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An Enantiospecific Entry to Indolizidines by Intramolecular Acylation of N-Pyrrole Esters

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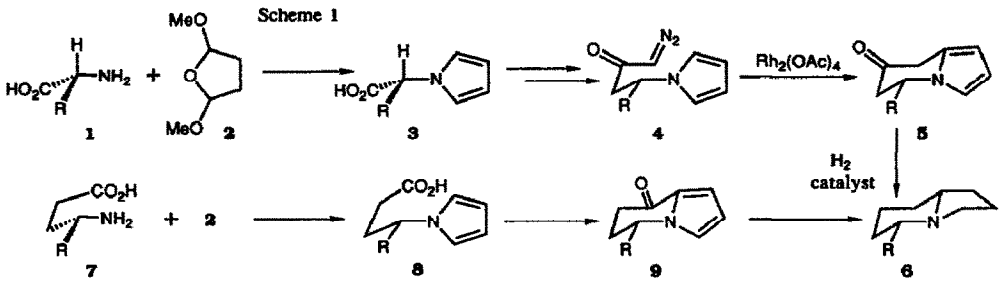
Abstract: L-Glutamic diethyl ester hydrochloride was converted to its pyrrole derivative **22** *by condensation with 2,5-dimethoxytetrahydrofuran in water. Cyclization of* **22** *with* BBr_3 *afforded (5S)-5,6-dihydro-5-ethoxycarbonyl-8(7H)-indolizinone (***23***). Catalytic hydrogenation of* **23** *over Pd/C in acetic acid gave exclusively (5S,9R)-5-ethoxycarbonylindolizidine in an overall yield of 41%, whereas hydrogenation over* Rh/Al_2O_3 *in ethanol gave predominantly (5S,8S,9S)-5-ethoxycarbonyl-8-hydroxyindolizidine in 48.5% overall yield.*

We recently devised a procedure for synthesizing enantiomerically pure 5-substituted and *cis*-3,5-disubstituted indolizidines from chiral α-amino acids.[1,2] Typically, an acid (**1**) is converted into its N-pyrrole derivative (**3**) by condensation with 2,5-dimethoxytetrahydrofuran (**2**) (Scheme 1). Extension of the side-chain by Arndt-Eistert homologation and adjunction of diazomethane affords the α-diazoketone **4** which by catalysis with rhodium acetate closes to the bicyclic pyrrole **5**. Formation of the desired diastereomeric indolizidine **6** is assured by substituent-directed catalytic hydrogenation of **5**. A logical modification of this sequence is to dispense with homologation by taking a suitable γ-amino acid (**7**) at the outset and effecting cyclization of the resulting N-pyrrole-butyric acid **8** to the pyrrole **9**. Catalytic hydrogenation, as before, would be expected to give **6**. However, previous experiments with aspartic acid and its esters[3,4] indicate that this approach might meet with mitigated success. For example, 2,5-diethoxytetrahydrofuran (**2a**) reacted poorly with L-aspartic acid (**10**), but efficiently with its mono- and diesters **13** and **16** to give the N-pyrrole derivatives **11**, **14**, and **17** (Scheme 2). Moreover, acid-catalyzed cyclization of **11** to **12** failed entirely whereas the treatment of **14** with phosphorous pentoxide furnished the bicyclic ketone **15** in only 37% yield.

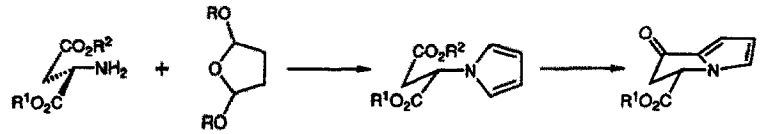
Scheme 1



We now describe a new non-racemizing procedure for the reaction of 2,5-dimethoxytetrahydrofuran (**2**) with L-aspartic and L-glutamic esters and a new method for the intramolecular acylation of the resulting N-pyrrole esters, which provides, in the case of diethyl L-glutamate, intermediates for the eventual synthesis of certain natural indolizidines.

Condensation of the hydrochlorides of dimethyl L-aspartate (**16**) and L-glutamate (**18**)[5] with **2** in glacial acetic acid and sodium acetate furnished the N-pyrrole derivatives **17** and **19** (Schemes 2 and 3). Despite the high yields, partial racemization invariably occurred (Table, entries 1 and 3). However, by simply repeating the reaction in water alone, **17** and **19** were obtained as completely optically pure products, but at the expense of yield (entries 2 and 4). By using diethyl L-glutamate hydrochloride (**21**) instead, yields were improved markedly in both acetic acid and water (entries 5 and 6), giving in the latter solvent the N-pyrrole derivative **22** as a single enantiomer.

Scheme 2



10 $R^1 = R^2 = H$ **2a** R = Et **11** $R^1 = R^2 = H$ **12** $R^1 = H$
13 R^1 = Me, $R^2 = H$ or **14** R^1 = Me, $R^2 = H$ **15** R^1 = Me
16 HCl, $R^1 = R^2$ = Me **2** R = Me **17** $R^1 = R^2$ = Me

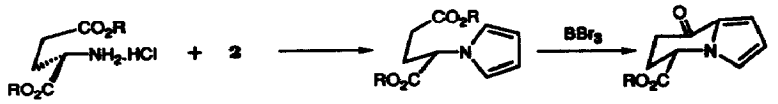
Next, the enantiomerically pure N-pyrrole esters **17**, **19** and **22** were cyclized to the bicyclic keto pyrroles **15**, **20** and **23** (Schemes 2 and 3). Normally, esters are not amenable to Friedel-Crafts acylation.[7,8] Nonetheless, submission of **17** to boron tribromide[9] gave a 44% yield of **15** in an enantiomeric excess of 82%.[10] In contrast, the pure enantiomers **19** and **22**, by similar exposure to boron tribromide, underwent intramolecular acylation to **20** and **23** with complete retention of configuration[11] in yields of 80 and 88% respectively.

Table Reaction of 2,5-Dimethoxytetrahydrofuran (**2**) with L-Aspartic (**16**) and L-Glutamic diester hydrochlorides (**18** and **21**) to give the corresponding N-pyrrole esters (**17**, **19** and **22**)

Entry	Educt	Procedure[a]	Product	Yield %	$[\alpha]_D^{20}$, conc., solvent[b]	Enantiomeric excess,[c] %
1	**16**	A	**17**	86	-45.5°, 1.34, $CHCl_3$	64
2	**16**	B	**17**	20	-76.6°, 1.23, $CHCl_3$	>98
3	**18**	A	**19**	70	-26.9°, 1.21, MeOH	86
4	**18**	B	**19**	23	-33.5°, 1.34, MeOH	>98
5	**21**	A	**22**	83	-16.6°, 1.04, EtOH	84
6	**21**	B	**22**	62	-21.9°, 1.11, EtOH	>98

a)In procedure A (a modification of that in ref. 6), a solution of the educt, **2**, NaOAc (each 10 mmol) in HOAc (100 ml) was warmed (80°C, 30 mins). Filtration through *Celite* and evaporation gave a residue. The solution of the latter in CH_2Cl_2 was washed (10% aq. HCl), dried and evaporated. Chromatography (SiO_2, hexane:Et_2O, 1:1) gave products. In procedure B, educt and **2** were dissolved in H_2O and warmed (80°C, 30 mins), when the products deposited (extraction with CH_2Cl_2). b)Values determined in $CHCl_3$ were stable, but drifted slightly in alcoholic solutions. c)Determined by gas chromatography at 135°C over Lipodex E (octakis-(2,6-di-O-pentyl-3-O-butyryl)-γ-cyclodextrin) coated on a fused silica column (25 m x 0.25 mm) (*Macherey-Nagel AG*, CH-4702 Oensingen).

Scheme 3



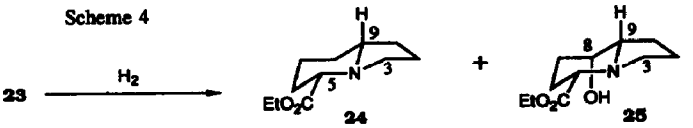
18 R = Me
21 R = Et

19 R = Me
22 R = Et

20 R = Me
23 R = Et

Finally, hydrogenation of the bicyclic keto pyrrole **23** in acetic acid over palladium-on-charcoal proceeded stereospecifically. Reduction occurred with hydrogenolysis of the carbonyl group to give (5S,9R)-5-ethoxycarbonylindolizidine (**24**) in 75% yield.[12] Hydrogenation over rhodium-on-alumina in ethanol was similarly directed in an all-*cis* fashion affording (5S,8S,9S)-5-ethoxycarbonyl-8-hydroxyindolizidine **25** in 89% yield together with 5% of **24**.[13,14]

Scheme 4



10% Pd/C, AcOH — 75% — 0%

5% Rh/Al_2O_3, EtOH-AcOH (99:1) — 5% — 89%

In conclusion, thanks to these new methods of pyrrole formation and cyclization, the innate chirality of L-glutamic diethyl ester is retained and serves to control the stereochemistry of the indolizidine products. Appropriate elaboration of **24** and **25** should permit the concise synthesis of various structurally related alkaloids such as the piclavines[15] and pumiliotoxins.[16] Applications of this methodology will be reported in due course.

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References and Notes

1. C.W. Jefford, Q. Tang, A. Zaslona, *J. Am. Chem. Soc.* **1991**, *113*, 3513.
2. C.W. Jefford, J.B. Wang, *Tetrahedron Lett.* **1993**, *34*, 3119.
3. A.D. Josey, E.L. Jenner, *J. Org. Chem.* **1962**, *27*, 2466.
4. S.J. Box, D.F. Corbett, *Tetrahedron Lett.* **1981**, *22*, 3293.
5. L-Aspartic and L-glutamic acids, of 99.7 and 99.5% enantiomeric purity respectively, were purchased from *Fluka Chemie AG*, CH-9470 Buchs, and quantitatively converted into their dimethyl ester hydrochlorides (**16** and **18**) by a standard procedure (R.B. Silverman, M.A. Levy, *J. Org. Chem.* **1980**, *45*, 815). Diethyl L-glutamate hydrochloride (**21**) was similarly prepared.
6. C. Kashima, T. Maruyama, K. Harada, S. Hibi, Y. Omote, *J. Chem. Res., Miniprint* **1988**, 601.
7. J. March, *Advanced Organic Chemistry*, 4th Edition, **1992**, J. Wiley & Sons, New York, pp 534-542.
8. To our knowledge, pyrroles have never been acylated with esters (see H.J. Anderson, C.E. Loader in "Pyrroles, Part One. The Synthesis and the Physical and Chemical Aspects of the Pyrrole Ring" (Ed. R.A. Jones), J. Wiley & Sons, New York, **1992**, pp 397-497).

9. The choice of boron tribromide was dictated by its known reactions with esters and lactones in which boronic derivatives, behaving like acylating agents, are supposedly formed (W. Gerrard, M.A. Wheelans, *J. Chem. Soc.* **1956**, 4296; H. Yazawa, K. Tanaka, K. Kariyone, *Tetrahedron Lett.* **1974**, 3995; G.A. Olah, R. Karpeles, S.C. Narang, *Synthesis* **1982**, 963). The action of BCl_3 was similar but less effective.

10. The ^1H- and ^{13}C-NMR spectra were identical to those already reported (ref. 4). A reaction time of 15 mins (see ref. 11) gave **15** with an $[\alpha]_D^{20}$ of -105.9° (c 1.01 $CHCl_3$). After 60 mins reaction, the value dropped to -65.9° (c 1.34, $CHCl_3$). The enantiomeric excesses were 82 and 50% respectively (estimated from the ^1H-NMR spectra in the presence of $Eu(hfc)_3$ (see M. Calmes, J. Daunis, R. Jacquier, J. Verducci, *Tetrahedron* **1987**, *43*, 2285). Therefore, it can be concluded that the previously prepared sample of **15** (ref. 4), characterized by an $[\alpha]_D^{20}$ of -95.5°, was partially racemic.

11. In a typical experiment, BBr_3 (5.5 ml of a 1.0M soln. in CH_2Cl_2) was added dropwise to **22** (1.267 g, 5 mmol) in CH_2Cl_2 (50 ml) under Ar and stirred at 20°C for 15 mins. Water (10 ml) was then added and the resulting mixture was neutralized (aq. $NaHCO_3$) separated and extracted (CH_2Cl_2). After drying the extracts (Na_2SO_4) and evaporation, the residue was subjected to flash chromatography (SiO_2, Et_2O) to give **23** as a yellowish oil (0.916 g, 88%): ^1H-NMR (400 MHz, $CDCl_3$): 1.28 (t, J = 7.2, 3H), 2.50-2.66 (m, 4H), 4.19-4.30 (m, 2H), 4.91-4.95 (m, 1H), 6.33 (dd, J = 3.2, 5.1, 1H), 6.90 (dd, J = 2.3, 3.2, 1H), 7.08 (dd, J = 2.3, 5.1, 1H), $[\alpha]_D^{20}$ = +12.7° (c 1.21, CH_2Cl_2). Optical purity was determined as ≥99:1 by GC Lipodex E at 180°C and by its ^1H-NMR spectrum in the presence of $Eu(hfc)_3$. No racemization was observed after longer reaction times.

12. Hydrogenations were conducted at 55 psi for 2 h at 20°C in a Parr apparatus. Acetic acid as solvent was necessary to ensure hydrogenolysis of the carbonyl group. In EtOH:AcOH (99:1), **24** and **25** were obtained in 39 and 51% yields respectively.

13. Indolizidine **24**, a colorless liquid, and **25**, a crystalline solid, m.p. 36-37°C, were purified by chromatography (neutral Al_2O_3, Et_2O) and characterized by the following data:
24: $[\alpha]_D^{20}$ = -106.3° (c 1.15, CH_2Cl_2); a single diastereomer as determined by its ^1H-NMR spectrum in the presence of $Eu(hfc)_3$. ^1H-NMR (400 MHz, $CDCl_3$): 1.26 (t, J = 7.0, 3H), 1.28-1.42 (m, 2H), 1.45-1.67 (m, 3H), 1.73-1.91 (m, 6H), 1.96 (q, J = 8.8, 1H), 2.73 (dd, J = 11.4, 2.6, 1H), 3.22 (td, J = 8.5, 1.8, 1H), 4.13-4.26 (m, 2H). NOESY cross peaks: C(5)H↔C(9)H; C(5)H↔C(3)H pseudoaxial. IR (neat): 2790 (s, Bohlmann band), 1748 cm^{-1} (vs, C=O).
25: $[\alpha]_D^{20}$ = -88.3° (c 1.51, CH_2Cl_2), a single diastereomer (^1H-NMR, $Eu(hfc)_3$). ^1H-NMR (400 MHz, $CDCl_3$): 1.28 (t, J = 7.0, 3H), 1.50 (tdd, J = 13.6, 5.2, 2.6 1H), 1.63-2.08 (m, 8H), 2.17-2.20 (m, 1H), 2.64 (brd, J = 7.7, 1H), 2.83 (dd, J = 11.8, 3.3, 1H), 3.25 (td, J = 8.1, 1.8, 1H), 3.82 (brs, 1H), 4.20 (q, J = 7.0, 2H). NOESY cross peaks: C(9)H↔C(8)H; C(9)H↔C(5)H; C(8)H↔C(7)H axial, C(5)H↔C(3)H pseudoaxial. IR (neat): 3499 (s, OH), 2796 (s, Bohlmann band), 1732 cm^{-1} (vs, C=O).

14. Compounds **23**, **24** and **25** gave acceptable elemental analyses.

15. M.F. Raub, J.H. Cardellina II, T.F. Spande, *Tetrahedron Lett.* **1992**, *33*, 2257.

16. J.P. Michael, *Nat. Prod. Rep.* **1994**, *11*, 17; J.W. Daly, H.M. Garaffo, T.F. Spande in "The Alkaloids" (Ed. G.A. Cordell), Academic Press, San Diego, 1993, vol. 43, chap. 3.

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