late, relative to the quinuclidines, than it is toward methyl tosylate would be expected from the concept of steric hindrance. However, the observation that the relative reactivity of 1-azabicycloheptane toward the more hindered isobutyraldehyde-2-*d* is less than it is toward acetone-$d_6$ is counter to the expectations of steric hindrance. Of course, the van der Waals equation contains attractive as well as repulsive terms and suitable combination of these would seem to explain our results but in the absence of appropriate calculations we cannot claim to have explained them.

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## An Efficient Regio- and Stereoselective Synthesis of (±)-Monomorine I via the Highly Regioselective α-Alkynylation of a 1-Acylpyridinium Salt

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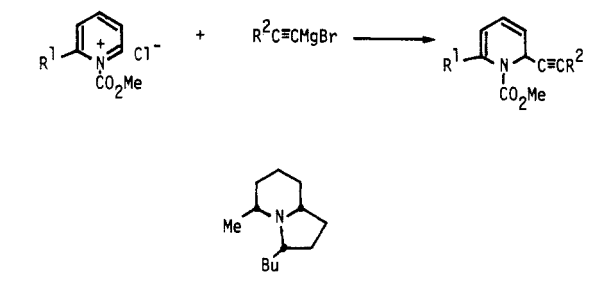
We have recently reported that nucleophilic addition of alkynyl Grignard reagents to 1-methoxycarbonylpyridinium chloride takes place at the α-position in a highly regioselective manner to give 2-substituted 1-methoxycarbonyl-1,2-dihydropyridines exclusively. This methodology is applicable to the synthesis of (±)-solenopsin A as well as indolizidine and quinolizidine.[1,2] In further extension of this α-alkynylation methodology to the synthesis of naturally occurring nitrogen heterocycles, we now describe an efficient regio- and stereoselective synthesis of (±)-monomorine I (1), a trail pheromone of the pharaoh ant,[3,4] using the above regioselective α-alkynylation of 1-acylpyridinium salt[5,6] as a key reaction (Scheme I).

Reaction of 2-methylpyridine with 3-(2-tetrahydropyranyloxy)heptynylmagnesium bromide (2) in the presence of methyl chloroformate afforded the α-alkynylated 1,2-dihydropyridine (3) exclusively in high yield. Without purification, 3 was hydrogenated over 5% Pt-C, followed by deprotection of the hydroxyl group, to give a cis-2,6-disubstituted piperidine derivative (4) in 83% isolated yield.[7] No other regioisomer could be detected by NMR or GLC analysis, clearly indicating the general and high α-regioselectivity in the reaction of alkynyl Grignard reagents with 1-acylpyridinium salts.

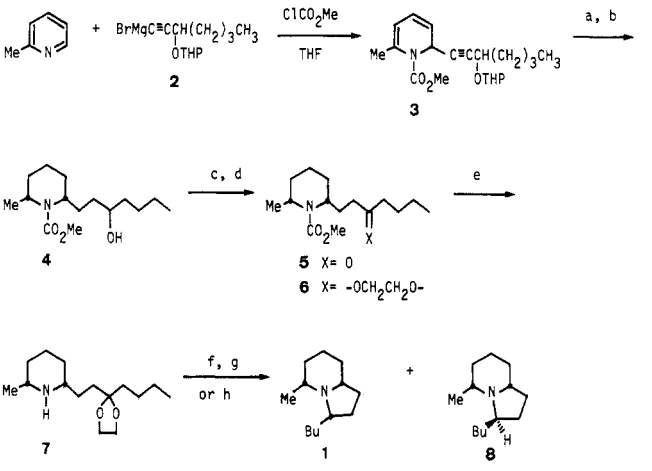
Jones oxidation of 4 followed by protection of the carbonyl group with ethylene glycol gave 6. Basic hydrolysis of 6 in the presence of hydrazine hydrate afforded a crucial intermediate, 7, in 96% yield. The last step required stereoselective reductive cyclization of 7 to monomorine I (1). At first we examined intramolecular reductive amination with $NaBH_3CN$.[8] Thus, acidic deprotection of 7,

**Scheme I**



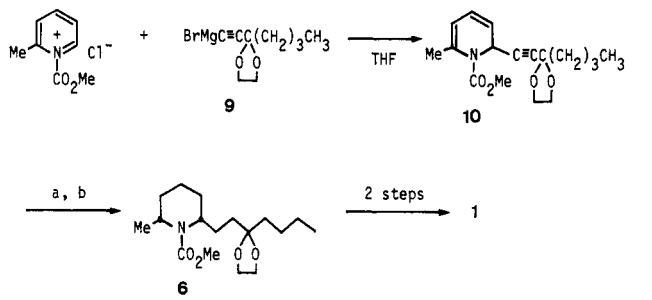
1, Monomorine I

**Scheme II**



Reagents: (a) $H_2$, Pt-C/MeOH; (b) Amberlyst H-15/MeOH; (c) $CrO_3$-$H_3O^+$/acetone; (d) $(CH_2OH)_2$, p-TsOH/PhH; (e) KOH, $NH_2NH_2$ $H_2O$/$(CH_2OH)_2$; (f) aq. HCl/THF; (g) $NaBH_3CN$/aq. HCl-MeOH; (h) $H_2$, Pd-C/aq. HCl-MeOH

**Scheme III**



Reagents: (a) $H_2$, Pt-C/MeOH; (b) $(CH_2OH)_2$, p-TsOH/PhH

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0022-3263/87/1952-2094$01.50/0 

followed by reduction with $NaBH_3CN$ in aqueous HCl–MeOH gave 1 and its $C_9$ epimer (8) in 63% yield (1:8 = 70:30). We found, however, that when 7 was subjected to catalytic hydrogenation conditions in acidic media[4e] the stereoselectivity was close to 100%. Thus, treatment of 7 over 10% Pd-C under $H_2$ in aqueous HCl–MeOH gave 1 in 60% yield. The stereoisomer (8) could not be detected by GLC analysis (Scheme II).

We next pursued a shorter route to the key intermediate (6). The required 3,3-(ethylenedioxy)-1-heptyne was easily prepared from bis(trimethylsilyl)acetylene.[9] Reaction of 1-methoxycarbonyl-2-methylpyridinium chloride with the Grignard reagent (9) proceeded again in a highly regioselective manner to give 10 exclusively in high yield. It should be noted here that the pyridinium salt must be preformed in this case; otherwise, reaction of the Grignard reagent with methyl chloroformate takes place in a competitive manner. Without purification, 10 was hydrogenated over 5% Pt-C and then reacetalized, because partial deacetalization occurred during the hydrogenation. Thus, the key intermediate (6) could be obtained in three steps from 2-methylpyridine in 55% overall yield (Scheme III).

In summary, we have demonstrated the versatile utility of the highly regioselective $\alpha$-alkynylation of 1-acylpyridinium salts with alkynyl Grignard reagent to the synthesis of indolizidine alkaloids. Thus, (±)-monomorine I (1) could be obtained regio- and stereoselectively from 2-methylpyridine in five steps in 32% overall yield.

## Experimental Section

The IR spectra were recorded on a JaSCO IR-810 spectrometer. The mass spectra were taken by using a Hitachi RMS-4 mass spectrometer. The $^1H$ and $^{13}C$ NMR spectra were obtained on Varian EM-390 and JEOL FX-90Q spectrometers, $Me_4Si$ being chosen as the internal standard. Analytical GLC were carried out on a Shimadzu GC-4C gas chromatography with 10% SE-30 and 10% PEG-20M on Chromsorb W columns. The microanalyses were performed by Kyoto University Elemental Analysis Center. Tetrahydrofuran (THF) was distilled from benzophenone ketyl before use.

***cis*-2-(3-Hydroxyheptyl)-1-methoxycarbonyl-6-methylpiperidine (4).** To a mixture of 2-methylpyridine (1.110 g, 11.8 mmol) and the alkynyl Grignard reagent (2), prepared from 3-(2-tetrahydropyranyloxy)-1-heptyne (1.969 g, 10.1 mmol) and EtMgBr (7.5 mL, 1.36 M, 10.2 mmol), in THF (18 mL) was slowly added a solution of methyl chloroformate (0.90 mL, 1.10 g, 11.6 mmol) in THF (10 mL) over 1.5 h under ice-cooling. The reaction mixture was stirred for an additional 2 h, poured into 10% aqueous $NH_4Cl$, and extracted with ether. The organic solution was washed with water and brine and dried ($Na_2SO_4$). The solvent was evaporated to give almost pure 3 (3.32 g, 95%): IR (neat) 2250, 1720 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.43–6.03 (m, 4 H), 4.68–5.06 (m, 1 H), 4.20–4.53 (m, 1 H), 3.76 (s, 3 H), 3.33–4.00 (m, 4 H), 2.16 (s, 3 H), 1.20–2.00 (m, 10 H), 0.87 (dist t, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 154.1 (s), 135.0 (s), 123.3 (d), 120.0 (d), 112.0 (d), 95.4 (d), 82.6 (s), 81.9 (s), 65.0 (d), 62.1 (t), 53.0 (q), 44.2 (d), 35.4 (t), 30.6 (t), 27.6 (t), 25.7 (t), 22.5 (t), 21.5 (q), 19.5 (t), 14.1 (q). Without purification, 3 was immediately dissolved in dry MeOH (100 mL) and completely hydrogenated over 5% Pt-C (0.80 g) at atmospheric pressure of $H_2$. After the catalyst was removed by filtration through Celite, the solvent was evaporated. The residue was dissolved in dry MeOH (29 mL), and to this solution was added Amberlyst H-15 (0.30 g). The mixture was stirred at 45 °C for 1 h, and Amberlyst was removed by filtration. The solvent was evaporated, and the residue was purified by Kugelrohr distillation to give 4 (2.252 g, 83% based on 3): bp 140 °C (0.7 mmHg); MS $m/e$ (rel intensity) 188 (4), 170 (55), 156 (58), 85 (100); IR (neat) 3450, 1780, 1680 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.03–4.57 (m, 2 H) 3.53–3.73 (m, 1 H), 3.70 (s, 3 H), 1.07–1.90 (m, 19 H), 3.58 (d, 3 H, $J$ = 7.5 Hz), 0.90 (dist t, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 156.9, 156.8 (s), 72.0, 72.6 (d), 52.4 (q), 50.6, 49.9 (d), 41.6 (d), 37.5, 37.2 (t), 34.8, 34.5 (t), 31.2, 30.9 (t), 30.3 (t), 28.1, 28.0 (t), 27.7, 27.3 (t), 22.8 (t), 20.6 (q), 14.1 (t), 13.9 (q). Anal. Calcd for $C_{15}H_{29}NO_3$: C, 66.38; H, 10.77. Found: C, 66.17; H, 10.78.

***cis*-1-Methoxycarbonyl-6-methyl-2-(3-oxoheptyl)piperidine (5).** To a solution of 4 (1.973 g, 7.3 mmol) in acetone (15 mL) was added Jones reagent, prepared from $CrO_3$ (430 mg, 4.3 mmol), water (3.1 mL), and concentrated $H_2SO_4$ (0.4 mL), and the mixture was stirred for 2 h at room temperature. The reaction mixture was poured into water and extracted with $CH_2Cl_2$. The organic solution was washed with 10% aqueous $Na_2S_2O_3$ and brine and dried ($Na_2SO_4$). The solvent was evaporated to give almost pure 5 (1.947 g, 99%): bp 123 °C (0.28 mmHg) (bath temp); MS $m/e$ (rel intensity) 269 ($M^+$, 2), 169 (41), 156 (100); IR (neat) 1700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.00–4.55 (br, 2 H), 3.66 (s, 3 H), 2.25–2.60 (m, 4 H), 1.10–2.00 (m, 12 H), 1.15 (d, 3 H, $J$ = 7.5 Hz), 0.83 (dist t, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 209.5 (s), 156.6 (s), 52.3 (q), 49.9 (d), 46.1 (d), 42.5 (t), 40.2 (t), 30.3 (t), 28.8 (t), 28.4 (t), 26.0 (t), 22.5 (t), 20.6 (q), 14.1 (t), 13.9 (q). Anal. Calcd for $C_{15}H_{27}NO_3$: C, 66.88; H, 10.10. Found: C, 66.76; H, 10.37.

***cis*-2-(3,3-Ethylenedioxyheptyl)-1-methoxycarbonyl-6-methylpiperidine (6).** A mixture of 5 (1.144 g, 4.2 mmol), ethylene glycol (0.680 g, 11.0 mmol), and *p*-TsOH (0.034 g) in PhH (40 mL) was refluxed by suing a Dean-Stark separator. After the reaction was completed, the solvent was removed by distillation. The residue was dissolved in $CH_2Cl_2$, washed with 10% aqueous NaOH, and dried ($Na_2SO_4$). The solvent was evaporated to give 6 (1.318 g, 99%): bp 129 °C (0.27 mmHg) (bath temp); MS $m/e$ (rel intensity); 313 ($M^+$,1), 156 (100); IR (neat) 1700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 4.03–4.53 (m, 2 H), 3.93 (s, 4 H), 3.68 (s, 3 H), 1.10–1.90 (m, 16 H), 1.18 (d, 3 H, $J$ = 7.5 Hz), 0.88 (dist t, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 156.6 (s), 117.7 (s), 64.9 (t), 52.3 (q), 50.6 (d), 46.1 (d), 36.9 (t), 34.5 (t), 30.3 (t), 29.3 (t), 28.0 (t), 26.0 (t), 23.0 (t), 20.5 (q), 14.2 (t), 14.1 (q). Anal. Calcd for $C_{17}H_{31}NO_4$: C, 65.14; H, 9.97. Found: C, 65.34; H, 10.15.

**Preparation of 6 via 10.** To a mixture of 1-methoxycarbonyl-2-methylpyridinium chloride, prepared from 2-methylpyridine (0.375 g, 4.0 mmol) and methyl chloroformate (0.23 mL, 0.290 g, 3.1 mmol), in THF (18 mL) was added the alkynyl Grignard reagent, prepared from 3,3-(ethylenedioxy)-1-heptyne (0.310 g, 2.0 mmol) and EtMgBr (1.45 mL, 1.38 M, 2.0 mmol), in THF (12 mL) under ice-cooling over 10 min. The reaction mixture was stirred at that temperature for 1.5 h. After addition of water (15 mL) and then $CH_2Cl_2$ (50 mL), the mixture was washed with 5% aqueous HCl several times and then with water and dried ($Na_2SO_4$). The solvent was evaporated to give 10 (0.544 g, 89%): IR (neat) 1720 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 5.80–6.10 (m, 1 H), 5.45–5.80 (m, 3 H), 3.85–4.20 (m, 4 H), 3.0 (s, 3 H), 2.16 (s, 3 H), 1.10–2.00 (m, 6 H), 0.87 (dist t, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 154.1 (s), 135.1 (s), 123.6 (d), 119.5 (d), 112.0 (d), 103.4 (s), 81.1 (s), 80.5 (s), 64.6 (t), 64.4 (t), 53.0 (q), 44.0 (d), 38.8 (t), 26.1 (t), 22.6 (t), 21.4 (q), 14.0 (q). Without purification, 10 was immediately dissolved in dry MeOH (30 mL) and completely hydrogenated over 5% Pt-C (0.18 g) under atmospheric pressure of $H_2$. After the catalyst was removed by filtration through Celite, the solvent was evaporated. Since NMR analyses indicated that the residue was a mixture of 5 and 6, it was subjected to the acetalization reaction in a manner similar to the above to give almost pure 6 (0.345 g, 55% based on the alkyne).

***cis*-2-(3,3-Ethylenedioxyheptyl)-6-methylpiperidine (7).** A mixture of 6 (2.096 g, 6.7 mmol), KOH (12.60 g), and 100% $NH_2NH_2 \cdot H_2O$ (2.2 mL) in ethylene glycol (63 mL) was stirred under reflux for 6 h. The cooled solution was poured into water and extracted with $CH_2Cl_2$. The organic solution was washed with 20% aqueous NaOH several times and dried ($Na_2SO_4$). The solvent was evaporated to give almost pure 7 (1.638 g, 96%): bp 110 ° (0.45 mmHg) (bath temp); MS $m/e$ (rel intensity) 255 ($M^+$, 1), 143 (100); IR (neat) 3350, 1460, 1100 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 3.93 (s, 4 H), 2.30–2.80 (m, 2 H), 1.10–1.90 (m, 17 H), 1.05 (d, 3 H, $J$ = 7.5 Hz), 0.88 (dist t, 3 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 111.8 (s), 64.9 (t), 57.5 (d), 52.6 (d), 37.0 (t), 34.5 (t), 33.6 (t), 32.2 (t), 31.6 (t), 26.0 (t), 24.9 (t), 23.1 (d), 23.0 (q), 14.1 (q). Anal. Calcd for $C_{15}H_{29}NO_2$: C, 70.54; H, 11.45. Found: C, 70.79; H, 11.74.

**Synthesis of (±)-Monomorine I (1). a. Reductive Cyclization with $NaBH_3CN$.** To a solution of 7 (0.479 g, 1.9 mmol)

(9) Alexakis, A.; Commercon, A.; Coulentianos, C.; Normant, J. F. *Pure Appl. Chem.* **1983**, *55*, 1759.

in THF (35 mL) was added 1 N HCl (5.5 mL) under ice-cooling. The mixture was stirred at room temperature for 24 h and basified with 1 N $NaHCO_3$ (6 mL). The organic material was extracted with $CH_2Cl_2$ and dried ($Na_2SO_4$). After evaporation of the solvent, the residue was dissolved in MeOH (5 mL). To this solution was added 1 N HCl (1.5 mL) to adjust the pH to 4 and then $NaBH_3CN$ (0.100 g, 1.6 mmol). The mixture was stirred at room temperature for 6 h and poured into 2 N NaOH (20 mL). The organic material was extracted with ether, and the organic solution was dried ($Na_2SO_4$). The solvent was evaporated, and the residue was purified by Kugelrohr distillation (100 °C (20 mmHg)) to give a mixture of 1 and 8 (0.232 g, 63%, 1:8 = 70:30 by GLC).

**b. Catalytic Reductive Cyclization with 10% Pd–C.** A mixture of 7 (0.1660 g, 0.65 mmol), 1 N HCl (0.2 mL), and 10% Pd-C (0.056 g) in MeOH (10 mL) was stirred under an atmosphere of $H_2$ for 4 days. The catalyst was removed by filtration through Celite, and the filtrate was poured into 1 N NaOH (20 mL). The organic material was extracted with $CH_2Cl_2$, and the organic solution was dried ($Na_2SO_4$). The solvent was evaporated, and the residue was purified by Kugelrohr distillation (85 °C (15 mmHg)) to give 1 (0.076 g, 60%). The isomer 8 was not detected by GLC or NMR analysis. 1: MS *m/e* (rel intensity) 195 ($M^+$, 2), 180 (3), 138 (100); $^1H$ NMR ($CDCl_3$) $\delta$ 0.75–3.00 (br m, 22H), 1.13 (d, 3 H, $J$ = 6 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 67.2 (d), 62.8 (d), 60.2 (d), 39.8 (t), 36.0 (t), 31.1 (t), 30.5 (t), 29.8 (t), 29.4 (t), 25.1 (t), 23.0 (t), 22.9 (q), 13.9 (q). The $^{13}C$ NMR spectrum of 1 was identical with the reported one.[4e]

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## A Stereoselective Synthesis of (±)-*cis*-α-Irone

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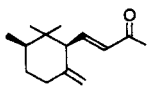
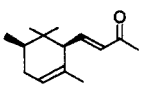
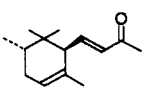
The main constituents of natural iris oil, *cis*-γ-irone (1), *cis*-α-irone (2), and *trans*-α-irone (3),[1,2] have received much attention from synthetic chemists for a long time. Most



1



2

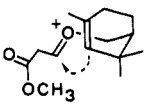


3

of the known[3] syntheses, however, produce mixtures of isomers that are difficult to separate on a preparative scale. So far, only one stereoselective approach has been described for 3,[4] but none for 1 and 2. We now report a stereoselective synthesis of (±)-*cis*-α-irone (2) from readily available[5] (2,2,4-trimethyl-3-cyclohexen-1-yl)methanol (4) in which the side chain is introduced by a conceptually novel method (Scheme I).

Addition of alcohol 4 to methyl propiolate in the presence of *N*-methylmorpholine[6] afforded the (*E*)-β-alkoxyacrylate 5 (88% yield). Upon exposure of 5 to catalytic amounts of methanesulfonic acid in dichloromethane at −10 °C, smooth cyclization to the 3-oxabicyclo[3.3.1]nonene derivative 6 occurred (yield 94%). For cleavage of the tetrahydropyran moiety, the bicyclic ester 6 was first hydrolyzed with aqueous base to the crystalline acid 7 (yield 78%), which was then treated with 2 equiv of LDA in THF at −70 °C, followed by warmup to 0 °C and quenching to give acid 8 in 88% yield after crystallization.[7] Making use of the hydroxymethyl group of 4, the side chain had thus been introduced in four steps with complete stereocontrol and simultaneous shift of the ring double bond. The synthesis was completed by first reducing the hydroxymethyl group of 8 via the corresponding mesylate 9, which was then treated with zinc and sodium iodide in refluxing DME[8] to give the crystalline acid 10 (yield 71%). Finally, reaction of 10 with methyllithium in diethyl ether afforded the title compound 2 in 89% yield. The (±)-*cis*-α-irone (2) thus obtained proved to be very pure; no other isomers could be detected by capillary GC or 400-MHz $^1H$ NMR analysis.

The key step of the above synthesis is the β-alkoxyacrylate–olefin cyclization reaction 5 → 6, which ensures the cis relationship of the substituents. This transformation most likely proceeds through the oxonium ion **a**.



**a**

The endo configuration[9] at C-4 in the cyclization product 6 points to a chairlike transition state with the carbomethoxymethyl group in a quasi-equatorial position. The corresponding transition state with this substituent in an axial position would suffer from a severe 1,3-diaxial interaction.

Except Johnson's pioneering work[10] on acetal–olefin cyclizations, which occur in an exocyclic mode with respect to the initiator and thus give carbocyclic products, oxonium ion initiated cyclizations have not received much attention. Recently, however, a number of papers[11] describe endocyclic acetal–olefin cyclizations leading to oxacyclic products. To the best of our knowledge, enol ethers have not been used previously as starter units in cationic olefin cyclizations.

In conclusion, *cis*-α-irone (2) has been stereoselectively synthesized for the first time via a novel β-alkoxyacrylate–olefin cyclization 5 → 6. Mechanistic details as

(1) (a) Rautenstrauch, V.; Ohloff, G. *Helv. Chim. Acta* **1971**, *54*, 1776; *Ibid.* **1972**, *55*, 2686. (b) Ohloff, G.; Otto, E.; Rautenstrauch, V.; Snatzke, G. *Helv. Chim. Acta* **1973**, *56*, 1874. (c) Rautenstrauch, V.; Willhalm, B.; Thommen, W.; Ohloff, G. *Helv. Chim. Acta* **1984**, *67*, 325.

(2) Krick, W.; Marner, F.-J.; Jaenicke, L. *Helv. Chim. Acta* **1984**, *67*, 318.

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