(*R*)-(+)-3-Amino-2-phenylpropanoic Acid: a Revised Absolute Configuration based on an Enantioselective Synthesis and an X-Ray Crystal Structure of the Salt with (1*S*)-(+)-Camphor-10-sulfonic Acid

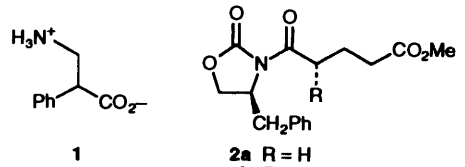
Alice A. D'Souza, Majid Motevalli, Andrew J. Robinson and Peter B. Wyatt†
Department of Chemistry, Queen Mary and Westfield College, University of London, Mile End Road, London E1 4NS, UK

Amidoalkylation of the lithium enolate of (4*S*,5*R*)-4-methyl-5-phenyl-3-(phenylacetyl)oxazolidin-2-one **5** by 1-(*N*-benzyloxycarbonylaminomethyl)benzotriazole **2c**, followed by cleavage of the oxazolidinone chiral auxiliary and of the *N*-benzyloxycarbonyl group, gave (*R*)-(+)-3-amino-2-phenylpropanoic acid **1**, the absolute configuration of which was determined by X-ray crystallography on the salt **8** with (1*S*)-(+)-camphor-10-sulfonic acid.

Derivatives of 3-amino-2-phenylpropanoic acid **1**, an isomer of phenylalanine, are of biological interest. For example, (−)-**1** is the side chain in the semisynthetic penicillin betacine,[1] whereas the ethyl ester of (±)-**1** has neurological activity.[2] The amino acid **1** has been resolved[1] *via* its camphor-10-sulfonate salt and (+)-**1** has been assigned the *S*-configuration by a chemical correlation with (+)-(*S*)-1-amino-2-phenylbutane and by ORD studies;[3] however, no previous asymmetric synthesis of **1** has been reported. We chose **1** as a target in order to explore the stereoselective aminomethylation of chiral enolates.

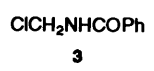
Evans *et al.* have reported that the titanium enolate of the acyloxazolidinone **2a** reacts with *N*-(chloromethyl)benzamide **3** to give the amidoalkylation product **2b**, stereoselectively and in high yield.[4] However, the reagent **3** deteriorates on storage[5] and the ultimate removal of the *N*-benzoyl group would normally require heating with mineral acid, conditions under which an acid such as **1** might be expected to racemize.

1-(Aminomethyl)benzotriazoles and their *N*-acyl derivatives can also function as aminomethylating agents.[6] Recent work by Page and co-workers[7] has shown that the reagents **4a** and **4b** may be used to effect the stereoselective aminoalkylation of ketone enolates containing the 1,3-dithiane 1-oxide auxiliary. We reasoned that 1-(*N*-benzyloxycarbonylaminomethyl)-benzotriazole **4c** would be a particularly useful aminomethylating agent because the benzyloxycarbonyl group could readily be removed by catalytic hydrogenolysis. The stable, crystalline reagent **4c**, m.p. 119–120 °C (from toluene),‡ was prepared in 62% yield by refluxing 1-(hydroxymethyl)benzotriazole[8] and benzyl carbamate with a catalytic amount of toluene-4-sulfonic acid in toluene, using a Dean–Stark trap.

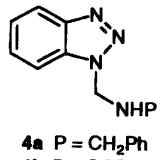


1

2a R = H
2b R = $CH_2NHCOPh$

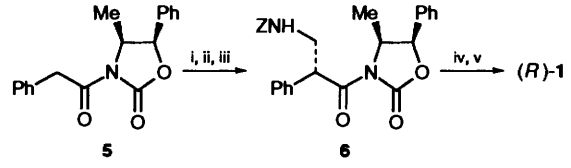


3



4a P = CH_2Ph
4b P = COPh
4c P = Z

The lithium enolate of the 3-(phenylacetyl)oxazolidinone[8] **5** was generated (LDA–THF, −78 °C) and then treated with **4c**. The mixture was allowed to warm up to +20 °C over 5 h, and then maintained at this temperature for 1 h before being quenched with saturated NH_4Cl (aq.) and subjected to an aqueous work up. A 250 MHz ^1H NMR spectrum of the crude organic product was consistent with the formation of the protected amino acid **6** and the deacylated oxazolidinone **7** as the principal products in a *ca.* 3:1 molar ratio: presumably **7** arises by decomposition of the enolate of **5** at the relatively high temperatures needed for the amidoalkylation. Flash chromatography, using EtOAc–light petroleum (b.p. 40–60 °C) as eluent, gave **6** as a foam, $[\alpha]_D$ +84 (*c* 1.1 in EtOAc), in 65% yield.‡ The chiral auxiliary was then removed hydrolytically and the Z group was hydrogenolysed to give, after recrystallisation from aqueous ethanol, (+)-3-amino-2-phenylpropanoic acid **1** (68% yield from **6**).§



5 **6**

Scheme 1 *Reagents and conditions:* i, LDA, THF, −78 °C; ii, **4c**; iii, warm to 20 °C; iv, LiOH, H_2O_2, H_2O, 0 °C, 1 h, then H^+; v, H_2 (3 atm), Pd–C, AcOH

It was expected that the amidomethylation would occur selectively on the less hindered, *si* face of the chelated, *Z* form of the enolate of **5**, which is the preferred site for alkylation of this type of enolate,[9] thus leading to the synthesis of (*R*)-**1**; yet the $[\alpha]_D$ data in ref. 3 implied that the *S*-enantiomer had been produced. In order to resolve this inconsistency, (+)-**1** was treated with (1*S*)-(+)-camphor-10-sulfonic acid to give the salt **8**, which after crystallisation from EtOH–Et_2O had $[\alpha]_D$ +61 (*c* 0.5 in H_2O) {lit.,[1] $[\alpha]_D$ +63 (*c* 0.5 in H_2O)} and for which

† E-mail: p.b.wyatt@qmw.ac.uk.
‡ Compounds **4c** and **6** had spectroscopic and high resolution mass spectrometric data in full agreement with the structures proposed; a satisfactory microanalysis was also obtained for **4c**.

§ Data for (+)-**1**: m.p. 222–224 °C (decomp.), $[\alpha]_D$ +94 (*c* 0.2 in H_2O) {lit.,[3] m.p. 224–225 °C (decomp.), $[\alpha]_D$ for (*S*)-**1** +95 (*c* 0.2 in H_2O)}; δ_H(250 MHz, D_2O) 3.30 (1 H, dd, *J* 12 and 7 Hz), 3.49 (1 H, dd, *J* 12 and 7 Hz), 3.81 (1 H, t, *J* 7 Hz) and 7.3–7.5 (5 H, m).

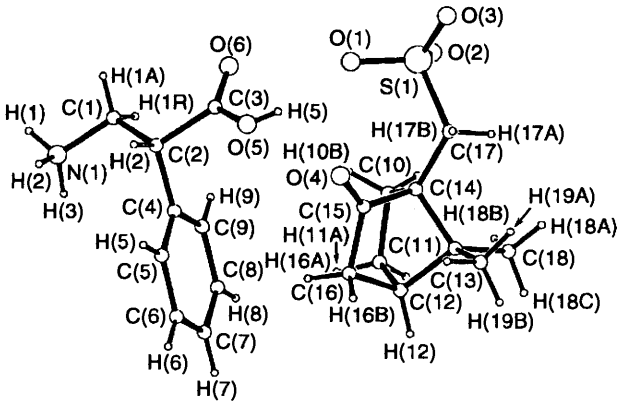
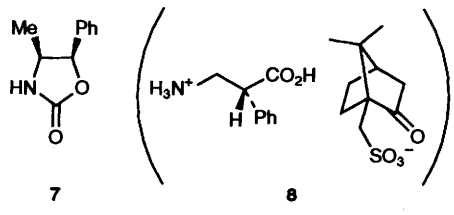


Fig. 1 X-Ray crystal structure of compound **8**

the *R*-configuration of the amino acid **1** was proved by a single crystal X-ray structure determination (Fig. 1).*

Thus, we have shown that the reagent **4c** does deliver a conveniently *N*-protected aminomethyl group to the enolate of the *N*-acyloxazolidinone **5**, in the same stereochemical sense as has been observed [9] for simple alkylations. We have also shown



7 **8**

that the absolute configuration of **1** was incorrectly assigned in ref. 3.

Acknowledgements

We thank the EPSRC (formerly SERC) for studentships (A. A. D. S. and A. J. R.). We also thank Miss J. Isaacs, Mr. P. Cook and Mr. G. Coumbarides for measuring spectra.

References

1 E. Testa, G. Cignarella, G. Pifferi, S. Füresz, M. T. Timbal, P. Schiatti and G. Maffii, *Il Farmaco (Sci. Ed.)*, 1964, **19**, 895.
2 F. Leonard, A. Wajngurt, M. Klein and C. M. Smith, *J. Org. Chem.*, 1961, **26**, 4062.
3 J. A. Garbarino and O. Nuñez, *J. Chem. Soc., Perkin Trans. 1*, 1981, 906.
4 D. A. Evans, F. Urpi, T. C. Somers, J. S. Clark and M. T. Bilodeau, *J. Am. Chem. Soc.*, 1990, **112**, 8215.
5 J. J. Getz, R. J. Prankerd and K. B. Sloan, *J. Org. Chem.*, 1992, **57**, 1702.
6 A. R. Katritzky, X. Lan and W.-Q. Fan, *Synthesis*, 1994, 445.
7 P. C. B. Page, S. M. Allin, E. W. Collington and R. A. E. Carr, *J. Org. Chem.*, 1993, **58**, 6902.
8 K. Fries, H. Güterbock and H. Kühn, *Annalen*, 1934, **511**, 213.
9 D. A. Evans, M. D. Ennis and D. J. Mathre, *J. Am. Chem. Soc.*, 1982, **104**, 1737.
10 G. M. Sheldrick, SHELXS-86 Program for structure solution, *Acta Crystallogr., Sect. A*, 1990, **46**, 467.
11 G. M. Sheldrick, Program for crystal structure refinement, *J. Appl. Crystallogr.*, in preparation.
12 H. D. Flack, *Acta Crystallogr., Sect. A*, 1983, **39**, 876.

Paper 4/06444E
Received 21*st October* 1994
Accepted 3*rd November* 1994

* *Crystal Structure Determination for Compound* **8**.—Data were collected at 293 K on an Enraf–Nonius CAD-4 diffractometer. $C_9H_{12}NO_2^+$ $C_{10}H_{15}SO_4^-$, M 397.48, monoclinic, space group $P2_1$, a = 6.280(2), b = 11.563(4), c = 13.804(3) Å, U = 987.6(5) Å^3, $F(000)$ = 424; Z = 2, D_c = 1.337 g cm^{-3}, Mo-Kα, λ = 0.710 69 Å, μ(Mo-Kα) = 0.199 mm^{-1}, 2503 independent reflections. The structure was solved by direct methods using SHELXS-86 [10] and refined on F^2 by full matrix, least-squares techniques using SHELXL-93.[11] All atoms were refined isotropically, except O and S atoms. H atoms were placed at calculated positions using the AFIX command in SHELXL-93. Displacement parameters of H atoms were kept fixed at the isotropic values of parent atoms. The absolute configuration was confirmed by the Flack factor,[12] x = −0.3(2), in SHELXL-93. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See 'Instructions for Authors (1994)', *J. Chem. Soc., Perkin Trans. 1*, 1995, Issue 1. The final residuals for reflections with $I > 2\sigma(I)$ were R_1 = 0.0557, wR_2 = 0.1096.