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A Three-step, Highly Enantioselective Synthesis of (*R*)-2-Methyl Tryptophane Ethyl Ester : Comparison with Chemical Resolution.

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Abstract : (*R*)-2-Methyltryptophan ethyl ester, (*R*)-**2**, having an enantiomeric purity >,=96% was obtained in 3 steps and using (*SSS*)-hydroxypinanone, **1**, as the recoverable chiral auxiliary. The synthesis of the alkylating agent, **5a**, was improved (to a reproduceble 55% overall yield from 2,3-dimethylindole). The resolution of *racemic*-**2** through chromatographic separation of the corresponding iminoester derived from (*RRR*)-**1** also proved to be easy and efficient (~25% yield).
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Since the discovery that 5-methyltryptophan inhibited the growth of *Bacterium coli*[1] many substituted tryptophans have been synthesized but in their racemic forms.[2] Tryptophans substituted in position 2, although having less bioactivity, prevent side reactions during incorporation into peptides[2d] and/or are used to restrict the conformation of the final peptide. Racemic ethyl 2-methyltryptophan, *racemic*-**2**, has already been synthesized by the 'gramine' synthesis[2a] and we report here a chemical resolution and the first enantioselective (ee > 96%) and short (3 steps) synthesis of (*R*)-ethyl 2-methyltryptophan, (*R*)-**2**, both methods using the hydroxypinanone **1** as chiral auxiliary.[3]

Resolution :

The racemic amino ester **2**, *racemic*-**2**,[4] was prepared in 3 steps and 71% yield using Gilchrist's method.[5] The iminotryptophan **3a** was then synthesized, as a 1/1 mixture of the two possible diastereomers (**3aI** and **3aII**) from (*RRR*)-hydroxypinanone **1** and *racemic*-**2** following a known procedure.[6] The diastereomers **3aI** and **3aII** were then separated by chromatography[7] and isolated in pure form (as seen from CCM and 200 MHz ^{1}H NMR) in ~45% and 43% yield respectively.

Diastereomer **3aII** was then submitted to hydrolysis (citric acid 15% in THF, 1 day at ambient) to provide 83% of the desired (*R*)-ethyl 2-methyltryptophan, (*R*)-**2** having a *minus* sign of rotation in $CHCl_3$ and ^{1}H and ^{13}C NMR spectra identical to those of racemic-**2**. The chiral auxiliary (*RRR*)-**1** was recovered in 87% yield by extraction of the aqueous phase.

Diastereomers **3aI** and **3aII** are easily distinguished using the chemical shift of one of the methyls belonging to the *gem*-dimethyl group (Me_a) and by the chemical shift of the axial proton in position-9 (which is only coupled with the equatorial H_9-proton), Scheme 1.

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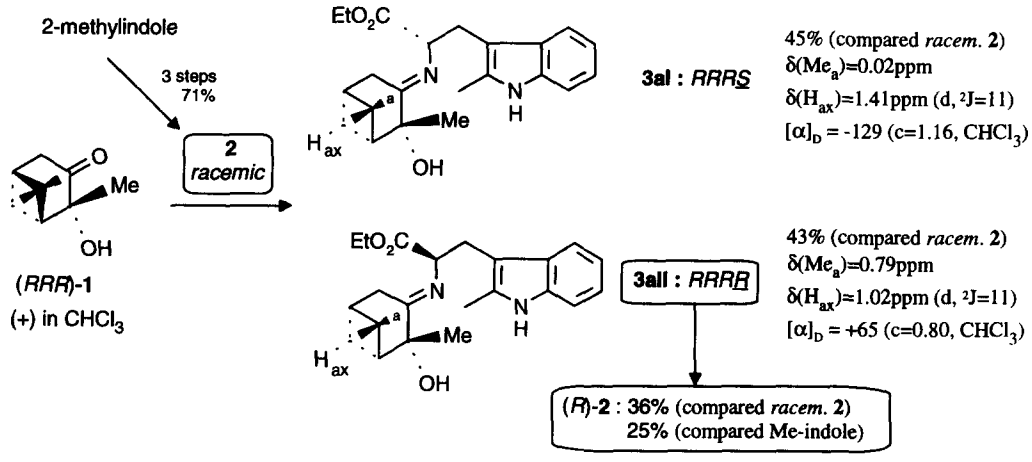
Scheme 1

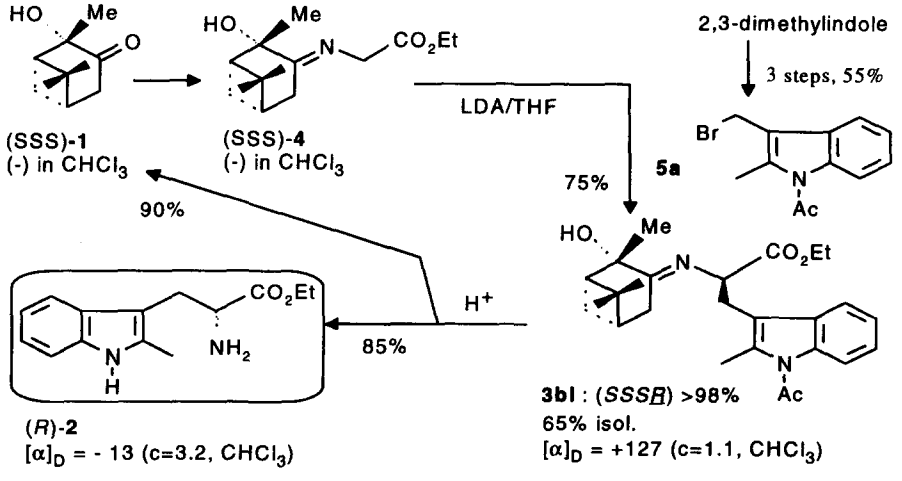


Alkylation of iminoglycinate **4** :

According to previous syntheses of known amino esters[8] and to our model of approach,[9] one can say that (*SSS*)-**1** will provide the (*R*)-amino esters as the *major* (or unique) isomer while the (*RRR*)-**1** will lead to the (*S*)-amino esters. The iminoglycinate **4** derived from (*SSS*)-**1** was thus used to provide the desired *R*-configuration for the amino ester **2**, Scheme 2.

The (*SSS*)-iminoglycinate, **4**, was prepared[6] in 95% yield from (*SSS*)-**1** and ethyl glycinate. Alkylation at -50°C of the lithium enolate of **4**[10] with **5a** afforded the desired adduct **3b** as a single diastereomer (**3bI**) (as seen from ^{1}H NMR at 200 MHz of the crude product of the reaction) and in 75% conversion. After chromatography (hexane/Et_2O, 1/9) **3bI** was isolated in pure form (as seen from 400 MHz ^{1}H NMR)[11] in 65% yield and then submitted to hydrolysis (citric acid 15% in THF, 1 day at ambient) to give 85% of the desired (*R*)-ethyl 2-methyltryptophan, (*R*)-**2**, having a *minus* sign of rotation in $CHCl_3$.

Scheme 2

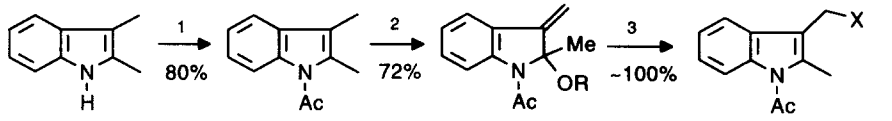


It is worth noting that the chiral auxiliary **1** was also recovered (~90%) by Et_2O extraction of the hydrolysis-mixture and can thus be re-used.

Because the precision of 400 MHz NMR is ±1% to 2% and that racemisation was never observed during hydrolysis of type **3** iminoesters,[6,8,9] one can conclude that the enantiomeric purity of both samples of (*R*)-**2** is identical to the diastereomeric purity of **3aII** and/or **3bI** (>,= 96%). On the basis of previous results[8] and of our model of approach for alkylation of iminoglycinate **4**,[8c,9] the *R*-configuration was assigned to the enantiomer of the amino ester **2** obtained from alkylation and having a *minus* sign of the rotation in $CHCl_3$.

The alkylating agent **5a** was obtained in 3 steps, Scheme 3. N-Acetyl-2,3-dimethylindole, **6**, was obtained in 80% isolated yield, instead of 60%,[12] by lowering the reflux temperature (70°C instead of 140°C). The second step being conducted in CH_2Cl_2 (which, if not well purified, contains EtOH) EtOH must be used instead of MeOH[13] to get pure **7a** (and not a mixture of **7a** and **7b**). Compound **7a**[14] (72%) was then separated from the starting **6** by chromatography (silicagel 60 ; toluene:Et_2O, 9:1). The last step must be performed at -78°C, using highly purified CH_2Cl_2, and a mixture of HBr 33% in AcOH (1 eq.) and NaBr (2 eq.). After washing with H_2O (until pH ~6), the organic phase was dried and the solvent evaporated to give **5a**[15] (95%) as a brown solid which decomposed rapidly and must thus be used immediately. It must be noted that 100% conversion was obtained, but that **5a** was contaminated by up to 5% of **5b.** Formation of **5c** is prevented by washing with H_2O instead of brine.

Scheme 3



6 **7a** R = Et **7b** R = Me **5a** X = Br ; **5b** X = OEt **5c** X = Cl

1) Ac_2O/CSA cat., 70°C. 2) Br_2 (0.9 eq.)/ CH_2Cl_2, EtOH (2 eq.), -78°C, NEt_3 (2 eq.), -78°C-15°C. 3) HBr 33% AcOH (1 eq.), NaBr (2eq.)/CH_2Cl_2, -78°C

(*R*)-Ethyl 2-methyltryptophan, (*R*)-**2**, can thus be obtained by a short (3 steps) and enantioselective (ee>96%) synthesis in which the alkylating agent **5a** is prepared in 3 steps. In this convergent synthesis the chiral auxiliary is recovered and can thus be re-used. Changing the configuration of the chiral auxiliary from *SSS* to *RRR* allows preparation of the (*S*)-enantiomer of **2** in the same way. The overall yield is ~52% (from the chiral auxiliary, 3 steps) and ~30% from the 2,3-dimethylindole used to prepare **5a** (5 steps).

(*R*)-Ethyl 2-methyltryptophan, (*R*)-**2**, can also be obtained through resolution of *racemic*-**2** prepared in 3 steps from 2-methylindole and the overall yield is ~25% (5 steps). The (S)-enantiomer is obtained simultaneously in the same ~25% yield.

Therefore the resolution technique, apart from the necessity to store the unwanted enantiomer, has about the same efficiency as the enantioselective synthesis because of the necessity, in this case, to prepare the alkylating agent **5a**.

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References and notes.

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2 a) Rydon H..N. *J. Chem. Soc.* **1948**, 705 (R=Me). b) Kissman H.M., Witkop B. *J. Am. Chem. Soc.* **1953**, *75*, 1967 (R=Ph). c) Jaeger E., Thamm P., Knof S., Wunsch E., Hoppe-Seyler's Z. *Physiol. Chem.* **1978**, *359* 1629 (R= tBu). d) Li J.P., Newlander K.A., Yellen T.O. *Synthesis*, **1988**, 73 (R=benzyl, C_6H_{11}, tBu, Pyridyl).

3 Discovered by Wagner in **1894** (*Ber. Chem. Gessels. 27*, 2272) the hydroxypinanone **1** was then described by Delepine M. (*Bull. Soc. Chim. Fr.* **1937**, *4*, 1669), Kuwata (*J. Am. Chem. Soc.* **1937**, *59*, 2509) and our group (*Bull. Soc. Chim. Fr.* **1989**, 544 and *Tetrahedron Lett.* **1997**, *38*, 5851). This compound was used for the first time as chiral auxiliary by Yamada S.I, Shioiri T. et al in **1976** (ref. 6a).

4 *Racemic*-**2** and (*R*)-**2** : ^{1}H NMR ($CDCl_3$) δ : 1.21 (t, 3H) ; 2.43 (s, 3H) ; 3.08 (AB of an ABX, 2H, ^{2}J=14Hz, ^{3}J ~ 5, 8Hz, Δν = 50Hz), 3.79 (dd, X of the ABX, 1H) ; 4.15 (q, 2H); 7.09 (m, 2H); 7.27 (m, 1H); 7.52 (m, 1H); 7.84 (bs, 1H). ^{13}C NMR ($CDCl_3$) δ : 11.8 ; 14.1; 30.1; 55.3; 60.9; 107.1; 110.2; 118.0; 119.4; 121.2; 128.3; 132.6; 135.3; 175.4. All the samples exhibited correct elemental analyses.

5 Gilchrist T.L., Lingham D.A., Roberts T.G. *J.C.S. Chem-Comm.* **1979**, 1089.

6 a) Yamada S.I., Oguri T., Shioiri T., *JCS Chem. Comm.* **1976**, 136. b) Solladié-Cavallo A., Schwarz J., Burger V. *Tetrahedron : Asymm.* **1994**, *5*, 1621.

7 Merck Silicagel 60 (0.5-40 μm) ; solvent : hexane/ether 2/1 to 1/9 ; 15 mm Hg vacuum at the botton of the column.

8 a) Oguri T., Kawai N., Shioiri T., Yamada S. *Chem. Pharm. Bull.* **1978**, *26*, 803. b) El Achqar A., Boumzebra M., Roumestant M.L., Viallefont P. *Tetrahedron*, **1988**, *44*, 5319 (cf p. 5321). c) Solladié-Cavallo A., Simon-Wermeister M.C., *Tetrahedron Lett.* **1989**, *30*, 6011.

9 Solladié-Cavallo A., Simon-Wermeister M.C., Schwarz J., *Organometallics*, **1993**, *12*, 3743.

10 Two equivalents of LDA were used and no $MgBr_2$ was added because with analogues of benzyl halides the diastereoselectivities at -78°C are already high, ≥ 90%.

11 **3bI** : Mp. 55-56°C. ^{1}H NMR ($CDCl_3$) δ : 0.02 (s, 3H) ; 1.11 (s, 3H) ; 1.27 (t, 3H) ; 1.30 (s, 3H) ; 1.40 (d, 1H, ^{2}J= 11Hz) ; 1.75 (m, 3H) ; 2.16 (dtd, 1H, ^{2}J=11, ^{3}J=6,6, 2.5 Hz) ; 2.36 (dd, 1H, ^{2}J=18Hz, ^{3}J=3Hz) ; 2.37 (s, 3H) ; 2.71 (s, 1H) ; 3.30 (AB of an ABX, 2H, ^{2}J=14Hz, ^{3}J=4, 10Hz, Δν=40Hz) ; 4.21 (q, 2H); 4.67 (dd, X of ABX, 1H) ; 7.06 (m, 2H); 7.21 (m, 1H); 7.53 (m, 1H); 7.78 (b, 1H). ^{13}C NMR ($CDCl_3$) δ : 11.8 ; 14.1 ; 21.4 ; 27.0 ; 27.7 ; 27.9; 28.5 ; 32.6 ; 37.8 ; 38.1 ; 49.8 ; 60.9 ; 62.5 ; 76.3 ; 107.4 110.1 ; 117.7 ; 119.2 ; 120.9 ; 128.3 ; 132.4 ; 135.2 ; 172.1 ; 178.2.

12 Dave V., Warnhof E.W. *Can. J. Chem.* **1971**, *49*, 194.

13 a) Vice S.F., Copeland C., Forsey S.P., Dmitrienko G.I. *Tetrahedron Lett.* **1985**, *26*, 5253. b) Vice S.F., Dmitrienko G.I. *Can.J. Chem.* **1982**, *60*, 1233.

14 **7a :** ^{1}H NMR ($CDCl_3$) δ : 1.17 (t, 3H) ; 1.76 (s, 3H); 2.52 (s, 3H); 3.10 (dq, A of an ABX_3, 1H ^{2}J=9Hz, ^{3}J=7Hz); 3.30 (dq, B of the ABX_3, 1H, ^{2}J=9Hz, ^{3}J=7Hz); 5.21 (s, 1H); 5.69 (s, 1H) ; 7.08 (t, 1H) ; 7.29 (t, 1H); 7.46 (d, 1H); 8.42 (d, 1H). In **7b** the ABX_3 system disappeared and is replaced by a singlet at 3.04 for MeO. All other δ are very similar.

15 **5a :** ^{1}H NMR ($CDCl_3$) δ : 2.60 (s, 3H); 2.72 (s, 3H); 4.67 (s, 2H); 7.30 (m, 2H); 7.60 (m, 1H); 7.88 (m, 1H). In **5b** CH_2 is found at 4.63 (s, 2H) together with the ethyl group at : 3.6 (q. 2H) and 1.25 (t, 3H). In **5c** the CH_2X signal is at 4.77 (s. 2H).