Iterative Reductive Alkylation Approach to Alkaloids: A Synthesis of (±)-Monomorine I and Its C-3 Epimer

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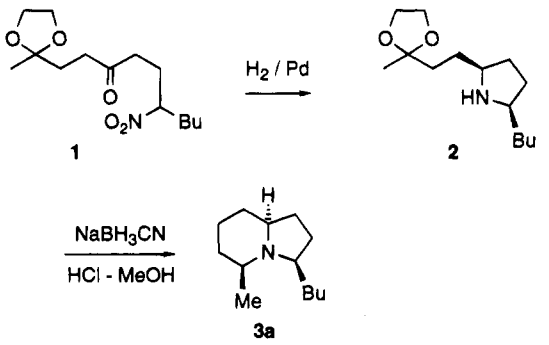
Received February 1, 1994

Due to their large number, structural diversity, and medicinal importance, alkaloids and their synthesis are important topics in organic chemistry. Contained in the structure of many alkaloids is a fused, bicyclic tertiary amine. One of the more direct ways of synthesizing this structural feature is an intramolecular, sequential reductive alkylation reaction between an amine and a dicarbonyl moiety.[1] This approach was used most notably by Stevens[1a] in a synthesis of the indolizidine alkaloid monomorine I (**3a**).[2] In this way (Scheme 1), the carbonyl groups were submitted to the conditions of reductive alkylation in a sequential manner, the first carbonyl group being present at the time of conversion of the nitro group of **1** to the amine, while the second carbonyl group was protected as the dioxolane until the conversion of **2** to **3a**.

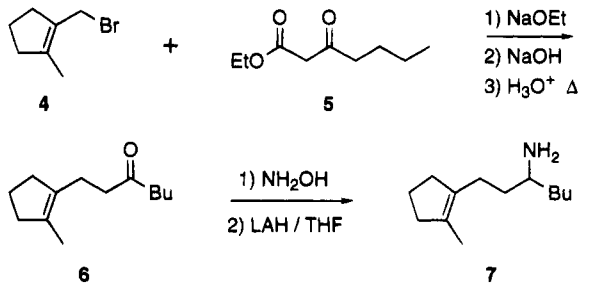
Scheme 1



A more direct method for this overall transformation was sought which would obviate the need for carbonyl protecting groups and provide precursors (analogous to **1**) for alkaloid synthesis which would be amenable to more elaborate arrays of functional groups. We hypothesized that the generation of a dicarbonyl compound from an alkene with the amino group already in place (or protected as the ammonium salt) would provide such an opportunity. This has been shown to be moderately effective in an *intermolecular* reaction between a primary amine and the ozonate of a cycloalkene, giving cyclic tertiary amines.[1b,c] However, the application of this method to the *intra*molecular case which would result in the desired fused, bicyclic system has not been described. Because of its relative simplicity, a 3,5-disubstituted indolizidine such as monomorine I provides a good target for testing this strategy; however, its synthesis does involve the creation of two new asymmetric centers. We report herein the successful application of this strategy to the synthesis of the indolizidine alkaloids (±)-monomorine I (**3a**) and (±)-3-*epi*-monomorine I (**3b**).

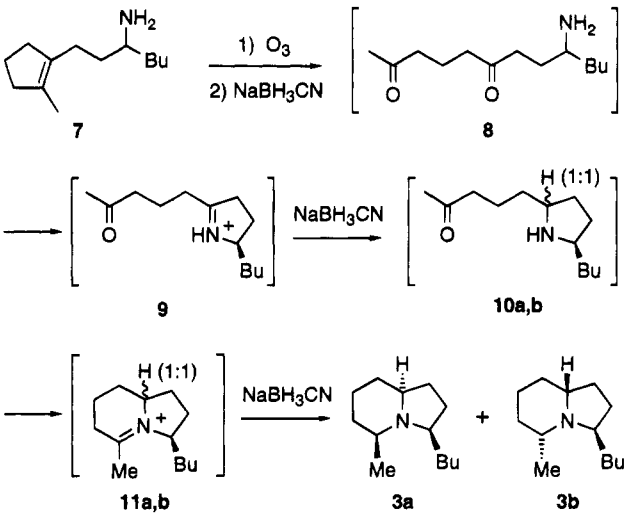
The synthesis of cyclization precursor **7** (Scheme 2) was carried out in a straightforward sequence starting from allylic bromide **4**. Alkylation of the sodium salt of ethyl 3-oxoheptanoate[3] (**5**) was followed by alkaline hydrolysis and decarboxylation to give ketone **6**. Conversion of this ketone to the required primary amine **7** was effected by LAH reduction[4] of the oxime derivative of **6**,[5] in 42% yield from **4**.

Scheme 2



Ozonolysis of **7** in methanol was carried out on the hydrochloride salt to prevent amine oxidation (Scheme 3). After removal of excess ozone using a stream of nitrogen, sodium cyanoborohydride was added directly to the reaction mixture. This gave 74% of a 1:1 mixture of indolizidines (>97% pure by GC) which were separated by silica gel chromatography. These components were identified as (±)-monomorine I (34% isolated yield) and-(±)-3-*epi*-monomorine I (27% isolated yield) by comparison with published proton NMR and mass spectra.[6]

Scheme 3



The addition of hydride to **11a** (H α, giving **3a**) using cyanoborohydride has been shown to be highly stereo-

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selective.[1a] Evidently, addition of hydride to **11b** is also stereoselective, giving a single indolizidine isomer corresponding to (±)-3-*epi*-monomorine I. Variation of C-3 stereochemistry appears to result from a nonselectve addition of hydride to pyrrolinium ion **9**, giving 2,5-disubstituted pyrrolidines **10a** and **10b**. This result is in concert with those of L'hommet wherein addition of hydride from sodium cyanoborohydride produced a 1:1 mixture of 2,5-disubsituted pyrrolidines from the corresponding 1-pyrroline.[7] Steric hindrance of one face of the pyrrolinium ion **9** by the butyl group would be expected to bias hydride addition (especially for larger hydride sources) in favor of the *cis* isomer. This outcome was observed by Stevens[1a] with the use of heterogeneous catalysis. Investigations concerning the effects of reaction conditions, reducing agent, and substrate structure on the stereochemistry of this process are in progress, and the application of this method to the synthesis of other and more complex alkaloids is also being pursued.

Experimental Section

General Methods. TLC analysis was performed on silica gel plates (Whatman 4420−220) and visualized by charring with 5% vanillin in 5% H_2SO_4−ethanol or by exposure to iodine vapor. Proton NMR spectra were recorded at 300 MHz using residual $CHCl_3$ as an internal standard. GLC analyses were performed using FID detection. Combustion analyses were performed by M-H-W Laboratories, Phoenix, AZ.

1-(Bromomethyl)-2-methylcyclopentene (4). (2-Methyl-1-cyclopentenyl)methanol[8] (2.38 g, 21.2 mmol) was dissolved in 50 mL of pentane and cooled to −5 °C in a brine/ice bath, and 7.15 g (42.4 mmol) of 48% HBr was added over 10 min. Once the addition was complete the solution was stirred at −5 °C for 30 min, brine was added, and the layers were separated. The organic layer was washed with saturated $NaHCO_3$ and brine and dried over Na_2SO_4, and the salts were washed twice with 10 mL of pentane. Concentration of the combined pentane filtrates yielded 3.64 g (98%) of an unstable pale yellow oil which was used immediately in the next step.

1-(2-Methylcyclopent-1-enyl)-3-heptanone (6). Sodium metal (95 mg, 4.2 mol) was dissolved in 50 mL anhydrous EtOH under N_2. After the mixture was stirred for 30 min, 160 mg (1.07 mmol) of NaI and 790 mg (4.59 mmol) of ethyl 3-oxoheptanoate (**5**)[3] were added. After an additional 1 h of stirring, 730 mg (4.17 mmol) of 1-(bromomethyl)-2-methylcyclopentene was added to the solution in one portion. The solution was refluxed for 2 h and cooled to rt, and ethanol was removed by rotary evaporation. The brown residue was partitioned between water and ether and washed once with brine, dried with $MgSO_4$, and concentrated to give 1.07 g of a greenish-black oil which was chromatographed on silica gel (hexanes, then 5% ether in hexanes) to afford 0.80 g (72%) of the desired keto ester as a clear oil. ^1H NMR ($CDCl_3$) δ: 0.89 (t, 3H, J = 7.2 Hz); 1.2−1.3 (m, 2H); 1.24 (t, 3H, J = 7.1 Hz); 1.48−1.58 (m, 2H); 1.60 (br s, 3H); 1.73 (pentet, 2H, J = 7.6 Hz); 2.23 (br t, 4H, J = 7.5 Hz); 2.43 (dt, 1H, J = 7.2, 17.4 Hz); 2.53 (dt, 1H, J = 7.3, 17.4 Hz); 2.60 (d, 2H, J = 7.7 Hz); 3.59 (t, 1H, J = 7.7 Hz); 4.15 (m, 2H). IR (film): 1632, 1646, 1718, 1745, 2875 cm^{-1}.

To the above keto ester (3.33 g, 12.5 mmol) dissolved in 1.1 mL of EtOH was added 11 mL of a 15% NaOH solution, and the reaction was heated at 60 °C for 2 h. After cooling, 8 mL of glacial acetic acid was added in one portion (immediate CO_2 evolution), and the reaction was refluxed for 1 h. The mixture was cooled and diluted with ether and water. The ether layer was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. Concentration of the ethereal solution gave 3.56 g of a brown oil, which was chromatographed on silica gel with 5% ether in hexanes (R_f = 0.26) to give 2.30 g (94%) of a pale brown oil. ^1H NMR ($CDCl_3$) δ: 0.89 (t, 3H, J = 7.3 Hz); 1.28 (m, 2H); 1.54 (m, 2H); 1.60 (s, 3H); 1.74 (pentet, 2H, J = 7.7 Hz); 2.24 (t, 2H, J = 7.4 Hz); 2.28−2.48 (br m, 8H). IR (film): 1620, 1710, 2933, 2960 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.37; H, 11.35.

1-(2-Methylcyclopent-1-enyl)-3-heptylamine (7). In 5.2 mL of 95% ethanol and 1 mL of H_2O were dissolved ketone **6** (2.49 g, 12.8 mmol) and hydroxylamine hydrochloride (1.4806 g, 21.31 mmol). With stirring, NaOH (2.60 g, 64.9 mmol) was added in one portion (exotherm). The reaction was refluxed for 1 h and cooled, and 10% HCl was added to pH = 2, stirred for 5 min, and neutralized with saturated $NaHCO_3$. The aqueous phase was extracted twice with 150 mL of ether, and the combined extracts were washed once with brine and dried over Na_2SO_4. Concentration of the dried ethereal phase afforded 2.48 g of a pale yellow oil (R_f = 0.39; 20% ether/hexanes) which was chromatographed on silica gel using 20% ether in hexanes giving 2.14 g (80%) of the off-white, oily oxime as a mixture of isomers. ^1H NMR ($CDCl_3$; integral values related to overlapping triplets at 0.9 ppm taken as 6H) δ: 0.91 (t, J = 7.2 Hz); 0.93 (t, J = 7.2 Hz); 1.37 (m, 4H); 1.48 (m, 4H); 1.61 (br s, 6H); 1.76 (m, 4H); 2.15−2.4 (br m, 16H), 8.92 (br s, 2H). IR (film): 1455, 1657, 1714, 3105, 3238 cm^{-1}. Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.25; H, 11.16; N, 6.98.

$LiAlH_4$ (1.01 g, 26.7 mmol) was suspended in 50 mL of THF, 2.14 g (10.2 mmol) of the above oxime dissolved in 50 mL THF was introduced at rt over 25 min, and the reaction was refluxed for 3 h. The reaction mixture was cooled to 0 °C and quenched by the sequential addition of 1 mL of H_2O, 1 mL of 15% NaOH, and 3 mL of H_2O. After the mixture was stirred for 1 h, the salts were filtered using a glass frit, washed three times with 25 mL of dry THF, and concentrated to give 1.72 g of pale yellow oil. The oil was chromatographed on silica gel eluting with ether and then with NH_3 saturated ether. Removal of solvent afforded 1.40 g (70%) of the desired material as a colorless oil. ^1H NMR ($CDCl_3$) δ 0.89 (t, 3H); 1.22−1.52 (br m, 11H); 1.60 (br s, 3H); 1.73 (pentet, 2H, J = 7.4 Hz); 2.07 (m, 2H); 2.25 (br t, 4H, J = 7.4 Hz); 2.62 (m, 1H). IR (film): 1603, 2841, 2925, 3297, 3370 cm^{-1}. Anal. Calcd for $C_{13}H_{25}N$: C, 79.93; H, 12.90; N, 7.17. Found: C, 79.96; H, 12.79; N, 7.36.

Ozonolysis/Cyclization of Aminoalkene 7: (±)-Monomorine I (3a) and (±)-3-*epi*-Monomorine I (3b). Aminoalkene **7** (438 mg, 2.24 mmol) was dissolved in 20 mL of methanol and brought to pH 5 by the addition of an excess of 1 M HCl in MeOH followed by solid NaOAc to adjust the pH upward. After the mixture was cooled to −78 °C, ozone was bubbled through a gas dispersion tube until the blue color persisted. Excess ozone was removed by passing nitrogen through a gas dispersion tube for 15 min whereupon 549 mg (8.74 mmol) of sodium cyanoborohydride and about 750 mg of 4-Å molecular sieves were added. Cooling was removed and the reaction stirred at rt for 42 h.

Workup consisted of the addition of 10% HCl to pH 1, stirring for 15 min, filtration and concentration. The yellow sludge that remained was partitioned between half-saturated aqueous K_2CO_3 and CH_2Cl_2, and the layers were separated. The aqueous phase was extracted with 100 mL of CH_2Cl_2, and the organic phases were combined, dried with $MgSO_4$ (salts washed 4× with 50 mL total CH_2Cl_2), and concentrated to give 359 mg of a yellow oil. Chromatography of this yellow oil on silica gel (ammonia-saturated 20% ether in hexanes) resulted in two products. The faster eluting band gave 150 mg of a clear oil which was determined by ^1H NMR to be monomorine I while the slower moving band afforded 120 mg of clear oil which was identified as (±)-3-*epi*-monomorine by ^1H NMR.[6] GLC analysis of combined impure fractions (52 mg) showed the presence of (±)-monomorine I and (±)-3-*epi*-monomorine in a 3:2 ratio for total yields of 39% and 35%, respectively.

Acknowledgment. Support for this research was provided by Bucknell University and a Bristol-Myers Squibb Award of Research Corporation. The purchase of a 300 MHz NMR spectrometer was provided for by the National Science Foundation (CHE-9122660) and the Keck Foundation.

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