Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 17 Sep 2007.

To cite this article: Barnaby C. H. May & Andrew D. Abell (1999) A Convenient Preparation of (2SR,3S)-3-Amino-2-hydroxy-4-phenylbutanoic Acid; an Important Peptide Bond Isostere, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:14, 2515-2525, DOI: 10.1080/00397919908086259

To link to this article: http://dx.doi.org/10.1080/00397919908086259

SYNTHETIC COMMUNICATIONS, 29(14), 2515-2525 (1999)

A CONVENIENT PREPARATION OF (2*SR*,3*S*)-3-AMINO-2-HYDROXY-4-PHENYLBUTANOIC ACID; AN IMPORTANT PEPTIDE BOND ISOSTERE

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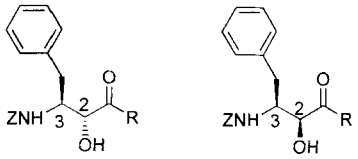
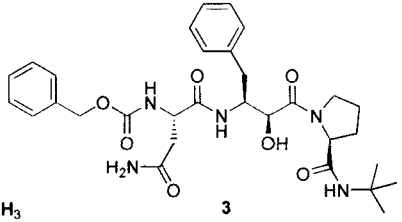
Abstract: We present an efficient synthesis of *N*-Z-(2*SR*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acids by hydroxylation of an enolate derived from methyl (3*S*)-*N*-Z-3-amino-4-phenylbutanoate with oxodiperoxymolybdenum (pyridine) (hexamethyl phosphoric triamide) complex (MoOPH).

The unusual amino acids, *N*-(benzyloxycarbonyl)-(2*RS*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid (**1a** and **1b**), [*N*-Z-(2*RS*,3*S*)-AHPBA] are important core isosteres of inhibitors of proteolytic enzymes,[1] most notably HIV protease[2] (eg. **3**[3]). Consequently, much attention has been devoted to the synthesis of **1a** and **1b**,



1a, (2*R*,3*S*), R=OH
2a, (2*R*,3*S*), R=OCH$_3$

1b, (2*S*,3*S*), R=OH
2b. (2*S*.3*S*), R=OCH$_3$



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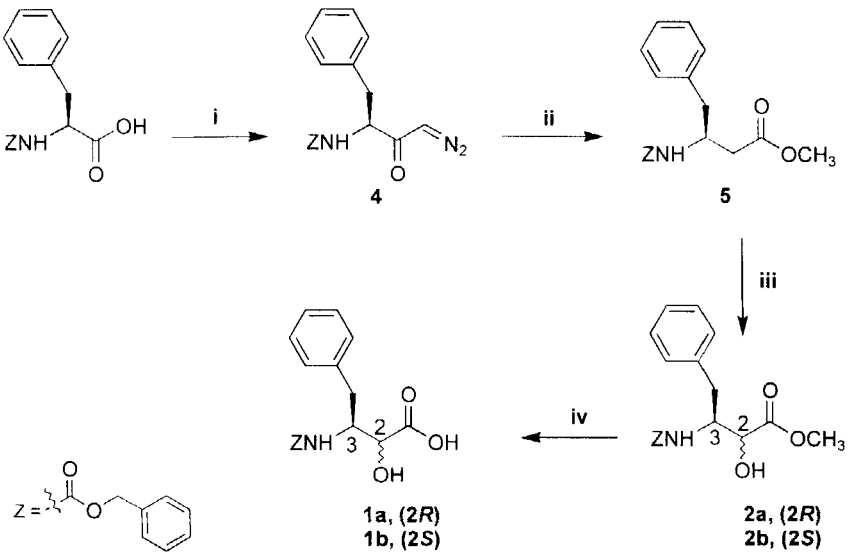
and its C3 epimers. A remarkable variety of stereoselective synthesise of **1a** and **1b**, have been published, among which may be noted; the halocyclocarbamation of allyamines,[4] the condensation of *N*-acyl-α-aminoacetophenone and glyoxylic acid followed by reduction,[5] hydroxyamination of methyl 4-phenyl-2-butenoate,[6] the benzylation of a *L*-malic acid derivative,[7] cycloaddition of an imine and benzoylketene,[8] and the azidation of a *D*-glucose derivative,[9] and ring opening of aziridine diols.[10] The practicality of these methods is limited by their complexity, and the demand for unusual reagents and synthetic intermediates. There are also several non-stereoselective synthesise, including a sequence based on the ozonolysis and reduction of peptidyl α-ethoxy vinyl ketones.[11] The most cited synthetic procedure involves formation of cyanohydrins from α-amino aldehydes, followed by acidic hydrolysis, and chromatographic separation of the C2 isomers.[12,13] This procedure was found, in our hands, to be low yielding and to suffer from problems associated with the formation of undesired side products. This led us to develop a simple route to the 3-amino-2-hydroxy acids **1a** and **1b**, starting from commercially available *N*-(benzyloxycarbonyl)-*L*-phenylalanine. The key step in the sequence is the direct oxidation of the β-aminoester **5** using MoOPH[14] as an electrophilic source of oxygen, to provide the methyl esters **2a** and **2b**. The isomeric methyl esters were readily separable by flash chromatography, and were obtained in good yield and high purity. Compounds **2a** and **2b** were then hydrolysed to give the desired 3-amino-2-hydroxy acids, **1a** and **1b**.

The essential problem in the synthesis of **1a** and **1b** is construction of the desired diasteriomeric C2, C3 portion. Initially we envisaged introduction of the required functionality by direct hydroxyamination of methyl 4-phenyl-2-butenoate, according the procedure of Sharpless *et al.*[15] Treatment of this olefin with potassium osmate, benzyl carbamate, and the chiral ligand hydroquinine 1,4-phthalazinediyl diether [$(DHQ)_2PHAL$], gave low yields (<5%) of **2a**, which proved difficult to purify. In addition, significant amounts of the undesired regioisomer, methyl *N*-(benzyloxycarbonyl)--2-amino-3-hydroxy-4-phenylbutanoate, were also produced, but not isolated.

Next we attempted the introduction of the α-hydroxy functionality of **1a** and **1b** by direct hydroxylation[16,17] of an appropriate substrate, according to a method developed for the synthesis of the taxol side chain, [(2*R*,3S)-*3*-amino-2-hydroxyl-3-phenylpropanoic acid].[18] The key β-aminoester **5**, was prepared from *N*-(benzyloxycarbonyl)-*L*-phenylalanine as detailed in scheme 1. Treatment of the mixed anhydride with diazomethane,[19] gave the diazoketone **4**, which underwent a Wolff rearrangement, catalysed by silver benzoate, in the presence of methanol, to give methyl *N*-(benzyloxycarbonyl)-(3*S*)-3-amino-4-phenylbutanoate, **5**,[20] with retention of configuration at C3.[21] Purification of the crude reaction mixture by flash chromatography, followed by a single recrystallisation, gave methyl ester **5** in 83% yield. The reaction of **5**, under strictly anhydrous conditions, with potassium hexamethyldisilazide (KHMDS, 6 equiv., -78°C to -25°C, THF) gave the corresponding potassium enolate. The enolate was reacted with MoOPH (1.5

Scheme 1



Reagents and conditions: i) EtOCOCl, NEt_3, THF/ether, CH_2N_2, -15°C, 18h. ii) PhCOOAg, CH_3OH, NEt_3, THF, rt, 1h. iii) KHMDS (6 equiv.), THF, MoOPH, -78°C, 3h iv) NaOH, H_2O/CH_3OH, rt, 2h.

equiv.) at -60°C, to give **2a** and **2b** as a 53:47 *syn/anti* mixture by ^{1}H NMR. Purification of the crude reaction mixture by flash chromatography gave *N*-Z-(2*R*,3*S*)-AHPBA methyl ester (**2a**), and *N*-Z-(2*S*,3*S*)-AHPBA methyl ester (**2b**) in 35% and 32% yield respectively, based on recovered starting material. A single recrystallisation (ethyl acetate/petroleum ether) gave samples of the methyl esters **2a** and **2b**, which were essentially pure by ^{1}H NMR. The *syn/anti* selectivity, and product yields were unaffected by the nature of the base (KHMDS, NaHMDS or LiHMDS) used to generate the enolate of **5**, the reaction temperature, or reaction time. Saponification of methyl esters, **2a** and **2b**, using sodium hydroxide (1.4 equiv., methanol/H_2O), gave the desired free acids **1a** and **1b** in 80% and 85%

yield respectively.[13] The C-2 configuration of these compounds were unequivocally assigned on the basis of a spectral comparison of ^{1}H nmr data previously published.[13]

In conclusion, the method reported here, provides a convenient synthesis of *N*-Z-(2*R*,3*S*)-AHPBA (**1a**), and *N*-Z-(2*S*,3*S*)-AHPBA (**1b**), in 36% overall yield, from commercially available *N*-Z-*L*-phenylalanine. Standard synthetic methods were employed in the synthesis of an enolisable substrate, to which the C2 hydroxyl functionality was directly introduced using the MoOPH complex. Practically this method was found to be superior in terms of simplicity and efficiency, to those methods already published.

EXPERIMENTAL

General Methods. Melting points were obtained using a capillary melting point apparatus, and are uncorrected. NMR spectra were recorded at 300 MHz (^{1}H) and at 75 MHz (^{13}C) on either a Varian CFT300 or XT300, in $CDCl_3$, with TMS as an internal standard, and at a probe temperature of 23°C. IR spectra were recorded on a Shimadzu FTIR-821PC spectrophotometer. Mass spectra were obtained using a Kratos MS80RFA spectrometer. Optical rotations were measured on a JASCO J-20C recording spectropolarimeter, and $[\alpha]_D^{20}$ values are given in units of 10^{-1} deg cm^2 g^{-1}, with the concentration given in units gcm^{-3}. Flash chromatography employed E. Merck silica gel (Kiesel gel 60, 200-400 mesh). Analytical thin layer chromatography (TLC) was carried out on silica gel (Merck,

60 F_{254}). Potassium, lithium, and sodium hexamethyldisilazide (KHMDS, LiHMDS, NaHMDS), and hexamethylphosphoric triamide, were obtained from the Aldrich® chemical company, and used fresh. Tetrahydrofuran (THF), and ether were freshly distilled from sodium and benzophenone. Pyridine was used freshly distilled from barium oxide, and all reactions were carried out under an atmosphere of nitrogen, as indicated.

Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) (MoOPH);[14] MoOPH was freshly prepared according to the procedure of Vedejs *et al.*[14] Molybdenum oxide (0.2 mmol, 30 g), and 30% aqueous hydrogen peroxide (150 mL) were stirred, by a mechanical paddle, in a 500 mL three-necked flask equipped with an internal thermometer. The mixture was heated in a 40°C oil bath, until the internal temperature reached 35°C. At this time an exothermic reaction was initiated. The oil bath was removed and replaced with a water bath to maintain the internal temperature below 40°C.[22] The mixture was then stirred at 40°C for 3.5 h. to give a yellow solution, with a small amount of white particulate. The solution was cooled to rt, and filtered through a plug of celite. The resulting yellow filtrate was cooled in an ice bath to 10°C, and hexamethylphosphoric triamide (HMPA) (0.21 mol, 37.3 g) was added dropwise with stirring over 5 min. Stirring was continued for 15 min at 10°C to give a yellow crystalline precipitate which was filtered, and air dried using a vacuum aspirator. The yellow solid was recrystallised from methanol, and the resulting yellow needles were isolated, and washed with cold methanol, to give

oxodiperoxymolybdenum(aqua)(hexamethylphosphoric triamide). The crystalline product was dried over phosphorous pentoxide at 10^{-1} mmHg for 24 h. to give oxodiperoxymolybdenum(hexamethylphosphoric triamide) as a hygroscopic yellow solid. A sample of this material, (0.10 mol, 36 g) was dissolved in dry THF (150 mL), and the solution was filtered through a celite plug. The filtrate, collected in a Buchner funnel, equipped with a magnetic stirrer, was placed in a 20°C water bath. Dry pyridine (0.10 mol, 8.0 g) was added portion-wise to the stirred solution over 10 min, to give a yellow crystalline precipitate. The solid was isolated, washed with dry THF (25 mL), and dry ether (200 mL), and finally dried at 10^{-1} mmHg. Oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) was thus obtained as a finely divided crystalline yellow solid (35 g); mp, 111-112°C (lit.[14] mp, 103-105°C).

Methyl *N*-(Benzyloxycarbonyl)-(3*S*)-3-amino-4-phenylbutanoate, (5);[20] A solution of diazoketone **4**[19] (9.6 mmol, 3.0 g) and dry methanol (1.3 equiv., 13 mmol, 0.4g, 0.5 mL) in dry THF (100 mL) was stirred at rt in a flame dried flask, under nitrogen. A solution of silver benzoate (0.1 equiv., 1.0 mmol, 0.25 g) in triethylamine (2.9 equiv., 29 mmol, 2.9 g, 4.0 mL) was added dropwise to the stirred solution, and the reaction was stirred for 2 h. Volatiles were removed under reduced pressure, and the resulting brown residue was taken up in ethyl acetate, washed with 10% aqueous HCl (2 x 10 mL), saturated aqueous $NaHCO_3$ (2 x 10mL), saturated aqueous NaCl (2 x 10mL), dried ($MgSO_4$), filtered and evaporated. The crude reaction mixture was purified by flash column

chromatography (10% ethyl acetate/petroleum ether) and a single recrystallisation (ethyl acetate/petroleum ether) to give **5** as a pale solid (2.7 g, 84%): mp, 54-55°C (lit.[20] mp, 53-55°C): ^{1}H NMR ($CDCl_3$), and ^{13}C NMR ($CDCl_3$) of **5** were identical to that already published.[20]

Methyl *N*-(Benzyloxycarbonyl)-(2*RS*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoates (2a and 2b): A solution of KHMDS (0.5 M in toluene, 6 equiv., 2.5 mmol, 5.2 mL) in dry THF (2 mL) was stirred and cooled to -78°C, in a flame dried flask under nitrogen. A solution of **5** (0.43 mmol, 140 mg) in dry THF (4 mL) was prepared in a flame dried flask under nitrogen, and was added dropwise to the solution of KHMDS. The reaction mixture was warmed to -25°C, then cooled back down to -78°C, prior to the addition of MoOPH (1.5 equiv., 0.64 mmol, 360 mg) as a single portion. The reaction mixture was warmed to -60°C, and stirred for 3 h. The reaction was quenched with saturated aqueous Na_2SO_3 (1 mL) and saturated aqueous NH_4Cl (1 mL), warmed to rt, and stirred until dissolution of the white solids. The aqueous layer was extracted with THF (3 x 10 mL), and the combined organic layers were washed with 10% aqueous HCl/saturated aqueous NaCl (1:1, 2 x 10 mL), 2% aqueous Na_2CO_3 (2 x 10 mL), saturated aqueous NaCl (2 x 10mL) and dried ($MgSO_4$). After filtration, solvent was removed under reduced pressure to give a yellow oil. The crude reaction mixture was purified by flash column chromatography (30% ethyl acetate/petroleum ether) to give unreacted starting material, **5** (52 mg, 35%), and methyl esters **2a** and **2b**.

N-Z-(2*R*,3*S*)-AHPBA methyl ester, **2a**; (34 mg, 35%); mp, 95-96°C (lit.[13] mp, 94-95°C), $[\alpha]_D^{20}$-68° (c=0.0036, methanol) (lit.[13] $[\alpha]_D^{20}$ -82° c=0.83, methanol); ^{1}H NMR ($CDCl_3$) δ 2.93 (m, 4-H_2), 3.69 (s, OCH_3), 4.08 (bs, 2-H), 4.32, (q, J=9 Hz, 3-H), 5.03 (s, Z-H_2), 5.16 (d, J=9.9 Hz, NH), 7.20-7.36 (m, ArH); ^{13}C NMR ($CDCl_3$) δ 38.22 (4-CH_2), 52.83 (OCH_3), 54.69 (3-CH), 66.72 (Z-CH_2), 70.09 (2-CH), 126.69, 127.88, 128.03, 128.44, 128.58, 129.34 (ArCH), 136.34, 137.24 (ArC), 155.67 (Z-CO), 174.08 ($COOCH_3$); IR ($CDCl_3$, cm^{-1}) 3529, 3435, 3033, 2956, 2252, 1732, 1508, 1456, 1442, 1220; TLC (analytical, 30% ethyl acetate/petroleum ether) R_f 0.20; EI MS *m/z* 91(100), 108(70), 143(15), 203(20).

N-Z-(2*S*,3*S*)-AHPBA methyl ester, **2b**; (32%, 31 mg); mp, 121-122°C (lit.[13] mp, 121-122°C), $[\alpha]_D^{20}$ –3° (c=0.013, methanol) (lit.[13] $[\alpha]_D^{20}$ -6° c=0.85, methanol); ^{1}H NMR ($CDCl_3$) δ 2.80 (m, 4-H_2), 3.55 (s, OCH_3), 4.34 (bs, 2-H), 4.37 (m, 3-H), 5.03 (s, Z-H_2), 5.13 (d, J=9 Hz, NH), 7.17-7.32 (m, ArH); ^{13}C NMR ($CDCl_3$) δ 35.58 (4-CH_2), 52.54 (OCH_3), 54.61 (3-CH), 66.76 (Z-CH_2), 72.17 (2-CH), 126.64, 127.96, 128.04, 128.35, 128.43, 129.40 (ArCH), 136.27, 136.80 (ArC), 155.87 (Z-CO), 172.95 ($COOCH_3$); IR ($CDCl_3$, cm^{-1}) 3531, 3436, 3031, 2956, 2252, 1720, 1510, 1456, 1440, 1220; TLC (analytical, 30% ethyl acetate/petroleum ether) R_f 0.12; EI MS *m/z* (rel. intensity) 91(100), 108(60), 143(5), 203(25).

Acknowledgments: The authors gratefully acknowledge the financial support of the Marsden Fund, New Zealand, the acquisition of mass spectra by B. Clark,

University of Canterbury, and Andrew Harvey, University of Canterbury, for the large scale synthesis of methyl *N*-(benzyloxycarbonyl)-(3*S*)-3-amino-4-phenylbutanoate.

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(Received in Japan 12 November 1998)