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Construction of *cis*- and *trans*-octahydroisoquinoline-7-ones via a tandem ring-opening and -closing strategy

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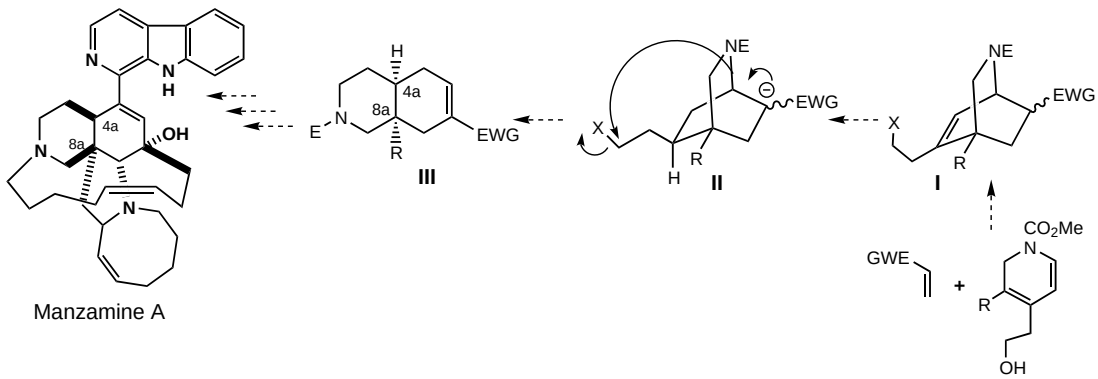
Abstract—*cis*- and *trans*-Octahyroisoquinolines can be efficiently constructed via a tandem ring-opening and -closing strategy. The precursors required to achieve this transformation are easily obtained by a Diels–Alder reaction followed by a stereoselective hydrogenation. © 2001 Elsevier Science Ltd. All rights reserved.

Decahydroisoquinoline rings are found in structurally diverse alkaloids, as well as several important clinical agents such as manzamine A and quinine.[1,2] Because of the wide occurrence and pharmacological importance of these compounds, the development of new stereospecific routes to this ring system remains an important objective in organic synthesis.

During the course of a program directed towards the development of a strategy for the synthesis of the marine alkaloids, we examined the feasibility of using a tandem ring-opening and -closing strategy to introduce the required hydroisoquinoline *cis*- or *trans*-ring-junction stereochemistry. Based on previous experimentation[3] and experience with the azabicyclo[2.2.2]octane ring system we designed a strategy that would allow preparation of either stereochemistry (Scheme 1), intermediate **II** to **III**. Such a route would have the advantage of preserving the relative configuration of the R group and H_{4a} during the transformation to the hydroisoquinoline.[4] Access to an azabicyclo[2.2.2]octane, like **I**, was seen to arise from a Diels–Alder reaction of a dihydropyridine derivative and an electron deficient dienophile. Introduction of the hydroxyethyl side-chain stereochemistries would rely upon stereoselective reduction of the alkene (Scheme 1).

To investigate the potential of this strategy, 4-hydroxyethyl pyridine **2** and 3,4-lutidine **1** were chosen as starting substrates (Scheme 2). This would demonstrate the feasibility of constructing hydroisoquinoline systems with either a substituted or unsubstituted ring juncture. One carbon homologation[5] of 3,4-lutidine via deprotonation with a 1:1 complex of LDA and HMPA



Scheme 1.

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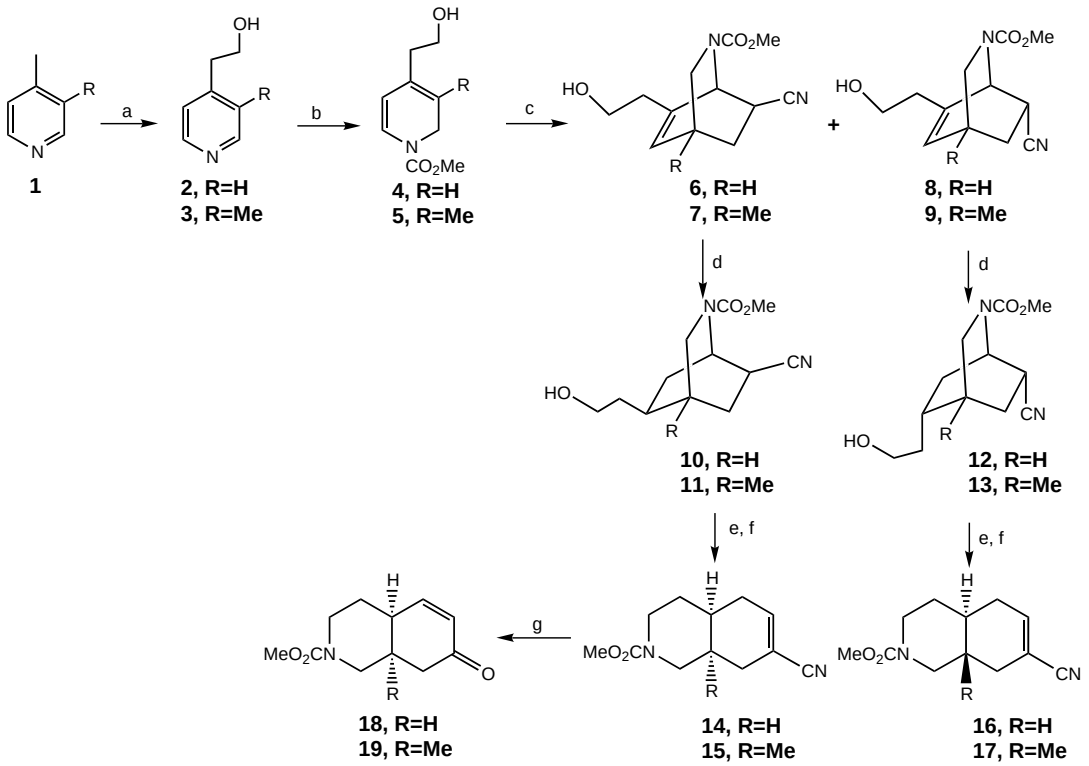
in THF at 0°C followed by treatment with paraformaldehyde afforded **3** in good yield. Reaction of alcohols **2** and **3**, separately, with methyl chloroformate and sodium borohydride[6] furnished dihydropyridines **4** and **5** respectively.[7] ^{1}H NMR analysis revealed that reduction of pyridine **3** also gave approximately 15% of 1,6-dihydropyridine isomer, which was unable to be separated from **5**. The polar dienes were directly subjected to Diels–Alder reaction with excess acrylonitrile to give a mixture of diastereoisomers. Separation by column chromatography gave the *exo* and *endo* isomers **6** and **7** in a 2.1:1 ratio in 65% yield, and **8** and **9** in a 1.8:1 ratio in 62% yield.[8] The structure of the each isomer was confirmed by selective proton decoupling and COSY-NMR experiments.

Hydrogenation of **6** at 1 atmosphere of hydrogen pressure with PtO_2, as a catalyst, produced a single product in 92% yield after 2 h. Similarly, **7** was transformed to a homogenous product in good yield. However, 15 h were required to complete the reaction. Extensive ^{1}H and ^{13}C NMR studies on the two diastereoisomers proved that *exo*-nitrile generated **10** and *endo*-nitrile provided **11**. No other isomers could be detected in a careful search of chromatographic fractions. Repeating the process with the more substituted dienes led to similar results (Scheme 2).

The success of PtO_2catalyzed hydrogenation of the various stereoisomers appears to be peculiar to this catalyst. For instance, the use of Pd/C, Rh/Al_2O_3, $Pd(OH)_2$ or Raney nickel gave either no, very slow reduction, or in some cases over reduction. The high degree of facial selectivity of this reaction seems to be due steric hindrance and not a haptophilic (or electronic) effect.[9] The *endo* (or bottom) face of **6**/**7** is shielded by two hydrogens while the top face is hindered by the π-bond of the sp^2 hybridized carbamate and a hydrogen. This suggests that a π-bond exerts a larger steric influence than a hydrogen. In **8**/**9**, the nitrile group is seen to project directly below the face of the alkene thus overriding the steric hindrance noted above and forcing the approach of the catalyst from the *endo* face.

The facial selectivity realized in the Diels–Alder reaction plays an important role in determining the stereochemical outcome of the catalytic hydrogenation. Therefore, in an effort to try and alter the *endo*/*exo* ratio, other dienophiles were examined; these included methyl acrylate, methyl vinyl ketone, and acrolein. Unfortunately, none of these dienophiles gave exclusively one isomer, and the *exo*/*endo* ratios for the Diels–Alder reactions ranged from 1:2 to 1:1. This lack of stereoselectivity is not surprising considering previous experiments with dienes of this nature.[10] All attempts to isomerize either cycloadduct under basic or acid conditions failed. Moreover, attempted cycloaddition, using a variety of Lewis acids ($ZnCl_2$, $Eu(fod)_3$, $SnCl_4$, $TiCl_4$), at a diversity of temperatures (−78 to 0°C) gave unsatisfactory results. In each case, extensive decomposition of the dienophile was observed and only minor amounts of cycloadduct were obtained (ca. 5–



Scheme 2. *Conditions and reagents*: (a) LDA, HMPA, $(HCOC)_n$, THF, 0°C; (b) $ClCO_2Me$, $NaBH_4$, MeOH, −78°C; (c) acrylonitrile, $C_6H_5CH_3$, relux, 48 h; (d) PtO_2, MeOH, 2 h; (e) PPh_3, I_2, imidazole, CH_3CN, Et_2O; (f) LDA, THF, 0°C; (g) **16**, LDA, HMPA (1:1), THF, camphorsulfonyloxaziridine, −78°C.

10%). Although disappointing, from a practical standpoint, the *exo*-isomers could be produced in 40–45% overall yield by using acrylonitrile, while the *endo*-isomers can be generated in similar yields by simply switching the dienophile to methyl acrylate. With this flexibility, and the fact that the substrates are generated in a rapid fashion, the impact of the lack of high selectivity in the cycloaddition is diminished.

With the hydroxyethyl stereochemistries now set, conversion of the alcohol in adducts **10–13** to their corresponding iodides was effectively carried out by treatment with PPh_3, I_2 and imidazole.[11] Deprotonation of each iodide at 0°C with LDA smoothly furnished the *cis*- and *trans*-fused hydroisoquinolines[12] **14–17** in moderate to good yields (Scheme 2). The stereochemistries of these compounds were confirmed by extensive 1D and 2D ^1H and ^{13}C NMR studies, including H–H COSY, HMQC, HMBC and DEPT experiments.

To further probe the utility of this strategy, deprotonation of the gamma hydrogen[13] in **14** and **15** with a 1:1 complex of LDA and HMPA (THF, −78°C) followed by treatment with Davis' camphorsulfonyloxaziridine,[14] or O_2,[13] gave enones **18** and **19**[7] in yields ranging from 50 to 65%. Although not examined to the same extent, oxidative decyanation of **16** proceeded in a similar manner. We believe the advanced features of enones **18** and **19** can potentially be exploited for the construction of the hydroisoquinoline portion of quinine and the manzamine alkaloids. Our efforts are currently being directed at exploring this possibility.

References

1. Bentley, K. W. *Nat. Prod. Rep.* **1999**, *16*, 367.
2. Lednicer, D.; Mitcher, L. A. *The Organic Chemistry of Drug Synthesis*; Wiley: Toronto, 1997; Vol. 7.
3. Lee, M. L. Ph.D. Thesis; University of New Brunswick, 1999.
4. The numbering scheme used is adapted from Tsuda, M.; Kobayashi, J. *Heterocycles* **1997**, *46*, 765.
5. Kaiser, E. M. *Synthesis* **1975**, 705.
6. Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321.
7. All compounds were characterized by ^1H and ^{13}C NMR, IR and HRMS analysis.
8. **General procedure for preparation of cycloadducts**: To a mixture of alcohol (20 mmol) and $NaBH_4$ (40 mmol) in MeOH (40 mL) at −78°C was added methyl chloroformate (30 mmol) in ether (5 mL) dropwise. The resulting mixture was stirred for 30 min and then poured into ice water (20 mL), stirred for 15 min and extracted with ether. The crude dihydropyridine and acrylonitrile (2.5 mL) in toluene (10 mL) was heated at reflux for 48 h. The resulting solution was concentrated and purified by SiO_2 chromatography to give the cycloadducts as colourless oils. Compound **6′**: ^1H NMR (400 MHz, $CDCl_3$): δ 6.13+6.12 (d, 1H, $J=6.2$), 5.03+4.87 (dd, 1H, $J=1.7$, 6.2), 3.76 (t, 2H, $J=6.3$), 3.74+3.71 (s, 3H), 3.46 (dd, 1H, $J=2.2$, 10.4), 3.06 (t, 1H, $J=11.1$), 2.79 (d, 1H, $J=9.1$), 2.59 (m, 1H), 2.43 (dt, 2H, $J=1.2$, 6.3), 1.91 (m, 2H), 1.81 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 156.1+155.6, 146.2+145.8, 125.2+124.7, 121.2+121.1, 60.4+60.3, 52.8, 48.0+47.5, 47.3+46.9, 36.8, 34.3+30.2, 34.0+30.0, 27.6+27.3. Compound **7**: ^1H NMR (400 MHz, $CDCl_3$): δ 6.12 (t, 1H, $J=4.0$), 5.03+4.87 (d, 1H, $J=6.3$), 3.74+3.70 (s, 3H), 3.72 (t, 2H, $J=7$), 3.20 (d, 1H, $J=11.0$), 2.89 (m, 1H), 2.60 (m, 1H), 2.49 (t, 2H, $J=7.0$), 2.37 (m, 1H), 1.82 (dd, 1H, $J=2.0$, 5.0), 1.25 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 156.0+155.4, 147.5+147.1, 124.4+123.9, 120.9, 60.7, 53.4+53.0, 52.7, 48.1+47.5, 37.4+37.1, 35.2+34.9, 33.0, 29.8+29.5. Compound **8**: ^1H NMR (400 MHz, $CDCl_3$): δ 6.24+6.13 (dd, 1H, $J=6.0$, 13.7), 5.02+4.87 (d, 1H, $J=5.1$), 3.77 (m, 2H), 3.70+3.67 (s, 3H), 3.45+3.27 (dd, 1H, $J=2.2$, 10.4), 3.09 (m, 1H), 3.00+2.61 (m, 1H), 2.82 (m, 1H), 2.50 (t, 1H, $J=6.3$), 2.43+2.42 (t, 1H, $J=6.3$), 2.13 (m, 1H), 1.91 (m, 1H), 1.73+1.70 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 156.2+155.6, 146.3+145.9, 125.1+124.6, 121.1+120.8, 60.3+60.2, 52.7, 48.0+47.4, 47.2+46.9, 37.0+36.8, 34.4+34.1, 33.9+30.2, 27.9+27.5. Compound **9**: ^1H NMR (400 MHz, $CDCl_3$): δ 6.24 (dd, 1H, $J=5.6$, 13.6), 5.03+4.90 (m, 1H), 3.79 (t, 2H, $J=6.8$), 3.70+3.67 (s, 3H), 3.10 (m, 1H), 3.03 (d, 1H, $J=10.0$), 2.8 (t, 1H, $J=8.0$), 2.47 (t, 2H, $J=6.8$), 2.08 (brs, 1H), 1.90 (t, 1H, $J=13.2$), 1.57 (dt, 1H, $J=4.0$, 13.2); ^{13}C NMR (400 MHz, $CDCl_3$): δ 155.2, 148.4+148.0, 123.6+123.1, 120.8, 60.8, 52.7+52.6, 47.4, 47.0, 37.4+37.2, 35.6, 33.2, 29.7+29.5, 19.4.
9. MaGee, D. I.; Lee, M. L. *J. Org. Chem.* **2000**, *64*, 2549.
10. Mariano, P. S.; Dunaway-Mariano, D.; Huesmann, P. L. *J. Org. Chem.* **1979**, *44*, 124.
11. Garegg, P. J.; Johansson, R.; Samuelsson, B. *Synthesis* **1984**, 163.
12. **General procedure for hydrogenation and isoquinoline formation**: A mixture of the alcohol (ca. 5 mmol) and PtO_2 (70 mg) in MeOH (10 mL) was stirred under atmospheric hydrogen pressure until no more hydrogen uptake was observed (2–15 h). The resulting alcohols were then added to a mixture of PPh_3, imidazole and I_2 in acetonitrile/Et_20 (1:3, 15 mL) and stirred for 1 h. The heterogenous solution was diluted with hexane and filtered through a pad of SiO_2. After evaporation of the solvent, the iodide was added dropwise in THF (2 mL) to a cooled solution (0°C) of LDA and stirred for 2 h. The solution was quenched with NH_4Cl and after work-up and purification by SiO_2 chromatography gave the saturated alcohols as colourless oils. Compound **14**: ^1H NMR (400 MHz, $CDCl_3$): δ 6.55 (dt, $J=2.1$, 5.0, 1H), 4.02 (brd, $J=24.6$, 1H), 3.83 (brd, $J=28.2$, 1H), 3.70 (s, 3H), 3.05 (d, $J=13$, 1H), 2.93 (t, $J=2.3$, 1H), 2.45 (dm, $J=19.8$, 1H), 2.21 (m, 2H), 2.09 (dm, $J=19.8$, 1H), 2.00–1.92 (m, 2H), 1.54–1.37 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 156.3, 142.5, 119.1, 110.7, 52.6, 47.2, 43.2, 30.8, 30.7, 30.7, 26.9, 25.7; HRMS (M^+–$C_2H_3O_2$): 161.10761. Compound **15**: ^1H NMR (400 MHz, $CDCl_3$): δ 6.48 (br, 1H), 4.14 (br, 1H), 3.76 (br, 1H), 3.66 (s, 3H), 2.7 (1H), 2.50 (d, $J=17.3$, 1H), 2.33 (d, $J=16.0$, 1H), 1.93 (d, $J=16.0$, 1H), 1.45 (m, 1H), 1.33 (m, 2H), 0.88 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 156.0, 144.2, 119.2, 111.7, 52.6, 48.9, 44.2, 35.8, 35.2 34.8, 32.4, 31.8, 29.9; HRMS (M^+–$C_2H_3O_2$): 175.12377. Compound **16**: ^1H NMR (400 MHz, $CDCl_3$): δ 6.48 (br, 1H), 4.14 (br, 1H), 3.76 (br, 1H), 3.66 (s, 3H), 2.7 (1H), 2.50 (d, $J=17.3$,

1H), 2.33 (d, $J=16.0$, 1H), 1.93 (d, $J=16.0$, 1H), 1.45 (m, 1H), 1.33 (m, 2H), 0.88 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 156.5, 141.9, 119.2, 109.4, 55.6, 51.0, 43.5, 33.9, 30.9, 26.3, 25.4; HRMS ($M^+-C_2H_3O_2$): 161.10809. Compound **17**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 (m, 1H), 4.27 (br, 1H), 3.90 (br, 1H), 3.71 (s, 3H), 2.75 (br, 1H), 2.47 (br, 1H), 2.30–1.7 (m, 4H), 1.65–1.30 (m, 3H), 0.85 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 156.2, 143.6, 119.3, 110.4, 55.6, 52.7, 44.5, 40.0, 38.3 37.5, 32.6, 31.2, 29.6; HRMS ($M^+-C_2H_3O_2$): 175.12381.

13. Watt, D. S.; Kyler, K. S.; Freerksen, R. W.; Selikson, S. J.; Wroble, R. R. *J. Org. Chem.* **1983**, *48*, 4087.
14. Davis, F. A.; Sheppard, A. C.; Chen, B. C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679.