Pergamon

Tetrahedron Letters 40 (1999) 7123–7126

TETRAHEDRON LETTERS

Asymmetric Synthesis of Arylglycine Amino Acids Using (*S,S*)-(+)-Pseudoephedrine Derived Amides

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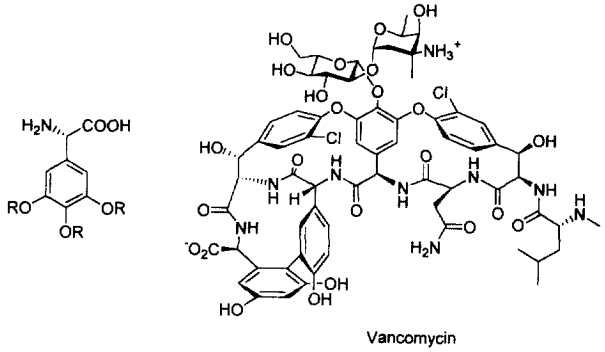
Received 10 June 1999; accepted 2 August 1999

Abstract: Arylglycine aminoacids were obtained in good yields and with enantiomeric excesses higher than 99% by using an asymmetric amination reaction protocol on (*S,S*)-(+)-pseudoephedrine based arylacetamide enolates with di-*tert*-butylazodicarboxylate. Subsequent hydrazinolysis and hydrolysis yielded the target aminoacids.

Amino acids are the basic structural units of proteins and important chiral building blocks for organic synthesis. The centrality of this synthon in both chemistry and biology has inspired a vast array of synthetic methodologies directed towards the asymmetric synthesis of amino acid derivatives.[1] In particular arylglycine amino acids were recently shown to be selective antagonists of the glutamate receptors of the central nervous system[2] as well as being key components of some widely used β-lactam antibiotics like amoxicillins, norcardicins and cephalexins. In addition some arylglycines are contained in the main structure of vancomycin, ristocetin, teicoplanin and related glycopeptide antibiotics.[3]

Figure 1



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0040-4039/99/$ - see front matter
PII: S0040-4039(99)01475-6

Even though a large number of synthetic methodologies are available for the asymmetric synthesis of amino acids, most of them involve carbon-carbon bond forming reactions on chiral glycine enolates[4] which is not a useful approach for the synthesis of these particular racemization-prone derivatives[5] and other routes have to be carried out.[6] Although many of these methods are quite effective, they often require multistep synthesis, the use of highly toxic reagents, laborious separation of diastereoisomers, harsh reaction conditions or they lack the required high chemo- and diastereoselectivity for subsequent synthetic purposes. Herein, and in connection with our studies in the asymmetric synthesis of isoquinoline alkaloids using phenylglycine derivatives as chiral inductors,[7] we describe a general 4-step route for the synthesis of arylglycine amino acids using (*S*,*S*)-(+)-pseudoephedrine as a chiral auxiliary.[8]

Our basic idea is shown in scheme 1. It has previously been reported that enolates can be aminated by dialkyl azodicarboxylate reagents.[9] Thus the arylacetic acid derived (*S*,*S*)-(+)-pseudoephedrine amides **1** prepared as previously reported[10] were deprotonated under kinetic conditions and subjected to reaction with di-*tert*-butyl azodicarboxylate (DTBAD) at -78°C.[11] The resulting adducts **2** were obtained in >95% d.e. as could be observed by ^{1}H-NMR spectroscopy. The amination reaction was observed to be fast and was completed within a few minutes (in contrast with other reactions of pseudoephedrine derived enolates with different electrophiles that required the aid of LiCl salts to accelerate the reaction).[8,12]

Scheme 1

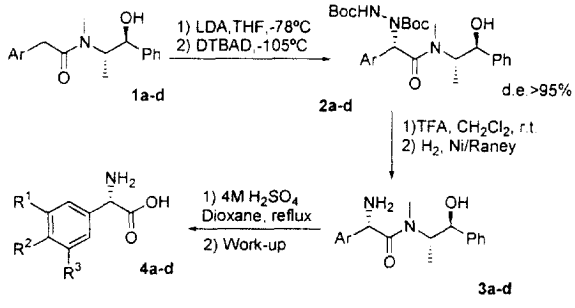

Table 1

Prod	R^1	R^2	R^3	Yield	d.e. [a]	Prod	Yield	Prod	Yield	e.e. [b]
2a	OMe	OMe	H	89	>95	**3a**	78	**4a**	86	>99
2b	OCH_2O		H	91	>95	**3b**	79	**4b**	89	>99
2c	OMe	OMe	OMe	90	>95	**3c**	78	**4c**	91	>99
2d	OBn	OMe	OBn	86	>95	**3d**	75	**4d**	88	>99

[a] Determined by ^{1}H-NMR. [b] Determined by chiral HPLC analysis of their corresponding methyl esters (Chiralcel OD, UV detector, Hexanes/*iso*-propanol 50:50. Flow rate 0.60mL/min.)

The adducts **2** were hydrolyzed with trifluoroacetic acid and hydrogenation of the resulting solution over Ni/Raney yielded the required arylglycine based (*S,S*)-(−)-pseudoephedrine amides **3** which, upon acid hydrolysis yielded the corresponding amino acids **4** in good yields after ion exchange chromatography purification (DOWEX 50 ion exchange resin). Also the chiral auxiliary (*S,S*)-(+)-pseudoephedrine could be recovered from the reaction mixture in 88% yield and with no racemization. The e.e. of the arylglycines **4** had to be calculated *via* transformation to the parent methyl ester derivatives which showed e.e.'s of >99% by chiral HPLC analysis after comparing with a racemic standard. This confirmed that all the transformations performed on the adducts **2** proceeded without epimerization in any of the steps.

The stereochemistry of the newly created chiral centre was assigned to be *S*, which was later confirmed on the final arylglycine **4c** by derivatization to the corresponding *N*-benzyloxycarbonyl protected compound and comparison of the obtained $[\alpha]_D^{20}$ value with data found in the literature for the same compound.[13]

In summary a general and highly stereoselective method has been developed for the asymmetric synthesis of arylglycine amino acids by electrophilic amination of chiral enolates derived from (*S,S*)-(+)-pseudoephedrine amides. The good yields and excellent enantioselectivities obtained make this method to be a very versatile one for the synthesis of any arylglycine derivative simply by changing the starting arylacetic acid precursor.

Acknowledgments: The authors acknowledge PETRONOR, S.A. (Muskiz, Bizkaia) for the generous gift of solvents. Financial support from the Basque Government (a fellowship to J.L.V. and E.A.), from the University of the Basque Country (Project UPV37/98) and the spanish DGES (Project PB98-0600) is gratefully acknowledged.

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11. In a representative experimental procedure. to a cooled (-78°C) solution of LDA (2.0mmol) in dry THF (100mL) was added a THF (50mL) solution of **1** (1mmol). The reaction was stirred for 1h at this temperature, 15min at 0°C and 5min at r.t. after which time the mixture was cooled again to -78°C at which temperature a solution of DTBAD (1.1 mmol) in dry THF was added dropwise within 10min. The resulting solution was stirred for 3h at -78°C, allowed to reach to r.t. and quenched with a saturated NH_4Cl solution (30mL). The mixture was extracted with CH_2Cl_2 (3x50mL) and the combined organic fractions were collected, dried over Na_2SO_4, filtered and the solvent was removed *in vacuo* to afford a yellowish oil which was purified by flash column chromatography.
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13. For (*S*)-(+)-*N*-(benzyloxycarbonyl)-1-(3,4,5-trimethoxyphenyl)glycine $[\alpha]_D^{20}$=+98.9 (c=2.0 EtOH). Lit. $[\alpha]_D^{20}$=+97.6 (c=1.95 EtOH) see ref. 6c.