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The Enantiospecific Synthesis of (-)-Monomorine from L-Glutamic Ester

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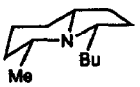
Abstract: Diethyl L-glutamate hydrochloride (3) was converted to its N-pyrrole derivative 5. Submission of 5 to butyryl chloride in boiling toluene gave the 2-butyryl derivative, and by treatment with $NaBH_3CN$ and ZnI_2, the 2-butyl analogue 9. Cyclization of 9 with BBr_3 afforded (5S)-3-butyl-5-ethoxycarbonyl-5,6-dihydro-8(7H)-indolizinone (10). Hydrogenation of 10 over Pd/C in acidified EtOH gave (3S,5S,9R)-3-butyl-5-ethoxycarbonylindolizidine. By successive reduction of the latter to the primary alcohol, formation of the chloride and reductive dechlorination with tributyltin hydride, (3S,5R,9R)-3-butyl-5-methylindolizidine, or (-)-monomorine, was obtained in 8 steps from 3 in a yield of 25%.

The indolizidine alkaloids have excited much interest on account of their exotic provenance and potent biological activity.[1] Unfortunately, they are only isolable in minuscule amounts from natural sources. Consequently, many methods have been devised for their synthesis.[2] A pertinent example is (+)-monomorine (**1**), the trail-laying pheromone of the Pharaoh ant, *Monomorium pharaonis* L. So far, six strategies, of varying length and efficiency, have been formulated. One involves asymmetric deprotonation of N-benzyloxycarbonylnortropinone,[4] while the others exploit the innate chirality of diethyl L-tartrate,[5,6] S-pyroglutamic acid,[7] and L-alanine[8,9] as starting materials.

1

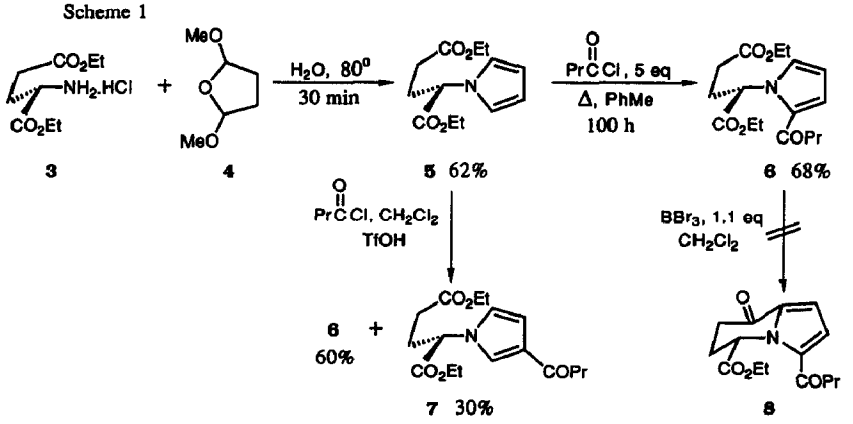


2

We now describe a new synthesis of the non-natural antipode, (-)-monomorine (**2**),[10] which exemplifies an improved procedure for constructing enantiomerically pure indolizidines by the intramolecular acylation of a suitable N-substituted pyrrole and the substituent-directed hydrogenation of the resulting bicyclic intermediate.[11] In the present instance, the enantiogenic chirality was provided by diethyl L-glutamate hydrochloride (**3**).[12,13] Its condensation with 2,5-dimethoxytetrahydrofuran (**4**) in warm water readily furnished the optically pure N-pyrrole derivative **5** in 62% yield (Scheme 1).[11] The future butyl group was then introduced by adding an equivalent of trifluoromethanesulfonic acid (TfOH) to a mixture of **5** and butyryl chloride.[14] Reaction was instantaneous and exothermic giving the desired 2-butyryl derivative **6**, but also the 3-substituted isomer **7**, in yields of 60 and 30% respectively.[15] Although chromatographic separation was entirely feasible,[16] heating **5** with excess butyryl chloride alone in toluene for 100 hours proved simpler[17] and gave **6** in 68% yield with no detectable trace of **7**, the thermodynamically favored isomer.[18,19] Next, direct closure to the bicyclic diketone **8** was attempted. However, the action of 1.1 equivalents of boron tribromide on **6** was without any effect, owing, no doubt, to deactivation of the pyrrole ring by the acyl substituent.

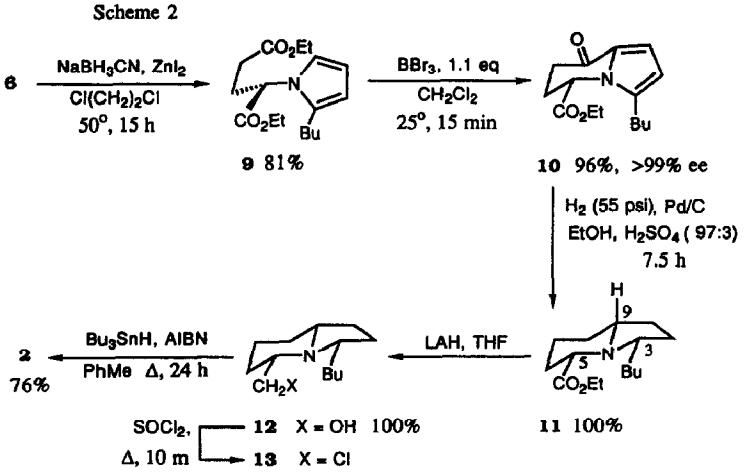
Consequently, the more nucleophilic butylated analogue **9** was prepared from **6** in 81% yield by reductive deoxygenation[20] with sodium cyanoborohydride and zinc iodide in 1,2-dichloroethane (Scheme 2). Subsequent treatment of **9** with 1.1 equivalents of boron tribromide for just 15 minutes was successful. Intramolecular acylation to the bicyclic keto pyrrole **10** occurred regioselectively with complete retention of configuration in 96% yield.

Scheme 1



The crucial process of hydrogenating **10** was accomplished over palladium-on-charcoal in slightly acidified ethanol solution.[21] After 7.5 hours of reaction time, it was reduced to (3S,5S,9R)-3-butyl-5-ethoxycarbonylindolizidine (**11**) in quantitative yield.[22] In keeping with precedent,[8,11,12] saturation of the pyrrole ring took place in an all-*cis* manner, being totally controlled by the stereogenic center. At the same time, the acidic conditions were conducive to removal of the benzylic carbonyl group by hydrogenolysis.[23,24]

Scheme 2



All that remained was the transformation of the remaining ester group into the 5-methyl substituent by a standard procedure.[25] The action of lithium aluminum hydride on **11** afforded the alcohol **12**, which was converted *in situ* to the chloride **13**. Finally, by reductive dechlorination of **13** with tributyltin hydride, (-)-monomorine (**2**) was obtained in 76% yield as a single isomer.[25] It was spectroscopically identical and optically congruent with those previously prepared.[26]

The present synthesis of **2**, compared with the others,[4-10] is short and practical requiring only eight simple operations to deliver enantiomerically pure product in an overall yield of 25%. Applications of this N-substituted pyrrole methodology for synthesizing other naturally occurring indolizidines are foreseeable and will be disclosed in due course.

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References and Notes

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10. (-)-Monomorine has been synthesized once before from chiral 2-cyano-6-oxazolopiperidine (J. Royer, H.-P. Husson, *J. Org. Chem.* **1985**, *50*, 670).
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12. For an example starting from L-aspartic acid see: C.W. Jefford, J.B. Wang, *Tetrahedron Lett.* **1993**, *34*, 3119.
13. Diethyl L-glutamate hydrochloride of >99% purity, was purchased from *Fluka Chemie AG*, CH 9470 Buchs.
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15. The ratio of **6**:**7** remained constant regardless of the degree of external cooling (-78° or 25°C) and even with 0.002 equivalent of TfOH under conditions of reflux.
16. Extraction of the mixture with CH_2Cl_2, drying of the extract ($MgSO_4$), evaporation and flash chromatography (SiO_2, Et_2O:hexane, 1:1) gave **6** (Rf 0.3) and **7** (Rf 0.12) as colorless oils.
17. We are indebted to Dr. J.M. Muchowski, Syntex Research, Institute of Organic Chemistry, Palo Alto, CA 94304, USA, for suggesting these conditions.

18. As a rule, N-substituted pyrroles undergo preponderant 3-acylation under the Vilsmeier-Haack conditions (J.M. Muchowski in "Advances in Medicinal Chemistry", Eds. B.E. Maryanoff and C.A. Maryanoff, vol. 1, JAI Press, Greenwich, CT, USA, 1992, p. 117; C.W. Jefford, Q. Tang, J. Boukouvalas, *Tetrahedron Lett.* **1990**, *31*, 995). The 2-acyl substituent of the kinetic product, when catalysts are present, rearranges to the 3-position (J.R. Carson, N.M. Davis, *J. Org. Chem.* **1981**, *46*, 839).

19. Despite the long reaction time, some of the reactant **5** always remained behind indicating that acylation was incomplete.

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21. Hydrogenation was performed in a Parr apparatus at 55 psi.

22. The new compounds, **6**, **9**, **10**, **11** and **12**, were purified by flash chromatography (**6**, **9**, **10** over SiO_2; **11** and **12** over neutral Al_2O_3, hexane:Et_2O, 4:1). All were colorless oils, except **12** which was a crystalline solid, m.p. 54-56°C. They gave acceptable elemental analyses and were fully characterized. Optical rotations ($[\alpha]_D^{20}$) were determined in CH_2Cl_2 and had the following values: **6**, -15.4° (c 1.07); **9**, -28.1° (c 1.00); **10**, -22.8° (c 1.00); **11**, -2.3° (c 1.04); **12**, +5.7° (c 1.0). The enantiomeric excess of **10** was estimated as >99% according to the ^{1}H-NMR spectrum taken in the presence of Eu(hfc)$_3$ (see M. Calmes, J. Daunis, R. Jacquier, J. Verducci, *Tetrahedron* **1987**, *43*, 2285). ^{1}H-NMR (400 MHz, $CDCl_3$): **6**, 0.96 (t, *J* = 7.4 Hz, 3H), 1.23 (t, *J* = 7.0 Hz, 3H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.70 (m, 2H), 2.19-2.24 (m, 3H), 2.58 (m, 1H), 2.74 (t, *J* = 7.4 Hz, 2H), 4.10 (q, *J* = 7.0 Hz, 2H), 4.18 (q, *J* = 7.0 Hz, 2H), 5.95 (m, 1H), 6.22 (dd, *J* = 3.8, 1.8 Hz, 1H), 7.02 (dd, *J* = 3.8, 1.4 Hz, 1H), 7.04 (m, 1H); **9**, 0.93 (t, *J* = 7.3 Hz, 3H), 1.24 (t, *J* = 7.4 Hz, 6H), 1.39 (sextet, *J* = 7.4 Hz, 2H), 1.59 (m, 2H), 2.13-2.33 (m, 3H), 2.40-2.52 (m, 3H), 4.12 (q, *J* = 7.4 Hz, 2H), 4.18 (qd, *J* = 7.4, 3.6 Hz, 2H), 4.76 (dd, *J* = 9.5, 5.8 Hz, 1H), 5.88 (m, 1H), 6.13 (t, *J* = 3.3 Hz, 1H), 6.69 (dd, *J* = 3.0, 1.5 Hz, 1H); **10**, 0.94 (t, *J* = 7.3 Hz, 3H), 1.26 (t, *J* = 7.3 Hz, 3H), 1.41 (m, 2H), 1.63 (m, 2H), 2.53-2.66 (m, 6H), 4.24 (qd, *J* = 7.3, 0.8 Hz, 2H), 4.91 (m, 1H), 6.12 (d, *J* = 4.0 Hz, 1H), 7.07 (d, *J* = 4.0 Hz, 1H); **11**, 0.8 (t, *J* = 7.3 Hz, 3H), 1.30-1.46 (m, 10H), 1.21 (t, *J* = 7.3 Hz, 3H), 1.65-1.90 (m, 6H), 1.92-2.00 (m, 1H), 2.18-2.29 (m, 1H), 2.66 (dd, *J* = 10.3, 3.3 Hz, 1H), 4.03-4.20 (m, 2H); **12**, 0.88 (t, *J* = 6.7 Hz, 3H), 1.18-1.55 (m, 9H), 1.56-2.00 (m, 8H), 2.04-2.30 (m, 2H), 2.51-2.61 (m, 1H), 3.54 (dd, *J* = 11.1, 2.8 Hz, 1H), 3.78 (dd, *J* = 11.1, 4.3 Hz, 1H).

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24. Related molecules which lack a carbonyl group in the six-membered ring undergo catalytic hydrogenation more slowly and with less stereocontrol (D.R. Artis, I.-S. Cho, S. Jaime-Figueroa, J.M. Muchowski, *J. Org. Chem.* **1994**, in press).

25. Improvement of the yield of **2** from **11** should be feasible since the same conversion, but in the racemic mode, has been achieved in 96% yield (M. Vavrecka, M. Hesse, *Helv. Chim. Acta* **1991**, *74*, 438).

26. (-)-Monomorine (**2**) was obtained as an oil and purified by chromatography (neutral Al_2O_3, hexane: Et_2O, 4:1). $[\alpha]_D^{20}$ = -35.0° (c 0.52, n-hexane). IR 2954 (vs), 2929 (vs), 2871 (m), 2858 (m), 2787 (Bohlmann band) (w), 2713 (w), 2581 (w), 1454 (m), 1378 (m), 1341 (w), 1319 (m), 1300 (m), 1261 (w), 1227 (w), 1204 (m), 1167 (m), 1124 (m), 1106 (m), 1084 (m), 1052 (m), 1020 (m), 962 (w), 928 (w). The ^{1}H- and ^{13}C-NMR spectra of **2** were identical to those reported for the (+) enantiomer (ref. 8).

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