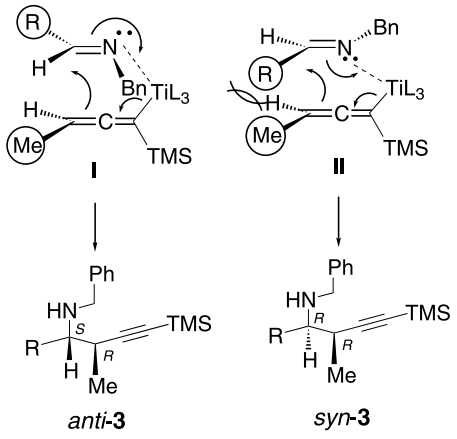
With the above approach, other indolizidine alkaloids having an alkyl substituent at the 5-position might be efficiently prepared by choosing a proper *N*-methoxy-*N*-methylalkanoamide instead of *N*-methoxy-*N*-methylhexanoamide for the conversion of **5** to **6** shown in Scheme 1. However, indolizidines with unsaturated substituents at this position, such as (−)-**235B** and (−)-**205A**, could not be accessible by this method due to the involvement of the hydrogenation step. We therefore prepared (8*R*,9*S*)-(−)-hexahydro-8-methyl-5-indolizinone (**10**), which is the known precursor for synthesizing 5,8-disubstituted indolizidines including those having unsaturated substituents at the 5-position,[14] as shown in Scheme 3. The acetylide generated from **5** and *n*-BuLi was treated with ethyl chloroformate to give unsaturated ester **9** in 85% yield. Subsequent hydrogenation of **9** over Pd/C gave (−)-**10** as a white solid in almost quantitative yield.[15] Although we could not separate (−)-**10** and its diastereomer (8-*epi*-**10** or *ent*-8-*epi*-**10**), 5,8-disubstituted indolizidines prepared from which might be obtained in pure form by column chromatography, as observed in the synthesis of (−)-indolizidine **209B** mentioned above.

The reaction of a racemic allenyltitanium with imines, which predominantly affords the *anti*-products, has been reported by Yamamoto et al., and they proposed that the reaction proceeds predominantly via the transition state I shown in Scheme 4 rather than the transition state II, which is destabilized by the steric repulsion between the Me and R groups.[6] The stereochemical outcome of the addition of the optically active allenyltitanium with the imine mentioned above could be elucidated by this rationale.

In conclusion, an efficient entry to optically active 5-substituted-8-methylindolizidine alkaloids has been developed starting from readily available optically



Scheme 3. *Reagents and conditions*: (i) *n*-BuLi (1.1 equiv.), −78°C (2 h), then ethyl chloroformate (1.5 equiv.), −78 to 0°C; (ii) Pd/C (10%), H_2, MeOH, 12 h.



Scheme 4.

active secondary propargyl phosphate **1**, where the asymmetric addition of the optically active allenyltitanium to the imine **2** is the key reaction. It should be noted that, in addition to indolizidines with an 8-methyl substituent, the present method is applicable to indolizidines with other alkyl substituents at this position using the corresponding optically active 1-alkyl-3-trimethylsilylprop-2-ynyl phosphate as the starting compound.

Acknowledgements

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7. Compound **1** was prepared in 60% overall yield from methyl (*S*)-lactate in a five-step reaction. See Refs. 4a and 4c for the synthesis and the determination of optical purity.
8. The reaction proceeded with somewhat lower diastereoselectivity than that reported by Yamamoto (see Ref. 6), which is probably due to the presence of the silyloxy group in the imine substrate and/or the differences in the reaction conditions, such as the solvent and the presence of magnesium salt resulted in the process of formation of the allenyltitanium.
9. Procedure: To a solution of **1** (765 mg, 2.75 mmol) and Ti(O-*i*-Pr)$_4$ (1.01 mL, 3.44 mmol) in dry diethylether (15 mL) was added *i*-PrMgCl (5.1 mL, 1.35 M in ether) dropwise at −50°C and the solution was stirred at −50 to −40°C for 1.5 h. Imine **2**, freshly prepared from 4-(*tert*-butyldimethylsilyloxy)-butanal (444 mg, 2.2 mmol) and benzylamine (236 mg, 2.2 mmol) in the presence of anhydrous $MgSO_4$ (1.2 g), was then added to the above allenyltitanium solution and the reaction mixture was allowed to warm to 0°C. After stirring at this temperature for 1 h, aqueous saturated $NaHCO_3$ (2 mL) was added to quench the reaction followed by solid NaF (2 g) and Celite (1 g). Upon filtrating off the precipitate, the filtrate was concentrated and purified by column chromatography (silica gel, ether:hexane 1:5) to afford **3** as a pale yellow oil (800 mg, 87%).
10. The overall chirality transfer from **1** to *anti*-**3** is calculated to be >97% based on the e.e. value of **1**. As the chirality transfer from **1** to the allenyltitanium is >97% (see Ref. 4), it is therefore inferred that the reaction of the allenyltitanium with imine **2** proceeds with almost complete chirality transfer.
11. The ^{1}H and ^{13}C NMR spectra of (−)-**7** were identical to those reported in the literature (Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543); $[\alpha]_D^{27} = -93.3$ (*c* 0.85, MeOH) (lit. $[\alpha]_D^{21} = -87.7$ (*c* 1.26, MeOH)).
12. The ^{1}H and ^{13}C NMR spectra of the minor product were identical to those of (±)-8-*epi*-indolizidine **209B** reported in the literature (Michael, J. P.; Gravestock, D. *Synlett* **1996**, 981). Its absolute configuration was not determined.
13. The reaction might proceed successively through saturation of the triple bond, debenzylation, intramolecular condensation of the resulting secondary amine with the ketone moiety to an iminium intermediate, and its diastereoselective reduction to give **7**. Highly diastereoselective reduction of the iminium intermediate to afford indolizidines has been reported, see: Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398 and references cited therein.
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15. The product contained about 10% 8-*epi*-**10** or *ent*-8-*epi*-**10**. The ^{1}H and ^{13}C NMR spectra of the major diastereomer (−)-**10** were identical to those reported in Ref. 14a.