

# TOTAL SYNTHESIS OF (+)-MONOMORINE I VIA ASYMMETRIC $\alpha$ -KETONIC CLEAVAGE OF 8-AZABICYCLO[3.2.1]OCTAN-3-ONE

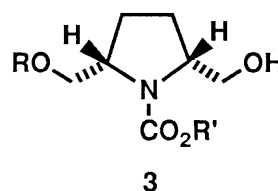
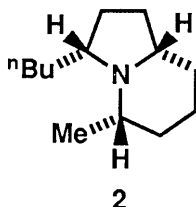
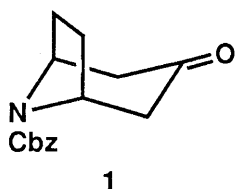
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The total synthesis of (+)-monomorphine I and preparation of *cis*-2,5-difunctionalized pyrrolidines, as a chiral synthon, starting with asymmetric cleavage of the 'fork head' ketone of 8-azabicyclo[3.2.1]octan-3-one are described.

**KEYWORDS** (+)-monomorphine I; asymmetric  $\alpha$ -ketonic cleavage; 'fork head' ketone; asymmetric deprotonation; 8-azabicyclo[3.2.1]octan-3-one;  $\sigma$ -symmetric bicyclic ketone; ant pheromone;  $\sigma$ -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.<sup>1)</sup> In a study associated with the asymmetric deprotonation of  $\sigma$ -symmetric bicyclic ketones according to the Koga's method,<sup>2)</sup> 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.<sup>3)</sup> 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 monomorphine I (2)<sup>4)</sup> and indolizidine 223AB. Here we describe the total synthesis of (+)-2,<sup>5,6,7)</sup> 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  $\sigma$ -symmetric pyrrolidine derivative 3 as a chiral building block.



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<sup>2)</sup> [chiral base 4, *n*-butyllithium (*n*-BuLi), excess trimethylsilyl chloride (TMSCl)] to afford the corresponding trimethylsilyl enolate 5<sup>8)</sup> in 90% ee<sup>9)</sup> (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, [ $\alpha$ ]<sub>D</sub><sup>26</sup> -12.3° (*c*, 1.24, CHCl<sub>3</sub>). 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<sub>2</sub>, PdCl<sub>2</sub>, CuCl) smoothly proceeded to give the ketone 12 in 84% yield. Final hydrogenation of 12 over Pd/C in methanol gave (+)-monomorphine I (2), [ $\alpha$ ]<sub>D</sub><sup>26</sup> + 33.2° (*c* 0.6, hexane), in 70% yield after recrystallization of its

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

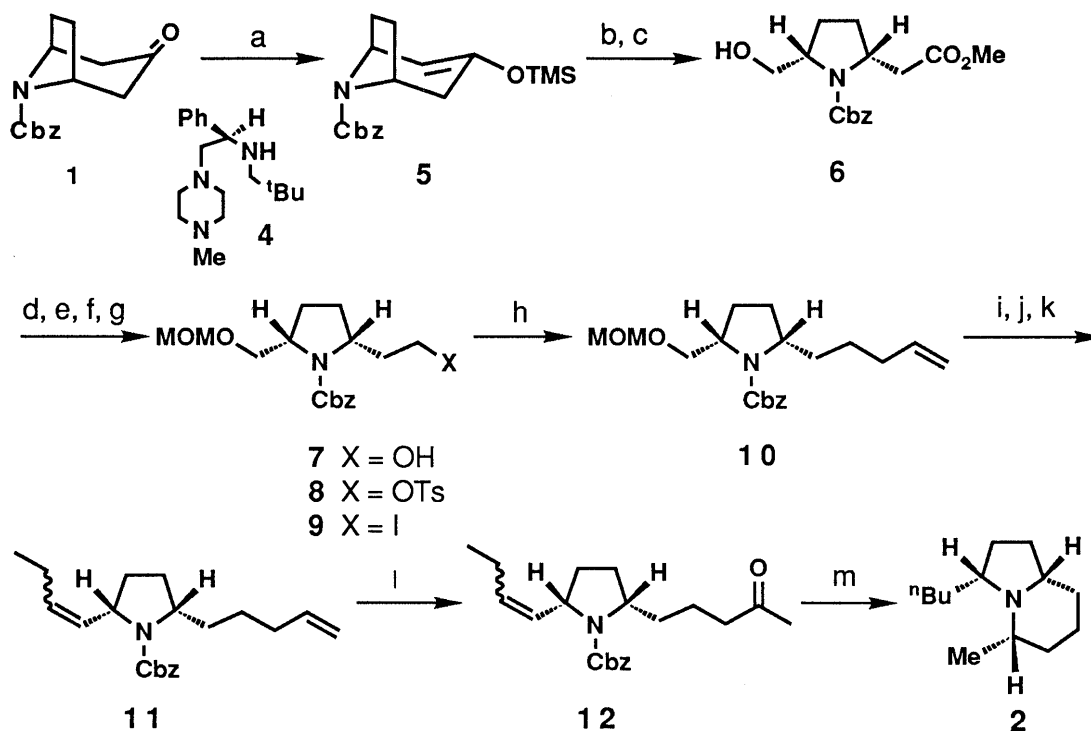


Chart 1

To add to the above synthesis, the  $\sigma$ -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<sup>10)</sup> in 60% yield.

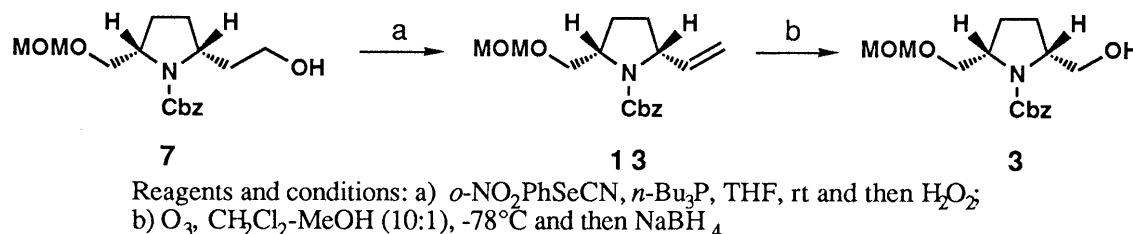


Chart 2

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 (-)-monomarine I and other indolizidine alkaloids are under investigation.

**ACKNOWLEDGEMENT** We are grateful to Professor K. Koga, Tokyo University, for his useful advice for the preparation and properties of the chiral amine **4**, and indebted to Professor C. Kibayashi, Tokyo College of Pharmacy, for his kindly providing us with the  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR and mass spectra of (+)-monomorphine I.

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- 6) For chiral synthesis of (+)-monomorphine I, see: N. Yamazaki and C. Kibayashi, *Tetrahedron Lett.*, **29**, 5767 (1988).
- 7) For chiral synthesis of (-)-monomorphine 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**;  $^1\text{H}$ -NMR (270 MHz,  $\text{CDCl}_3$ ) $\delta$ : 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  $\delta$  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  $\text{D}_2\text{O}$ ), 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  $\text{C}_{16}\text{H}_{21}\text{NO}_5$ ; 307.1419. Found; 307.1459. For **10**;  $^1\text{H}$ -NMR (270 MHz,  $\text{CDCl}_3$ ) $\delta$ : 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  $\text{C}_{20}\text{H}_{29}\text{NO}_4$ ; 347.2097. Found; 347.2140. For **12**;  $^1\text{H}$ -NMR (270 MHz,  $\text{CDCl}_3$ ) $\delta$ : 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  $\delta$  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  $\text{C}_{21}\text{H}_{29}\text{NO}_3$ ; 343.2145. Found; 343.2138.
- 9) Determined by HPLC using the chiral column OJ (Daicel Chemical Industries, Ltd.).
- 10) A colorless oil;  $^1\text{H}$ -NMR (270 MHz,  $\text{CDCl}_3$ ) $\delta$ : 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  $\text{D}_2\text{O}$ ), 4.50~4.69 (2H, brs), 5.14 & 5.19 (2H, ABq,  $J=12.8$  Hz), 7.31~7.38 (5H, m).  $[\alpha]_{\text{D}}^{26}$  -8.3° (c 0.78,  $\text{CHCl}_3$ ).

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