



S0957-4166(96)00111-5

The Synthesis of Chiral 1-(1H-Pyrrole) Derivatives

Charles W. Jefford,* Fabienne de Villedon de Naide,
and Krzysztof Sienkiewicz

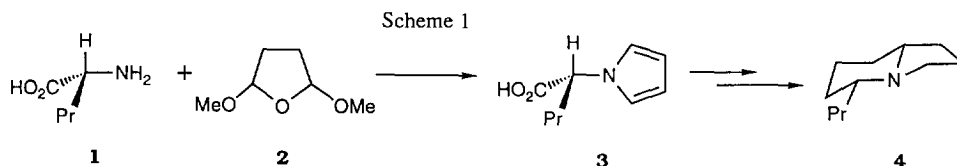
Department of Organic Chemistry, University of Geneva
CH-1211 Geneva 4, Switzerland

Abstract: Enantiomerically pure primary amines possessing an epimerizable center, such as α -amino acids and their ester hydrochlorides, undergo condensation with tetrahydro-2,5-dimethoxyfuran **2** in acetic acid or acetic acid containing sodium acetate at 80°C for 30 min. to give the corresponding 1-(1H-pyrrolyl) derivatives with partial racemization (9-18%). By replacing the solvent with a stirred mixture of aqueous acetic acid and 1,2-dichloroethane in the case of the acids and with water-1,2-dichloroethane for the ester hydrochlorides, repetition of the previous experiment gives the corresponding pyrroles in high yield and with complete retention of configuration. β -Aminoalcohols are also efficiently converted to their 1-(1H-pyrrolyl) derivatives in a stirred, warm mixture of aqueous acetic acid and 1,2-dichloroethane.

Copyright © 1996 Elsevier Science Ltd

INTRODUCTION

We recently developed a three-part method¹ for synthesizing enantiomerically pure indolizidine alkaloids which starts with the condensation of a chiral α -amino acid, exemplified by D-norvaline **1**, and tetrahydro-2,5-dimethoxyfuran **2** to give the corresponding 1-pyrrolyl derivative **3** (Scheme 1). Subsequent homologation and cyclization followed by catalytic hydrogenation then affords indolizidine 167B **4**. The validity and generality of the method hinges on the conservation of the implanted stereogenic center. Consequently, the condensation step is all-important. It is acid-catalysed and usually performed by simply heating a solution of the requisite amino acid and **2** in acetic acid with or without added sodium acetate for no more than 30 minutes.^{2,3}

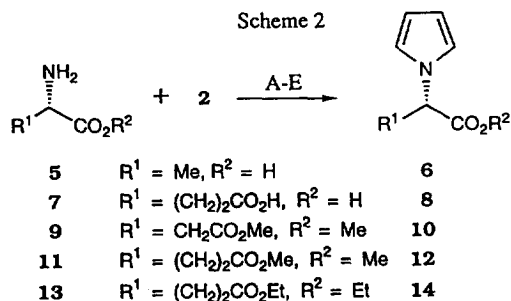


Although the mechanism has not been studied, it can be supposed to be similar to that operating in the related Paal-Knorr⁴ and Clauson-Kaas⁵ syntheses of 1-substituted 1H-pyrroles in which primary amines react with γ -diketones and **2** or its equivalents⁶ respectively. *A priori*, there was no reason to suspect that the chirality of the amine precursor or the ensuing intermediates would be compromised by these mildly acidic conditions. In

fact, in the first report² the constancy of the specific rotations of products obtained in different experiments was taken as indirect, but not conclusive, evidence of optical homogeneity. In the second,³ it was found that the degradation of pyrrolyl derivatives similar to **3**, by hydroxylamine or by ozonolysis, left the optical activity of the α -amino acid so liberated unaltered from what it was originally. We too were satisfied that the condensation was uncomplicated because the specific rotation observed for **4** was the same, given the margin of experimental error, as that previously reported.⁷ Moreover, (+)-monomrine synthesized by the same route had a rotation identical to those of other specimens.⁸ However, later a doubt arose over a sample of indolizidine 209D, similarly prepared,⁹ which had a specific rotation lower than expected.^{7,10} We therefore realized that it was high time to examine this classic reaction with special regard to the enantiomeric purity of the products. We now describe our results and disclose an improved method for preparing chiral 1-(1H-pyrrole) derivatives.¹¹

RESULTS AND DISCUSSION

First of all, the typical α -amino acids, L-alanine **5** and L-glutamic acid **7** were allowed to react with tetrahydro-2,5-dimethoxyfuran **2** under the Clauson-Kaas conditions, namely in warm acetic acid for 30 minutes (Table 1, entries 1 and 4). In both cases, the yield of pyrrole products **6** and **8** was poor (Scheme 2). More surprising was the occurrence of pronounced racemization as attested by the enantiomeric excesses (e.e.) of 72 and 88% respectively. Repeating the experiment, but in the presence of an equivalent of sodium acetate (Table 1, entries 2 and 5), left the yield of **6** unchanged, but improved it a bit for **8**. The e.e. values for **6** and **8** jumped to 82 and 94% respectively, but still fell short of an synthetically acceptable level (cf. Entries 1 and 2, and entries 4 and 5).



These results indicate that the racemizing effect of acetic acid is buffered by sodium acetate, but insufficiently so. In other words, acid is required for condensation, but its continued presence is deleterious. Accordingly, removing the pyrrole product from the acid medium as soon as it forms would prevent it from racemizing. In practice, running the condensation in a strongly stirred, two-phase mixture of warm aqueous acetic acid and 1,2-dichloroethane was entirely effective in the anticipated sense. Both L-alanine **5** and L-glutamic acid **7** gave the pyrrolyl derivatives **6** and **8** in an essentially enantiomerically pure state (>99%) (Entries 3 and 6). The specific rotations observed can be considered to be the maximum values. Moreover, markedly better yields were achieved.

Table 1. Preparation of *N*-pyrrole derivatives **6**, **8**, **10**, **12**, **14**, **16**, **18** by the condensation of α -amino acids (**5**, **7**), ester hydrochlorides **9**, **11**, **13**, and β -amino alcohols **15**, **17** with tetrahydro-2,5-dimethoxyfuran **2** under different reaction conditions.

Entry	Educt	Product	Conditions ^{a)}	Yield ^{b)} (%)	e.e. (%)	$[\alpha]_D^{20}$ (c, solvent)
1	5	6	A	49*	72	+15.4 (1.0, MeOH)
2			B	45*	82	+16.6 (1.2, MeOH)
3			C	73	>99	+20.9 (1.5, MeOH)
4	7	8	A	2	88	-13.7 (0.8, MeOH)
5			B	53	94	-15.1 (1.1, MeOH)
6			C	59	>99	-16.7 (1.1, MeOH)
7	9^{c)}	10	B	86	64	-45.5 (1.3, CHCl ₃)
8			D	20	>99	-76.6 (1.2, CHCl ₃)
9			E	69	>99	-76.4 (1.2, CHCl ₃)
10	11^{c)}	12	B	70	86	-26.9 (1.2, MeOH)
11			D	23	>99	-33.5 (1.3, MeOH)
12			E	75	>99	-29.4 (1.7, CHCl ₃)
13	13^{c)}	14	B	83	84	-16.6 (1.0, EtOH)
14			D	62	>99	-21.9 (1.1, EtOH)
15			E	81	>99	-12.2 (1.3, CHCl ₃)
16	15	16	A	69*	^{d)}	-25.3 (1.6, MeOH)
17			C	83	^{d)}	-25.0 (0.7, MeOH)
18	17	18	C	90*	>99	-22.2 (1.2, MeOH)

^{a)}The educt was condensed with **2** in: AcOH, 80°C, 30 min. (A); AcOH, AcONa (1 equiv.), 80°C, 30 min. (B); AcOH-H₂O-ClCH₂CH₂Cl, 80°C, 45 min (C); H₂O, 80°C, 30 min (D); H₂O-ClCH₂CH₂Cl, 80°C, 45 min (E) (see experimental part for details).

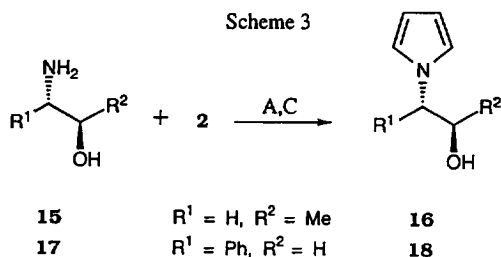
^{b)}Products were purified either by column chromatography or bulb-to-bulb distillation*.

^{c)}As the hydrochloride. ^{d)}Not determined.

It was reported earlier that aspartic acid condensed poorly with 2,5-diethoxytetrahydrofuran on acetic acid-catalysis giving the pyrrole in 10% yield, whereas the dl-dimethyl ester hydrochloride was more effective affording the analogous pyrrole ester in 90% yield.¹² As expected, submission of dimethyl L-aspartate **9**, as its hydrochloride, to a warm mixture of acetic acid containing sodium acetate and **2** was successful (Scheme 2). The desired pyrrole-protected derivative **10** was obtained in high yield though marred by an e.e. of 64% showing that extensive racemization had occurred (Entry 7). Its homologues, the hydrochlorides of dimethyl and diethyl L-glutamate **11** and **13**, were more impervious to racemization affording under the same conditions the pyrroles **12** and **14** in similar high yield (Entries 10 and 13).

In the original procedures, the hydrochlorides of esters such as **9**, **11**, and **13** were treated with sodium acetate or triethylamine, in addition to solution in acetic acid, the idea being that the ester would be freed for reaction.^{2,3} However, the hydrochlorides, as they already embody a molecule of acid, do not need to be neutralized and re-acidified for catalysed reaction with **2**. Indeed, merely dissolving the hydrochlorides of **9**, **11** and **13** in warm water containing **2** was enough to bring about their reaction, albeit in moderate yield (Entries 8, 11, and 14). The pyrrole esters so formed **10**, **12**, and **14**, being insoluble in water, deposited and were found to be of high enantiomeric purity (e.e. >99%). Performing the same experiment with the adjunction of 1,2-dichlorethane with strong stirring to extract the nascent pyrrole, gave products of the same high enantiomeric purity and, equally importantly, in preparatively useful yields (Entries 9, 12, and 15).

The two-phase procedure also worked well for the conversion of β -amino alcohols into their pyrrole derivatives. The usual method employing acetic acid¹³ requires a four-fold excess of the amine component which is wasteful when it is chiral. In the case of (R)-1-amino-2-propanol **15**, such an excess was necessary to get an adequate yield of the pyrrole **16** (Entry 16) (Scheme 3). A better yield was achieved more economically by just mixing an equivalent each of **15** and **2** in warm, stirred aqueous acetic acid and 1,2-dichloroethane (Entry 17). As there is no epimerizable center, the enantiomeric excess of **16** remained the same under both sets of conditions. Similar treatment of L-(+)- α -phenylglycinol **17** was equally satisfactory. The pyrrole **18** was obtained in high chemical and enantiomeric yield (Entry 18).



The preceding results confirm that the non-basic 1H-pyrrole derivatives of α -amino acids and esters, like their similarly deactivated N-acetyl and benzoyl analogues,¹⁴ are susceptible to partial racemization by acetic acid, the extent of which depends on the length of exposure to acid. On reviewing our first approach to the synthesis of (+)-monomorphine,¹ it is now seen that the choice of a reaction times of a few minutes was fortunate in that little racemization occurred. The crucial chiral building block **6** was constructed from L-alanine **5** and **2** by dissolving them in acetic acid containing six equivalents of sodium acetate and warming the resulting mixture for only 5 minutes. Under these conditions, **6** was formed in yields less than 50%. Nevertheless, its specific rotation ($[\alpha]_D^{20} = +20.6$ (c 0.73 MeOH)) was the same as that of the sample obtained by the present more efficient, two-phase procedure (Table 1, entry 3).

It is also possible that the short exposure times used earlier² and more recently¹⁵ for the condensation of L-glutamic acid **7** with **2** and its diethoxy analogue under the above-mentioned conditions gave pyrrole **8** with the same degree of high enantiomeric excess.

Longer contact times with acid cause more racemization. For example, the specific rotation of **12** previously obtained³ ($[\alpha]_D^{25} = -26.6$ (c 1.2, MeOH)) by warming **11** and **2** in acetic acid containing an equivalent of sodium acetate for 30 minutes was the same as that of the sample having an e.e of 86% (Table 1, entry 10). It is therefore likely that all pyrroles so prepared suffered racemization to about the same extent.³

CONCLUSION

The present findings reveal the limitations of the classic reaction and demonstrate that optically pure 1*H*-pyrrole derivatives are obtainable in high yield from α -amino acids and β -amino alcohols by letting them react with tetrahydro-2,5-dimethoxyfuran **2** in a warm, stirred mixture of water, acetic acid and 1,2-dichloroethane for 30 minutes. α -Amino ester hydrochlorides can be converted with comparable efficiency under the same conditions, without the help of acetic acid. Clearly, the two-phase procedure applied to aspartic and glutamic ester hydrochlorides provides useful chiral building blocks (e.g. **10** and **14**) which on cyclization will give access to a variety of pyrrolizidines and indolizidines. Although indolizidine 167B has yet to be prepared from **14**, simple functional group interchange of the latter has already been accomplished affording economical approaches to certain 5-alkyl, 3,5- and 5,8-dialkylindolizidines. Examples are the syntheses of enantiomerically pure (-)-monomarine,¹⁶ indolizidines 209B and 209D, and piclavine A.¹⁷ An application exploiting **16** is its successive inter- and intramolecular acylation to afford a practical synthesis of a rare 2-acetylpyrrole of marine origin.¹⁸

EXPERIMENTAL

General. M.p. was determined on a Reichert hot-stage microscope, not corrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Gas chromatographic analyses (GC) were performed on a Hewlett Packard 5890 instrument. Bulb-to-bulb distillations (BBD) were effected in a Büchi GKR-50 apparatus. ¹H and ¹³C-NMR spectra were recorded in CDCl₃, at 400 and 100 MHz respectively, on a Bruker AMX-400 spectrometer; chemical shifts (δ) being expressed in ppm with reference to Me₄Si, coupling constants (J) in Hz. The different kinds of C-atom were identified by APT or DEPT pulse sequence methods. Elemental analyses were made by Dr. H.J. Eder, Microanalytical Service, Department of Pharmaceutical Chemistry, University of Geneva.

L-Aspartic and L-glutamic **7** 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 **9** and **11** hydrochlorides by a standard procedure.¹⁹ Diethyl L-glutamate **13** hydrochloride was similarly prepared. L-Alanine **5**, (R)-1-amino-2-propanol **15** and L-(+)- α -phenylglycinol **17** of >99.5, >98.0 and 99.9% enantiomeric purity respectively were purchased from Fluka and used as received.

The preceding amino compounds were converted into 1-(1*H*-pyrrolyl) derivatives **6**, **8**, **10**, **12**, **14**, **16**, and **18** by procedures A-E, the details of which are described below. However, the yields are gathered in Table 1. For all procedures, the progress of condensation and the efficiency of extraction during work-up were monitored by thin layer chromatography (SiO₂) by using a mixture of 3% anisaldehyde and 4% sulfuric acid as a visualizing agent. The enantiomeric excess of **6** was determined by converting it to its methyl

ester by treatment with excess diazomethane in diethyl ether and examining the ester by GC at 100°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). In similar fashion, **8** was converted into its dimethyl ester **12** ($[\alpha]_D^{20} = -29.1$ (c 2.0, CHCl₃) for the enantiomerically pure product) and analysed by GC at 135°C. The pyrroles **10**, **12**, and **14** were also analysed by GC over *Lipodex E* at 135°C. The enantiomeric purity of **18** was determined by ¹H-NMR analysis of the ester formed from (R)-(-)- α -methoxy- α -trifluoromethylphenylacetic acid chloride (Mosher's acid chloride).²⁰ The optical rotations for the products were determined for each procedure; values of >99% for the enantiomeric excess (e.e.) indicate that the other antipode is essentially absent (Table 1). The optically pure, new products (Table 1, entries 3, 6, 9, 12, 15, and 18) gave satisfactory elemental analyses: C \pm 0.28, H \pm 0.12, N \pm 0.15, except for **8**: C \pm 0.69, H \pm 0.14, N \pm 0.22.

(2S)-2-(1H-Pyrrol-1-yl)propionic acid **6** (according to procedure A). L-Alanine (**5**, 0.891 g, 10 mmol) and tetrahydro-2,5-dimethoxyfuran (**2**, 1.322 g, 10 mmol) were dissolved in acetic acid (20 ml) and heated at 80°C with stirring for 30 min. The reaction was then quenched by pouring over crushed ice (20 ml), and extracted with CH₂Cl₂. The combined organic extracts were washed (brine), dried (MgSO₄) and evaporated to give an oil which on purification by BBD (b.p. 120°C at 1 Torr) furnished **6** (0.68 g, 49%) as a colorless solid, m.p. 78° C. Procedure B: the above experiment was repeated, except that sodium acetate (0.82 g, 10 mmol) was added to the mixture. Work-up was the same as before giving **6** (45%). Procedure C: L-alanine (**5**, 0.891 g, 10 mmol) and tetrahydro-2,5-dimethoxyfuran (**2**, 1.322 g, 10 mmol) were dissolved in water (10 ml), acetic acid (5 ml) and 1,2-dichloroethane (15 ml) and heated at 80°C with vigorous stirring for 45 min. After cooling to room temperature, the aqueous layer was separated and extracted several times with CH₂Cl₂. The combined organic extracts were dried (MgSO₄) and carefully evaporated to give a solid which on purification by column chromatography (CC) (SiO₂, Et₂O) furnished **6** (1.015 g, 73%) as colorless crystals, m.p. 79-80°C. Repetition of the experiment and final purification by BBD (b.p. 120°C at 1 Torr) also afforded **6** (0.96 g, 69%). ¹H-NMR: d 1.77 (d, J = 7.4, 3H), 4.80 (q, J = 7.6, 1H), 6.21 (t, J = 2.2, 2H), 6.75 (t, J = 2.2, 2H), 9.20 (br. s, 1H). ¹³C-NMR: d 17.94 (CH₃), 56.63 (CH), 108.87 (CH), 119.75 (CH), 177.00 (C=O). The NMR data are in agreement with those reported,³ however the previous m.p. 68-70.0°C and $[\alpha]_D^{20} = +19.0$ (c 1.2, MeOH) are lower.

(2S)-2-(1H-Pyrrol-1-yl)glutamic acid **8**. Procedures A, B and C were repeated with L-glutamic acid **7** giving **8** as an oil. ¹H-NMR: d 2.19-2.43 (m, 3H), 2.46-2.57 (m, 1H), 4.78 (dd, J = 9.9, 5.1, 1H), 6.22 (t, J = 2.2, 2H), 6.73 (t, J = 2.2, 2H), 8.30 (br. s, 2H). ¹³C-NMR: d 27.42 (CH₂), 29.61 (CH₂), 60.22 (CH), 109.35 (CH), 120.11 (CH), 175.76 (C=O), 178.36 (C=O). This product has been described before, but characterized as the dicyclohexylamine salt.² Brief mention without details has also been made.¹⁵

(2S)-Dimethyl 2-(1H-pyrrol-1-yl)succinate **10** (according to procedure E). To a solution of dimethyl L-aspartate (**9**) hydrochloride (1.975 g, 10 mmol) in water (15 ml) was added successively 1,2-dichloroethane (15 ml) and **2** (1.322 g, 10 mmol). The resulting heterogeneous mixture was vigorously stirred and heated at 80°C for 45 min. After cooling to room temperature, the aqueous layer was separated, extracted with CH₂Cl₂ and worked up as before. Purification by CC (SiO₂, hexane-ethyl ether, 1:1) gave **10** as colorless crystals,

m.p. 35-37°C. ¹H-NMR: δ 2.95 (dd, *J* = 16.9, 6.6, 1H), 3.28 (dd, *J* = 16.9, 8.1, 1H), 3.69 (s, 3H), 3.74 (s, 3H), 5.12 (dd, *J* = 7.9, 6.6, 1H), 6.18 (t, *J* = 2.2, 2H), 6.71 (t, *J* = 2.2, 2H). ¹³C-NMR: δ 37.47 (CH₂), 52.19 (CH₃), 57.80 (CH), 109.18 (CH), 120.04 (CH), 169.96 (C=O), 170.29 (C=O). The preceding experiment was repeated by dissolving the same quantities of **9** and **2** in water alone (20 ml) (Procedure D). Procedure B (as for **8** above) was repeated with **9**; however, the product **10** was purified by CC. Only the racemic form of **10** has been previously reported, m.p. 33-36°C, without spectral data.¹²

(2*S*)-Dimethyl 2-(1*H*-pyrrol-1-yl)glutarate **12**. Dimethyl L-glutamate **11** hydrochloride was condensed with **2** according to procedures B, D, and E giving **12** as an oil. ¹H-NMR: δ 2.09-2.34 (m, 3H), 2.40-2.49 (m, 1H), 3.66 (s, 3H), 3.73 (s, 3H), 4.74 (dd, *J* = 10.0, 5.2, 1H), 6.19 (t, *J* = 2.2, 2H), 6.71 (t, *J* = 2.2, 2H). ¹³C-NMR: δ 27.97 (CH₂), 29.59 (CH₂), 51.73 (CH₃), 52.59 (CH₃), 60.55 (CH), 108.96 (CH), 120.03 (CH), 170.69 (C=O), 172.77 (C=O). Brief mention has been made of **12** without details.¹⁵

(2*S*)-Diethyl 2-(1*H*-pyrrol-1-yl)glutarate **14** Diethyl L-glutamate **13** hydrochloride was similarly reacted according to procedures B, D, and E, giving **14** as an oil. ¹H-NMR: δ 1.22-1.27 (m, 6H), 2.09-2.32 (m, 3H), 2.39-2.44 (m, 1H), 4.12 (q, *J* = 7.4, 2H), 4.20 (qd, *J* = 7.0, 2.2, 2H), 4.70 (dd, *J* = 9.9, 5.5, 1H), 6.18 (t, *J* = 2.2, 2H), 6.72 (t, *J* = 2.2, 2H). ¹³C-NMR: δ 14.02 (CH₃), 14.13 (CH₃), 28.04 (CH₂), 29.92 (CH₂), 60.57 (CH₂), 60.78 (CH), 61.60 (CH₂), 108.82 (CH), 120.02 (CH), 170.20 (C=O), 172.32 (C=O).

(2*R*)-1-(1*H*-Pyrrol-1-yl)-2-propanol **16** (according to procedure A). To (2*R*)-1-amino-2-propanol (**15**, 1.2 g, 16 mmol) in acetic acid (20 ml) was added **2** (0.53 g, 4 mmol). The resulting solution was concentrated to half its volume by distillation from an oil bath at 120°C. The residue was mixed with water (20 ml) and extracted with CH₂Cl₂. The extract was washed with brine, an aqueous solution of sodium carbonate, dried (Na₂SO₄) and evaporated. The residue was dissolved in MeOH (20 ml) and an aqueous solution of NaOH (20% w/w, 10 ml), stirred (1 h), and extracted with CH₂Cl₂. Washing and drying of the extract as before, followed by evaporation, gave **16** as an oil, which was purified by CC (SiO₂, hexane-ethyl ether, 1:1). ¹H-NMR: δ 1.21 (d, *J* = 6.3, 3H), 1.70 (br. s, 1H), 3.74 (dd, *J* = 14.0, 8.1, 1H), 3.93 (dd, *J* = 14.0, 3.3, 1H), 4.04 (m, 1H), 6.17 (t, *J* = 2.2, 2H), 6.68 (t, *J* = 2.2, 2H). ¹³C-NMR: δ 20.11 (CH₃), 57.09 (CH₂), 67.99 (CH), 108.54 (CH), 121.14 (CH). Procedure C: a solution of **15** (0.375g, 5 mmol) and **2** (0.661 g, 5 mmol) in water (5ml), acetic acid (2.5 ml) and 1,2-dichloroethane (7.5 ml) was stirred vigorously and heated at 80°C for 4 h. After cooling to room temperature, the aqueous layer was separated, and extracted several times with CH₂Cl₂. The combined organic extracts were neutralized by shaking with aqueous sodium hydroxide (3*N*). The remaining aqueous layer was extracted again with CH₂Cl₂. The combined organic extracts were dried and evaporated giving **16** as a crude product which was purified by CC.

(2*S*)-2-(1*H*-Pyrrol-1-yl)-2-phenylethanol **18**. Repeating the preceding experiment with L-(+)-α-phenylglycinol **17** gave **18** as a colorless solid, m.p. 37-38°C. Purification was effected by BBD (b.p. 175°C at 0.6 Torr.). ¹H-NMR: δ 1.80 (br. s, 1H), 4.22 (m, 2H), 5.27 (dd, *J* = 8.1, 5.2, 1H), 6.26 (t, *J* = 2.2, 2H), 6.82 (t, *J* = 2.2, 2H), 7.15-7.18 (m, 2H), 7.30-7.40 (m, 3H). ¹³C-NMR: δ 64.79 (CH), 65.06 (CH₂), 108.57 (CH), 119.91 (CH), 126.55 (CH), 127.93 (CH), 128.68 (CH), 138.45 (C).

ACKNOWLEDGMENTS

We are indebted to the *Swiss National Science Foundation* for support of this research (grant No. 20-38'939.93). We also thank Messrs. A. Pinto and J.P. Saulnier for the NMR measurements.

REFERENCES

1. Jefford, C.W., Tang, Q., Zaslona, A. *J. Am. Chem. Soc.* **1991**, *113*, 3513-3518.
2. Gloede, J., Poduska, K., Gross, H., Rudinger, J. *Coll. Czech. Chem. Commun.* **1968**, *33*, 1307-1314.
3. Kashima, C., Maruyama, T., Harada, K., Hibi, S., Omote, Y. *J. Chem. Res. Miniprint* **1988**, 601-645.
4. Bean, G.P., in *Pyroles, Part One. The Synthesis and the Physical and Chemical Aspects of the Pyrrole Ring*, R.A. Jones, Ed.; J. Wiley and Sons, New York, N.Y., **1992**, pp 206-222.
5. Tyle, Z., Clauson-Kaas, N., *Acta Chem. Scand.* **1952**, *6*, 667-670; Elming, N., Clauson-Kaas, N. *Acta Chem. Scand.* **1952**, *6*, 867-874; Josey, A.D., Jenner, E.L. *J. Org. Chem.* **1962**, *27*, 2466-2470.
6. Chan, T.H. Lee, S.D. *J. Org. Chem.* **1983**, *48*, 3059-3061.
7. Polniaszek, R.P., Belmont, S.E. *J. Org. Chem.* **1990**, *55*, 4688-4693. The optical rotation of naturally occurring indolizidine 167B is not available for comparison.
8. Munchhof, M.J., Meyers, A.I. *J. Am. Chem. Soc.* **1995**, *117*, 5399-5400 and references cited therein.
9. Jefford, C.W., Wang, J.B. *Tetrahedron Lett.* **1993**, *34*, 3119-3122.
10. Åhman, J., Somfai, P. *Tetrahedron Lett.* **1995**, *36*, 303-306.
11. Preliminary paper: Jefford, C.W., Thornton, S.R., Sienkiewicz, K. *Tetrahedron Lett.* **1994**, *35*, 3905-3908.
12. Box, S.J., Corbett, D.F. *Tetrahedron Lett.* **1981**, *22*, 3293-3296.
13. Carpio, H., Galeazzi, E., Greenhouse, R., Guzmán, A., Velarde, E., Antonio, Y., Franco, F., Leon, A., Pérez, V., Salas, R., Valdés, D., Ackrell, J., Cho, D., Gallegra, P., Halpern, O., Koehler, R., Maddox, M.L., Muchowski, J.M., Prince, A., Tegg, D., Thurber, T.C., Van Horn, A.R., Wren, D. *Canad. J. Chem.* **1982**, *60*, 2295-2312.
14. Bergmann, M., Zervas, L. *Biochem. Ztschr.* **1928**, *203*, 280; Bergmann, M., Zervas, L. *Chem. Ber.* **1932**, *65*, 1192-1201.
15. Bond, T.J., Jenkins, R., Ridley, A.C., Taylor, P.C. *J. Chem. Soc., Perkin Trans. I* **1993**, 2241-2242; Bond, T.J., Jenkins, R., Taylor, P.C. *Tetrahedron Lett.* **1994**, *35*, 9263-9266. The assertions about the enantiomeric purity of **8** and **12** in the first communication and of their partial racemization in the second are not substantiated by any data
16. Jefford, C.W., Sienkiewicz, K., Thornton, S.R. *Tetrahedron Lett.* **1994**, *35*, 4759-4762.
17. Jefford, C.W., Sienkiewicz, K., Thornton, S.R. *Helv. Chim. Acta* **1995**, *78*, 1511-1524.
18. Jefford, C.W., Sienkiewicz, K., Thornton, S.R. *Tetrahedron Lett.* **1994**, *35*, 6271-6274.
19. Silverman, R.B., Levy, M.A. *J. Org. Chem.* **1980**, *45*, 815-818.
20. Dale, J.A., Mosher, H.S. *J. Am. Chem. Soc.* **1973**, *95*, 512-519.