applied with the program SHELXA, with transmissions 0.71–0.82. The structure was solved by direct methods and subjected to full-matrix least-squares refinement on F^2 (SHELXL-93), non-H atoms except B refined anisotropically, phenyl and closed-face carborane H atoms included with a riding model, open-face carborane H atoms located from difference syntheses and refined with B–H distance restraints. Restraints were also applied to the temperature factors of the light atoms and ring planarity. Refinement proceeded to $wR(F^2) = 0.055$ for 6269 reflections, 713 parameters and 588 restraints, conventional $R(F) = 0.023$, $S(F^2) = 1.09$, max. $\Delta\rho = 0.33\ e\,Å^{-3}$. **2**·$CH_2Cl_2$, $C_{89}H_{92}As_2Au_4B_{18}Cl_2P_4$, $M_r = 2488.69$, triclinic, space group $P\bar{1}$, $a = 14.368(3)$, $b = 16.094(3)$, $c = 20.145(3)$ Å, $\alpha = 88.22(2)$, $\beta = 87.04(2)$, $\gamma = 83.60(2)°$. $V = 4622(2)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.788$ Mg m^{-3}, $\mu = 7.2$ mm^{-1}, $F(000) = 2384$, $T = -100\,°C$. Data were collected from two crystals (Siemens P4 diffractometer): 1) tablet, $0.25 \times 0.2 \times 0.1$ mm, 10154 reflections to $2\theta 50°$, transmissions by ψ scan correction 0.498–0.933; 2) platelet, $0.55 \times 0.1 \times 0.03$ mm, 12387 reflections to $2\theta 45°$, transmissions 0.779–0.988. The datasets were merged with appropriate scaling to give 13513 unique reflections, $R_{int} = 0.064$. The structure was solved by direct methods, with other data as for complex **1**. Refinement proceeded to $wR(F^2) = 0.068$ for 13513 reflections, 570 parameters and 218 restraints, conventional $R(F) = 0.0387$, $S(F^2) = 0.834$, max. $\Delta\rho = 1.4\ e\,Å^{-3}$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100011. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: Int. code +(1223) 336-033; e-mail: deposit@chemcrys.cam.ac.uk).

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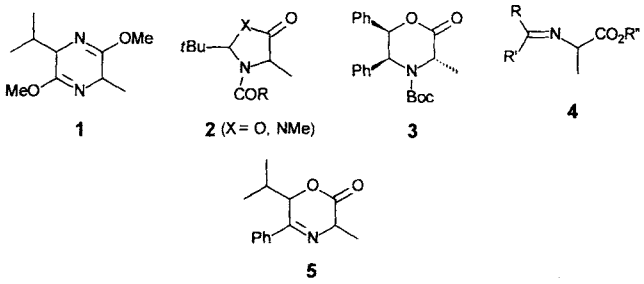
Asymmetric Synthesis of α-Methyl α-Amino Acids by Diastereoselective Alkylation of Optically Active 6-Isopropyl-3-methyl-2,3-dihydro-6*H*-1,4-oxazin-2-ones**

Rafael Chinchilla, Larry R. Falvello, Nuria Galindo, and Carmen Nájera*

Dedicated to Professor Dieter Seebach on the occasion of his 60th birthday

The present, high interest in the synthesis of nonproteinogenic amino acids is based on their remarkable pharmacological and conformational properties, both as free amino acids and as components of biologically active peptides. α-Methyl α-amino acids (AMAA) are important members in the family of modified amino acids. Some representative examples are a) naturally occurring α-aminoisobutyric acid (Aib) and (*R*)-2-amino-2-methylbutyric acid (D-Iva), which are constituents of peptaibols (microbial peptide antibiotics that form transmembrane ion channels),[1] b) (*S*)-α-methyl-DOPA (Aldomet), which is an inhibitor of DOPA decarboxylase (an important commercial antihypertensive);[2] c) (*S*)-α-methyltyrosine, which (as a substitute of tyrosine 4 in angiotensin II) results in a peptide that is resistant to chymotryptic degradation,[3] and d) (*R*)-α-methylaspartic acid,[4] (*R*)- or (*S*)-2-methylglutamic acids,[4b] as well as (*R*)- and (*S*)-α-methylserine,[5] which can be used to stabilize β-turn and α-helical conformations in short peptides.

The most direct synthetic approach to enantiomerically pure AMAAs is α-alkylation of chiral alanine anion equivalents;[6] the most noticeable are cyclic derivatives such as Schöllkopf's bis(lactim) ether **1**, Seebach's oxazolidinones and imidazolidinones **2**, and Williams' diphenyloxazinones **3**. High diastereoselectivities have been achieved by enolization with strong bases (such as *n*BuLi, LDA, and LHMDS) at low temperature followed by reaction with electrophiles. An easily enolizable, chiral alanine derivative is desirable for preparing optically active AMAAs under simple and mild reaction conditions. Due to the high acidity of their α-hydrogen atoms, imines derived from amino acid esters **4** are unique substrates for alkylation with solid–liquid phase-transfer catalysis (PTC)[7] and Pd-catalyzed allylation under neutral conditions[8] at room temperature.[9] Chiral imino esters[10] (up to 55% *ee*), cinchona-derived, quaternary ammonium salts[11] (up to 66% *ee*), and a sultam-derived glycine imine synthon[12] (up to 99.5% *de*) have been used in the asymmetric synthesis of amino acids under PTC alkylation conditions.



1 **2** (X = O, NMe) **3** **4**

5

Searching for iminic alanine derivatives, we focused our attention on 2,3-dihydro-6*H*-1,4-oxazin-2-ones **5**[13] for the following reasons: a) These compounds are cyclic imines of an alanine ester derived from an aromatic ketone; the phenyl group should favor easy formation of a highly stabilized enolate. b) They have a stereogenic center at the 6-position, which can be used to transfer its chirality to the 3-position for alkylation of the planar enolate. c) They can be easily hydrolyzed (this last step is very difficult for α,α-dialkylated α-amino acid derivatives).[14] d) They can be easily prepared enantiomerically pure using alanine as the source of chirality. Here we describe the diastereoselective alkylation of **5** under very mild conditions and their hydrolysis to the corresponding AMAAs.

Chiral oxazinones **5** were obtained by the reaction of α-bromoisovalerophenone with the potassium salt of *N*-Boc-L-alanine in DMF (Scheme 1).[15] Esters **6** were formed in a diastereomeric ratio of approximately 1:1, separated by flash chromatography, and isolated in 31% yield each. The Boc group of (*S*,*R*)-**6** was deprotected with HCl(g) in EtOAc, and treatment of the resulting hydrochloride with the base Et_3N in the presence of molecular sieves provided **5** in 70% yield. These compounds were obtained as a mixture of *cis*–*trans* diastereomers in a ratio of about 1:20 due to facile epimerization of the stereogenic C-3 center. Since C-3 will be part of the planar enolate after deprotonation, its configurational stability is irrelevant for the diastereoselectivity of the alkylation. Re-

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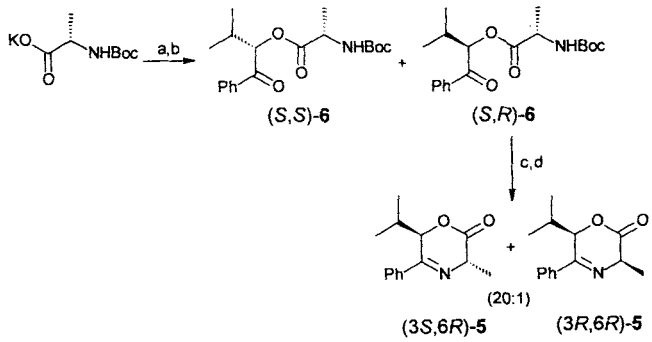


Scheme 1. a) PhCOCHBr*i*Pr, DMF, RT, 1 d. b) Flash chromatography on silica gel. c) HCl(g), EtOAc, 1 h. d) Et_3N, CH_2Cl_2, molecular sieves (4 Å); filtration through florisil.

crystallization afforded pure *trans* diastereomer (3*S*,6*R*)-**5**, whose relative configuration was determined by NOE experiments and X-ray structure analysis (Figure 1). Molecular me-

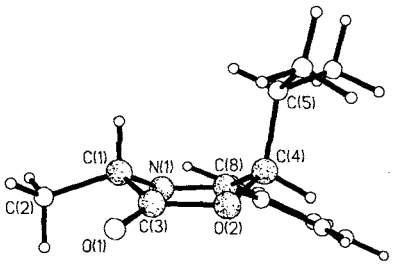


Figure 1. Crystal structure of (3*S*,6*R*)-**5** [18].

chanics calculations[16] corroborated that these 3,6-substituted oxazinones **5** prefer a quasi-boat conformation with the isopropyl group in an axial position. A similar orientation of the isopropyl group, which allows effective blocking of one of the faces and preferred anti-attack at the 3-position by electrophiles (1,4-induction), was predicted for the corresponding enolate.

When (*S*,*S*)-**6** was transformed into **5**, a mixture of *cis*–*trans* diastereomers in a ratio of about 1:2.5 was obtained. Surprisingly, the specific rotation of the *trans* derivative was considerably lower than that of the corresponding enantiomer (3*S*,6*R*)-**5**, which shows that epimerization at C-6 also occurred. This prevented the use of the enolate of oxazinones (6*S*)-**5** as enantiomeric counterparts of enolates from (6*R*)-**5**. As an alternative synthetic route (*S*,*R*)-**6** could be prepared by DCC-mediated (DCC = dicyclohexylcarbodiimide) esterification of (*R*)-α-hydroxyisovalerophenone[17] and *N*-Boc-L-alanine; this would avoid chromatographic separation.

The reaction of (6*R*)-**5** with different electrophiles (such as activated alkyl halides, paraformaldehyde, and methyl acrylate) in the presence of K_2CO_3 (3 equiv) and tetra-*n*-butylammonium bromide (TBAB, 0.1 equiv) in CH_3CN at room temperature provided the oxazinones **7** generally in good yields and diastereoselectivities (Table 1). The relative configuration of these heterocycles was confirmed by NOE experiments [(3*S*,6*R*)-**7a**] and X-ray diffraction analysis[18] [(3*S*,6*R*)-**7b**, Figure 2].

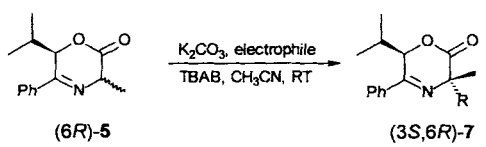


Table 1. Alkylation of oxazinone (6*R*)-**5** under solid–liquid phase-transfer catalysis.

Electrophile	R	No.	*t* [h]	Yield [%] [a]	Diastereomeric ratio [b]
$CH_2{=}CHCH_2I$	$CH_2{=}CHCH_2$	**7a**	24	62	96:4
$HC{\equiv}CCH_2Br$	$HC{\equiv}{\equiv}CCH_2$	**7b**	12	70	>98:2
$PhCH_2Br$	$PhCH_2$	**7c**	8	75	>98:2
EtO_2CCH_2I	EtO_2CCH_2	**7d**	24	60	95:5
(*E*)-$MeO_2CCH{=}CHCH_2Br$	(*E*)-$MeO_2CCH{=}CHCH_2$	**7e**	12	68	92:8
$(CH_2O)_n$	$HOCH_2$	**7f**	12	63	80:20
$CH_2{=}CHCO_2Me$	$CH_2CH_2CO_2Me$	**7g**	12	60	95:5

[a] Yield of isolated product after flash chromatography (silica gel); partial decomposition was observed. [b] Determined by NMR spectroscopy (300 MHz) and GC analysis of the crude product.

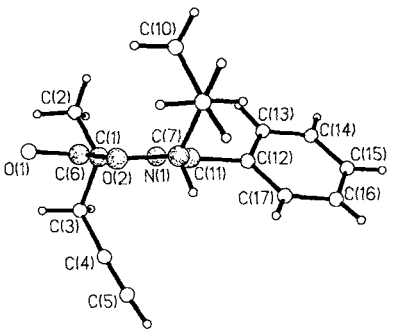


Figure 2. Crystal structure of (3*S*,6*R*)-**7b** [18].

The reaction of (6*R*)-**5** with allylic carbonates proceeded smoothly with $[Pd(PPh_3)_4]$ (5 mol%) and 1,2-bis(diphenylphosphino)ethane (dppe, 5 mol%) as catalyst in THF at room temperature. In general, substitution was regio- and highly diastereoselective to afford the corresponding oxazinones **7** (Table 2). When unsymmetrically substituted carbonates were

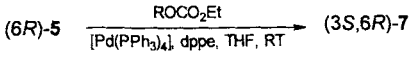
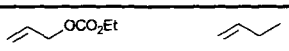
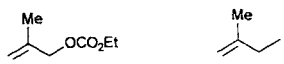
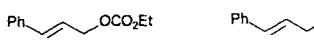
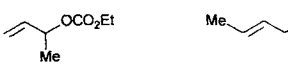
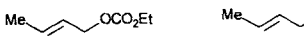
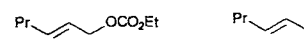


Table 2. Pd^0-catalyzed allylation of oxazinone (6*R*)-**5**.

Entry	Carbonate	R	No.	*t* [h]	Yield [%] [a]	Diastereomeric ratio [b]
1			**7a**	2	60	>98:2
2			**7h**	2	65	>98:2
3			**7i**	2	53 [c]	91:9
4			**7j**	3	65 [d]	92:8
5			**7j**	3	60 [d]	92:8
6			**7k**	3	56 [e]	85:15
7			**7l**	3	53	94:6

[a] Yield of isolated product after flash chromatography (silica gel); partial decomposition was observed. [b] Determined by NMR spectroscopy (300 MHz) and GC analysis of the crude product. [c] 28%, [d] 13%, and [e] 21% of the other regioisomer was also obtained (NMR).

  0570-0833/97/3609-0996 $ 17.50+.50/0

employed, attack on the (η^3-allyl)palladium complexes took place preferentially (entries 3–6) or exclusively (entry 7) at the less substituted position. The configuration of the double bond in the allylic group R is (*E*) for **7i–l**.

The alkylation conditions were also varied: The lithium enolate of (3*S*,6*R*)-**5** reacted with allyl acetate under Pd-catalyzed substitution at −60 °C to give the corresponding substituted allyl derivative **7a** in 45% yield and a diastereomer ratio of 96:4. Moreover, low-temperature alkylations with LDA as base were also performed with (3*S*,6*R*)-**5** for synthesizing **7a** and **7c**, but no improvements were achieved in yield or diastereoselectivity.

Representative alkylated oxazinones **7** were hydrolyzed with 6N aqueous HCl at 150 °C (pressure tube), and the obtained hydrochlorides transformed into the corresponding optically active (*S*)-AMAAs **8** by treatment with propylene oxide in ethanol (Table 3). The *ee* values for these amino acids correlated well with the corresponding *de* values for (3*S*,6*R*)-**7**.

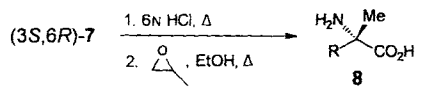


Table 3. Synthesis of α-methyl α-amino acids **8** by hydrolysis of oxazinones (3*S*,6*R*)-**7**.

R	No.	Yield [%] [a]	$[\alpha]_D^{25}$ (H_2O) {literature value}	*ee* [%] [b]
$PhCH_2$	**8c**	80	−21.5 (*c* = 1) {−22.0 (*c* = 1) [c]}	98
HO_2CCH_2	**8d**	78	+49.1 (*c* = 1) {−52.9 [d]}	92
$HOCH_2$	**8f**	75	+3.7 (*c* = 1) {+6.3 (*c* = 1) [e]}	58
$HO_2C(CH_2)_2$	**8g**	70	+22.1 (*c* = 2.7) [f] {+23.7 (*c* = 4) [f] [g]}	90

[a] Yield of isolated product. [b] Determined by comparing [α] values. [c] See ref. [19]. [d] (*R*) enantiomer, see ref. [20]. [e] See ref. [21]. [f] Measured at 436 nm in 6N HCl, see ref. [20]. [g] ≥97% *ee*.

A second, milder cleavage method that is ideal for isolating acid-sensitive amino acids was used in the case of the allyl derivative **7a**, which was obtained by PTC alkylation (Table 1). The imine group was hydrolyzed with 2N HCl in THF at room temperature for 1 h, and the ester group with LiOH (3 equiv) in THF/H_2O also at room temperature for 6 h. Subsequent Dowex chromatography gave (*S*)-α-allylalanine in 57% yield and 93% *ee*.[22]

We have found a practical and experimentally simple method for the synthesis of optically active (*S*)-AMAAs by alkylation or allylation of substituted 2,3-dihydro-6*H*-1,4-oxazinon-2-ones under solid–liquid PTC and Pd catalysis, respectively, followed by final hydrolysis. The method features simple preparation of starting materials from commercially available compounds and very mild reaction conditions. These heterocycles are promising chiral templates for the asymmetric synthesis of other types of α-amino acids.

Experimental Section

PTC alkylation of (6*S*)-**5**: A heterogeneous mixture of (6*S*)-**5** (231 mg, 1 mmol), TBAB (33 mg, 0.1 mmol), finely ground, technical-grade K_2CO_3 (400 mg, 3 mmol), and the corresponding electrophile (1.5 mmol) in CH_3CN (3 mL) was stirred at room temperature until the starting material had been totally consumed (GC, see Table 1). The mixture was filtered through a pad of silica gel, the solvent removed by 15 Torr, and the residue purified by flash chromatography on silica gel to afford **7**.

Pd-catalyzed allylation of (6*S*)-**5**: A solution of $[Pd(PPh_3)_4]$ (29 mg, 0.025 mmol) and dppe (28 mg, 0.07 mmol) in dry THF (0.5 mL) was added to a solution of (6*S*)-**5** (116 mg, 0.5 mmol) and the corresponding allylic carbonate (0.5 mmol) in dry THF (1 mL) and stirred at room temperature until the reaction was completed (see Table 2). The solvent was removed by 15 Torr, and the residue purified by flash chromatography on silica gel to afford **7**.

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