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Synthesis of dendrobatid alkaloid (+)-167B and (+)-209D and the investigation of diastereoselectivity using DFT calculations†

Wen-Hua Chiou* and Hao-Yu Chen

The synthesis of dendrobatid alkaloid (+)-167B and (+)-209D has been developed on the basis of the effective preparation of chiral tropinone 7-azabicyclo[3.2.1]octan-6-ol. DFT calculations have been applied to explain the observed diastereoselectivity.

Recently, indolizidine alkaloids commonly found in amphibian skin have received a great deal of attention due to their medicinal interest and diverse physiological properties.[1] These indolizidine alkaloids isolated from the dendrobatid family were found to be noncompetitive blockers of the neuromuscular transmission receptor and nicotinic acetylcholine receptors, which allowed these compounds to be promising drug candidates for epilepsy, schizophrenia, Parkinson disease and Alzheimer disease.[2,3] Since Daly's pioneering work in the 1970s, numerous valuable indolizidines with interesting structures have been isolated from poison-dart frogs,[4,5] and 5-mono, 3,5-di-substituted or 3,5-di-substituted indolizidines occupy a large portion of the discovered structures.[6,7] (Fig. 1). Accordingly, novel strategies for the asymmetrical synthesis of these azabicycles continue to receive considerable attention from the synthetic community.[8] As part of our interests in the synthesis of the dendrobatid alkaloids,[9] we wish to demonstrate a general and efficient protocol to prepare these alkaloids. Here we report syntheses of (+)-167B and (+)-209D as an application of our efficient preparation of enantiomerical tropanol, and a rationale of the observed diastereoselectivity using the DFT calculations.

Our approach to indolizidine 209D and 167B relies on efficient preparation of enantiopure 7-benzyloxycarbonylazabicyclo-[3.2.1]octan-6-one (**1**), readily available in both dextrorotatory and levorotatory forms by diastereomeric recrystallization of 7-azabicyclo[3.2.1]octan-6-ol with tartaric acid, and then protection of the free amine and subsequent oxidation of the hydroxyl group on basis of our previous progress (~20% overall yield after 3 steps and resolution).[10] The process proved to be an effective and reliable procedure for multi-gram scale production of enantiopure 7-azabicyclo[3.2.1]octan-6-ol with excellent chiral integrity. Bicyclic ketone **1** was subjected to Baeyer-Villiger oxidative ring expansion with *m*-CPBA in dichloromethane to give bicyclic (−)-lactone **2**, which was a quite unstable substance in either acidic or oxidative conditions. Treatment of crude lactone **2** with a mixture of $BF_3 \cdot OEt_2$ and trimethylallylsilane resulted in cleavage of the oxabicyclic ring and formation of a transient *N*-acyl iminium ion which was captured by trimethylallylsilane, affording a 2,6-disubstituted piperidine **3** as a single diastereomer in 84% yield over two steps. The relative stereo configuration would be determined in the latter stage by comparison with known structures because the nOe signals of two key methines in piperidine **3** were so ambiguous (*vide infra*). Lactone **2** was a useful intermediate for

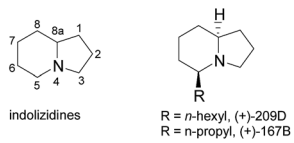
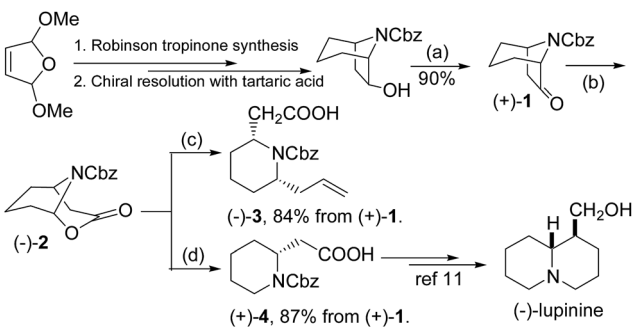


Fig. 1 Substituted structure and numbering of indolizidines.



Scheme 1 Preparation of *cis*-2,6-disubstituted piperidine and piperidinyl acetic acid from chiral 6-tropanol derivative. (a) TEMPO, NaOCl, KBr, $NaHCO_3$, acetone, 0 °C. (b) mCPBA, Na_2HPO_4, CH_2Cl_2, rt. (c) BF_3–Et_2O, $Me_3SiCH_2CH{=}CH_2$, CH_2Cl_2, −78 °C. (d) BF_3–Et_2O, Et_3SiH, CH_2Cl_2, −78 °C.

Department of Chemistry, National Chung Hsing University, Taichung, Taiwan, 402, ROC. E-mail: wchiou@dragon.nchu.edu.tw; Fax: +886-4-22862547; Tel: +886-4-22840411-420

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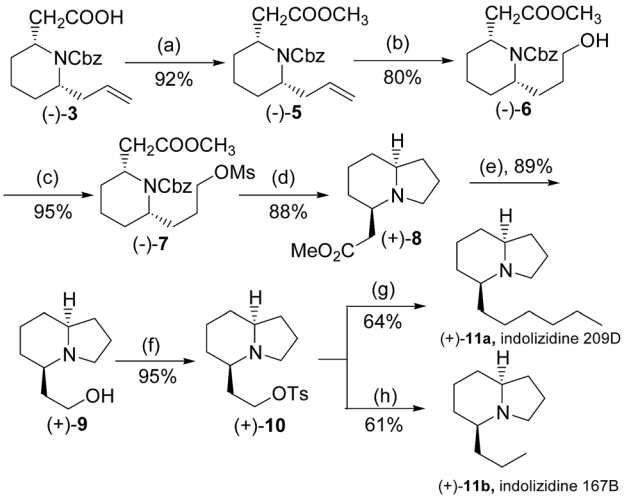
syntheses of piperidine or quinolizidine compounds. For example, treatment with triethylsilane in the conditions would produce homopipecolic acid **4**, which can be converted to (−)-lupinine, a quinolizidine alkaloids, according to the Davies's procedure.[11] Here we would like to point out that enantiomerically pure 2,6-disubstituted piperidine **3** would be a versatile building block for syntheses of indolizidine or quinolizidine compounds, due to the two differential side chains for further construction of the second ring moiety (Scheme 1).

To complete the synthesis of the target molecules, treatment of acid **3** with $SOCl_2$ in cold methanol resulted in the formation of methyl ester **5** in 92% yield. The allyl portion of **18** was converted to a linear alcohol group using the modified Kabalka's hydroboration–oxidation procedure,[12] *i.e.* sodium perborate, to furnish alcohol **6** in 80% overall yield. The temperature control was critical in this reaction. If the reaction temperature was higher, *i.e.* 0 °C, it would resulted in yield loss to 40%, probably due to the reduction of the ester moiety.[13] Alcohol **6** was reacted with MsCl in the presence of Et_3N in dichloromethane to produce mesylate **7**, which was treated under ambient hydrogen pressure to remove the benzyl group, and initiated cyclization to yield indolizidine **7** in 88% yield. Having achieved the synthesis of the crucial indolizidine intermediate **7**, we continued to use the product to complete the syntheses of 209D and 167B. Reduction of ester **8** group with $LiAlH_4$ yielded 89% yield of primary alcohol **9**, which was further converted to the corresponding tosylate **10** in 92% yield. The resulting tosylate **10** was alkylated with dibutylcyanocuprate, a high order cyanocuprate prepared by treatment of cupper cyanide with two-fold butylithium, to furnish butylated product **11a** in 64% yield. The ^{13}C signals of **11a** were identical to the reported values of *cis*-(5*R*,8*aS*)-5-hexyl-indolizidine,[14] while the specific rotation of the compound ($[\alpha]_D^{25}$ +92.6° (*c*: 1.0, CH_2Cl_2), literature value: +86.6° (*c*: 1.3, CH_2Cl_2)) also compared favourably.[15] Similarly, tosylate **10** was also reacted with dimethylcyanocuprate to produce the product **11b** in 61% yield, in which the ^{13}C signals and the specific rotation of **11b** were consistent with the reported values of *cis*-(5*R*,8*aS*)-5-propyl indolizidine[16] ($[\alpha]_D^{25}$ +115.0° (*c*: 1.3, CH_2Cl_2), literature value for its enantiomer: −111.3° (*c*: 1.3, CH_2Cl_2)) (Scheme 2).[15]

To explain the resulting stereochemistry outcome, we propose the addition proceeded in a two-step manner.[17] BF_3-mediated coordination on the lactone moiety immediately results in the ring cleavage, and therefore the formation of the transient *N*-acyliminium intermediate. Subsequent silane addition on the intermediate furnishes the *cis*-2,6-disubstituted piperidine stereoselectively. First of all, we consider the prototype reaction in which trimethylallylsilane reacts on a substituent-free *N*-methoxycarbonyl Δ^1-piperideinium. Trimethylallylsilane may take either axial or equatorial approach to react on the piperideinium bearing either *s-trans* or *s-cis* configuration, which is achieved by rotation of the carbamate bond.[18] Thus, we perform the DFT calculations at the level of B3LYP/6-31++G (d, p) to obtain all four possible TS geometries during the silane addition (Fig. 2).

The results in Table 1 have disclosed the stabilities of these four transition states appear to be concerned with the



Scheme 2 Synthesis of indolizidine 167B and 209D. (a) $SOCl_2$, MeOH, 0 °C. (b) (i) BH_3–THF, THF, −50 °C, (ii) $NaBO_3$, H_2O, rt. (c) MsCl, Et_3N, CH_2Cl_2, rt. (d) Pd/C, H_2, Et_3N, MeOH, rt. (e) $LiAlH_4$, THF, rt. (f) TsCl, Et_3N, CH_2Cl_2, rt. (g) CuCN, MeLi, Et_2O, 0 °C. (g) CuCN, *n*-BuLi, Et_2O, −78 °C.

piperideinium conformations and electrostatic attractions between two major dipoles, the iminium and the carbonyl groups. The *s-cis*-configuration guarantees best coulombic attraction by disposing the most positive iminium carbon atom (C-2) as close in space to the most negative carbonyl oxygen atom (O-1) as possible.[19] In addition, with a pseudo-chair conformation, $TS_{ax\text{-}cis}$ and $TS_{ax\text{-}trans}$ structures involved with the axial approach are more stable than $TS_{equ\text{-}cis}$ and $TS_{equ\text{-}trans}$ which bears with a twist boat conformation. In fact, the conformation distortion can be best characterized and evaluated by the dihedral angle ϕ_1, the angle of the iminium hydrogen and the equatorial hydrogen at the C-3 position (Table 1). Severe deviation from the typical *gauche* angle (∼60°) is noticed ($\Delta\phi_1 \sim 45°$) and strong eclipsing interaction is also

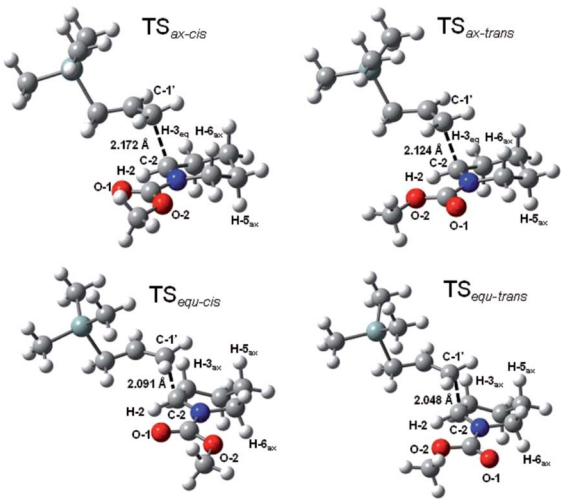


Fig. 2 Four TS geometries describing axial and equatorial silane additions on *N*-methoxycarbonylpiperidenium with *s-cis* and *s-trans* configuration.

Table 1 Relative energies, imaginary frequency, dihedral angle and distance in four TS geometries[a]

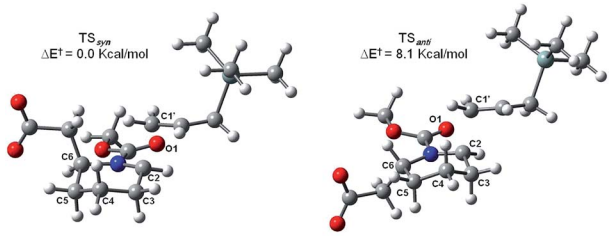
	Rel *E*	Imag *ν*	ϕ_1	C_2–$C_{1'}$
$TS_{ax\text{-}cis}$	0.0	208	55.0	2.172
$TS_{ax\text{-}trans}$	+ 2.3	232	54.5	2.174
$TS_{equ\text{-}cis}$	+ 3.0	246	15.2	2.091
$TS_{equ\text{-}trans}$	+ 5.8	259	15.8	2.048

[a] Energy in kcal mol^{-1}, imagine frequency in cm^{-1}, ϕ_1 is the dihedral angle $\angle H_2$–C_2–C_3–H_{3equ}, distance in Å.

expected. A large angle deviation implies a local eclipse conformation, and naturally results in a relative unstable twist boat conformation, while a small deviation ensures a stable pseudo-chair conformation. Thus, we conclude that the axial addition on the *s-cis*-carbamate substrate dominates among these four possible reaction routes since the $TS_{ax\text{-}cis}$ is the most stable among the four possible transition state geometries. It is worthy to point out that the electrostatic interactions and the ring conformations seem to contribute roughly equally in the stabilities of these transition states, and a longer reaction distance in the transition state geometries will be allowed in case of that either beneficial factor is hold.

Next, we consider two possible *syn* and *anti* approach in the axial addition manner on the *Z-N*-methoxycarbonyl Δ^1-piperideinium bearing an acetic group at the C-6 position on the basis of the favored transition state $TS_{ax\text{-}Z}$, and obtain two TS structures TS_{syn} and TS_{anti} which lead the *cis*- and *trans*-2,6-disubstituted adduct respectively (Fig. 3). The results show the TS_{syn} is favoured over TS_{anti} by 8.1 kcal mol^{-1}, indicating the silane addition prefers to proceed in "*syn* addition" to yield the *cis*-2,6-disubstituted adduct.

In the TS_{syn} structure, the piperideinyl ring with the axial substituent on the C-6 position keeps a less strained conformation because of small deviations from the parent structure



	TS_{syn}	TS_{anti}	$TS_{ax\text{-}Z}$
rel E	0.0	8.1	-------
C_2-$C_{1'}$	1.951	1.870	2.172
ϕ_1	59.5	55.3	55.0
ϕ_2	162.2	144.1	168.2
ϕ_3	2.7	15.0	0.5
ϕ_4	176.7	161.8	179.6

Fig. 3 *syn* and *anti* approach TS geometries with axial silane addition on 6-substituted *N*-methoxycarbonyl Δ^1-piperideinium. Energy in kcal mol^{-1}, distance in Å, ϕ_1: $\angle H_2$–C_2–C_3–H_{3equ}, ϕ_2: $\angle C_{5ax}$–C_5–C_6–C_{6ax}, ϕ_3: $\angle C_2$–N–C═O_1, ϕ_4: $\angle C_2$–N–C–OMe.

($\Delta\phi_2 = 6°$). In addition, analysis of the TS_{syn} structure reveals good planar geometry in the carbamate group ($\phi_3 = 2.7°$ and $\phi_4 = 176.7°$), suggesting the double bond character in the carbamate remains nearly intact during silane approaching. The distortion of the piperideinium ring is best illustrated by dihedral angle ϕ_2, the angle of the two axial substituents at the C-5 and C-6 position, while dihedral angle ϕ_3 and ϕ_4 are used to describe the planarity of the carbamate. Since the *syn* approach to the *cis*-2,6-disubstituted piperidine adduct does not distort either the planarity or the ring conformation, a long distance between $C_{1'}$–C_2 in transition state has been allowed. Comparing to the TS_{syn} geometry, the TS_{anti} geometry shows that the *anti* addition does not only alter the dihedral angle ϕ_2 to 144 degree, but also change the dihedral angle ϕ_4 to 162 degree, significantly attenuate the planarity of the carbamate group ($\phi_3 = 15.0°$ and $\phi_4 = 161.8°$) and twist the conformation of the Δ^1-piperideinium ring to suffer more strain compared to that in the non-substituent case ($\Delta\phi_2 = 24.1°$). Both the piperideinyl moiety and the carbamate moiety need to be distorted to accommodate the equatorial substituent as the *anti* approach progressed. Thus, *anti* addition will result in the instability of the corresponding transition state, and the absence of the 2,6-*trans* product. The traditional explanation argues that a stable reactant conformation dominates stereo outcome: since the $A^{1,3}$-strain exerted from a substituent on the nitrogen has imposed an pseudoaxial orientation on the C-6 substituent as a stable reactant conformation, only an nucleophilic addition is only allowed from the least hindered face, *i.e.* an axial addition, to afford the *cis*-2,6-disubstituted product.[20]

Our calculations provide different perspectives, in which the stable transition state is crucial to determine the possible reaction routes. Three major factors, distortion in the ring conformation, intactness of carbamate planarity and electrostatic attraction, contribute to the stabilities of the transition states and dominate the silane addition to proceed in the *syn*-approach on the C-6 substituted Δ^1-piperideinium with *s-cis*-carbamate configuration in the axial manner.

In conclusion, we have presented syntheses of two dendrobated alkaloids, (+)-indolizidine 209D and (+)-indolizidine 167B, featuring applications of readily available enantiomerical 6-tropinonol to the 2,6-disubstituted piperidines and 5-substituted indolizidines *via* Baeyer-Villiger oxidation. The DFT results described above provides a transition state-based rationale of the observed *cis*-selectivity for the formation of only *cis*-2,6-disubstituted piperidine product. Further applications to interesting targets and extension of calculations are under active investigation.

Acknowledgements

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