Asymmetric Synthesis of (+)-Monomorine I by way of a Diastereoselective Reaction of 1,3-Oxazolidine with a Grignard Reagent

Kimio Higashiyama, Keiji Nakahata and Hiroshi Takahashi
Faculty of Pharmaceutical Science, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

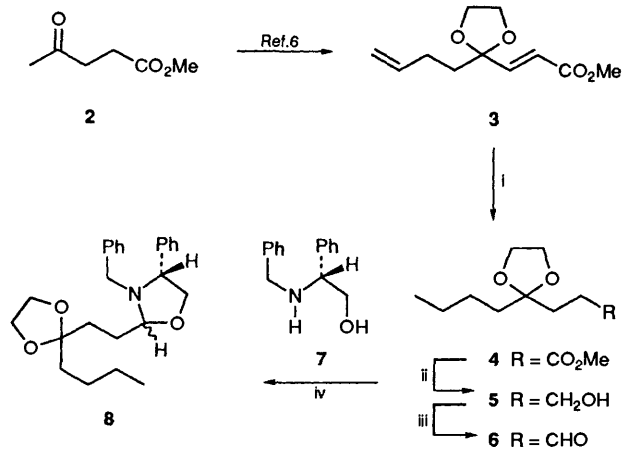
The indolizidine alkaloid, (+)-monomorine I **1**, has been prepared in an asymmetric synthesis employing the highly diastereoselective reaction of a 1,3-oxazolidine with a Grignard reagent.

Chiral 1,3-oxazolidines, readily synthesized by condensing (*S*)- or (*R*)-*N*-alkyl-2-hydroxyethylamines such as (*S*)-*N*-alkylvalinol or (*R*)-*N*-alkylphenylglycinol with carbaldehydes,[1] react with various organometallic reagents in a highly diastereoselective manner, ultimately providing a route for generating chiral amines in high chemical and optical yields.[2] We have already reported the application of such reactions to the synthesis of two piperidine alkaloids, (*R*)-(−)-coniine and (2*R*,6*S*)-(+)-dihydropinidine.[3]

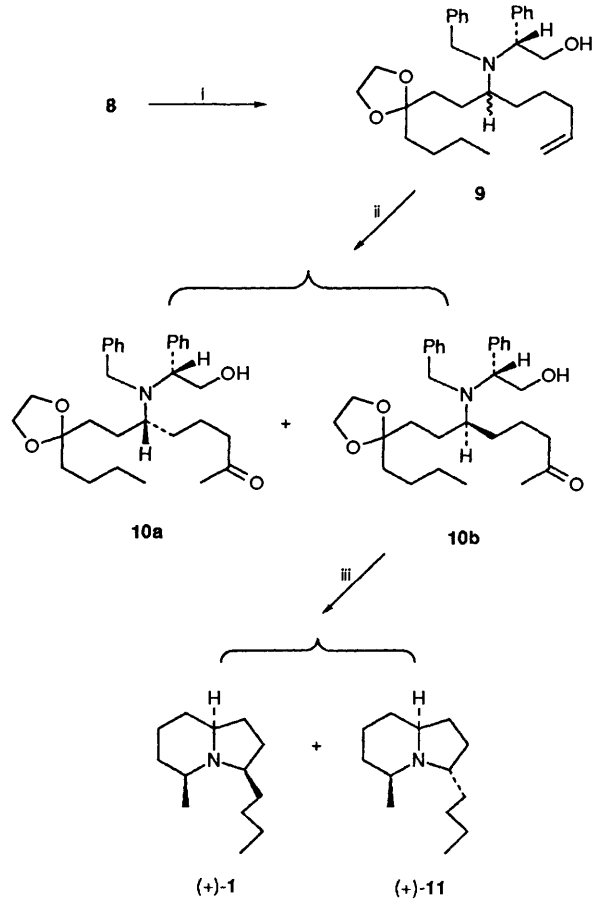
We have now extended this work, with the enantioselective total synthesis of (+)-monomorine I **1**, by a diastereoselective reaction of a 1,3-oxazolidine derived from (*R*)-phenylglycinol with a Grignard reagent. (+)-Monomorine I **1** was earlier isolated from the tropical Pharoah's ant *Monomorium pharaonis*[4] as a major component having trail-following activity.[5]

Results and Discussion

The key intermediate in the synthesis of the title alkaloid, the starting chiral 1,3-oxazolidine, was prepared as follows. Methyl 4,4-(ethylenedioxy)octa-2,7-dienoate **3**, readily available from methyl levulinate **2** by a known procedure,[6] was converted into the aldehyde **6** (57% overall yield) by the sequence: catalytic hydrogenation, reduction with lithium aluminium hydride and oxidation with pyridinium chlorochromate (PCC). Condensation of **6** with *N*-benzylphenylglycinol **7** in dichloromethane in the presence of anhydrous magnesium sulfate gave a quantitative yield of the desired 1,3-oxazolidine **8**. Although the ^{1}H NMR results for this product showed that it was a thermodynamic mixture[7] as a result of the asymmetric centre at the 2-position, since the minor component was <7%, the oxazolidine was used for the subsequent reaction without purification (see Scheme 1).



Scheme 1 *Reagents and conditions:* i, H_2, 10% Pd/C, MeOH, room temp., 23 h (91%); ii, $LiAlH_4$, THF, room temp., 1 h (91%); iii, PCC, CH_2Cl_2, room temp., 4 h (67%); iv, *N*-benzylphenylglycinol **7**, $MgSO_4$, CH_2Cl_2, room temp., 6 h (89%)



Scheme 2 *Reagents and conditions:* i, CH_2=$CH(CH_2)_3MgBr$, THF, −15 °C then room temp., 72 h (73%); ii, O_2, $PdCl_2(MeCN)_2$, $CuCl_2$, MeOH, room temp., 2 h (**10a**, 3%; **10b**, 75%); iii, H_2, 10% Pd/C, MeOH–3% HCl, room temp., 96 h (**1**, 78%; **11**, 8%)

The reaction of **8** with pent-4-enylmagnesium bromide in tetrahydrofuran at −15 °C furnished the alcohol **9** (73%) as an inseparable diastereoisomeric mixture in a ratio of 91.5:8.5. This, when subjected to the Wacker procedure, afforded a 4:96 mixture of the methyl ketones **10a** and **10b** (78% total yield). After separation of the two isomers by silica gel column chromatography, **10b** was submitted to catalytic hydrogenation (Pd/C) to provide (+)-monomorine I **1** (78%) along with its C-3 epimer (+)-indolizidine 195B **11** (8%) (see Scheme 2). The spectroscopic data and the specific optical rotation of synthetic (+)-**1** were identical with those reported.[8]

Experimental

General Methods.—M.p.s were measured with a Yanagimoto-Micro Melting Point apparatus and are uncorrected. IR spectra were recorded on a 215 Hitachi Grating I.R. spectro-

photometer. ^{1}H NMR spectra were obtained on a JEOL PMX 270 instrument, and chemical sifts are reported in ppm on the δ scale from internal tetramethylsilane. Mass spectra were measured with a JEOL JMS D-300 spectrometer by using the chemical ionization (CI) (isobutane) methods. Optical rotation were taken with a JASCO-DIP-370 polarimeter.

Methyl 4,4-*Ethylenedioxyoctanoate* **4**.—A solution of compound **3** (1.0 g, 4.71 mmol) in methanol (30 cm^3) was hydrogenated over 10% palladium on carbon (100 mg) at atmospheric pressure for 23 h. The catalyst was filtered off and washed with methanol and the combined filtrate and washings were evaporated under reduced pressure. The residual oil was distilled to afford the ester **4** (0.93 g, 91%) as a colourless oil, b.p. 90 °C at 3.0 mmHg (Found: C, 61.0; H, 9.5. Calc. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32%); ν_{max}(film)/cm^{-1} 2940 (CH) and 1730 (C=O); δ_H(270 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 7.3, CH_3), 1.26–1.33 (4 H, m, $CH_3CH_2CH_2$), 1.56–1.62 [2 H, m, $CH_3(CH_2)_2CH_2$], 1.99 (2 H, t, *J* 7.3, $CH_2CH_2CO_2CH_3$), 2.37 (2 H, t, *J* 7.3, $CH_2CO_2CH_3$), 3.69 (3 H, s, OCH_3) and 3.93 (4 H, s, OCH_2CH_2O); *m/z* (CI, isobutane) 217 (M^+ + H) and 157 ($M^+ - CO_2CH_3$).

4,4-*Ethylenedioxyoctanol* **5**.—To a suspension of lithium aluminium hydride (0.26 g, 6.58 mmol) in dry THF (50 cm^3) at room temperature was added dropwise a solution of the ester **4** (1.0 g, 4.62 mmol) in THF (20 cm^3) over a 20 min period. The reaction mixture was stirred for 1 h after which the excess of hydride was decomposed by the slow addition of water (1 cm^3) and the mixture was filtered through a little Celite. Evaporation of the filtrate gave a colourless oil, which was distilled to give the alcohol **5** (0.73 g, 91%) as a colourless oil, b.p. 96 °C (0.5 mmHg); ν_{max}(film)/cm^{-1} 3400 (OH) and 2940 (CH); δ_H(270 MHz; $CDCl_3$) 0.89 (3 H, t, *J* 7.3, CH_3), 1.30–1.76 [10 H, m, $CH_3(CH_2)_3$, $(CH_2)_2CH_2OH$], 2.34 (1 H, br s, OH), 3.64 (2 H, t, *J* 6.1, CH_2OH) and 3.95 (4 H, m, OCH_2CH_2O); *m/z* (CI, isobutane) 189 (M^+ + H) and 157 (M^+ − OH).

4,4-*Ethylenedioxyoctanal* **6**.—To a solution of PCC (1.00 g, 9.23 mmol) in dry CH_2Cl_2 (100 cm^3) at room temperature was added dropwise a solution of the alcohol **5** (1.16 g, 6.16 mmol) in dry CH_2Cl_2 (20 cm^3) over a 20 min period. After being stirred for 4 h at room temperature, the reaction mixture was diluted with ether (100 cm^3), and filtered through a little Celite. Evaporation of the filtrate gave a brown oil, which was purified by distillation to give the aldehyde **6** (0.77 g, 67%) as a colourless oil, b.p. 80 °C at 1.0 mmHg (Found: C, 64.2; H, 9.9. Calc. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74%); ν_{max}(film)/cm^{-1} 2940 (CH) and 1715 (C=O); δ_H(270 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 6.7, CH_3), 1.25–1.39 [4 H, m, $CH_3(CH_2)_2$], 1.52–1.69 [2 H, m, $CH_3(CH_2)_2CH_2$], 2.30 (2 H, t, *J* 6.7, CH_2CH_2CHO), 2.44 (2 H, dt, *J* 6.7 and 1.8, CH_2CH_2CHO), 3.91 (4 H, m, OCH_2CH_2O) and 9.70 (1 H, t, *J* 1.8, CHO); *m/z* (CI, isobutane) 187 (M^+ + H).

(2R,4R)-3-*Benzyl*-2-(3,3-*ethylenedioxyheptyl*)-4-*phenyl*-1,3-*oxazolidine* **8**.—To a solution of *N*-benzylphenylglycinol **7** (0.77 g, 3.38 mmol) in dry CH_2Cl_2 (40 cm^3) in the presence of anhydrous $MgSO_4$ (5.0 g) was added dropwise a solution of the aldehyde **6** (0.70 g, 3.75 mmol) in dry CH_2Cl_2 (10 cm^3) over a 10 min period at room temperature. After the reaction mixture had been stirred for 6 h it was filtered through a little Celite and the filtrate concentrated under reduced pressure. The residue was crystallized to afford the oxazolidine **8** (1.2 g, 89%) as colourless prisms, m.p. 56 °C (from MeOH); $[\alpha]_D^{25}$ −30.60 (*c* 1.05, $CHCl_3$) (Found: C, 76.1; H, 8.5; N, 3.3. Calc. for $C_{25}H_{33}NO_3$: C, 75.91; H, 8.41; N, 3.54%); ν_{max}(film)/cm^{-1} 2950 (CH); δ_H(270 MHz; $CDCl_3$) major component; 0.87 (3 H, t, *J* 6.7, CH_3), 1.21–1.34 [4 H, m, $(CH_2)_2$], 1.36–1.51 [4 H, m, $(CH_2)_2$], 1.53–1.83 (2 H, m, CH_2), 3.49 (1 H, d, *J* 14.0, $PhCH_2N$), 3.67 (1 H, t, *J* 7.9, $PhCHCH_2O$), 3.75–3.92 (6 H, m, $PhCH_2N$, $PhCHCH_2O$, OCH_2CH_2O), 4.12 (1 H, t, *J* 7.3, $PhCHCH_2O$), 4.37 (1 H, dd, *J* 3.1 and 5.5, NCHO), 7.15–7.41 (10 H, m, ArH); minor component; 4.61–4.65 (1 H, m, NCHO); *m/z* (CI, isobutane) 369 (M^+ + H).

6-[N-*Benzyl*-N-(2-*hydroxy*-1-*phenylethyl*)*amino*]*tridec*-1-*en*-9-*one Ethylene Acetal* **9**.—To a stirred solution of pent-4-enylmagnesium bromide, prepared from pent-4-enyl bromide (0.57 g, 3.82 mmol) and Mg (0.1 g, 4.11 mmol), in dry THF (10 cm^3) was added dropwise at 0 °C a solution of the oxazolidine **8** (0.50 g, 1.26 mmol) in dry THF (10 cm^3) under nitrogen over a 1 h period. After the reaction mixture had been stirred at room temperature for 72 h it was quenched with water (1 cm^3) and filtered through a little Celite. The filtrate was dried (Na_2SO_4) and concentrated to give a pale yellow oil which was subjected to column chromatography on silica gel with hexane–ether (2:1) to give a diastereoisomeric mixture (91.5:8.5 as determined by ^{1}H NMR) of **9** (0.43 g, 73%) as a colourless oil (Found: C, 77.1; H, 9.3; N, 3.0. Calc. for $C_{30}H_{45}NO_3$: C, 77.38; H, 9.31; N, 3.01%); ν_{max}(film)/cm^{-1} 3540 (OH), 2945 (CH) and 1640 (C=C); δ_H(270 MHz; $CDCl_3$) (major component) 0.87 (3 H, t, *J* 6.7, CH_3), 0.93–1.75 [14 H, m, $(CH_2)_7$], 1.85–2.03 (2 H, m, $CH_2CH{=}CH_2$), 2.44 (1 H, br s, OH), 2.56–2.59 (1 H, m, CHN), 3.44–3.96 (9 H, m, $PhCH_2N$, $PhCHCH_2OH$, OCH_2CH_2O), 4.82–5.07 (2 H, m, $CH{=}CH_2$), 5.72–5.89 (1 H, m, $CH{=}CH_2$) and 7.25–7.39 (10 H, m, ArH); (minor component) 5.52–5.67 (1 H, m, $CH{=}CH_2$); *m/z* (CI, isobutane) 466 (M^+ + H).

(6S,1'R)-6-[N-*Benzyl*-N-(2-*hydroxy*-1-*phenylethyl*)*amino*]-*tridecane*-2,9-*dione* **10**.—Oxygen gas was bubbled into a stirred mixture of compound **9** (807 mg, 1.73 mmol), $(MeCN)_2PdCl_2$ (200 mg, 0.78 mmol) and $CuCl_2$ (300 mg, 2.23 mmol) in methanol (50 cm^3) at room temperature for 2 h. The catalyst was filtered off and the catalyst was washed with methanol and the combined filtrates were evaporated under reduced pressure. The resulting residue was dissolved in 10% aqueous ammonium hydroxide (20 cm^3) and extracted with benzene (3 × 20 cm^3) and the combined extracts were washed with brine (20 cm^3), dried (Na_2SO_4) and concentrated to give a pale brown viscous oil. This was subjected to column chromatography on silica gel with hexane–ether (2:1). The first fractions gave the minor ketone **10a** (23 mg, 3%) as a colourless gum; ν_{max}(film)/cm^{-1} 3480 (OH), 2925 (CH) and 1700 (C=O); δ_H(270 MHz; $CDCl_3$) 0.66–0.80 (1 H, m, CH_2), 0.81–1.00 (1 H, m, CH_2), 0.92 (3 H, t, *J* 7.3, CH_3), 1.12–1.40 [3 H, m, $(CH_2)_2$], 1.41–1.81 [5 H, m, $(CH_2)_3$], 2.02 (3 H, s, $COCH_3$), 2.06 (2 H, t, *J* 7.3, CH_2CO), 2.16 (1 H, br s, OH), 2.30–2.69 (5 H, m, 2 × CH_2CO, CHN), 3.47–3.51 (1 H, m, $PhCHCH_2OH$), 3.55 (1 H, d, *J* 14.0, $PhCH_2N$), 3.76–3.93 (3 H, m, $PhCH_2N$, $PhCHCH_2OH$) and 7.24–7.41 (10 H, m, ArH); *m/z* (CI, isobutane) 438 (M^+ + H). The second fractions gave the major ketone **10b** (571 mg, 75%) as a colourless gum, $[\alpha]_D^{25}$ −34.40 (*c* 1.02, EtOH) (Found: C, 76.7; H, 9.1; N, 3.2. Calc. for $C_{28}H_{39}NO_3$: C, 76.85; H, 8.98; N, 3.20%); ν_{max}(film)/cm^{-1} 3450 (OH), 2925 (CH) and 1700 (C=O); δ_H(270 MHz; $CDCl_3$) 0.88 (3 H, t, *J* 6.7, CH_3), 1.13–1.32 [5 H, m, $(CH_2)_3$], 1.35–1.59 [4 H, m, $(CH_2)_2$], 1.72–1.89 (1 H, m, CH_2), 2.04–2.11 (2 H, m, CH_2CO), 2.11 (3 H, s, $COCH_3$), 2.15 (2 H, t, *J* 7.3, CH_2CO), 2.25 (1 H, br s, OH), 2.35 (2 H, t, *J* 6.7, CH_2CO), 2.51–2.63 (1 H, m, CHN), 3.57–3.61 (1 H, m, $PhCHCH_2OH$), 3.64 (1 H, d, *J* 14.0, $PhCH_2N$), 3.92 (1 H, d, *J* 14.0, $PhCH_2N$), 3.84–3.95 (2 H, m, $PhCHCH_2OH$), 7.26–7.41 (10 H, m, ArH); *m/z* (CI, isobutane) 438 (M^+ + H).

(+)-*Monomorine* I **1** *and* (+)-*Indolizidine* 195B **11**.—A solution of the ketone **10b** (761 mg, 1.74 mmol) in methanol (20 cm^3) and 3% aqueous HCl (4 cm^3) was hydrogenated over 10% palladium on carbon (80 mg) under 4.0 kg cm^{-2} of hydrogen for 96 h at room temperature. The reaction mixture was then filtered through a little Celite and the filtrate was evaporated under reduced pressure to give a residue. This was dissolved in 10% aqueous KOH (30 cm^3) and extracted with ether (3 × 10 cm^3). The combined extracts were washed with brine (10 cm^3), dried (Na_2SO_4) and concentrated at < 30 °C at 20 mmHg to give a pale yellow oil, which was subjected to column chromatography on aluminium oxide with hexane–ether (9 : 1) as eluent. The first fractions gave (+)-monomorine I **1** (313 mg, 78%) as pale yellow oil, $[\alpha]_D^{25}$ +35.1 (*c* 1.33, hexane) {lit.,[8d] (3*R*,5*S*,9*S*)-**1** $[\alpha]_D^{25}$ +34.30 (*c* 1.02, hexane)}; δ_H(270 MHz; $CDCl_3$) 0.87 (3 H, t, *J* 7.0, CH_3), 1.13 (3 H, d, *J* 6.2, CH_3), 1.15–1.96 [16 H, m, $(CH_2)_8$], 2.07 (1 H, m), 2.21 (1 H, m) and 2.46 (1 H, m). The spectroscopic data are identical with those reported.[8d] The second fraction gave (+)-indolizidine 195B **11** (32 mg, 8%) as pale yellow oil, $[\alpha]_D^{25}$ +101.19 (*c* 0.28, MeOH) {lit.,[9] (3*S*,5*S*,9*S*)-**11** $[\alpha]_D^{25}$ +98.0 (*c* 0.30, MeOH)}; δ_H(270 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 7.1, CH_3), 1.10 (3 H, d, *J* 6.1, CH_3), 0.95–1.94 [16 H, m, $(CH_2)_8$], 2.33–2.55 (2 H, m) and 3.27 (1 H, m). The spectroscopic data are identical with those reported.[9]

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Paper 3/06241D
Received 19*th October* 1993
Accepted 28*th October* 1993