Synthesis of (−)-Monomorine I

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Abstract: (−)-Monomorine I has been synthesized using a stereoselective intramolecular 1,6-conjugate addition of a hydroxylamine to a dienyl ester, followed by a tandem hydrogenation–lactamization reaction.

Key words: Michael addition, tandem reaction, alkaloid, lactam, heterocycle

The synthesis of indolizidine alkaloids remains a field of great interest, not only due to the biological properties of many of these alkaloids, but also due to the challenge of achieving effective and efficient control of the stereochemistry.1 Amongst the indolizidine alkaloids, a large number possess alkyl substituents at positions 3 and 5. Amongst these 3,5-dialkylindolizidines, (+)-monomorine I, a pheromone of the pharaoh ant,2 as well as its enantiomer, (−)-monomorine I (1), and its racemic form, have become frequent targets for synthetic chemists and are widely used to demonstrate the efficacy of synthetic methodology (Figure 1).3–5

Figure 1 (−)-Monomorine I

The problem of controlling the relative stereochemistry of the piperidine ring was solved with great elegance by Stevens and Lee in work that has become a classic application of stereoelectronic control.4 Numerous other methods have been devised for controlling the stereochemistry of the pyrrolidine ring, and the issue of absolute stereochemistry. While there are excellent methods for controlling stereochemistry during five-membered-ring formation, six-membered rings tend to be more reliable and predictable as they can adopt a well-understood chair conformation. With this thought in mind, we set out to apply our recently reported 1,2-oxazine method6 to the synthesis of (−)-monomorine I (1) and, thus, demonstrate a rapid and efficient route to indolizidines. In particular, we anticipated that the use of tandem reactions would shorten the synthesis and that we would be able to establish the two chiral centers of the pyrrolidine by formation of a six-membered tetrahydro-1,2-oxazine ring 2 (Scheme 1), then relay those stereocenters into the desired five-membered ring by a sequence of a ring-opening and a reclosing reaction.

Scheme 1 (−)-Monomorine I retrosynthesis

Commercially available hex-1-ene oxide was subjected to hydrolytic kinetic resolution using Jacobsen’s catalyst.7 The unreacted (S)-epoxide 3 (>99% ee by chiral GC) was then treated with allylmagnesium bromide to give second-ary alcohol 4. Substitution of the hydroxy group with N-hydroxyphthalimide under Mitsunobu conditions8 proceeded satisfactorily provided that the reaction was maintained at room temperature. It was also found that this reaction proceeded with complete inversion most reliably when conducted in toluene, rather than tetrahydrofuran.9 Cross-metathesis of the N-alkoxyphthalide 5 with crotonaldehyde, employing Grubbs’ second-generation catalyst, followed by Wittig reactions with the appropriate ylides yielded the desired dienes 7a and 7b (Scheme 2). While the intermediate aldehyde 6 may be isolated, this is not necessary. The ylide may be added to the crude product of the cross-metathesis, provided that the excess crotonaldehyde has been removed in vacuo.

The first of the two planned tandem reactions, deprotection-1,6-conjugate addition, was achieved using the previously reported method.6 Liberation of the hydroxylamine of 7a on treatment with hydrazine hydrate gave the tetrahydro-1,2-oxazine 8 as a single stereoisomer (Scheme 3). The ring stereochemistry was assigned to be trans in accordance with previous studies;6 although the 1H NMR signals for the protons at C3 and C6 were not resolved. This assignment was subsequently confirmed by conversion into the natural product. In contrast, when the corresponding methyl ketone 7b was employed in an analogous sequence, attempted liberation of the hydroxylamine under the same conditions yielded a complex mixture, possibly due to competing condensation with the ketone carbonyl.
monomorine thus obtained was in good agreement with that reported by others.3–5,11 An optical rotation of –35.5 was obtained for the synthetic compound, which may be compared to +35.1 reported for the natural product.2

Scheme 4  Monomorine synthesis

(–)-Monomorine I (1) has been prepared by a flexible route that may be adapted for the synthesis of analogues and the opposite antipode. The overall yield, from resolved hexene oxide, is 26% and the synthesis is complete in just nine steps including a tandem deprotection–intramolecular Michael addition and a tandem double hydrogenation–lactamization. The application of this method to indolizidines with other substitution patterns is under way.

THF was distilled from Na/benzophenone, CH2Cl2 was distilled from CaH2 and Et2O was obtained from a solvent purifier (alumina column). Other reagents and solvents were commercial and used as received. IR spectra were recorded on a Bio-Rad FTS 165 spectrophotometer either neat or as Nujol mulls using NaCl plates.1 H NMR spectra were recorded on a Bruker Advance DPX300 at 300 MHz with residual protic solvent as the reference.13C spectra were recorded at the corresponding frequency on the same instrument. Mass spectra were recorded on a Finnigan Trace GC Ultra instrument at 70 eV with El mode. HRMS were recorded on a Finnigan MAT95XP instrument, also using El mode. Specific rotations, [α]D, were recorded on an Jasco P-1030 polarimeter and are given with units of 10–1deg·cm2·g–1. Elemental analysis was carried out at Nanyang Technological University.

(5)-Non-1-en-5-ol (4)14 Allyl bromide (15 mL, 60 mmol) was slowly added dropwise to Mg turnings (2.7 g, 112.8 mmol) in anhyd Et2O. The mixture was stirred for 1.5 h and the resulting Et2O soln was transferred by cannula to a new flask. 1,2-Epoxyhexane (3.0 g, 3.6 mL, 30 mmol) was added slowly. The mixture was stirred for 1 h and then sat. aq NH4Cl (20 mL) and H2O (20 mL) were added. The mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (3 × 10 mL) and dried (MgSO4) (20 mL) and H2O (20 mL) were added. The mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (3 × 10 mL) and dried (MgSO4). The solvent was evaporated to afford 4 (3.6 g, 85%) as a colorless oil, which was used without purification; Rf = 0.49 (hexanes–EtOAc, 9:1).

[α]D25 = –0.9 (c 1.32, CH2Cl2).

1H NMR (300 MHz, CDCl3): δ = 0.91 (t, J = 6.9 Hz, 3 H), 1.32–1.56 (m, 8 H), 2.12–2.21 (m, 2 H), 3.61–3.64 (m, 1 H), 4.97 (ddt, J = 10.1, 2.2, 1.2 Hz, 1 H), 5.05 (ddt, J = 17.2, 1.8, 1.6 Hz, 1 H), 5.84 (ddt, J = 6.7, 10.2, 17.1 Hz, 1 H).

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**13**C NMR (75 MHz, CDCl₃): δ = 138.7, 114.7, 71.5, 37.2, 36.5, 30.1, 27.8, 22.7, 14.0.

(R)-5-[(1,3-Dioxo-1,3-dihydro-2H-isooindol-2-yl)oxy]non-1-ene (5)

Alcohol 4 (3.6 g, 25 mmol), PhthNOH (4.08 g, 25 mmol), and Ph₃P (6.56 g, 25 mmol) were dissolved in toluene (100 mL). DIAD (6.06 g, 5.9 mL, 30 mmol) was added dropwise at 0 °C and the mixture was stirred at r.t. overnight. The solvent was evaporated and the residue was purified by flash chromatography (hexane–EtOAc, 90:10) to afford 5 (7.2 g, 99%) as a colorless oil that solidified during refrigeration; Rf = 0.3 (hexanes–EtOAc, 9:1).

IR (NaCl): 3000, 2954, 2931, 1789, 1693, 1371, 1124, 877 cm⁻¹.


MS (EI): m/z (%) = 288.11 [M + H] +, 230.11, 125.27, 164.13, 129.4, 129.1, 129.0, 123.4, 114.9, 87.64, 32.1, 31.6, 29.1, 27.0, 22.7, 14.0.

Aldehyde (0.42 g, 0.49 mL, 6 mmol) was added and the mixture was heated at reflux for 3 h under N₂. The volatiles were evaporated and the residue was taken up in CH₂Cl₂ (18 mL). Methyl (triphenylphosphorane) (208 mg, 0.66 mmol) were dissolved in MeCN (4 mL) and heated at reflux for 36 h under N₂. The mixture was pre-absorbed on silica gel (1 g) and purified by flash chromatography (silica gel, hexane–EtOAc, 9:1) to give 6 (0.07 g, 60%) as a colorless oil; Rf = 0.33 (hexanes–EtOAc, 3:1).

IR (NaCl): 3000, 2870, 2860, 1730, 1645, 1597, 1447, 1277, 1128 cm⁻¹.

HRMS (EI): m/z (%) = 316.07 [M + H] +, 192.20 (100), 135.19, 135.0, 129.4, 129.1, 129.0, 123.4, 87.4, 32.2, 31.5, 28.4, 27.1, 22.8, 14.0.

Methyl (35,6R,8E)-6-(Butyltetrahydro-2H-1,2-oxazin-3-yl)but-3-en-6-one (8)

Dienyl ester (1.2 g, 3.2 mmol) was dissolved in CH₂Cl₂ (10 mL) and hydrazine hydrate (0.6 mL, 20.2 mmol) was added. The mixture was stirred at r.t. for 10 h. The mixture was filtered through Celite and the filtrate was evaporated. The residue was purified by flash chromatography (hexane–EtOAc, 95:5) to afford 8 (750 mg, 96%) as a colorless oil; Rf = 0.39 (EtOAc).

**Alkene** 5 (0.6 g, 2.1 mmol) and Grubbs II catalyst (0.04 mmol) were dissolved in CH₂Cl₂ (12 mL). Crotonaldehyde (0.42 g, 4.9 mL, 6 mmol) was added and the mixture was heated at reflux for 2 h under N₂. The volatiles were evaporated and the residue was purified by flash chromatography (hexane–EtOAc, 90:10) to afford 6 (600 mg, 92%) as a colorless oil; Rf = 0.38 (hexanes–EtOAc, 3:1).

IR (NaCl): 3000, 2954, 2931, 1789, 1372, 1371, 1188, 797 cm⁻¹.

HRMS (EI): m/z (%) = 356.07 [M + H] +, 192.20 (100), 135.19, 135.0, 129.4, 129.1, 129.0, 123.4, 87.4, 32.2, 31.5, 28.4, 27.1, 22.8, 14.0.

Methyl (35,6R,8E)-6-(Butyltetrahydro-2H-1,2-oxazin-3-yl)but-3-en-6-one (8)

Dienyl ester 7a (1.2 g, 3.2 mmol) was dissolved in CH₂Cl₂ (10 mL) and hydrazine hydrate (0.6 mL, 20.2 mmol) was added. The mixture was stirred at r.t. for 10 h. The mixture was filtered through Celite and the filtrate was evaporated. The residue was purified by flash chromatography (hexane–EtOAc, 95:5) to afford 7a (750 mg, 96%) as a colorless oil; Rf = 0.39 (EtOAc).

**Alkene** 5 (0.6 g, 2.1 mmol) and Grubbs II catalyst (0.04 mmol) were dissolved in CH₂Cl₂ (12 mL). Crotonaldehyde (0.42 g, 4.9 mL, 6 mmol) was added and the mixture was heated at reflux for 2 h under N₂. The volatiles were evaporated and the residue was taken up in CH₂Cl₂ (18 mL). Methyl (triphenylphosphoranylidene)acetate (0.07 g, 2.3 mmol) was added and the mixture was stirred at r.t. under N₂ overnight. The solvent was evaporated and the residue was purified by flash chromatography (hexane–EtOAc, 75:25) to afford 7a (0.07 g, 60%) as a colorless oil; Rf = 0.33 (hexanes–EtOAc, 3:1).

IR (NaCl): 3000, 2954, 2931, 1789, 1372, 1371, 1215, 977 cm⁻¹.

HRMS (EI): m/z (%) = 242.18 [M + H] +, 184.22, 168.30, 144.24, 135.19, 135.0, 129.4, 129.1, 129.0, 123.4, 87.4, 32.2, 31.5, 28.4, 27.1, 22.8, 14.0.

**Methyl (35,6R,8E)-6-(Butyltetrahydro-2H-1,2-oxazin-3-yl)but-3-en-6-one (8)**

Dienyl ester 7a (1.2 g, 3.2 mmol) was dissolved in CH₂Cl₂ (10 mL) and hydrazine hydrate (0.6 mL, 20.2 mmol) was added. The mixture was stirred at r.t. for 10 h. The mixture was filtered through Celite and the filtrate was evaporated. The residue was purified by flash chromatography (hexane–EtOAc, 95:5) to afford 8 (750 mg, 96%) as a colorless oil; Rf = 0.39 (EtOAc).

IR (NaCl): 3000, 2953, 2933, 1789, 1372, 1188, 977 cm⁻¹.

HRMS (EI): m/z (%) = 288.11 [M + H] +, 192.20, 135.19, 135.0, 129.4, 129.1, 129.0, 123.4, 87.4, 32.2, 31.5, 28.4, 27.1, 22.8, 14.0.
(R)-6-[R]-3-Hydroxyheptylpiperidin-2-one (10)

**Experimental Procedure**: 

PotO (10 mg, 0.04 mmol) and CD3CO2 (10 mg, 0.1 mmol) were added to a soln of oxazine 8 (100 mg, 0.414 mmol) in MeOH (6 mL). The mixture was stirred under H2 (balloon) for 1 h. The mixture was filtered and the filtrate was evaporated. The residue was purified by flash chromatography (EtOAc–MeOH, 95:5) to give 10 (75 mg, 88%) as a low melting point white solid; mp 63–65 °C; Rf = 0.13 (EtOAc).

**NMR Data**: 

**1H NMR (300 MHz, CDCl3)**: δ = 4.71–4.80 (s, 1 H), 1.76 (m, 12 H), 1.90–1.92 (m, 2 H), 2.27–2.41 (m, 2 H), 3.31–3.45 (m, 2 H).

**13C NMR (75 MHz, CDCl3)**: δ = 172.5, 83.0, 52.6, 38.6, 34.1, 31.8, 31.2, 30.0, 28.1, 27.1, 22.4, 19.6, 8.53.


**MS (EI)**: m/z (%) = 195.15 [M]+, 180.22, 138.16 (100), 124.29, 123.32.

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We previously reported similar transformations which proceeded satisfactorily with Pd/C: (a) The difference is likely to be due to the different batches and suppliers of Pd/C. Variability in this material has been reported: Bates, R. W.; Boonsombat, J. Org. Biomol. Chem. 2005, 3, 520. (b) Ikawa, T.; Sajiki, H.; Hirota, K. Tetrahedron 2004, 60, 6189.

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