TOTAL SYNTHESIS OF (+)-MONOMORINE I *VIA* ASYMMETRIC α-KETONIC CLEAVAGE OF 8-AZABICYCLO[3.2.1]OCTAN-3-ONE

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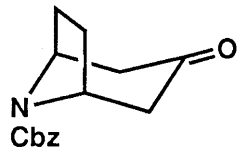
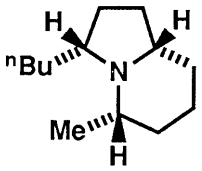
The total synthesis of (+)-monomorine I and preparation of *cis*-2,5-difunctionalized pyrrolidines, as a chiral synthon, starting with asymmetric cleavage of the 'fork head' ketone of 8-azabicyclo[3.2.1]octan-3-one are described.

KEYWORDS (+)-monomorine I; asymmetric α-ketonic cleavage; 'fork head' ketone; asymmetric deprotonation; 8-azabicyclo[3.2.1]octan-3-one; σ-symmetric bicyclic ketone; ant pheromone; σ-symmetric pyrrolidine; ozonolysis

A 2,5-disubstituted pyrrolidine or 2,6-disubstituted piperidine moiety constitutes a large family of naturally occurring alkaloids, many of which display significant biological activities.[1] In a study associated with the asymmetric deprotonation of σ-symmetric bicyclic ketones according to the Koga's method,[2] the asymmetric cleavage of the 'fork head' ketone of 9-azabicyclo[3.3.1]nonan-3-one was found to proceed in high enantiomeric excess (ee) to lead to the *cis*-2,6-difunctionalized piperidine derivative.[3] We examined the application of this procedure to the 8-azabicyclo[3.2.1]octan-3-one system with a view to obtaining a *cis*-2,5-disubstituted pyrrolidine synthon as a chiral building block for the syntheses of natural products with a pyrrolidine skeleton such as monomorine I (**2**)[4] and indolizidine 223AB. Here we describe the total synthesis of (+)-**2**,[5,6,7] a trail pheromone of the pharaoh ant, *via* a 'chiral pyrrolidine' route starting with the asymmetric cleavage of the azabicyclic 'fork head' ketone and also the synthesis of the σ–symmetric pyrrolidine derivative **3** as a chiral building block.



1



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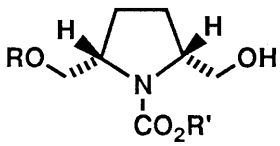
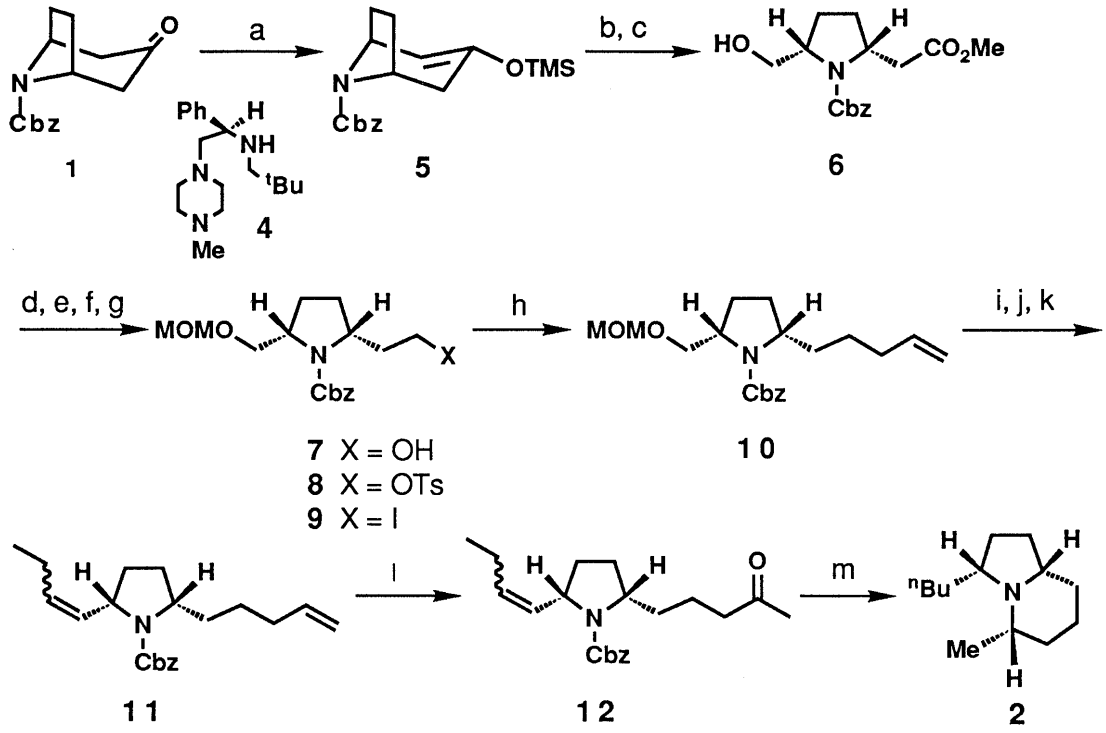


3

An *N*-protected 8-azabicyclo[3.2.1]octan-3-one (**1**) was subjected to the kinetic deprotonation procedure according to the method of Koga[2] [chiral base **4**, *n*-butyllithium (*n*-BuLi), excess trimethylsilyl chloride (TMSCl)] to afford the corresponding trimethylsilyl enolate **5**[8] in 90% ee[9] (89% yield) (Chart 1). Ozonolysis of the silyl enol ether **5** and subsequent sodium borohydride reduction followed by esterification of the resulting carboxylic acid afforded the *cis*-2,5-disubstituted pyrrolidine derivative **6**, $[\alpha]_D^{26}$ -12.3° (*c*, 1.24, $CHCl_3$). Protection of the hydroxyl in **6** with methoxymethyl chloride (MOMCl) followed by reduction with lithium triethylborohydride (Super-Hydride) afforded the alcohol **7** in 84% yield. Compound **7** was converted into the iodide **9**, *via* the tosylate **8**, which was transformed by the Grignard cross coupling reaction with allylmagnesium chloride in the presence of a copper(I) salt into the olefin **10** in 70% yield. Further carbon-chain elongation of **10** was carried out through removal of the methoxymethyl group and the Swern oxidation of the resulting alcohol followed by the Wittig reaction (propyltriphenylphosphonium bromide, *n*-BuLi) to give the diolefin **11** in 77 % yield. Site-selective oxidation of **11** under the Wacker process (O_2, $PdCl_2$, CuCl) smoothly proceeded to give the ketone **12** in 84% yield. Final hydrogenation of **12** over Pd/C in methanol gave (+)-monomorine I (**2**), $[\alpha]_D^{26}$ + 33.2° (*c* 0.6, hexane), in 70% yield after recrystalization of its

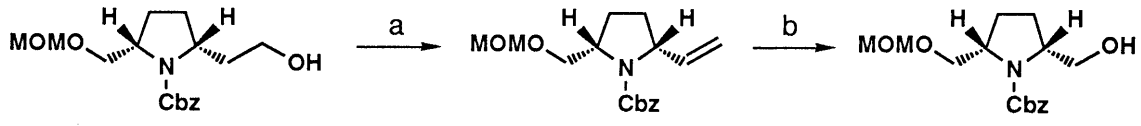
hydrochloride from ether-ethanol, which was identical in its ^{1}H- and ^{13}C-NMR and mass spectra with an authentic specimen [$[\alpha]_D^{22}$ + 34.3° (*c* 1.02, hexane)].[6] The present synthesis is the first entry to the indolizidine alkaloid starting from the chiral pyrrolidine synthon.



Reagents and conditions: a) **4**, *n*-BuLi, TMSCl-HMPA, -100°C; b) O_3,CH_2Cl_2-MeOH(10:1), -78°C and then $NaBH_4$; c) CH_2N_2; d) MOMCl, $(iso\text{-}Pr)_2EtN$; e)Super-Hydride, THF, 0°C~rt; f) TsCl, pyridine; g) NaI, acetone; h) allylmagnesium chloride, CuI, THF, -78~-36°C; i) c.HCl, MeOH; j) $(COCl)_2$, DMSO, Et_3N, -78°C; k) $CH_3CH_2CH{=}PPh_3$, 0°C~rt; l) O_2, $PdCl_2$, CuCl; m) 5% Pd/C, MeOH.

Chart 1

To add to the above synthesis, the σ–symmetric pyrrolidine **3** was synthesized from **7** *via* the following sequences (Chart 2). Treatment of the alcohol **7** with *o*-nitrophenyl selenocyanate followed by oxidation with hydrogen peroxide gave the olefin **13** in 60% yield. Ozonolysis of **13** and subsequent sodium borohydride reduction furnished the pyrrolidine derivative **3**[10] in 60% yield.



Reagents and conditions: a) *o*-$NO_2PhSeCN$, *n*-Bu_3P, THF, rt and then H_2O_2; b) O_3, CH_2Cl_2-MeOH (10:1), -78°C and then $NaBH_4$

Chart 2

Compound **3** is a potential chiral building block for the divergent synthesis of both enantiomers of pyrrolidine alkaloids. Further transformations of **3**, for example, to (-)-monomorine I and other indolizidine alkaloids are under investigation.

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6) For chiral synthesis of (+)-monomorine I, see: N. Yamazaki and C. Kibayashi, *Tetrahedron Lett.*, **29**, 5767 (1988).

7) For chiral synthesis of (-)-monomorine I, see: J. Royer and H.-P. Husson, *J. Org. Chem.*, **50**, 670 (1985).

8) Satisfactory analytical and spectral data were obtained for all new compounds: for example, for **6**; ^{1}H-NMR (270 MHz, $CDCl_3$)δ; 1.60~1.86 (2H, br m), 1.93~2.13 (2H, br m), 2.31~2.60 (1H, br), 2.64~2.80 (1H, br), 3.40~3.70 (4H,br, including at δ 3 56, 3H, br s), 3.79~3.91 (1H, br m), 3.92~4.07 (1H, br), 4.09~4.21 (1H, br, exchangeable with D_2O), 4.25~4.41 (1H, br), 5.11 & 5.16 (2H, AB q, *J*=12.0 Hz), 7.28~7.44 (5H, m). HRMS: Calcd. for $C_{16}H_{21}NO_5$; 307.1419. Found; 307.1459. For **10**; ^{1}H-NMR (270 MHz, $CDCl_3$)δ; 1.22~1.47 (3H, m), 1.53~1.75 (1H, m), 1.84~2.20 (6H, m), 3.30 (3H, br s), 3.35~3.50 (1H, br), 3.52~3.77 (1H, br), 3.85 (1H, br), 4.07(1H, br), 4.60 (2H, br s), 4.92 (1H, d-like, *J*=10.1 Hz), 4.95 (1H, d-like, *J*=16.5 Hz), 5.13 (2H, s), 5.74~5.86 (1H, m), 7.28~7.37 (5H, m). HRMS: Calcd. for $C_{20}H_{29}NO_4$; 347.2097. Found; 347.2140. For **12**; ^{1}H-NMR (270 MHz, $CDCl_3$)δ; 0.80~1.10 (3H, br), 1.25~1.43 (1H, m), 1.51~1.74 (5H, m), 1.85~2.15 (7H, m, including at δ 2.10, 3H, br s), 2.44 (2H, br), 3.89 (1H, br m), 4.60 (1H, br m), 5.11 (2H, br s), 5.25 (1H, t-like, *J*=8.6 Hz), 5.34 (1H, br), 7.27~7.38 (5H, m).HRMS: Calcd. for $C_{21}H_{29}NO_3$; 343.2145. Found; 343.2138.

9) Determined by HPLC using the chiral column OJ (Daicel Chemical Industries, Ltd.).

10) A colorless oil; ^{1}H-NMR (270 MHz, $CDCl_3$)δ; 1.92~2.08 (4H, br), 3.30 (3H, s), 3.45~3.65 (3H, brs), 3.77~3.98 (1H, br), 4.00~4.16 (2H, brm), 4.25~4.40 (1H, br, exchangeable with D_2O), 4.50~4.69 (2H, brs), 5.14 & 5.19 (2H, ABq, *J*=12.8 Hz), 7.31~7.38 (5H, m). $[\alpha]_D^{26}$ -8.3° (*c* 0.78, $CHCl_3$).

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