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Aza-[2,3]-Wittig Rearrangements of Vinylaziridines as a Novel Entry to Indolizidine Alkaloids. Enantioselective Total Synthesis of Indolizidine 209D

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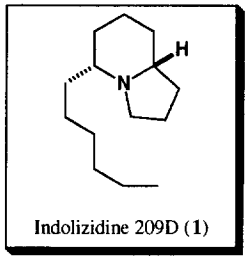
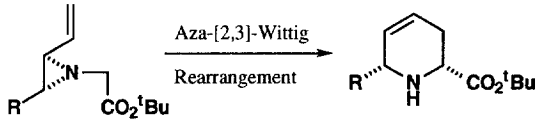
Abstract: An enantioselective total synthesis of indolizidine 209D (**1**) from epoxy alcohol **4** is described. The key step in the sequence involves an aza-[2,3]-Wittig rearrangement of vinylaziridine **7** to yield the *cis*-2,6-disubstituted tetrahydropyridine **8** in 98% yield and as a single detectable diastereomer.

Extracts from the skin secretions of neotropical frogs have furnished a number of pharmacologically potent alkaloids whose structural complexity has provided a stimulating impetus for the development of new synthetic methodology. Of these, the indolizidine alkaloids constitute a class with 22 members,[1] of which some have the ability to function as non-competitive blockers of neuromuscular transmission.[2] One of the structurally simpler members, indolizidine 209D (**1**), has been isolated only once in minute quantities from a single population of dendrobatid frogs and its absolute stereochemistry tentatively assigned as shown below.[1] To date three syntheses of **1** have been reported,[3] two of which yielded the target compound in high enantiomeric excess.[3b,c] Recently we demonstrated that substituted vinylaziridines **2** are excellent substrates for the aza-[2,3]-Wittig rearrangement, yielding the corresponding *cis*-2,6-disubstituted tetrahydropyridines **3** in high yield and as a single detectable diastereomer.[4] As a continuation of this work we now wish to report on the application of this rearrangement for the synthesis of indolizidine 209D (**1**).

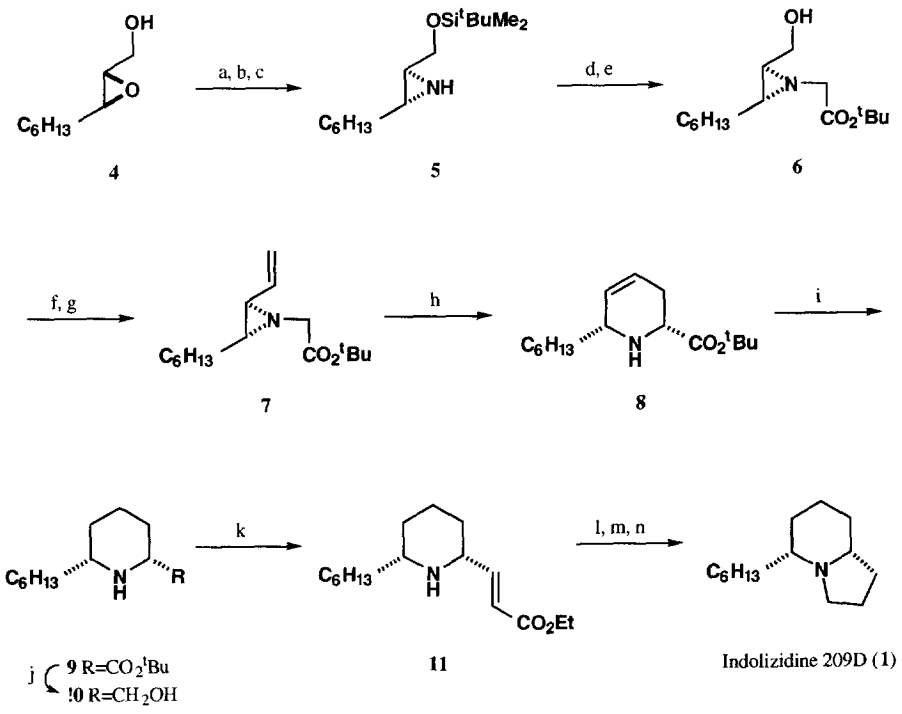


Indolizidine 209D (**1**)



2 **3**

The key intermediate, rearrangement precursor **7**, was prepared in a straightforward manner from the known epoxy alcohol **4** (>95% ee) as shown in the Scheme.[5] Exposure of compound **4** to NaN_3 gave the corresponding azidodiols as a mixture of regioisomers.[6] Selective protection of the primary hydroxyl group

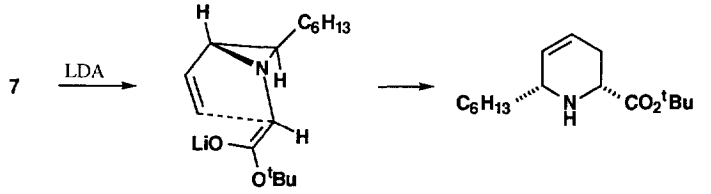


Scheme. (a) NaN_3, NH_4Cl, $MeOCH_2CH_2OH/H_2O$, 96% (b) $^tBuMe_2SiCl$, CH_2Cl_2, Et_3N, DMAP, 94% (c) Ph_3P, toluene, Δ, 96% (d) *tert*-butyl bromoacetate, K_2CO_3, 18-crown-6, THF, 67% (e) Bu_4NF, THF, 89% (f) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2 -78 °C (g) Ph_3PCH_2, THF, 82% (two steps) (h) LDA, THF, -78 °C, 98% (i) 5% Pd/C, H_2, EtOH, 83% (j) $LiAlH_4$, THF, 0 °C→RT, 94% (k) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2 -78 °C, then Ph_3PCHCO_2Et, 50% (l) 5% Pd/C, H_2, 4 psi, EtOH, 90% (m) Me_3Al, benzene, 69% (n) $LiAlH_4$, THF, Δ, 88%.

as a *tert*-butyldimethylsilyl ether followed by reductive cyclization[7] gave aziridine **5** (87% from **4**), its absolute stereochemistry being inverted as compared to the parent epoxide. The required anion-stabilizing group for the projected rearrangement was introduced by exposure of **5** to *tert*-butyl bromoacetate and K_2CO_3/18-crown-6 (cat.) in THF[8] which was followed by removal of the silyl group to yield compound **6** (60% from **5**). Alcohol **6** was then converted into vinylaziridine **7** by a Swern oxidation[9] followed by a Wittig olefination (82% from **6**).[10] It should be noted that aziridine **7** exists as a mixture of nitrogen invertomers at room temperature, but the composition of this mixture is of no consequence for the aza-[2,3]-Wittig rearrangement.

When compound **7** was treated with LDA at -78 °C in THF a smooth aza-[2,3]-Wittig rearrangement ensued, delivering the *cis*-2,6-disubstituted tetrahydropyridine **8** in 98% yield and as a single diastereomer.[4] The assignment of the relative stereochemistry of the product was based on previous examples[4] and ultimately confirmed by conversion of **8** into indolizidine 209D (*vide infra*). The outcome of the rearrangement can be rationalized by assuming that the reaction proceeds through **12** in which the vinyl group

adopts an *endo* conformation, projecting over the three-membered ring, while the enolate moiety is *exo* so as to avoid unfavourable steric interactions with the other aziridine substituents (Figure). Bond formation between the terminal olefinic carbon and the enolate with concomitant opening of the aziridine then gives the observed product.



12 8

Figure. Proposed transition state geometry for the stereoselective conversion of **7** to **8**.

The synthesis of **1** was then completed as shown in the Scheme. Since compound **8** proved to be somewhat labile and did not survive flash chromatography on silica gel without some decomposition, the crude reaction mixture was hydrogenated to yield the pipecolinic acid derivative **9** (81% from **7**).[11,12] Reduction of the ester moiety then gave amino alcohol **10**. Conversion of **10** into alkaloid **1** requires a two-carbon homologation, which was planned as an oxidation followed by an olefination. Initially we had some concerns as to whether the unprotected secondary amine functionality in **10** would interfere with this sequence; gratifyingly, however, when alcohol **10** was subjected to the one-pot Swern-Wittig protocol developed by Ireland,[13] the α,β-unsaturated ester **11** was obtained in 50% yield. Hydrogenation of **11** followed by $AlMe_3$ induced lactam formation[14] and $LiAlH_4$ reduction yielded indolizidine 209D (**1**, 55% from **11**), its spectroscopic data being in agreement with reported values.[12]

In conclusion, we have developed a novel entry to the indolizidine alkaloids and exemplified it by an enantioselective total synthesis of indolizidine 209D, the key step being a highly efficient and diastereoselective aza-[2,3]-Wittig rearrangement of vinylaziridine **7**. Further applications of this reaction in natural product synthesis will be reported in due course.

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   (c) The enantiomeric purity of **4** was determined by ^{1}H NMR spectroscopy on the the corresponding MTPA ester and comparing with a sample prepared from *rac*-**4**. (Ward, D. E.; Rhee, C. K. *Tetrahedron Lett.* **1991**, *32*, 7165.)
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11. The rearrangement product **8** is pure according to ^{1}H NMR analysis.
12. Spectroscopic data for (a) compound **9**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.19 (dd, 1H, J=11.5, 2.5 Hz), 2.45 (m, 1H), 2.97 (m, 1H), 2.84 (m, 2H), 2.62 (m, 1H), 1.52-1.18 (m, 21H), 1.02 (m, 1H), 0.86 (t, 3H, J=7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.7, 80.8, 59.8, 56.4, 37.2, 32.1, 29.5, 29.4, 28.1, 25.9, 24.7, 22.6, 14.1; IR (film) 3340, 2930, 1760, 1455, 1368, 1160 cm^{-1}; $[\alpha]_D$ +12.2 (*c* 3.21, $CDCl_3$); HRMS (CI+) Exact Mass Calc. for $C_{16}H_{32}NO_2$ (M+H): 270.2433. Found: 270.2448.
    (b) indolizidine 209D (**1**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.25 (dt, 1H, J=9.0, 2.0 Hz), 2.96 (q, 1H, J=9.0 Hz), 1.90-1.05 (m, 22H), 0.86 (t, 3H, J=7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 65.0, 63.9, 51.6, 34.7, 31.9, 31.1, 30.9, 30.6, 29.8, 25.8, 24.7, 22.6, 20.4, 14.1; IR (film) 2920, 2860, 2780, 1455, 1375, 1137 cm^{-1}; $[\alpha]_D$ -83.6 (*c* 0.77, CH_2Cl_2) [lit.[3b] $[\alpha]_D$ -80.4 (*c* 1, CH_2Cl_2); lit.[3c] $[\alpha]_D$ -76.5 (*c* 0.74, CH_2Cl_2)]; HRMS (CI+) Exact Mass Calc. for $C_{14}H_{28}N$ (M+H): 210.2222. Found: 210.2222.
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