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Efficient formal synthesis of the dendrobatid alkaloid, indolizidine (−)-209B

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Abstract—Condensation of the β-amino alcohol **7** derived from an enantiopure β-amino ester with the β-keto ester **8** provides the vinylogous urethane **9**, which is cyclized to give the dehydropiperidine **10**. Hydrogenation of **10** and subsequent cyclization mediated by Ph_3P/CBr_4 then afforded the bicyclic product **12**, a precursor of indolizidine (−)-209B. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

About sixty 5,8-disubstituted indolizidines have been isolated from the skins of amphibians. Most of them display interesting biological activities.[1] For example, indolizidines 209B, 207A, 205A and 235B (**1**–**4**, Fig. 1) were found to be an atypical and potent class of non-competitive blockers for muscle-type and ganglionic nicotinic receptor-channels.[2] As a result, they have become target molecules for many synthetic efforts in the past decade.[3] Two years ago Michael and Gravestock reported a concise synthesis of indolizidine 209B utilizing an enantiopure β-amino ester as a building block.[3b] Herein, we wish to describe an alternative and more efficient route to 5,8-disubstituted indolizidines from an enantiopure β-amino ester.[4] The protocol is exemplified by a formal synthesis of indolizidine 209B.

As outlined in Scheme 1, our synthesis started from the diastereoselective Michael addition of lithium (*R*)-*N*-benzyl-*N*-α-methylbenzylamide to (*E*)-methyl octenoate.[5] The generated β-amino ester **6** was subjected to Pd/C-catalyzed hydrogenolysis and then LAH reduction to provide the corresponding amino alcohol **7**. Next, we planned to condense **7** with the β-keto ester **8**[6] to obtain the vinylogous urethane **9**. Initial attempts to effect this transformation by acid-catalyzed azeotropic removal of water in toluene failed.[4e] After completing a number of experiments, we found that mixing the two reactants without solvent at room temperature afforded the desired product **9** in 70% yield. Obviously, the intramolecular cyclization of **9** to afford the dehydropiperidine **10** was a key step in the present synthesis. This transformation was found to be challenging and therefore many reaction conditions were explored. The results are summarized in Table 1.

Because in Michael's report[3b] excellent results were obtained when I_2/imidazole/Ph_3P was used to mediate a similar transformation in refluxing toluene, these reaction conditions were initially applied to our reaction. Unfortunately, the desired cyclization product **10** was obtained in only 23% yield (entry 1). At this point we

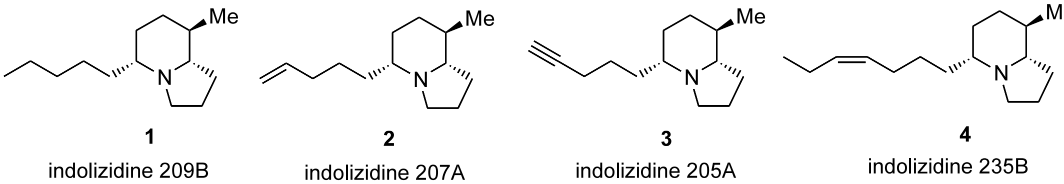

Figure 1.

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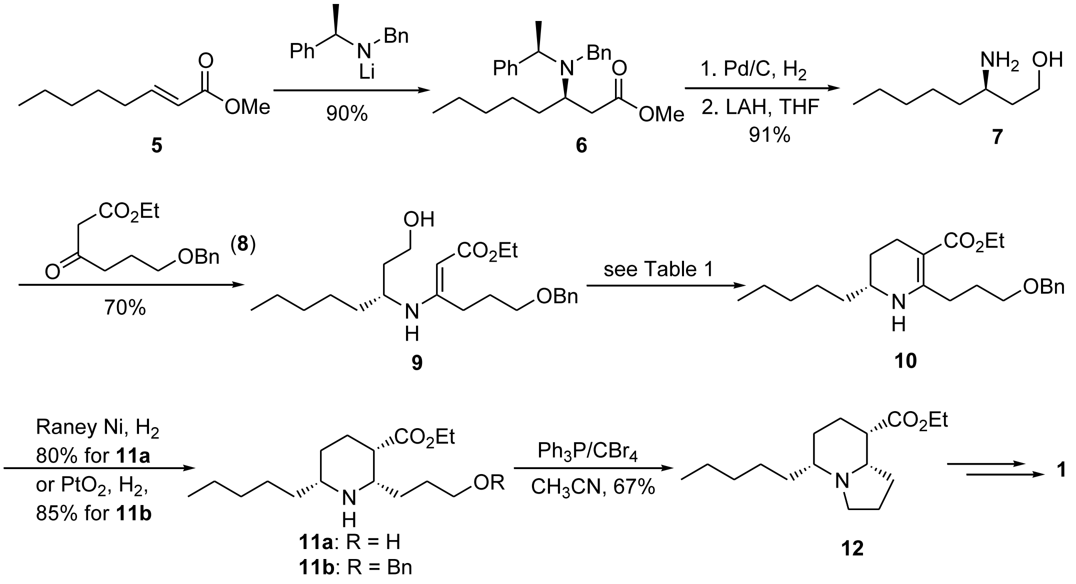
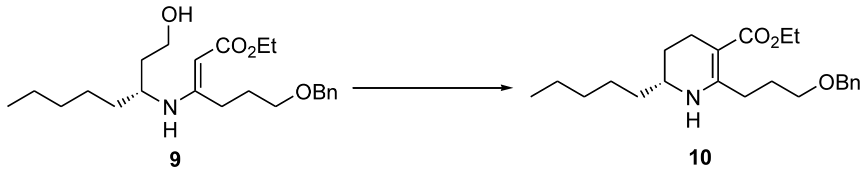


Scheme 1.

Table 1. Conversion of the alcohol **9** to the dehydropiperidine **10**



Entry	Reaction conditions	Yield of **10** (%)[a]
1	I_2, imidazole, Ph_3P, toluene, reflux	23
2	CBr_4, Ph_3P, CH_2Cl_2, 0°C to rt, then adding Et_3N, reflux	24[b]
3	CBr_4, Ph_3P, CH_3CN, 0°C to rt, then adding Et_3N, reflux	71
4	CBr_4, Ph_3P, DMF, 0°C to rt, then adding Et_3N, 100°C	–[c]
5	1. CBr_4, Ph_3P, CH_3CN, 0°C to rt; 2. LDA, THF, -78°C to rt	57
6	1. CBr_4, Ph_3P, CH_3CN, 0°C to rt; 2. KOH, EtOH, reflux	–[c]

[a] Isolated yield.

[b] The corresponding bromide was isolated in 40% yield.

[c] A complex product mixture was observed by TLC.

turned our attention to stepwise cyclization. Accordingly, bromination of **9** with CBr_4/Ph_3P in methylene chloride provided the corresponding bromide, which was subjected to cyclization by adding triethylamine in one-pot at reflux. However, in this case the yield for the desired product **10** was still lower, mainly because 40% unconverted bromide was isolated (entry 2). We reasoned that the reaction temperature might be too low for the cyclization step and changed the solvent to acetonitrile. As we expected, the cyclization reaction worked well in refluxing acetonitrile to give **10** in 71% yield (entry 3). Further attempts to improve the yield by increasing the reaction temperature failed (entry 4). In addition, using other bases to assist the cyclization of the bromide were unsuccessful (entries 5 and 6).

Hydrogenation of **10** in the presence of Raney Ni at 70 atm to hydrogenate the olefin moiety and deprotect the benzyl group afforded the desired 2,3,6-trisubstituted piperidine **11a** in 80% yield. No other isomers were obtained from this reaction. It is notable that hydrogenation of **10** catalyzed by Pd/C at 50 atm provided **11a** in low yield and with poor diastereoselectivity, and when PtO_2 was employed as the catalyst only **11b** was isolated in good yield, which showed that no deprotection of the benzyloxy group occurred. Finally, treatment of **11a** with PPh_3/CBr_4 furnished 5,8-indolizidine **12**, which can be converted to (–)-indolizidine 209B.[3b]

In conclusion, we have developed an efficient route to enantiopure 5,8-disubstituted indolizidines using β-amino esters as the starting material. This protocol should allow the synthesis of various substituted indolizidines by varying the β-amino ester and β-keto ester starting materials. Further application of this method is in hand.

2. Experimental

2.1. (*R*)-3-Aminooctanol, 7

A mixture of the β-amino ester **6** (5.5 g, 15 mmol), Pd/C (3 mmol) and acetic acid (1.5 mL) in methanol (60 mL) was stirred under hydrogen (50 atm) at 50°C for 20 h. The Pd/C was filtered off and the filtrate was concentrated to dryness. The residual oil was dissolved in THF (40 mL) and LAH (2.0 g, 50 mmol) was added at 0°C in portion. The resulting mixture was stirred at the same temperature for 2 h and then allowed to warm to room temperature. The reaction was quenched by adding water before the mixture was partitioned between chloroform and water. The organic layer was separated and the aqueous layer was extracted with chloroform. The combined organic layers were dried over Na_2SO_4, and concentrated to afford 2.0 g (91%) of crude **7**. $[\alpha]_D^{20}=-14.4$ (*c* 1.3, $CHCl_3$); IR (KBr) 3554, 3041, 2910, 1051 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.71–3.60 (m, 3H), 3.14 (br s, 3H), 2.85 (m, 1H), 1.63–1.21 (m, 10H), 0.89 (t, *J*=6.9 Hz, 3H); EI-MS *m/z* 146 (M$^+$), 128, 102, 74, 56; HRMS calcd for $C_8H_{19}NO$ (M$^+$) 145.1426, found 145.1428.

2.2. Condensation of 7 with β-keto ester, 8

A mixture of **7** (4.0 g, 27.6 mmol), β-keto ester **8** (7.3 g, 27.6 mmol) and freshly dried $MgSO_4$ (1.5 g) was stirred at room temperature for 2 days. Purification of the resulting mixture directly by column chromatography eluting with 1/3 ethyl acetate/*n*-hexane afforded **9** as a colorless oil (7.5 g, 70%). $[\alpha]_D^{20}=+8.9$ (*c* 2.6, $CHCl_3$); IR (KBr) 3063, 2930, 1742, 1716, 1647 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (br d, *J*=7.8 Hz, 1H), 7.31–7.20 (m, 5H), 4.51 (s, 2H), 4.40 (s, 1H), 4.11 (q, *J*=7.2 Hz, 2H), 3.60 (br m, 3H), 3.52 (m, 2H), 2.31 (m, 2H), 1.82 (m, 2H), 1.61–1.23 (m with t, *J*=6.3 Hz, 14H), 0.89 (t, *J*=7.3 Hz, 3H); EI-MS *m/z* 391 (M$^+$), 341, 301, 213, 170, 156, 91; HRMS calcd for $C_{23}H_{37}NO_4$ (M$^+$) 391.2721, found 391.2783.

2.3. (*R*)-2-Pentyl-5-ethoxycarbonyl-6-(3-benzyloxypropyl)-1,2,3,4-tetrahydropyridine, 10

To a stirred solution of **9** (997 mg, 2.55 mmol) in anhydrous acetonitrile (2.5 mL) was added CBr_4 (1088 mg, 3.28 mmol) at 0°C. After all CBr_4 was dissolved, Ph_3P (870 mg, 3.32 mmol) was added slowly. The resulting mixture was warmed to room temperature and stirring was continued until **9** disappeared (as indicated by TLC). To this solution triethylamine (0.5 mL) was added and the resulting solution was heated under reflux for 5 h. The solvent was removed in vacuo and the residue was chromatographed eluting with 1/15 ethyl acetate/*n*-hexane to afford **10** as a pale yellow oil (675 g, 71%). $[\alpha]_D^{20}=+86.5$ (*c* 1.23, $CHCl_3$); IR (KBr) 2929, 1677, 1585 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.20 (m, 5H), 4.51 (s, 2H), 4.30 (br s, 1H), 4.15 (q, *J*=7.1 Hz, 2H), 3.50 (t, *J*=6.3 Hz, 2H), 3.11 (m, 1H), 2.72 (t, *J*=7.3 Hz, 2H), 2.41 (dt, *J*=15, 5.1 Hz, 1H), 2.20 (m, *J*=5.5 Hz, 1H), 1.92 (m, 4H), 1.41–1.20 (m, 11H), 0.89 (t, *J*=7.0 Hz, 3H); EI-MS *m/z* 373 (M$^+$), 327, 281, 239, 168, 91; HRMS calcd for $C_{23}H_{35}NO_3$ (M$^+$) 373.2591, found 373.2576.

2.4. (1*S*,2*S*,6*R*)-1-(3-Hydroxypropyl)-2-ethoxycarbonyl-6-pentylpiperidine, 11a

To a suspension of Raney Ni (60 mg) in ethanol (20 mL) was added a drop of triethylamine, and a solution of **10** (150 mg, 0.4 mmol) in ethanol (1 mL). The resulting mixture was stirred under hydrogen (70 atm) at 60–70°C for 15 h. The cooled mixture was filtered and the filtrate was concentrated. The residual oil was chromatographed eluting with 1/10 methanol/ethyl acetate to afford **11a** (92 mg, 80%). $[\alpha]_D^{20}=-11$ (*c* 0.97, $CHCl_3$); IR (KBr) 3682, 1721, 11180 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (q, *J*=7.3 Hz, 2H), 3.70 (dt, *J*=11.6, 3.6 Hz, 1H), 3.51 (dt, *J*=11.7, 3.6 Hz, 1H), 2.6 (d, *J*=10.7 Hz, 1H), 2.5 (m, 2H), 2.1 (dq, *J*=11.9, 2.2 Hz, 1H), 1.81–1.20 (m with t, *J*=6.5 Hz, 20H), 0.89 (t, *J*=7.1 Hz, 3H); ESI-MS *m/z* 286 (M$^+$+H$^+$); HRMS calcd for $C_{16}H_{31}NO_3$ (M$^+$) 285.2303, found 285.2310.

2.5. (5*R*,8*S*,8a*S*)-5-Pentyloctahydroindolizidine-8-carboxylic acid ethyl ester, 12

To a stirred solution of **11** (15 mg, 0.053 mmol) in anhydrous methylene chloride (1.5 mL) was added CBr_4 (21 mg, 0.06 mmol) at 0°C. After all of the CBr_4 was dissolved, Ph_3P (21 mg, 0.06 mmol) was added. The resulting solution was stirred at room temperature for 17 h and the solvent was removed in vacuo. The residue was extracted with *n*-hexane and the hexane extract washed with brine. After removal of the solvent, the residue was chromatographed to afford **12** (9 mg, 67%). $[\alpha]_D^{20}=-31.5$ (*c* 0.25, $CHCl_3$); IR (KBr) 2781, 1738, 1461 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.2 (q, *J*=7.3 Hz, 2H), 3.5 (dt, *J*=7.7, 2.2 Hz, 1H), 2.67 (m, 1H), 2.15 (m, 2H), 1.91–1.21 (m with t, *J*=6.5 Hz, 20H), 0.89 (t, *J*=6.9 Hz, 3H); MS *m/z* 267 (M$^+$), 197, 196, 238, 222, 168, 122, 70; HRMS calcd for $C_{16}H_{29}NO_2$ (M$^+$) 267.2198, found 267.2207.

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