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Enantioselective Synthesis of β-Amino Acids. 6. High 1,2-Stereoinduction in the Preparation of Enantiopure 2(*R*)-Hydroxy-3(*R*)-*N*-benzoylamino-3-phenylpropionic Acid (*Like* Stereoisomer of Taxol's Side Chain).[1]

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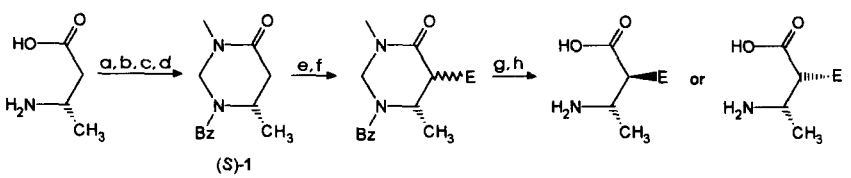
Abstract. The remarkably high 1,2-stereoinduction encountered in the hydroxylation of 1-benzoyl-3-methyl-6(*S*)-phenylperhydropyrimidin-4-one [(*S*)-**2**] allows for the preparation of enantiopure *N*-benzoyl (2*R*,3*R*)-3-phenylisoserine, the like stereoisomer of taxol's C-13 side chain.

Introduction

The moderately diastereoselective addition of the enolate **1**-Li, prepared from (*S*)-3-aminobutanoic acid, to several electrophiles was described recently.[2] Separation and hydrolysis of the resulting adducts afforded enantiopure *like* and *unlike* stereoisomers[3] of 2,3-dialkylated β-amino acids (Scheme I).

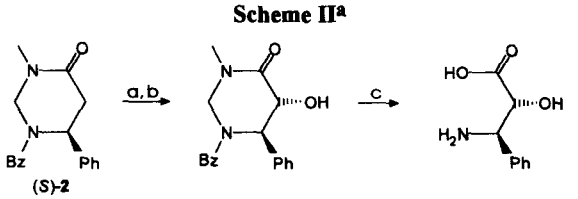
Scheme I[a]



[a] a, $(CH_3)_3SiCl/CH_3OH$; b, CH_3NH_2/CH_3OH; c, $(CH_2O)_n$; d, C_6H_5COCl/DMAP; e, LDA/THF; f, E^+; g, flash chromatography; h, 6 N aqueous HCl at 115-120°C, followed by ion-exchange column.

In this communication, we want to describe the high 1,2-stereoinduction[4] encountered in the hydroxylation of the phenyl analogue (*S*)-**2**, which allowed an efficient elaboration of enantiopure α-hydroxy-β-amino β-phenylpropionic acid (Scheme II).[5-8]

Scheme II[a]



[a] a, LDA; b, (+)-(camphorsulfonyl)oxaziridine; c, 6 N HCl at 105°C.

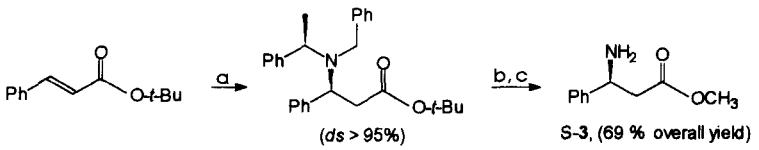
Results and Discussion

A. Preparation of 1-Benzoyl-3-methyl-6(*S*)-phenylperhydropyrimidin-4-one [(*S*)-2].

Methyl (*S*)-3-amino-3-phenylpropionate, (*S*)-**3**, was prepared according to the procedure described by Davies, et al.[9] via the highly diastereoselective addition of the lithium amide of (*R*)-

benzyl(α-methylbenzyl)amine[10] to *tert*-butyl cinnamate, followed by hydrogenolysis and esterification (Scheme III).

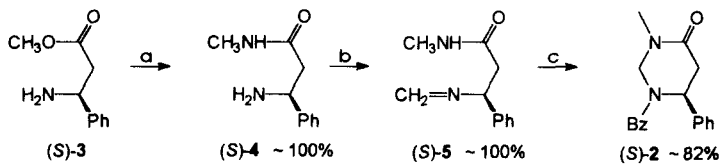
Scheme III[a]



[a] a, (*R*)-benzyl(α-methylbenzyl)amide; b, H_2, Pd/C, AcOH; c, $(CH_3)_3SiCl$, CH_3OH.

Conversion of ester (*S*)-**3** to the amide (*S*)-**4** was followed by Schiff base formation with paraformaldehyde. Imine (*S*)-**5** was used for the cyclization step without purification: treatment with benzoyl chloride/DMAP gave the desired perhydropyrimidinone (*S*)-**2** in good yield (Scheme IV).[11]

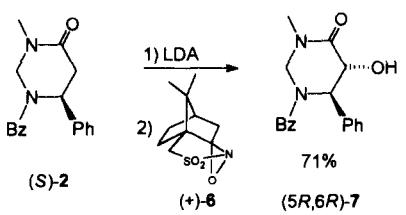
Scheme IV[a]



[a] a, CH_3NH_2/CH_3OH; b, $(CH_2O)_n$; c, BzCl/DMAP

B. Stereoselective Hydroxylation of Perhydropyrimidinone (*S*)-2.

Enolisation of heterocycle (*S*)-**2** using lithium diisopropylamide (LDA)[12] was followed by hydroxylation at -78°C with the oxaziridine (+)-**6**[13] to afford the expected[14] trans product (5*R*,6*R*)-**7** (eq 1)[15]. ^1H (270 MHz) and ^{13}C (67.5 MHz) NMR spectra show the exclusive formation of one hydroxylated product, whose configuration was assigned by correlation with known methyl (2*R*,3*R*)-3-benzoylamino-2-hydroxy-3-phenylpropionate, (2*R*,3*R*)-**9** (see below). The high diastereoselectivity observed in the hydroxylation of (*S*)-**2**-Li suggests a remarkable stereodirecting ability of the phenyl group at C(6) in the perhydropyrimidinone system.[16,17]

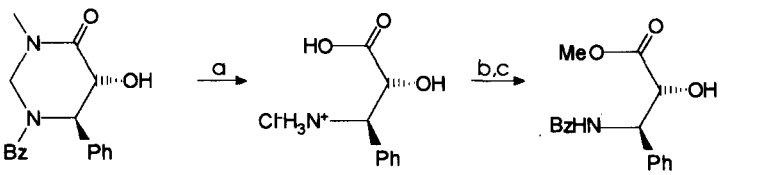


(eq. 1)

C. Hydrolysis of the Pyrimidinone Adduct 7 to Give the α-Hydroxy-β-phenyl-β-amino Acid.

The hydrolysis of heterocycle (5*R*,6*R*)-**7** was achieved by heating to 100-105°C with 6 N HCl in a sealed tube. Hydrochloride **8** was then converted to the known[7g,18] *N*-benzoylated methyl ester (2*R*,3*R*)-**9** by the sequence shown in Scheme V.

Scheme V[a]



(5*R*,6*R*)-**7** (2*R*,3*R*)-**8** (2*R*,3*R*)-**9** 41 % overall

[a] a, 6 N HCl at 105°C; b, $(CH_3)_3SiCl/MeOH$; c, $BzCl/Et_3N$.

References and Notes.

1. For Part 5, see: Murer, P.; Rheiner, B.; Juaristi, E.; Seebach, D. *Heterocycles* **1994**, *39*, 319.
2. Juaristi, E.; Escalante, J. *J. Org. Chem.* **1993**, *58*, 2282.
3. For a definition of the *like/unlike* stereochemical descriptors, see: (a) Seebach, D; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654. (b) See, also: Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis*; Wiley-Interscience: New York, 1991; p 52-54.
4. For discussions on 1,2-asymmetric induction, see: (a) Nógrádi, M. *Stereoselective Synthesis*; VCH Publishers: Weinheim, 1987; p 131. (b) Ref 3b; p 178.
5. Interestingly, taxol derivatives equipped with either enantiomer of the like side chain have been found to be almost as active as taxol itself.[6]
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8. For reviews on enantioselective synthesis of β-amino acids, see: (a) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichimica Acta* **1994**, *27*, 3. (b) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517.
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10. For the preparation of enantiopure alkyl (α-methylbenzyl)amines, see: Juaristi, E.; Murer, P.; Seebach, D. *Synthesis* **1993**, 1243.
11. **1-Benzoyl-3-methyl-6(*S*)-phenylperhydropyrimidin-4-one [(*S*)-2].** (*S*)-3-(Methyledeneamino)-*N*-methylbutanamide [(*S*)-**5**, 1.68 g, 8.8 mmol, prepared from methyl (*S*)-3-amino-3-phenylpropionate according to the general method of Juaristi and Escalante[2]] and 100 mL of benzene were treated with 0.96 g (7.9 mmol) of DMAP and 1.12 mL (9.6 mmol) of benzoyl chloride (dropwise addition) and

heated at reflux for 4 h. The precipitate that formed at this stage was removed by filtration, and the filtrate was concentrated on a rotary evaporator. The residue was separated by flash chromatography (hexane-ethyl acetate, 80:20 → 0:100) to afford 2.1 g (82 % yield) of (*S*)-**2** as a viscous oil: $[\alpha]^{28}_D$ = - 60.0 (c = 1.1, $CHCl_3$); ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.85 (3 H, br s, C*H*$_3$N), 2.7-3.0 (2 H, m, C*H*$_2$CH), 4.38 (1 H, d, *J* = 12 Hz, NC*H*H'N), 5.0 (1 H, br d, *J* = 12 Hz, NCH*H*'N), 5.6 (1H, br, C*H*CH$_2$), 7.25 (10 H, s, arom); ^{13}C NMR (67.8 MHz, $CDCl_3$, at 50°C) δ 32.0, 36.5, 53.5, 59.0, 126.4, 127.0, 128.1, 128.7, 129.0, 130.6, 134.7, 138.8, 167.7, 170.7.

12. Cf. Juaristi, E.; Quintana, D.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1991**, *56*, 2553.
13. Davis, F. A.; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387.
14. Cf. Juaristi, E.; Escalante, J.; Lamatsch, B.; Seebach, D. *J. Org. Chem.* **1992**, *57*, 2396.

15. **1-Benzoyl-3-methyl-5(*R*)-hydroxy-6(*R*)-phenylperhydropyrimidin-4-one [(5*R*,6*R*)-7].** A solution of (*i*-Pr)$_2$NH (0.13 mL, 0.95 mmol) in 15 mL of anhydrous THF was cooled under nitrogen to -40°C before the slow addition of 0.45 mL (0.95 mmol) of *n*-BuLi in hexane (2.1 M). The resulting solution was stirred at -40°C for 30 min and then cooled down to -78°C before the addition of 0.215 g (0.73 mmol) of pyrimidinone (*S*)-**2** in 10 mL of THF. The resulting dark-brown solution was stirred at -78°C for 45 min and was then treated with 250 mg (1.09 mmol) of (+)-(camphorsulfonyl)oxaziridine [(+)-**6**]. The reaction mixture was stirred at this temperature for 1 h and at ambient temperature for 5 min. The mixture was then treated with 5 mL of saturated ammonium chloride solution and then with 10 mL of water. The aqueous phase was extracted with five 5-mL portions of ethyl acetate. The combined extracts were dried (Na_2SO_4), filtered, and evaporated to give 0.49 g of the crude product, which was purified by flash chromatography (hexane-ethyl acetate, 50:50 → 0:100) to give 0.16 g (71 % yield) of (5*R*,6*R*)-7: $[\alpha]^{28}_D$ = - 37.8 (c = 1.4, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.08 (3 H, br s, C*H*$_3$N), 4.1-5.1 (5 H, m, C*H*$_2$, C*H*-OH, O*H*, and C*H*Ph), 7.05-6.0 (10 H, m, arom); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ, 26.4, 57.9, 62.0, 66.6, 126.1, 127.2, 128.1, 128.5, 128.8, 130.6, 134.2, 139.8, 170.4.

16. So far we do not have additional information concerning the possibility of double stereodifferentiation ("matched/mismatched" combinations)[17] in the hydroxylation reaction.

17. Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

18. **Methyl 2(*R*)-hydroxy-3(*R*)-*N*-benzoylamino-3-phenylpropionate [(2*R*,3*R*)-9].** A suspension of 0.11 g (0.35 mmol) of hydroxylated heterocycle (5*R*,6*R*)-**7** in 4 mL of 6 N HCl was heated in a sealed ampule to 100-105°C for 12 h. The solution was then allowed to cool to ambient temperature, and extracted with two 3-mL portions of ethyl acetate. The aqueous phase was evaporated at reduced pressure to afford 0.09 g of the crude product, which was immediately dissolved in 5 mL of methanol, cooled to 0°C and treated with 0.09 mL (0.77 mmol) of $(CH_3)_3SiCl$. The reaction mixture was stirred for 12 h and then evaporated to give 0.1 g of hydrochloride (2*R*,3*R*)-**8**, which was redissolved in 15 mL of CH_2Cl_2 and treated dropwise with 0.26 mL (1.75 mmol) of triethyl amine. The resulting solution was stirred at ambient temperature for 20 min before the slow addition of benzoyl chloride (0.04 mL, 0.38 mmol) in 1 mL of CH_2Cl_2. Stirring was continued overnight and then the reaction mixture was diluted with 10 mL of CH_2Cl_2, and partitioned with 10 mL of water. The aqueous phase was extracted with three 5-mL portions of CH_2Cl_2, the combined organic extracts dried (Na_2SO_4), filtered and concentrated in a rotary evaporator to give 0.16 g of the crude product, which was purified by flash chromatography (hexane-ethyl acetate, 80:20 → 50:50). The desired product was isolated as a crystalline solid that was recrystallized from hexane-CH_2Cl_2 (95:5) to afford 0.043 g (41 % overall yield) of pure (2*R*,3*R*)-**9**: mp 161-162°C (lit.[7g] mp 153°C); $[\alpha]^{28}_D$ = - 9.9 (c = 1.01, CH_3OH) [lit.[7g] $[\alpha]^{28}_D$ = - 9.6 (c = 1.0, CH_3OH)]; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.25 (1 H, d, *J* = 6.6 Hz , O*H*), 3.70 (3 H, s, C*H*$_3$O), 4.69 (1 H, dd, J_1 = 6.6 Hz, J_2 = 3.3 Hz, C*H*-OCH$_3$), 5.61 (1 H, dd, J_1 = 8.5 Hz, J_2 = 3.3 Hz, C*H*-C$_6$H$_5$), 7.2 (1 H, br d, *J* = 8.5 Hz, N*H*), 7.25-7.52 (8 H, m, arom), 7.78-7.81 (2 H, m, arom); ^{13}C NMR (22.49 MHz, $CDCl_3$) δ 52.6, 55.6, 72.9, 127.1, 127.4, 128.3, 129.5, 131.7, 134.0, 136.5, 166.7, 172.1.

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