Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 2845–2850

TETRAHEDRON:
ASYMMETRY

New synthesis of enantiomerically pure (*S*)-3-amino-2-phenyl propanoic acid via the asymmetric transformation of its racemic *N*-phthaloyl derivative

Monique Calmes * and Françoise Escale

Laboratoire des Aminoacides, Peptides et Protéines, UMR 5810, Universités Montpellier I et II, UM II, Place E. Bataillon, 34095 Montpellier Cedex 5, France

Received 8 June 1998; accepted 3 August 1998

Abstract

The synthesis of racemic *N*-phthalyl 3-amino-2-phenyl propanoic acid and its asymmetric transformation via the corresponding prochiral ketene have been investigated, allowing the preparation of enantiomerically pure (*S*)-3-amino-2-phenyl propanoic acid. © 1998 Elsevier Science Ltd. All rights reserved.

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1. Introduction

β-Amino acids and their derivatives are an important class of compounds. They are present in biologically active peptides and in free form show interesting pharmacological effects.[1] They are also precursors of the β-lactam moiety found in some antibiotics.[1]

Many methods have been reported for the synthesis of racemic β-amino acids but only recently has the preparation of enantiomerically pure compounds emerged.[1,2]

The 3-amino-2-phenyl propanoic acid **1**, a counterpart of phenylalanine, is of particular interest since its (±)-ethyl ester has neurological activity[3] and (−)-**1** is part of the side chain in semisynthetic penicillin betacin.[4] Indeed, only a few preparations of the homochiral compound **1** have been reported.[4–6] In 1964, the racemic mixture was resolved via its (+)-camphor-10-sulfonate salt[4] and the (*S*)-configuration was for the first time assigned to the (+)-enantiomer by a chemical correlation with (+)-(*S*)-1-amino-2-phenyl butane and ORD studies.[7] Wyatt et al.[5] later described the asymmetric synthesis of (+)-3-amino-2-phenyl propanoic acid by aminomethylation of a chiral 3-(phenylacetyl)oxazolidinone with 1-(*N*-benzyloxycarbonyl aminomethyl) benzotriazole. However, an X-ray structure determination unambiguously assigned the opposite (*R*)-configuration to this enantiomer. Then, an elaborate synthesis[6]

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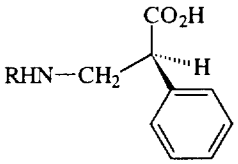
* Corresponding author. Fax: 04 67 14 48 66; e-mail: monique@ampir1.univ-montp2.fr

PII: S0957-4166(98)00313-9

using as key steps a palladium catalysed asymmetric allylic substitution and a modified Curtius reaction to introduce nitrogen, has been used to form the (+)-2-phenyl *t*-butyloxycarbonylamino derivative **2** in high enantiomeric excess but only moderate yield. Recently, the enantiomerically pure derivative **2** has been also obtained by using as the key step the acylation of metallated phenylacetonitrile with sultan carbonyl chloride.[8]

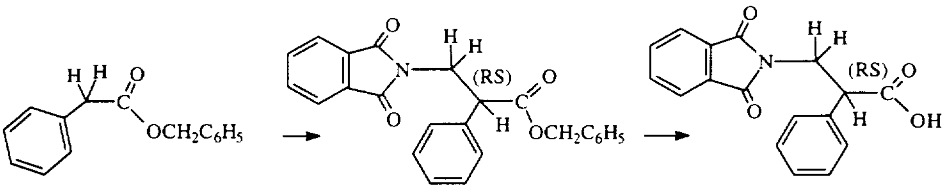


1 R = H
2 R = t-Boc

We showed in previous work[9] concerning deracemisation reactions, that the asymmetric transformation of racemic mixtures involving prochiral ketenes was a simple, convenient and effective reaction. We therefore decided to explore this method to prepare the homochiral 3-amino-2-phenyl propanoic acid.

2. Results and discussion

Prior to carrying out the asymmetric transformation, racemic 3-amino-2-phenyl propanoic acid had to be prepared with the amine function totally protected in order to avoid NH addition to the ketene. We developed a convenient method (Scheme 1) which directly produces the adequately *N*-protected substrate starting from phenyl acetic benzyl ester **3** (easily prepared from the cheap commercially available corresponding acid) and *N*-bromomethylphthalimide.



3 4 5

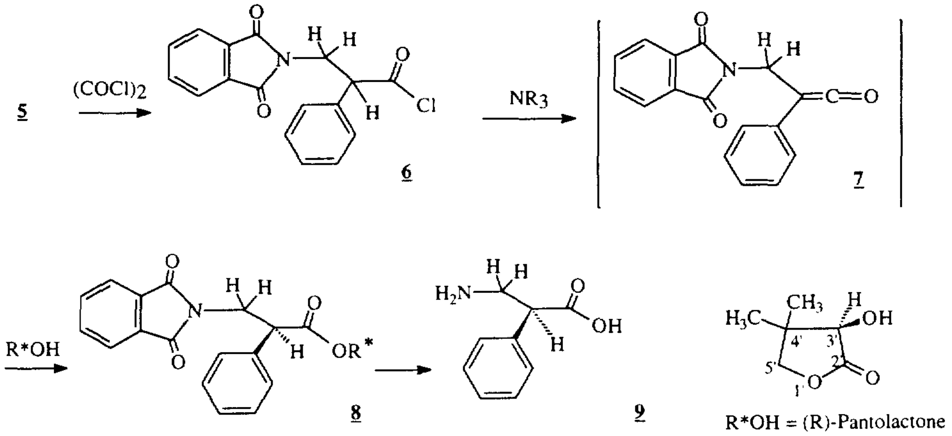
Scheme 1.

Alkylation of **3** was achieved in good yield (75%) in THF after deprotonation at low temperature (−78°C) by using lithium diisopropylamine as base and DMPU[10] as co-solvent. When the same reaction was carried out without DMPU, **4** was obtained in only modest yield (35%) even if another additive such as LiCl was used. The benzyl ester was easily cleaved by hydrogenolysis without degradation of the phthalyl group and the *N*-phthalyl 3-amino-2-phenyl propanoic acid **5** racemic mixture was obtained in quantitative yield.

According to the considered methodology, the asymmetric transformation of **5** involves the stereoselective addition of a chiral alcohol to the *N*-phthalyl-3-aminomethyl-2-phenyl ketene **7** (Scheme 2). This reaction was performed in THF, and (*R*)-pantolactone, a very efficient commercially available chiral auxiliary, was used as the chiral alcohol.

The ketene **7** was obtained in situ by dehydrochlorination of the corresponding acyl chloride **6** resulting from **5** after treatment at room temperature with oxalyl chloride. As shown previously[9,11] the tertiary base, used in excess, both catalysed the diastereoselective addition of an alcohol to a ketene and enhanced the stereoselectivity. Ketene formation and alcohol addition occurs in a one pot procedure.

First we controlled ketene formation. It could be assumed that, due to their similar structures, ketenes derived from **6** and from aryl propionic acids have comparable stabilities and reactivities. Therefore, in



Scheme 2.

a first attempt we used the same experimental conditions as those previously used for aryl propionic acids, i.e. generation of the ketene by treatment of **6** with triethylamine for 3 h at room temperature, but under these conditions side reactions were observed to take place. We next modified the experimental conditions: concentration, temperature and reaction time. We noted that a lower concentration was advisable because of, in particular, the low solubility of **6** in THF. In addition, only a small amount of ketene was formed using a lower temperature (0°C to −20°C). On the other hand, treatment of the acyl chloride **6** with triethylamine, first at 0°C then for 1 h at room temperature, allowed effective generation of the ketene, the corresponding methyl ester being quantitatively formed with high C_α deuteriation by trapping the mixture with CH_3OD. Subsequent addition of (*R*)-pantolactone to **7** at the same temperature afforded the *N*-phthalyl-(*S*,*R*)-3-amino-2-phenyl propanoic pantolactonyl ester **8** both in high chemical yield (88%) and with high diastereoisomeric excess (d.e.=94%).

The optically pure (*S*,*R*)-*N*-phthalyl pantolactonyl ester was easily obtained after one recrystallisation. Hydrolysis of **8** under acidic conditions[9] gave the corresponding (*S*)-3-amino-2-phenyl propanoic acid **9** without racemisation as verified by NMR analysis.[12] The (*S*)-configuration of **9** was assigned by comparison with the specific optical rotation value previously described,[5] thus enabling us to establish that of the ester **8**.

In conclusion, we have described an effective and highly stereoselective synthesis of (*S*)-3-amino-2-phenyl propanoic acid using as the key step a base-catalysed addition of (*R*)-pantolactone to the corresponding *N*-phthalyl ketene.

3. Experimental

Tetrahydrofuran (THF) was freshly distilled under argon from sodium and benzophenone; triethylamine (NEt_3) was distilled from KOH and ninhydrin; DMPU was stirred over CaH_2 for 1 h and then distilled at reduced pressure before use. Thin layer chromatography (TLC) was carried out on silica gel (60 F_{254}, Merck 5715) and spots were located with UV light or iodine vapour. (*R*)-Pantolactone (chemical and enantiomeric purities >99%) was purchased from Fluka Chemical Co. All other chemicals were commercially pure compounds and were used as received. Melting points were determined with a Büchi apparatus and are uncorrected. Optical rotation was measured on a Perkin–Elmer, 241 polarimeter. HPLC analysis was performed on a Waters 510 instrument with a variable detector. ^1H NMR spectra were recorded on a Bruker AC 250 spectrometer. Data are reported as follows: chemical shifts (δ) in ppm with respect to TMS, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad). The diastereoisomeric excess (d.e.) of **8** was determined for the crude product from the ^{1}H NMR spectra ($CDCl_3$) by integration of the 3′-C*H* signal of the pantolactonyl moiety of the pair of diastereoisomers and/or by HPLC (Chiracel OD column, 25 cm×4 mm, flow rate: 1 mL/min, hexane:isopropanol=80:20. To obtain racemic samples of the pantolactonyl ester **8**, (*SR*)-**5** was esterified with (*R*)-pantolactone in the presence of dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP). Racemisation during acid hydrolysis of **8** was verified by NMR analysis[12] (DMSO-d_6) after derivatisation with Marfey's reagent (1-fluoro 2,4-dinitrophenyl 5-(*S*) alanine amide).[13]

3.1. *Phenyl acetic benzyl ester 3*

The phenyl acetic benzyl ester **3** was prepared from phenyl acetic acid (1.36 g, 10 mmol) and benzyl alcohol as previously described in the literature[14] as an oil (2.1 g, 9.3 mmol, 93% yield); TLC (eluent hexane:AcOEt) R_f=0.53; ^{1}H NMR ($CDCl_3$) δ=3.74 (s, 2H, $C_6H_5CH_2CO$), 5.21 (s, 2H, $OCH_2C_6H_5$), 7.38 (m, 10H, *H*-phenyl).

3.2. N-*Phthalyl-(*RS*)-3-amino-2-phenyl propanoic benzyl ester 4*

A solution of *n*-butyllithium (2.5 M) in hexane (2.4 mL, 6 mmol) was added dropwise over 5 min to a stirred solution of diisopropylamine (0.91 mL, 6.5 mmol) in dry THF (12 mL) at −78°C under argon. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (3.5 mL) was added in one portion, and the mixture was then stirred at −78°C for 1 h. A solution of phenyl acetic benzyl ester (1.13 g, 5 mmol) in THF (7 mL) was added over 10 min, keeping the temperature below −78°C during the addition. After stirring the mixture for 1 h at −78°C, the *N*-bromomethylphthalimide (1.44 g, 6 mmol), was added dropwise in dry THF (9 mL) at the same temperature. The mixture was stirred for an additional hour at −78°C, and then allowed to warm slowly to room temperature. After being stirred for 16 h at room temperature, the reaction mixture was quenched with 1 M HCl (60 mL) and then extracted with ether (3×100 mL). The combined ether extracts were washed with water, dried and evaporated in vacuo to leave a yellowish solid. The solid was then purified by chromatography on silica gel (eluent CH_2Cl_2) R_f=0.55, to give **4** (1.45 g, 3.75 mmol, 75% yield), as white crystals. M.p. 98°C; ^{1}H NMR ($CDCl_3$) δ=4.20 (dd, J=8.4 Hz and J=13.6 Hz, 1H, *H*CH–N), 4.31 (dd, J=7.6 Hz and J=13.6 Hz, 1H, *H*CH–N), 4.38 (dd, J=8.4 Hz and J=7.6 Hz, 1H, C*H*–CH_2–N), 5.11 (d, J=12.4 Hz, 1H, *H*CHC_6H_5), 5.17 (d, J=12.4 Hz, 1H, *H*CHC_6H_5), 7.17 (m, 5H, *H*-phenyl), 7.59 (m, 2H, *H*-phthalyl), 7.67 (m, 2H, *H*-phthalyl). Anal. calcd for $C_{24}H_{19}NO_4$: C 74.79, H 4.97, N 3.63. Found: C 74.65, H 4.88, N 3.59.

3.3. N-*Phthalyl-(*RS*)-3-amino-2-phenyl propanoic acid 5*

N-Phthalyl-(*RS*)-3-amino-2-phenyl propanoic benzyl ester **4** (578 mg, 1.5 mmol) was added to a cooled (−20°C) solution of 20% palladium hydroxide on carbon (100 mg) in ethyl acetate (4 mL). The mixture was then stirred for 5–6 h at room temperature under H_2 (monitoring the reaction by TLC). After filtration through Celite, concentration of the filtrate gave the expected compounds **5** (420 mg, 1.4 mmol, 95% yield) as a white solid. M.p. 175°C (lit.,[15] m.p. 178–180°C); ^{1}H NMR ($CDCl_3$) δ=4.23 (m, 3H, CH_2–N and C*H*–CH_2–N), 7.28 (m, 5H, *H*-phenyl), 7.67 (m, 2H, *H*-phthalyl), 7.80 (m, 2H, *H*-phthalyl). Anal. calcd for $C_{17}H_{13}NO_4$: C 69.15, H 4.44, N 4.74. Found: C 69.21, H 4.35, N 4.67.

3.4. N-*Phthalyl-(*RS*)-3-amino-2-phenyl propanoic acid chloride 6*

A mixture of the *N*-phthalyl-(*RS*)-3-amino-2-phenyl propanoic acid (1 equiv.) and oxalyl chloride (10 equiv.) was stirred under argon at 30°C for 12 h. Evaporation of excess oxalyl chloride gave the corresponding *N*-phthalyl-(*RS*)-3-amino-2-aryl propionic acid chloride which was used as such in the following step.

3.5. *Preparation of the racemic* N-*phthalyl pantolactonyl ester 8*

To *N*-phthalyl-(*RS*)-3-amino-2-phenyl propanoic acid (295 mg; 1 mmol), (*R*)-pantolactone (130 mg, 1 mmol) and 4-dimethylaminopyridine (122 mg, 1 equiv.) in 6 mL of CH_2Cl_2, was added 1 equiv. of dicyclohexylcarbodiimide (206 mg) at 0°C. The mixture was then stirred at room temperature for an additional 12 h. The resulting mixture was filtered and washed with saturated aqueous solutions of citric acid (3×6 mL) and saturated $NaHCO_3$ (3×6 mL) dried over Na_2SO_4 and concentrated in vacuo. The racemic mixtures (*S,R*)/(*R,R*) of the pantolactonyl esters **8**, were analysed by NMR spectroscopy and HPLC.

3.6. *Diastereoselective addition of (*R*)-pantolactone to* N-*phthalylaminomethyl phenyl ketene 7*

To a stirred solution under argon of *N*-phthalyl-(*RS*)-3-amino-2-phenyl propanoic acid chloride **6** (313 mg; 1 mmol) in 3 mL of anhydrous THF cooled to 0°C, was added 154 μL (1.1 equiv.) of NEt_3 in THF (1 mL). After being stirred for 1 h at room temperature, a solution of 153 mg (1.2 mmol) of (*R*)-pantolactone in 1 mL of THF was added. After 3 h at this temperature (the reaction being monitored by TLC), a 1 N citric acid solution (5 mL) was added at 0°C and the solution was extracted with AcOEt (3×10 mL). The organic layer was then washed successively with water and a $NaHCO_3$ solution and finally dried over Na_2SO_4. Evaporation under vacuum gave mainly the (*S,R*)-pantolactonyl ester **8** (358 mg; 0.88 mmol; 88%) which was analysed by NMR spectroscopy and HPLC: d.e.=94%. Enantiomerically pure (*S,R*)-**8** was obtained by recrystallisation (ethyl acetate:ether). M.p. 156°C.

The HPLC and NMR data of compound **8** were deduced by comparison of the data of the racemic mixture and enantiomerically pure compound obtained above.

3.7. N-*Phthalyl-3-amino-2-phenyl propanoic pantolactonyl ester 8*

(*S,R*)-**8**: HPLC: r.t. 18.70 min; ^1H NMR ($CDCl_3$) δ=0.94 (s, 3H, 4′-C*H*$_3$), 1.06 (s, 3H, 4′-C*H*$_3$), 3.89 (d, J=9 Hz, 1H, 5′-HC*H*), 3.92 (d, J=9 Hz, 1H, 5′-HC*H*), 4.12 (dd, J=8 Hz and J=13.8 Hz, 1H, HCH–N), 4.27 (dd, J=8 Hz and J=13.8 Hz, 1H, HCH–N), 4.41 (t, $J_1=J_2=8$ Hz, 1H, *H*C–C_6H_5), 5.30 (s, 1H, 3′-C*H*), 7.20 (m, 3H, *H*–phenyl), 7.30 (m, 2H, *H*–phenyl), 7.60 (m, 2H, *H*–phthalyl), 7.72 (m, 2H, *H*–phthalyl).

(*R,R*)-**8**: HPLC: r.t. 20.80 min; ^1H NMR ($CDCl_3$) δ=0.70 (s, 3H, 4′-C*H*$_3$), 1.06 (s, 3H, 4′-C*H*$_3$), 3.92 (s, 2H, 5′-C*H*$_2$), 4.18 (dd, J=8.5 Hz and J=13.5 Hz, 1H, HCH–N), 4.26 (dd, J=7.2 Hz and J=13.5 Hz, 1H, HCH–N), 4.46 (dd, J=7.2 and J=8.5 Hz, 1H, *H*C–C_6H_5), 5.36 (s, 1H, 3′-C*H*), 7.20 (m, 3H, *H*–phenyl), 7.30 (m, 2H, *H*–phenyl), 7.60 (m, 2H, *H*–phthalyl), 7.72 (m, 2H, *H*–phthalyl).

Anal. calcd for $C_{23}H_{21}NO_6$: C 67.81, H 5.20, N 3.44. Found: C 67.78, H 5.13, N 3.36.

3.8. *Hydrolysis of* N-*phthalyl-3-amino-2-phenyl propanoic pantolactonyl ester 8*

A mixture of the *N*-phthalyl pantolactonyl ester **8** (0.5 mmol), acetic acid (1.4 mL) and a 6 N HCl solution (14 mL) was refluxed until completion of the hydrolysis (4–5 h), the reaction being monitored by TLC. The mixture was allowed to warm to room temperature and the volatile products were distilled at reduced pressure. Water (15 mL) was added to the residue and the mixture was washed with AcOEt (3×15 mL). Evaporation under vacuum of the aqueous layer followed by propylene oxide treatment gave the free (*S*)-3-amino-2-phenyl propanoic acid **9**. M.p. 220–222°C (lit.,[5] m.p. 222–224°C); ^{1}H NMR (DMSO-d_6) δ=3.00 (dd, J=6 Hz and J=12.8 Hz, 1H, HCH–N), 3.40 (dd, J=8.5 Hz and J=12.8 Hz, 1H, HCH–N), 4.00 (dd, J=6 Hz and J=8.5 Hz, 1H, *H*C–C_6H_5), 7.36 (m, 5H, *H*-phenyl); $[\alpha]_D$=−92 (c=0.2 in H_2O).

Acknowledgements

We thank Dr. J. Daunis for his support and helpful discussions.

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