APPLICATION OF THE INTRAMOLECULAR SCHMIDT REACTION TO THE ASYMMETRIC SYNTHESIS OF (-)-INDOLIZIDINE 209B FROM PULEGONE†

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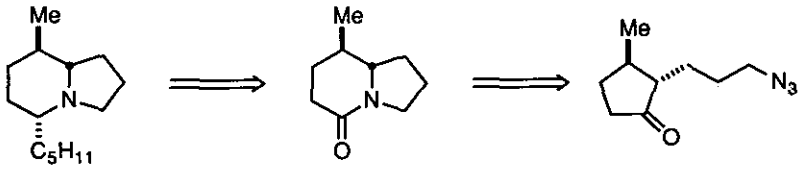
Abstract - A synthesis of enantiomerically pure indolizidine alkaloid 209B, beginning from naturally occurring pulegone, is described. The key step is the formation of a bicyclic lactam *via* the intramolecular Schmidt reaction of an alkyl azide with a cyclic ketone. The 11-pot synthesis was accomplished in an overall yield of 21.9%.

Chiral, optically pure natural products are valuable starting materials in chemical synthesis.[1] The wide variety of readily available terpenes renders this class an attractive starting point for asymmetric synthesis.[2] Naturally, the vast majority of effort in this area has focused on carbocyclic targets, with amino acids more commonly used for the synthesis of nitrogen-containing heterocyclic compounds.[3] Recent reports from these laboratories have introduced the acid-promoted reaction of alkyl azides with ketones as a useful method for the insertion of a substituted nitrogen group adjacent to a carbonyl group.[4] The easy introduction of azide into an appropriate ketone-bearing substrate recommends these new Schmidt-type reactions for the synthetic conversion of terpenes into alkaloids. In this paper, we illustrate this strategy in a synthesis of (-)-indolizidine 209B (**1**).[5] The key reaction, shown in the retrosynthesis below, is the conversion of azide(**3**)to lactam(**2**).



1, indolizidine 209B **2** **3**

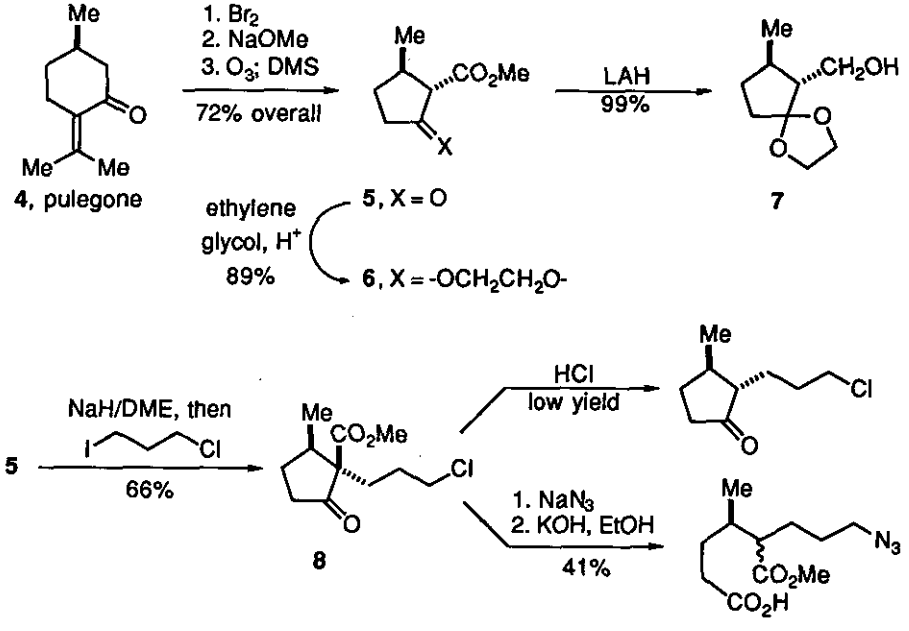
Indolizidine 209B belongs to a class of indolizidine alkaloids isolated from the skin secretions of poison frogs of the *Dendrobates* family.[6] As a group, these compounds have attracted synthetic interest because of their interesting biochemical properties, including antagonism at the acetylcholine receptor-ion channel complex.[6,7] Additionally, these relatively simple alkaloids provide tests of synthetic methodology useful for application to more complex congeners such as gephyrotoxin or pumiliotoxin A. Accordingly, several asymmetric syntheses of both enantiomers of indolizidine 209B[8] and related compounds[9] have appeared in the literature. Generally,

†Dedicated to Professor E.C. Taylor in honor of his decades of service to heterocyclic chemistry.

these syntheses have been chiral-auxiliary-based affairs, with exceptions involving the introduction of nitrogen into terpene[8d] or tartaric acid-derived[9a,c] starting materials.

The starting point for the synthesis was pulegone, which had previously been converted to the trans 2,3-disubstituted cyclopentanone derivatives (**5-7**) by Marx and Norman (Scheme 1).[10] The key reaction in this sequence is the Favorskii rearrangement encountered during the conversion of pulegone to **5**. We carried out this sequence according to this literature precedent, obtaining the yields shown. The stereochemical disposition of the C-2 and C-3 substituents (cyclopenantone numbering) is predominantly trans, as shown in the scheme, by a margin of about 13 : 1. The cis isomer is present as an impurity throughout most of the synthesis, as indicated by nmr; this isomer is not shown for simplicity and, at any rate, is ultimately removed by a fractional crystallization.

Scheme 1

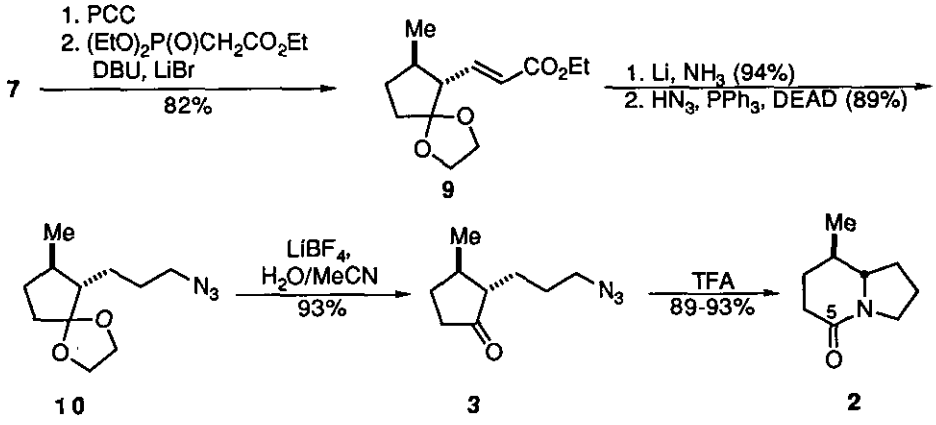


Initially, we hoped to simply attach the 3-carbon side chain needed for the synthesis of keto azide (**3**) by alkylation of the activated position in keto ester (**5**), followed by ester hydrolysis and decarboxylation. However, we encountered difficulties in the manipulation of **8**, which was presumably formed by alkylation of the enolate trans to the C-3 methyl group. Acidic hydrolysis/decarboxylation gave a very disappointing yield of the desired product along with baseline material (tlc), whereas treatment under basic conditions only led to the fragmentation product resulting from attack at the ketone. These results stand in stark contrast to the easy decarboxylation of keto esters lacking the methyl group and are probably due to steric hinderance of the ester

by the cis-disposed C-3 substituent. It is possible that the hydrolysis product obtained under acidic conditions results from selective reaction of a small amount of C-2 epimeric material likely to be present.

We opted to carry out the somewhat more linear route summarized in Scheme 2. Oxidation of alcohol (**7**) followed by Horner-Emmons extension of the side chain resulted in the α,β-unsaturated ester (**9**). Although the intermediate aldehyde could be isolated, superior overall yields were obtained when the crude aldehyde was directly subjected to olefination. Concomitant reduction of the double bond and the ester group was satisfactorily accomplished under dissolving metal conditions;[11] the resulting alcohol was smoothly converted to azide (**10**) under Mitsunobu conditions.[12] The ketal was removed in the presence of the azide functionality without incident under mild Lewis acid catalysis,[13] affording keto azide (**3**) in 93% yield. Finally, intramolecular Schmidt reaction[4a] was accomplished in excellent yield by dissolution of **3** in trifluoroacetic acid. At this stage, **2** could be recrystallized from hexanes to afford the isomerically pure material shown, as verified by its ultimate conversion to indolizidine 209B.

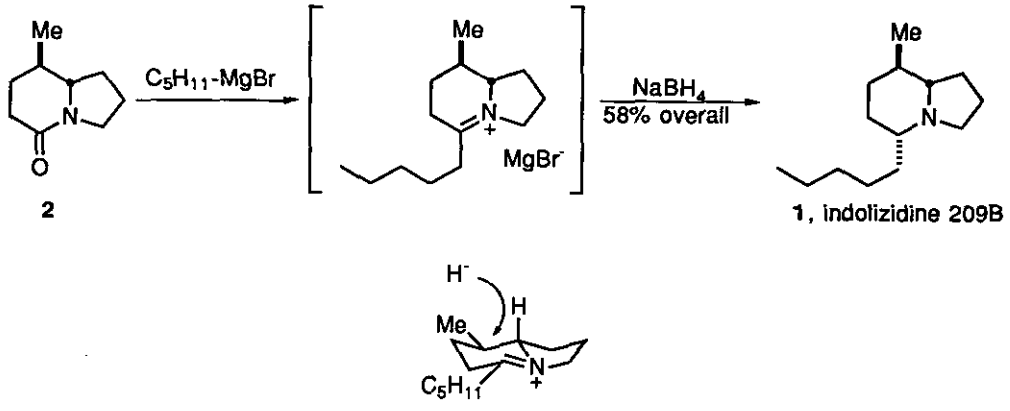
Scheme 2



Bicyclic lactam (**2**) *is a potential intermediate for the synthesis of a number of indolizidine alklaloids bearing* various side chains at C-5, including 209B, 205A, and 235B.[6] The synthesis of indolizidine 209B was accomplished using the straightforward method shown in Scheme 3. Addition of pentyl Grignard followed by acidification afforded an iminium ion intermediate, which was reduced from the pseudoaxial direction to give the target alkaloid in 58% overall yield. The stereochemical course of this reduction was expected based on the stereoelectronic principles of Stevens[14] and had been previously observed in this series of alkaloids.[9f] That alkaloid 209B was, in fact, obtained, was evident from the observation of Bohlmann bands in the ir spectrum, indicating all-equatorial stereochemistry about the six-membered ring, and from the ^{1}H- and ^{13}C-nmr data, which were in complete agreement with those reported for the natural product.[8c] Interestingly, only one of the α-amino protons appears at >2 ppm in the ^{1}H-nmr spectrum, suggesting that the three axial protons anti to the nitrogen lone pair might experience shielding. Although the optical rotation of the natural product is, strictly

speaking, unknown (due to paucity of material obtained from natural sources), the absolute configuration shown was proposed in analogy to related alkaloids and the absolute value of the optical rotation of our synthetic material ($[\alpha]_D$ -96.5, (c = 0.62, methanol)) is consistent with other reported values.[6,8]

Scheme 3



In summary, the total synthesis of indolizidine alkaloid 209B has been carried out from pulegone. The synthesis involves the purification of the products of 11 chemical steps and was realized in an overall yield of 21.9% yield. Despite the length of the synthesis, most of the steps are straightforward and easily carried out. The key bicyclic lactam(3)(10 steps, 37.8% yield) can be considered a central intermediate in the synthesis of other alkaloids in this series. Most importantly, the utility of the intramolecular Schmidt reaction in linking the terpene class of natural products with at least one family of alkaloids has been firmly established.

ACKNOWLEDGEMENTS. This work was supported by the National Institutes of Health (GM-39402). In addition, PSR warmly acknowledges a Warner-Lambert undergraduate research fellowship.

EXPERIMENTAL SECTION

General experimental procedures have been published.[15]

Ethyl (3'*R*, 2'*R*)-3-(3-methyl-1-oxocyclopent-2'-yl)acrylate, ethylene ketal (9). Alcohol (7)[10] (2.04 g, 11.9 mmol) was dissolved in dry CH_2Cl_2 (25 ml) and added via cannula to a stirred suspension of pyridinium chlorochromate (6.41 g, 29.7 mmol) in 50 ml of CH_2Cl_2 over 5 min. The reaction mixture became homogeneous, then a black precipitate formed. After 1.5 h, the reaction mixture was decanted from the precipitate, and the precipitate was dissolved in satd aq $NaHCO_3$ (50 ml). The aqueous solution was extracted with ether (1 x 100 ml), and the ether layer was extracted with brine (1 x 25 ml). The combined ether and CH_2Cl_2 layers were dried (Na_2SO_4) and concentrated to give an oil, which was immediately dissolved in dry

MeCN (140 ml). To this solution was added triethylphosphonoacetate (2.82 ml, 14.2 mmol), then LiBr (1.24 g, 14.2 mmol), then 1,8-diazabicycloundec-7-ene (1.77 ml, 11.9 mmol). A mild exotherm ensued, followed by formation of a precipitate. After 1 h, water (100 ml) was added, and the solution was extracted with ether (2 x 200 ml). The combined organic layers were washed with brine (1 x 50 ml), dried (Na_2SO_4), and concentrated to give an oil. The crude product was purified by *siliga gel chromatography (25% ethyl acetate/hexane)* to give **9** (2.33 g, 82% yield). ^{1}H Nmr (300 MHz, $CDCl_3$) δ 0.95 (d, J=6.2 Hz, 3H), 1.30 (t, J=7.2 Hz, 3H), 1.80-2.05 (m, 5H), 2.22 (t, J=9.9 Hz, 1H), 3.78-3.96 (m, 4H), 4.19 (q, J=7.2 Hz, 2H), 5.86 (dd, J=0.6, 15.8 Hz, 1H), 6.92 (dd, J=9.5, 15.8 Hz, 1H); ^{13}C nmr (75.6 MHz, $CDCl_3$) δ 14.2, 18.7, 31.7, 36.5, 38.1, 59.1, 60.1, 64.8, 64.8, 118.5, 123.1, 146.9, 166.2; ir (neat) 1710, 1640 cm^{-1}; ms (EI) *m/z* calc'd for $C_{13}H_{20}O_4$: 240.1362, found 240.1356; 240 ($M^{+\cdot}$), 195, 167, 138, 126, 99; $[\alpha]_D$ -46.4°(c=1.09, EtOH).

(3*R*, 2*S*)-2-(3-Hydroxypropyl)-3-methylcyclopentanone, ethylene ketal. α,β-Unsaturated ester (**9**) (2.09 g, 8.72 mmol) was dissolved in a mixture of *dry ether (20 ml) and dry ethanol* (25 ml). This solution was added via cannula to a flask containing liquid NH_3 (about 125 ml, distilled from sodium) at -78 °C. The solution was placed in an acetonitrile/dry ice bath (about -40 °C), and lithium (5.17 g, 750 mmol) was carefully added portionwise over 2 h. After the addition was complete, the blue color was discharged by careful addition of ethanol, followed by methanol/water. The NH_3 was then allowed to evaporate. The resulting copious precipitate was dissolved in water (300 ml). The aqueous solution was extracted with ether (3 x 100 ml), and the combined organic layers were washed with brine (1 x 100 ml), dried (Na_2SO_4), and concentrated to give an oil. The crude product was purified by flash chromatography (34-50% ethyl acetate/hexane) to give the title compound (*1.61 g, 93% yield*). ^{1}H *Nmr (300 MHz, $CDCl_3$)* δ 0.97 (d, J=6.4 Hz, 3H), 1.06-1.20 (m, 1H), 1.22-1.35 (m, 1H), 1.39-1.80 (m, 8H), 2.02 (br, 1H), 3.55 (t, J=6.3 Hz, 2H), 3.72-3.90 (m, 4H); ^{13}C nmr (75.6 MHz, $CDCl_3$) δ 20.3, 24.4, 30.5, 31.1, 35.7, 38.3, 52.6, 63.2, 64.8, 64.3, 118.5; ir (neat) 3440, 2936, 1015 cm^{-1}; $[\alpha]_D$ -34.0°(c=1.09, EtOH); analysis calc'd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07; found: C, 65.62; H, 10.18.

(3*R*, 2*S*)-2-(3-Azidopropyl)-3-methylcyclopentanone, ethylene ketal (10). The alcohol obtained from the previous experiment (0.254 g, 1.27 mmol) was dissolved in a benzene solution of HN_3[16] (0.770 ml of 2.14 M HN_3/benzene, 1.65 mmol) and the mixture was chilled in an ice bath. Triphenylphosphine (0.398 g, 1.52 mmol) was added, followed by diethylazodicarboxylate (0.240 ml, 1.52 mmol). Another portion of HN_3 solution (0.77 ml, 1.65 mmol) was added and the mixture was stirred at 0 °C. After 30 min, 15% KOH (10 ml) was added and the mixture was stirred for an additional 10 min. Water (50 ml) was added and the mixture was extracted with ether (2 x 100 ml). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated to give an oil. The crude product was purified by flash chromatography (5% ethyl acetate/hexane) to give **10** (0.255 g, 89% yield). ^{1}H Nmr (300 MHz, $CDCl_3$) δ 1.03 (d, J=6.5 Hz, 3H), 1.12-1.28 (m, 1H), 1.30-1.88 (m, 9H), 3.26 (dt, J=2.1, 6.7 Hz, 2H), 3.68-3.95 (m, 4H); ^{13}C nmr (75.6 MHz, $CDCl_3$) δ 20.3, 25.4, 27.4, 30.6, 35.7, 38.1, 51.9, 52.6, 63.9, 64.3, 118.4; ir (neat) 2080 cm^{-1}; ms (EI) *m/z* 225 ($M^{+\cdot}$), 198, 196, 183, 154, 113, 99, 86, 69, 55; $[\alpha]_D$ -38.8°(c=1.14, EtOH).

(3*R*, 2*S*)-2-(3-Azidopropyl)-3-methylcyclopentanone (3). Ketal (**10**) (1.27 g, 5.59 mmol) and $LiBF_4$ (1.05 g, 11.2 mmol) were dissolved in 2% water/acetonitrile (24 ml) and stirred. After 16 h, ether (200 ml) was added, and the solution was washed with water (50 ml) and brine (50 ml). The organic layer was dried (Na_2SO_4) and concentrated to give an oil. The crude product was purified by silica gel chromatography (10% ethyl acetate/hexane) to give **3** (0.958 g, 95% yield). ^{1}H Nmr (300 MHz, $CDCl_3$) δ 1.17 (d, J=7.4 Hz, 3H), 1.33-1.48 (m, 1H), 1.53-1.94 (m, 6H), 2.02-2.17 (m, 2H), 2.30-2.34 (m, 1H), 3.29 (t, J=6.2 Hz, 2H); ^{13}C nmr (75.6 MHz, $CDCl_3$) δ 19.5, 24.7, 26.4, 29.5, 37.0, 38.0, 51.6, 56.9, 220.6; ir (neat) 2083, 1730 cm^{-1}; ms (EI) *m/z* 182 ($M^{+\cdot}$), 154, 138, 125, 111, 96, 83, 55, 43; $[\alpha]_D$ +57.3°(c=1.10, EtOH).

(8*R*, 8a*S*)-3-Methyl-5-indolizidinone (2). Keto azide (**3**) (0.743 g, 4.10 mmol) was dissolved in trifluoroacetic acid (7.5 ml) in an ice bath; gas evolution ensued. The ice bath was removed and the solution was stirred. After 40 min, the mixture was concentrated to an oil. The oil was dissolved in CH_2Cl_2 (100 ml) and the solution was washed with satd aq $NaHCO_3$ (1 x 25 ml). The aqueous layer was extracted with CH_2Cl_2 (2 x 100 ml), and the combined organic layers were dried (Na_2SO_4) and concentrated to an oil. The crude product was purified by silica gel chromatography (acetone) to give **2** (0.558 g, 89% yield) as a ca. 13 : 1 mixture of stereoisomers. Two crystallizations from hexanes gave a single isomer: mp 59-62 °C; ^{1}H nmr (300 MHz, $CDCl_3$) δ 1.03 (d, J=6.0 Hz, 3H), 1.30-1.52 (m, 3H), 1.65-1.89 (m, 2H), 1.91-2.02 (m, 1H), 2.16 (pentet, J=5.7 Hz, 1H), 2.25-2.53 (m, 2H), 3.00 (sextet, J=5.0 Hz, 1H), 3.42-3.64 (m, 2H); ^{13}C nmr (75.6 MHz, $CDCl_3$) δ 18.1, 22.0, 29.9, 31.4, 32.2, 35.3, 45.2, 65.0, 168.9; ir (neat) 1612 cm^{-1}; ms (EI) *m/z* calc'd for $C_9H_{15}NO$: 153.1154, found 153.1151; 153 ($M^{+\cdot}$), 111, 83, 70, 55; $[\alpha]_D$ -21.7°(c=1.09, EtOH).

Indolizidine 209B. Lactam (**2**) (0.100 g, 0.654 mmol) was dissolved in dry ether (2.0 ml) and the solution was chilled in ice. A solution of *n*-pentylmagnesium bromide (0.980 ml of a 2.0 M solution, 1.96 mmol) was added and the ice bath was removed. After 4 h, the mixture was chilled in an ice bath and acetic acid (3.0 ml) was added, followed by $NaBH_4$ (0.050 g, 1.31 mmol). The ice bath was removed and the mixture was stirred. After 1 h, ether (100 ml) was added and the solution was washed with 7.5% KOH (50 ml). The aqueous layer was extracted with ether (1 x 100 ml), and the combined organic layers were washed with brine (1 x 25 ml), dried (Na_2SO_4), and concentrated to an oil. The crude product was purified by two successive flash chromatographies (ethyl acetate) to give the title compound (0.079 g, 58% yield) as a colorless oil. ^{1}H Nmr (300 MHz, $CDCl_3$) δ 0.87 d (6.5, 3H), 0.88 (t, J=6.6 Hz, 3H), 0.97 (td, J=4.2, 11.7 Hz, 1H), 1.14-1.53 (m, 11H), 1.55-2.00 (m, 8H), 3.26 (td, J=8.5, 1.8 Hz, 1H); ^{13}C nmr (75.6 MHz, $CDCl_3$) δ 14.0, 18.9, 20.3, 22.6, 25.5, 29.0, 31.2, 32.3, 33.7, 34.6, 36.6, 52.8, 63.5, 71.3; ir (neat) 2950, 2920, 2882, 2773, 2695, 1452 cm^{-1}; ms (EI) *m/z* calc'd for $C_{14}H_{27}N$: 209.2143, found 209.2130; 209 ($M^{+\cdot}$), 208, 196, 182, 164, 138, 96, 70, 55; $[\alpha]_D$ -96.5° (c=0.62, MeOH); lit.,[8a,c] $[\alpha]_D$ -94.3°(c=1.85, MeOH); lit.,[8b] $[\alpha]_D$ +98°(c=3, MeOH); lit.,[8d] $[\alpha]_D$ -91.3°(c=0.58, MeOH).

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Received, 7th December, 1992