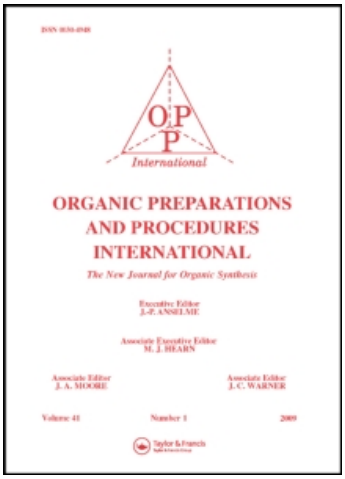

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

ASYMMETRIC SYNTHESIS OF (R)-N-(*t*-BUTOXYCARBONYL)-4-CYANOPHENYLALANINE METHYL ESTER

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To cite this Article Pecunioso, Angelo , Papini, Damiano , Tamburini, Bruno and Tinazzi, Francesco(1997) 'ASYMMETRIC SYNTHESIS OF (R)-N-(*t*-BUTOXYCARBONYL)-4-CYANOPHENYLALANINE METHYL ESTER', Organic Preparations and Procedures International, 29: 2, 218 — 221
To link to this Article: DOI: 10.1080/00304949709355188
URL: http://dx.doi.org/10.1080/00304949709355188

5. R. G. Harvey, *Tetrahedron*, **22**, 2561 (1966).

6. A. N. Pudovik, *Zh. Obshch. Khim.*, **22**, 462 (1952).

7. G. Sturtz, *Bull. Soc. Chim. Fr.*, 2333 (**1964**).

8. P. Savignac, A. Berque and F. Mathey, *Synth. Commun.*, **9**, 287 (1979).

9. D. D. Perrin and W. L. F. Armarego, "*Purification of Laboratory Chemicals*", Pergamon Press, 3rd Ed., p. 297, 1988.

10. a) P. O. I. Virtanen, H. Malo and H. Ruotsalainen, *Suom. Kemistilehti B*, **43**, 512 (1970); *Chem. Abstr.*, **74**, 63686b (1971); b) A. A. Khalaf, A. A. Abdel-Wahab, A. M. El-Khawaga and M. F. El-Zohry, *Bull. Soc. Chim. Fr.*, II, 285 (**1984**).

11. a) I. Lukac, J. Pilka, M. Kulickova and P. Hrdlovic, *J. Poly. Sci.*, **15**, 1645 (1977); b) F. G. Bordwell and W. T. Brannen, Jr., *J. Am. Chem. Soc.*, **86**, 4645 (1964); c) V. M. Solov'ev, N. E. Kurochkina and A. P. Skoldinov, *Zh. Obshch. Khim.*, **37**, 1233 (1967).

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ASYMMETRIC SYNTHESIS OF (R)-N-(*t*-BUTOXYCARBONYL)-4-CYANOPHENYLALANINE METHYL ESTER

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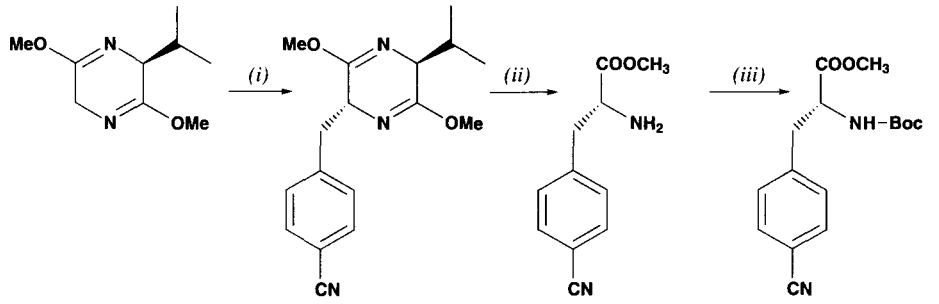
The unnatural amino acid (R)-4-cyanophenylalanine is an important precursor of a number of pharmacologically active substances.[1] Recently, detailed procedures have been reported for the preparation of both the (R)-4-cyanophenylalanine and its N-benzoyl derivative using either an enantioselective enzymatic hydrolysis of the racemic 4-cyanophenylalanine ethyl ester[1a] or the enantioselective catalytic hydrogenation of the corresponding N-benzoyl dehydro amino acid respectively.[2] We report here an alternative procedure for the preparation of the (R)-N-(*t*-butoxycarbonyl)-4-cyanophenylalanine methyl ester (**4**) *via* the asymmetric synthesis using the commercially available[3] chiral auxyliary **1**. Full spectroscopic and analytical characterizations for both compound **4** and the heterocyclic intermediates **2** are also reported.

Alkylation of the *bis*-lactim ether **1** with 4-cyanobenzyl bromide, under the conditions reported by Schollkopf *et al.*,[4] gave intermediate **2** in 62% yield as a single diastereoisomer. Hydrolysis



1 2 3 4

i) THF , BuLi , -78°; *ii)* 0.25 N HCl / THF 1/1 v/v / R.T. ; *iii)* $(Boc)_2O$, NEt_3 , DMF , 60°

of the dihydropyrazine ring was efficiently performed with a 0.25 N HCl/tetrahydrofuran solvent mixture. The crude recovered product (R)-4-cyanophenylalanine methyl ester (**3**), contaminated with (S)-valine methyl ester, was treated without further purification with di-*t*-butylpyrocarbonate/triethylamine reagent mixture[5] to give the two corresponding Boc-protected derivatives. The contaminant (S)-N-(*t*-butoxycarbonyl)-valine methyl ester was easily removed at this stage by flash chromatography to afford pure **4** in 68% overall yield starting from **2**. The enantiomeric excess of both the recovered (R)-N-(*t*-butoxycarbonyl)-4-cyanophenylalanine methyl ester (**4**) and the crude (R)-4-cyanophenylalanine methyl ester (**3**) were determined to be > 92% for both compounds by chiral HPLC.

EXPERIMENTAL SECTION

Melting points were recorded in capillary tubes. IR spectra were determined using a Bruker IFS48 spectrometer and values are expressed in cm^{-1}. ^1H NMR spectra were obtained using a Varian Unity 400MHz spectrometer and chemical shift are reported in δ ppm. MS analyses were carried out with a Fisons Instrument using a FAB ionisation technique. The elemental analyses were performed in a Carlo Erba EA1108 elemental analyser. Optical rotatory values were obtained on a Jasco DIP-360 instrument. HPLC analyses were performed on a Perkin Elmer Series 410 LC instrument connected with a Hewlett Packard 1040M II Diode Array Detector, using a Chiralpak AD (Daicel) column unless otherwise specified.

(2R,5S)-2-(4-Cyanobenzyl)-2,5-dihydro-3,6-dimethoxy-5-isopropylpyrazine.- A 1.6M solution of n-butyllithium in hexane (25.5 mL, 40.81mmol) was added at -78° under nitrogen to a stirred solution of (2S) 2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine (6.015g, 32.65mmol) in 200 mL of dry THF. After 45min a solution of 2-cyanobenzyl bromide (8.0g, 40.81mmol) in 60 mL of dry THF was added in 45 min. After stirring for 1 hr at -78°, the solution was allowed to warm up to ca -5 ° and a saturated solution of NH_4Cl (250 mL) was added. The resulting mixture was extracted with ethyl ether (3x300 mL) and the combined organic layers were dried with Na_2SO_4. After removing the solvent under vacuum, the crude pale yellow solid obtained was purified by chromatography on a short (10cm) silica gel column (cyclohexane/ethyl acetate = 95/5) and then tritured with petroleum ether (50 mL) to give a white solid (6.06g, 62% yield), mp. 77°; ^1H NMR ($CDCl_3$): δ 0.62 (d, 3H), 0.95 (d, 3H), 2.16 (m, 1H),

3.14 (m, 2H), 3.45 (*t*, 1H), 3.65 (s, 3H), 3.71 (s, 3H), 4.32 (m, 1H), 7.22 (m, 2H), 7.51 (m, 2H); IR (Nujol) 2228, 1693; MS: *m/z* 300 (MH^+), 256 (base peak); $[\alpha]_D^{20}$ = -47.2° (c = 1.03, CH_2Cl_2).

Anal. Calcd. for $C_{17}H_{21}N_3O_2$: C, 68.19; H, 7.08; N, 14.04. Found: C, 68.25; H, 7.03; N, 14.16

(R)-4-Cyanophenylalanine Methyl Ester.- A solution of 5.0g of (2R,5S)-2-cyanobenzyl-2,5-dihydro-3,6-dimethoxy-5-isopropylpyrazine in 260 mL of a 1/1 (v/v) 0.25M HCl/THF mixture was stirred at room temperature for 90 min; then ethyl ether (650 mL) was added to the solution and then the pH was adjusted to 9-10 by the dropwise addition of a 32% aqueous solution of ammonia. The organic layer was separated and the aqueous layer extracted with further 2x650 mL of ethyl ether. The combined organic layers were dried with Na_2SO_4 and concentrated under vacuum to give a pale red oil (3.8g) consisting of a mixture of methyl (R)-4-cyanophenylalanine **3** and valine methyl ester in ca 2/1 molar ratio as determined by ^1H NMR. The product **3** showed an R/S ratio > 96/4 (eluent:hexane-ethyl alcohol, 80:20 v/v, flow rate = 1 mL/min.). This crude material was used in the following step without further purification.

A fraction (0.35 g) of the crude oil was purified by chromatography on a silica gel column (dichloromethane-methanol, 96:4) followed by trituration with 6N HCl. The (R)-4-cyanophenylalanine methyl ester hydrochloride salt (85 mg) was collected and dried under vacuum for 24 hrs at room temperature. ^1H NMR (DMSO): δ 3.21 (m, 2H), 3.67 (s, 3H), 4.36 (m, 1H), 7.47 (d, 2H), 7.81 (d, 2H), 8.62 (bs, 3H); *m/z* 205 (MH^+); $[\alpha]_D^{20}$ = -48.3° (c = 0.84, EtOH); HPLC assay >99% a/a (Hypersil ODS column; eluent:ammonium phosphate buffer 10mM pH 7-CH_3CN, 60:40 v/v; flow rate = 1 mL/min; detection wavelenght = 230 nm).

Anal.: Calcd. for $C_{11}H_{12}N_2O_2$•HCl: C, 54.89; H, 5.44; N, 11.63. Found: C, 54.87; H, 5.45; N, 11.49

(R)-(N-*t*-Butoxycarbonyl)-4-cyanophenylalanine Methyl Ester.- A solution of $(Boc)_2O$ (3.2g, 14.6mmol) in dry DMF (19 mL) was added to a solution of the crude (R)-4-cyanophenylalanine methyl ester (2.22g) and triethylamine (2.8 mL, 19.9mmol) in dry DMF (35 mL). The solution was warmed to 60° for 30 min and then was allowed to cool down to room temperature. After removing solvent under vacuum the remaining oil was partitioned between water (350 mL) and CH_2Cl_2 (430 mL) and the aqueous layer extracted further with 3x190 mL of CH_2Cl_2. The combined organic layers were dried with Na_2SO_4 and concentrated under vacuum. The crude oil obtained (3.8g) was successively purified by flash chromatography (cyclohexane-ethyl acetate 8:2) to give 2.0g (67% starting from **2**) of a white solid, mp. 108-110°; ^1H NMR ($CDCl_3$): δ 1.42 (s, 9H), 3.08-3.23 (m, 2H), 3.74 (s, 3H), 4.63 (m, 1H), 5.03 (d, 1H), 7.26 (m,2H), 7.60 (m, 2H); IR ($CDCl_3$) 3437cm^{-1}, 2232, 1744-1680; *m/z*: 305 (MH^+), 205 (base peak); $[\alpha]_D^{20}$ = -54.0° (c = 0.940, $CHCl_3$).

Anal. Calcd.for $C_{16}H_{20}N_2O_4$: C, 63.13; H, 6.64; N, 9.21. Found: C, 63.27; H, 6.93; N, 9.05

The product **4** showed an R/S ratio = 96/4 (eluent:hexane-isopropyl alcohol, 80:20 v/v; flow rate = 1 mL/min.).

Acknowledgement.- We wish to thank Carla Marchioro, Mahmoud Hamdan and their collaborators for the support given to this work.

REFERENCES

1. a) B. Christophe *et al.*, *Fr. Demand,* FR 93-1686, **1993**; *C.A.* **123**: 144622 (1995); b) C. Kolar and W. Stueber, *Eur. Pat. Appl.*, EP 93-102048, **1993**; *C.A.* **120**: 107754 (1994); c) W. Stueber and G. Dickneite, *Eur. Pat. Appl.*, EP 92-105138, **1992**; *C.A.* **119**: 49920 (1993); d) A. Bernat *et.al.*, *Fr. Demand,* FR 86-1400, **1986**; *C.A.* **109**: 38238 (1988) and references cited therein.

2. S. Taudien and K. Schinkowski, *Tetrahedron Asymmetry*, **4**, 73 (1993).

3. The chiral auxyliary (2S)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine was supplied from MERCK-Schuchardt (Germany).

4. a) U. Schollkopf, U. Groth and C. Deng, *Angew. Chem. Int. Ed. Engl.*, **20**, 798 (1981); b) R. M. Williams, "*Synthesis of Optically Active α-Amino Acids*", Pergamon Press, Oxford, 1989.

5. J. McNulty and I. W. J. Still, *Synth. Commun.*, **22**, 979 (1992).

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A FACILE SYNTHESIS OF 3-FLUOROTHIOPHENE-2-CARBOXYLIC ACID

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In connection with an ongoing project in our laboratory, we required a convenient synthesis of 3-fluorothiophene-2-carboxylic acid (**1a**). This compound has previously been prepared by three research groups. In one synthesis, 3-fluorothiophene (**1b**) was lithiated with butyllithium, and the resulting 2-lithio carbanion was carboxylated with carbon dioxide.[1] The requisite 3-fluorothiophene itself was prepared from 3-bromothiophene (**1c**) *via* halogen/lithium exchange followed by fluorination with perchloryl fluoride, which is both hazardous and expensive.[1,2] An alternative and apparently attractive approach involved diazotization of methyl 3-aminothiophene-2-carboxylate (**1d**), followed by a Schiemann reaction in xylene.[3] However, in our hands the only product isolated (in >90% yield) was the azo compound **1e** which arose from coupling of the diazonium salt with the solvent xylene. The most recent synthesis of 3-fluorothiophene-2-carboxylic acid (**1a**, 32% overall yield) required four steps starting with 3-chlorothiophene (**1f**).[4] We now report a convenient, one-step synthesis of **1a** from thiophene-2-carboxylic acid (**2**).

1 a, X = CO_2H, Y = F
b, X = H, Y = F
c, X = H, Y = Br
d, X = CO_2Me, Y = NH_2
e, X = CO_2Me, Y = 2,4-$(CH_3)_2C_6H_3N_2$
f, X = H, Y = Cl