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TETRAHEDRON: *ASYMMETRY*

Expedient syntheses of indolizidines (–)-167B and (–)-209D

Guncheol Kim* and Eun-ju Lee

Department of Chemistry, College of Natural Science, Chungnam National University, Taejon 305-764, South Korea

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Abstract—Indolizidine alkaloids (–)-167B and (–)-209D were synthesized via an expedient route using hydroacylation and amination. © 2001 Published by Elsevier Science Ltd.

1. Introduction

The indolizidine alkaloids are contained in the toxic skin secretion of neotropical frogs belonging to the genus *Dendrodates*, and display a wide range of biological activities.[1] Some of the indolizidines in this class are non-competitive blockers of nicotinic receptor channels.[2]

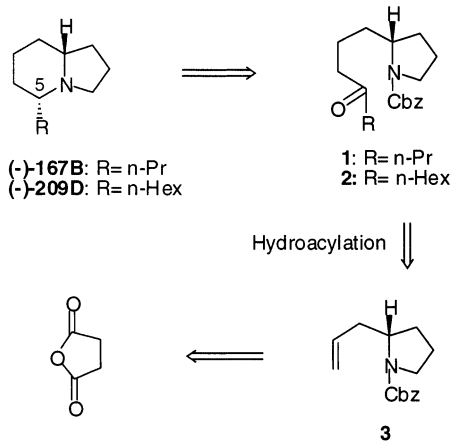
The simplest bicyclic gephyrotoxin alkaloids, 167B and 209D, have a single alkyl substituent at C(5) of the indolizidine ring, and the limited amount of these compounds available from natural sources as well as their interesting pharmacological properties has made them an attractive synthetic subject.[3]

We considered the keto-intermediates **1** and **2** to be appropriate final precursors for the synthesis, as hydrogenation of the compounds would control the stereochemistry at the developing stereogenic center to afford the alkaloids,[3c,3n] respectively, and these compounds could be prepared from intermediate **3**. To elongate the allylic side chain of **3** and afford the appropriate carbonyl compounds, we wanted to perform the process in a single step using a hydroacylation reaction (Scheme 1). In the related syntheses, manipulation of the allylic side chain required several steps and costly chemicals.[3n,4]

2. Results and discussion

Herein, we describe a concise route to the alkaloids using hydroacylation and amination. For the preparation of the known chiral intermediate **3**, we planned to use intermediate **5**, which was made by modifying the reported process.[5a,5b] Condensation of (*R*)-(–)-2-phenylglycinol with succinimide afforded imide **4** as described, which was partially reduced to a hydroxy imide using $SnCl_2$ and $NaBH_4$ in EtOH.[6] Acid treatment, selective allylation, separation of the 9:1 diastereomeric products by column chromatography, and deprotection of the chiral auxiliary using Na in NH_3 containing EtOH provided **5**. LAH reduction of the amide to pyrrolidine and treatment of the intermediate with benzyl chloroformate afforded **3** (Scheme 2).

The allylic compound **3** was then subjected to hydroacylation conditions. Recent development of a mild intermolecular hydroacylation has described the combined use of a Rh(I) complex, 2-amino-3-picoline, benzoic acid, and aniline.[7] However, an excess amount of simple alkenes has been used with mostly reactive benzaldehyde or its congeners. As the alkene **3** must be



Scheme 1.

* Corresponding author. E-mail: guncheol@cuvic.cnu.ac.kr

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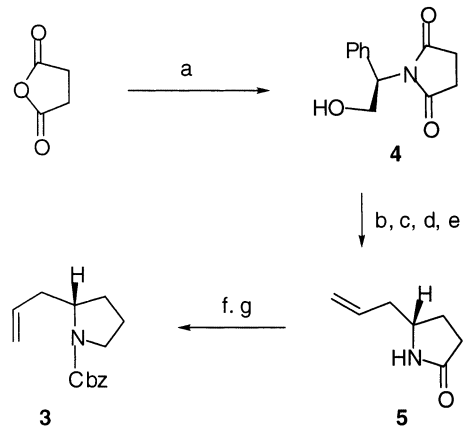


Scheme 2. *Reagents and conditions*: (a) (*R*)-(−)-2-phenylglycinol, toluene, Et_3N; (b) $NaBH_4$, $SnCl_2$, EtOH; (c) CF_3CO_2H, CH_2Cl_2; (d) $AllBu_3Sn$, $TiCl_4$, CH_2Cl_2; (e) Na, NH_3, THF, EtOH; (f) LAH, THF; (g) $ClCO_2Bn$, THF, Et_3N.

used as the limiting reagent, we wanted to find the optimal conditions for this case. When using 1 equiv. of heptaldehyde at 130°C over 2 h, only 10% of **2** was obtained with 80% recovery of the starting material **3**. Use of 5 equiv. of heptaldehyde at 150°C over 24 h increased the yield to 35% (45% recovery of **3**). In the case of butyraldehyde, 30% of **1** (55% recovery of **3**) was obtained under the same conditions. Although the yields are relatively low even under vigorous reaction conditions, the single step manipulation using commercially available aldehydes compensates for the moderate yields.

Finally, hydrogenation of **1** and **2** was carried out under 1 atm pressure of H_2 in MeOH containing 5% Pd on carbon, providing (−)-167B (80%, $[\alpha]_D^{24}$ −104.0 (*c* 0.80, CH_2Cl_2) [lit.[3a] $[\alpha]_D$ −111.3 (*c* 1.3, CH_2Cl_2)]) and (−)-209D (83%, $[\alpha]_D^{24}$ −81.4 (*c* 1.15, CH_2Cl_2) [lit.[3a] $[\alpha]_D$ −80.4 (*c* 1, CH_2Cl_2)]), respectively (Scheme 3).

3. Conclusion

The present study demonstrates the use of hydroacylation of intermediate **3** with commercial aldehydes, providing precursors **1** and **2** for indolizidines (−)-167B and (−)-209D in moderate yields, and the following hydrogenation made the expedient syntheses possible.

4. Experimental

4.1. General procedures

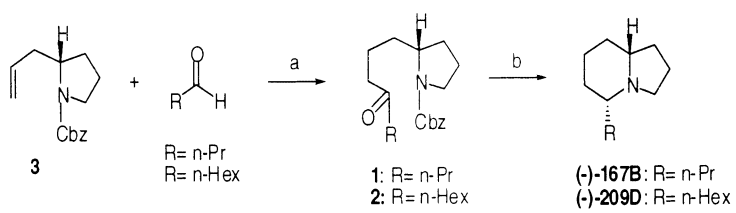
All reactions were performed in oven-dried glassware with magnetic stirring. Commercial grade reagents and anhydrous solvents were used without further purification.

4.2. Preparation of the known intermediate (5*S*)-propenyl pyrrolidinone 3[5a,5b]

Succinic anhydride (3.64 g, 36.4 mmol) and (*S*)-phenylglycinol (5 g, 36.4 mmol) were dissolved in toluene (300 mL). The mixture was heated under reflux for 1 h, and triethylamine (10 mL) was added and the mixture was heated again at reflux for 17 h. The resulting product was cooled to rt and concentrated. The crude product was separated by column chromatography eluting hex:EtOAc 5:1 to afford (*S*)-(+)-*N*-(1-phenyl-2-hydroxyethyl)succinimde **4** as an oil (6.45 g, 84%, $[\alpha]_D^{24}$ +17.4 (*c* 1.80, EtOH) [lit.[5a] $[\alpha]_D$ +16.5 (*c* 1.87, EtOH)]).

To a solution of this imide (3.50 g, 16.0 mmol) and tin(II) chloride (3.00 g, 16.0 mmol) in ethanol/CH_2Cl_2 (7:1, 160 mL) was added sodium borohydride (3.0 g, 80.0 mmol) at 0°C. The mixture was stirred at 0°C for 40 min and quenched with saturated aqueous $NaHCO_3$ solution. The resulting grey mixture was extracted with CH_2Cl_2 (5×100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated to afford a crude mixture, and this material was directly treated with trifluoroacetic acid (15 mL) in CH_2Cl_2 (200 mL). After stirring the solution for 20 min at rt, the solution was concentrated and separated by column chromatography to afford a bicyclic lactam intermediate (2.64 g, 90%, mp 65–68°C; $[\alpha]_D^{24}$ +153.5 (*c* 1.60, EtOH) [lit.[5a] $[\alpha]_D$ +154.1 (*c* 1.29, EtOH)]).

This lactam intermediate (2.20 g, 11.0 mmol) and allyltrimethylsilane (6.90 mL, 43.0 mmol) in CH_2Cl_2 (20 mL) was added to a solution of $TiCl_4$ (1 M solution in CH_2Cl_2, 27.0 mL, 27.0 mmol) in CH_2Cl_2 (100 mL) at −78°C under an argon atmosphere. The resulting solution was stirred at −78°C for 1 h and at 0°C for 2 h and quenched with saturated $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2 (3×100 mL), dried over MgSO4, filtered, concentrated and the crude product (~9:1 mixture of epimers) purified by silica gel column chromatography using hex:EtOAc = 5:1 provided *N*-[2-(2*R*-phenyl ethanol)]-5*S*-propenyl-2-pyrrolidinone as a clear oil (2.18 g, 81%), $[\alpha]_D^{24}$ +22.2 (*c* 1.70, CH_2Cl_2) [lit.[5b] $[\alpha]_D$ +21.9 (*c* 2.0, CH_2Cl_2)].



Scheme 3. *Reagents and conditions*: (a) $[Rh(PPh_3)_3Cl]$(2 mol%), 2-amino-3-picoline (20 mol%), benzoic acid (6 mol%), aniline (60 mol%), RCHO (500 mol%), toluene, 150°C, 24 h, 30% for **1**, 35% for **2**; (b) H_2, 5% Pd on C, MeOH, 80% for 167B, 83% for 209D.

To a solution of this pyrrolidinone (2.43 g, 13.20 mmol) in liquid NH_3 (70 mL) containing THF/ethanol (8 mL/8 mL) was added Na (1.52 g, 66 mmol) slowly at −78°C. The blue color persisted more than 3 min, and then the reaction was quenched by slow addition of solid NH_4Cl. After slow evaporation of liquid NH_3, the mixture was extracted with EtOAc (3×100 mL), washed with brine (30 mL), and dried over $MgSO_4$. Filtration, evaporation, and purification by silica gel column chromatography afforded 1.97 g of **5** (67%, $[\alpha]_D^{24}$ +1.95 (*c* 1.49, CH_2Cl_2) [lit.[5b] $[\alpha]_D$ +1.4 (*c* 2.0, CH_2Cl_2)]).

To a solution of **5** (1.0 g, 8.0 mmol) in THF (15 mL) was added LAH solution (24 mL of 1.0 M solution in ether, 24.0 mmol) at 0°C. The solution was heated under reflux for 5 h, and then 20% NaOH solution (3 mL) was added. The white solid was filtered through glass filter and the filtrate was concentrated. The crude product was directly treated with benzyloxycarbonyl chloride (2.87 g, 16.0 mmol) in THF (15 mL) containing Et_3N (1.0 mL), stirring at rt for 4 h. The reaction mixture was diluted with EtOAc (15 mL), washed with satd NH_4Cl solution and dried over $MgSO_4$. After concentration the crude product was purified by column chromatography to provide **3** (1.50 g, 77%, $[\alpha]_D^{24}$ −46.9 (*c* 1.18, $CHCl_3$) [lit.[5c] $[\alpha]_D$ −38.7 (*c* 1.13, $CHCl_3$)]).

4.3. Preparation of (*R*)-*1*-benzyloxycarbonyl-2-(4-oxo-nonyl)pyrrolidine 1

A mixture of **3** (0.20 g, 0.816 mmol), butyraldehyde (0.294 g, 4.08 mmol), toluene (0.25 mL), 2-amino-3-picoline (34.6 mg, 0.32 mmol), benzoic acid (12 mg, 0.10 mmol), and aniline (94 mg, 1.0 mmol) in a screwed vial was stirred at rt for 10 min, and $Rh(PPh_3)_3Cl$ (30 mg, 0.032 mmol) was added. The combined mixture was heated at 150°C for 24 h. The mixture was diluted with EtOAc (10 mL) and washed with 1N H_2SO_4, satd $NaHCO_3$ solution, and brine. After drying over $MgSO_4$, the organic layer was filtered and concentrated. Silica gel column chromatography afforded **1** (78 mg, 30%) and the recovered **3** (0.11 g, 55%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.37 (m, 5H), 5.12 (q_{AB}, J=19.5, 12.3 Hz, 2H), 3.80 (m, 1H), 3.35–3.43 (m, 2H), 2.30–2.43 (m, 4H), 1.33–1.94 (m, 10H), and 0.90 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.9, 155.7, 137.6, 129.0 (3), 128.5 (2), 67.2, 58.0, 47.0, 45.4, 43.1, 34.3, 30.8, 24.0, 20.9, 17.9, and 14.4; $[\alpha]_D^{24}$ −45.7 (*c* 1.20, EtOH) [lit.[3c] $[\alpha]_D^{21}$ −47.2 (*c* 2.00, EtOH)]); IR (thin film) 2961, 2934, 2879, 1715, 1699, 1684, 1648, 1415, 1356, 1099 and 1174 cm^{-1}; ESIMS m/z 317.9 ($M+H^+$, $C_{19}H_{27}NO_3$ requires 317.8). Anal. calcd for $C_{19}H_{27}NO_3$: C, 71.88; H, 8.51; N, 4.41. Found: C, 71.91; H, 8.59; N, 4.37%.

4.4. Preparation of (*R*)-*1*-benzyloxycarbonyl-2-(4-oxo-decyl)pyrrolidine 2

Similar procedure as above. 35% of **2** and 45% of recovered **3**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.26–7.34 (m, 5H), 5.09 (q_{AB}, J=20.4, 12.4 Hz, 2H), 3.80 (m, 1H), 3.33–3.44 (m, 2H), 2.30–2.40 (m, 4H), 1.23–1.91 (m, 16H), and 0.85 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.8, 155.3, 137.5, 128.8 (3), 128.2 (2), 66.8, 57.7, 46.7, 43.3, 42.8, 34.1, 32.0, 30.5, 29.3, 24.2, 23.8, 22.9, 20.7, 17.9, and 14.4; $[\alpha]_D^{24}$ −38.0 (*c* 1.50, $CHCl_3$); IR (thin film) 2943, 1710, 1700, 1558, 1417, 1358 and 1102 cm^{-1}; ESIMS m/z 360.1 ($M+H^+$, $C_{22}H_{33}NO_3$ requires 360.2). Anal. calcd for $C_{22}H_{33}NO_3$: C, 73.50; H, 9.19; N, 3.90. Found: C, 73.45; H, 9.26; N, 3.85%.

4.5. Synthesis of 167B

A solution of **1** (48 mg, 0.151 mmol) in MeOH (2 mL) containing Pd on carbon (5%, 5 mg) was stirred under H_2 at rt for 10 h. After filtration through Celite, the mixture was concentrated and filtered through short path of silica gel using EtOAc as an eluent to afford 167B (20 mg, 80%, $[\alpha]_D^{24}$ −104.0 (*c* 0.80, CH_2Cl_2) [lit.[3a] $[\alpha]_D$ −111.3 (*c* 1.3, CH_2Cl_2)].

4.6. Synthesis of 209D

Similar procedure using **2** as above afforded 209D (83%, $[\alpha]_D^{24}$ −81.4 (*c* 1.15, CH_2Cl_2) [lit.[3a] $[\alpha]_D$ −80.4 (*c* 1, CH_2Cl_2)].

Acknowledgements

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