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Stereoselective Synthesis of α-Hydroxy-β-amino Acids Using *D*-Glyceraldehyde as the Homochiral Source.

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Abstract: A systematic study of the diastereoselective addition of methyl organometallic compounds to the benzyl imine derived from conveniently protected *D*-glyceraldehyde in order to develop a new approach to enantiomerically pure α-hydroxy-β-amino acids is reported. Methylmagnesium bromide addition afforded the corresponding adduct, which can be further elaborated to give *(2S,3R)* 3-amino-2-hydroxybutanoic acid, with complete diastereoselectivity.

Of all the rare amino acids of biological relevance, in the past few years particular interest has focused on α-hydroxy-β-amino acids. This can be explained by the fact that many of them occur in nature as components of more complex biologically active molecules. The more striking examples are 3-phenylisoserine, present in the side chain of taxol,[1] an anti-tumour reagent, 2-hydroxy-3-amino-4-phenylbutanoic acid, the non-leucine part of bestatin,[2] a dipeptide endowed with inmuno-regulatory properties, or a component of a novel class of HIV-1 protease inhibitors,[2b] 3-amino-2-hidroxydecanoic acid, the N-terminal component of the linear peptapeptide microginin,[3] an ACE inhibitor, or cyclohexylnorstatine, the C-terminal moiety of KRI 1314[4] which inhibits renin. Consequently, numerous methods have been developed for synthesising enantiomerically pure α-hydroxy-β-amino acids. A remarkable variety of solutions has been devised, among which may be noted are nucleophilic ring opening of chiral epoxides[5] , β-lactam synthon methodologies,[6] hetero Diels-Alder reactions,[7] aldol reactions,[8] electrophilic hydroxylation of chiral enolates,[9] diastereoselective alkylation of malic acid and subsequent Curtius rearrangement,[10] addition of nucleophiles to chiral α-amino aldehydes,[11] and halocyclocarbamation of chiral allylamines.[12]

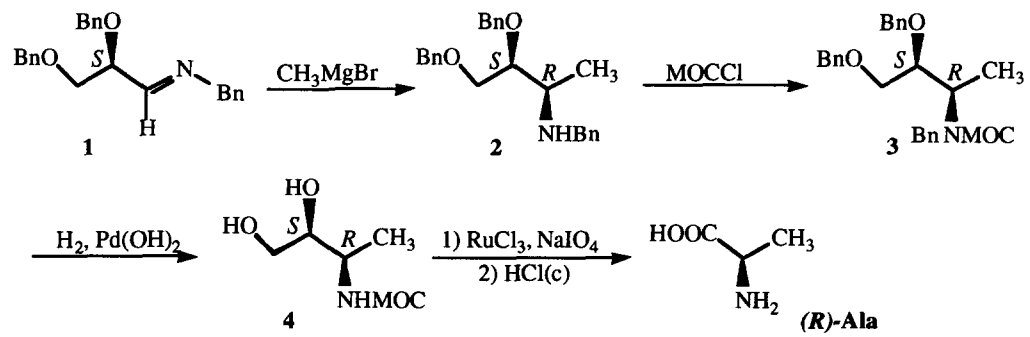
Although organometallic addition reactions to C=C and C=O bonds are well known and have been extensively studied in both 'achiral' and 'chiral versions' asymmetric additions to C=N bonds have only recently begun to attract attention. Asymmetric addition to chiral imines, to chiral hydrazones as well as additions to achiral derivatives in the presence of chiral mediators have all been well reported,[13] although the use of chiral imines derived from chiral carbonyl compounds, R*CH=N-R, is rare. A careful survey of the literature up to now on the addition of organometallic reagents to the imine bond revealed only two precedents for the latter case, the work of Terashima et al.[14] who have used a chiral imine derived from threose as a starting material in the synthesis of cyclohexylnorstatine, and that of Jäger et al.[15] who have obtained optically active amino alcohols by Grignard addition to *N,O*-dibenzylglyceraldimine and lactaldimine.

In view of this, and in connection with our studies on the asymmetric synthesis of amino acids from readily available and cheap starting materials we were interested in developing a general synthetic approach to α-hydroxy-β-amino acids based on the stereoselective addition reaction of an organometallic reagent to a chiral imine derived from *D*-glyceraldehyde as the key step.

N-Benzylimine derived from *(2R)*-2,3-di-*O*-benzylglyceraldeyde **1**, readily available[16] from mannitol, was chosen as a substrate as it has proven to be a good substrate for the addition of cyanide to the C=N bond affording the corresponding aminonitrile in high yield with very good stereoselectivity.[17] Several methyl organometallic reagents were tested as nucleophiles in order to optimise the proposed route.

The addition of CH_3MgBr to imine **1** was carried out in ether at 0 °C. Two equivalents of the organometallic reagent were required for complete consumption of the starting imine and the addition compound was obtained as a single diastereoisomer, as determined by ^{1}H-NMR spectroscopic analysis, in 51 % yield. In order to increase the reaction yields other organometallic reagents, e.g. CH_3Li and CH_3Cu, generated *in situ* from methylmagnesium bromide and copper (I) bromide prior to the addition reaction, were used and no reaction occurred with these organometallics. As better yields have been reported[18] for the addition of alkyl copper reagents, complexed with boron trifluoride etherate prior to use, to aldimines containing α-hydrogens we also tested $CH_3Cu.BF_3$ but unfortunately the reaction did not work at all. Finally, we also tried the methylmagnesium bromide reaction in the presence of several Lewis acids, e.g. ZnI_2, $TiCl_4$ and $CeCl_3$, of these only $CeCl_3$ gave the desired product but the results were similar to those previously obtained with CH_3MgBr.

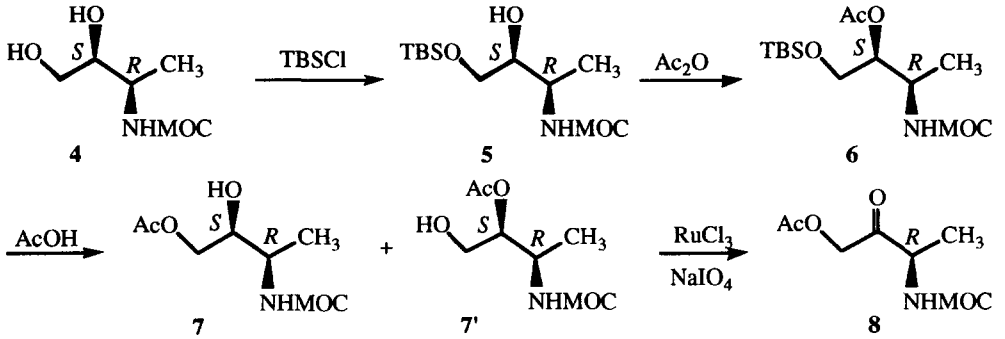
The absolute configuration of the addition reaction product was unambiguously determined by the transformation of compound **2** to alanine (scheme 1). Treatment of **2** with methylchloroformate in dry THF afforded compound **3** which was submitted to hydrogenolysis in the presence of palladium hydroxyde to afford the methoxycarbonylamino diol **4**. Treatment of the 1,2-diol with an excess of sodium periodate in the presence of ruthenium trichloride followed by hydrolysis of the resulting compound with hydrochloric acid under reflux conditions gave *(R)*-alanine whose specific rotation value allowed us to determine the absolute configuration of the newly formed stereogenic carbon and confirmed that compound **2** had been obtained as a single diastereoisomer.



Scheme 1

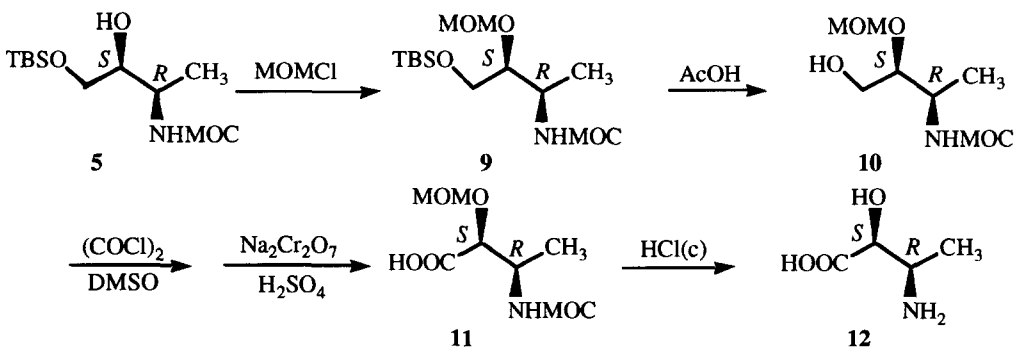
With **4** in hand elaboration to 3-amino-2-hydroxybutanoic acid was next attempted. First we tried selective protection and deprotection of hydroxy groups in order to be able to selectively oxidise the primary hydroxy group to the desired carboxy moiety. Thus treatment of **4** with *tert*-butyldimethylsilylchloride cleanly afforded compound **5** clearly which was subsequently acetylated with acetic anhydride to compound **6**. Selective *tert*-

butyldimethylsilyloxy hydrolysis with acetic acid afforded a mixture of regioisomers **7** and **7'**, presumably due to transacetylation of the initially formed regioisomer **7**. Oxidation of the regioisomeric mixture with an excess of sodium periodate in the presence of ruthenium trichloride resulted in the formation of ketone **8** as the major compound, indicating that the desired compound was the minor component of the mixture, only a 15%.



Scheme 2

Alternatively, compound **5** was treated with methoxymethylchloride to afford compound **9.** In this case selective hydrolysis of the *tert*-butyldimethylsilyloxy group under the same conditions used above afforded the desired compound **10** as a unique regioisomer from which we can easily isolate the free amino acid in three steps; 1) oxidation of the primary hydroxy group to the carboxy moiety by successive treatment with oxalyl chloride in DMSO and oxidation of the intermediate aldehyde with sodium dichromate in sulphuric acid, 2) acidic hydrolysis of methoxymethyl and methoxycarbonyl protecting groups by teatment of compound **11** with hydrochloric acid and 3) ion exchange chromatography to obtain the free amino acid. The free amino acid **12** obtained as a white solid had a mp > 225 °C (decomp.) and $[\alpha]^{25}_D$ = - 12.4 (c, 0.75 in water)



Scheme 3

In summary, we have developed a new approach to the synthesis of α-hydroxy-β-amino acids starting from the available "chiral pool" which is both flexible and practical since starting from a common substrate we can introduce a wide variety of substituents onto the side chain. The application of this new procedure to the stereoselective synthesis of α-hydroxy-β-amino acids present in taxol, bestatin, microginin and other interesting compounds is underway and will be published in due course.

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EXPERIMENTAL

Apparatus: Melting points were determined using a Büchi 510 capillary melting point apparatus and are uncorrected. Specific rotations were recorded using a Perkin-Elmer 241-C polarimeter with a thermally-jacketed 10 cm cell at 25°C. IR spectra were obtained on a Perkin-Elmer 1600 FTIR infrared spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in deuteriochloroform or deuterated water and referenced with respect to the residual solvent signal on a Varian Unity 300 or a Bruker AMX300 spectrometer. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ 0.00 ppm), and coupling constants *(J)* are measured in Hertz. Elemental analyses were performed on a Perkin-Elmer 200 C,H,N,S elemental analyser.

Chemicals: All reactions were carried out under argon with magnetic stirring. Solvents were dried prior to use. All reagents were purchased from the Aldrich Chemical Co. and used as received. TLC was performed on precoated silica-gel plates which were visualised using UV light and anisaldehyde/sulphuric acid/ethanol (2/1/100). Flash column chromatography was undertaken on silica gel (Kiesegel 60).

***(2S)-N*-(2,3-Dibenzyloxypropylidene)benzylamine 1.** A solution of *(2R)*-2,3-di-*O*-benzyl-*D*-glyceraldehyde (5.4 g, 20 mmol) in dry ether (80 ml) and anhydrous magnesium sulphate (4 g) was added to a stirred solution of benzylamine (2.15 g, 20 mmol) in dry ether (80 ml) at 0 °C. After 3 h the reaction mixture was filtered and evaporated to afford the crude imine **1** which was used as such in the next step. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.70-3.86 (m, 2H), 4.17-4.25 (m, 1H), 4.56 (s, 2H), 4.61 (AB system, 2H), 4.62 (AB system, 2H), 7.20-7.42 (m, 15H), 7.77 (dt, 1H, J = 5.4 Hz, J = 1.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 64.8, 71.3, 71.8, 73.4, 79.5, 127.0, 127.6, 127.6, 127.7, 127.9, 127.9, 128.3, 128.4, 128.5, 137.9, 138.0, 138.6, 164.8.

***(2R,3S)-N*-Benzyl-3,4-dibenzyloxy-2-butylamine 2.** A solution of the crude chiral imine (7.2 g, 20 mmol) in diethyl ether (50 ml) was added to a stirred solution of a Grignard reagent, prepared from methylmagnesium bromide 1M solution in dibutyl ether (50 ml, 50 mmol) and diethyl ether (50 ml) at 0 °C under argon over a period of 30 min. After being stirred for 15 h at room temperature, the reaction mixture was poured into saturated aqueous NH_4Cl (30 ml), the organic layer separated and the aqueous layer extracted with ether (2 x 50 ml). The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (ether/hexane 3:1 as eluent) afforded 3.8 g (51 % yield) of *(2R,3S)-N*-benzyl-3,4-dibenzyloxy-2-butylamine **2** as a colourless oil. $[\alpha]^{25}_D$ = - 21.6 (c, 1 in chloroform), IR (Nujol) 3328 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.10 (d, 3H, J = 6.6), 2.86 (brs, 1H), 2.93 (dq, 1H, J = 6.6, J = 6.6), 3.51 (ddd, 1H, J = 6.6, J = 5.4, J = 3.9), 3.63 (dd, 1H, J = 10.5, J = 5.4), 3.66 (d, 1H, J = 12.9), 3.75 (dd, 1H, J = 10.5, J = 3.9), 3.85 (d, 1H, J = 12.9), 4.53 (s, 2H), 4,54 (d, 1H, J = 11.7), 4.74 (d, 1H, J = 11.7), 7.23-7.37 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.3, 51.3, 53.5, 70.4, 72.8, 73.4, 82.0, 126.8, 127.6, 127.6, 127.7, 127.9, 128.1, 128.3, 128.3, 128.4, 138.3, 138.6, 140.7. Anal. Calcd for $C_{25}H_{29}NO_2$: C, 79.97; H, 7.78; N, 3.73. Found: C, 80.08; H, 7.87; N, 3.81.

***(2R,3S)-N*-Benzyl-3,4-dibenzyloxy-*N*-methoxycarbonyl-2-butylamine 3.** A solution of *(2R,3S)-N*-benzyl-3,4-dibenzyloxy-2-butylamine **2** (3.4 g, 9 mmol), methyl chloroformate (1.7 g, 18 mmol) and K_2CO_3 (7.5 g, 54 mmol) in dry THF (60 ml) was stirred at room temperature for 2 h. The reaction mixture was then filtered and concentrated *in vacuo* to afford a crude product which was purified by silica gel flash chromatography (ether/hexane 1:1 as eluent) to provide 3.75 g (96 % yield) of *(2R,3S)-N*-benzyl-3,4-dibenzyloxy-*N*-methoxycarbonyl-2-butylamine **3** as a colourless oil. $[\alpha]^{25}_D$ = - 24.8 (c, 1 in chloroform), IR (Nujol) 1698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.09 (d, 3H, J = 7.2), 3.49 (dd, 1H, J = 10.5, J = 5.1),

3.61 (dd, 1H, J = 10.5, J = 3.6), 3.62 (s, 3H), 3.75-3.87 (m, 1H), 4.04 (dq, 1H, J = 7.2, J = 7.2), 4.34 (d, 1H, J = 15.9), 4.43 (d, 1H, J = 11.7), 4,44 (d, 1H, J = 12.3), 4.51 (d, 1H, J = 12.3), 4.60 (d, 1H, J = 15.9), 4.66 (d, 1H, J = 11.7), 7.15-7.28 (m, 15H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 16.1, 50.6, 52.2, 55.0, 70.7, 72.9, 73.6, 80.6, 126.7, 127.4, 127.5, 127.6, 127.8, 128.2, 128.2, 128.3, 138.4, 138.9, 139.5, 157.2. Anal. Calcd for $C_{27}H_{31}NO_4$: C, 74.80; H, 7.21; N, 3.23. Found: C, 74.98; H, 7.08; N, 3.40.

***(2S,3R)*-3-Methoxycarbonylamino-1,2-butanediol 4.** A solution of *(2R,3S)-N*-benzyl-3,4-dibenzyloxy-*N*-methoxycarbonyl-2-butylamine **3** (3.5 g, 8 mmol) in methanol (50 ml) was hydrogenated with $Pd(OH)_2$ (750 mg) as catalyst at room temperature for 12 h. When the reaction was finished the catalyst was removed by filtration and the filtrate evaporated to dryness to afford 1.25 g (95 % yield) of *(2S,3R)*-3-methoxycarbonylamino-1,2-butanediol **4** as an oil. $[\alpha]^{25}_D$ = + 12.4 (c, 1 in chloroform), IR (Nujol) 3350, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.22 (d, 3H, J = 7.2), 2.62 (brs, 2H), 3.48-3.63 (m, 3H), 3.65 (s, 3H), 3.74-3.86 (m, 1H), 5.01 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.8, 47.7, 52.2, 63.6, 74.4, 157.5. Anal. Calcd for $C_6H_{13}NO_4$: C, 44.17; H, 8.03; N, 8.58. Found: C, 44.29; H, 7.91; N, 8.72.

Oxidation of *(2S,3R)*-3-methoxycarbonylamino-1,2-butanediol 4 to *R*-alanine. Small portions of $NaIO_4$ (1.7 g, 8 mmol) were added to a stirred solution of *(2S,3R)*-3-methoxycarbonylamino-1,2-butanediol **4** (326 mg, 2 mmol) in 2:2:3 acetonitrile-carbontetrachloride-water (30 ml). After being vigorously stirred for 5 min following completion of the addition the mixture was treated with $RuCl_3 \cdot H_2O$ (10 mg, 0.044 mmol) and stirring was allowed to continue for 2h. Dichloromethane (40 ml) was then added, the organic phase was separated and the aqueous phase extracted with dichloromethane (3 x 30 ml). The organic extracts were concentrated *in vacuo* and the black residue was hydrolysed by refluxing for 12 h with 20 % hydrochloric acid (30 ml). After filtration the aqueous solution was washed with dichloromethane and evaporated *in vacuo* to give the crude product which was purified by ion exchange chromatography (Dowex 50x8) to afford 130 mg (73 % yield) of *(R)*-alanine. Further purification was performed by silica gel column chromatography (eluent, water/acetonitrile 1:2)

***(2S,3R)*-1-*tert*-Butyldimethylsilyloxy-3-methoxycarbonylamino-2-butanol 5.** Triethylamine (2.4 g, 24 mmol), dimethylaminopyridine (73 mg, 0.6 mmol) and *tert*-butyldimethylsilylchloride (1.81 g, 12 mmol) were added to a stirred solution of *(2S,3R)*-3-methoxycarbonylamino-1,2-butanediol **4** (978 mg, 6 mmol) in dry dichloromethane (10 ml) at 0 °C. After being stirred for 20 h at room temperature the reaction mixture was dissolved in diethyl ether (100 ml), washed with 1M aqueous NH_4Cl and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (ether/hexane 2:1 as eluent) afforded 1.5 g (90 % yield) of *(2S,3R)*-1-*tert*-butyldimethylsilyloxy-3-methoxycarbonylamino-2-butanol **5** as an oil. $[\alpha]^{25}_D$ = + 9.5 (c, 1 in chloroform), IR (Nujol) 3434, 1704 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.04 (s, 6H). 0.87 (s, 9H), 1.21 (d, 3H, J = 6.9), 2.68 (brs, 1H), 3.45-3.51 (m, 1H), 3.55-3.61 (m, 2H), 3.63 (s, 3H), 3.66-3.74 (m, 1H), 5.04 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ - 5.4, 18.2, 18.6, 25.8, 47.8, 52.0, 64.7, 74.2, 156.9. Anal.Calcd for $C_{12}H_{27}NO_4Si$:C,51.95;H,9.81;N, 5.05. Found: 51.81; H, 10.03; N, 4.90.

***(2R,3S)*-3-Acetoxy-4-*tert*-butyldimethylsilyloxy-*N*-methoxycarbonyl-2-butylamine 6.** Dimethylaminopyridine (24 mg, 0.2 mmol), triethylamine (404 mg, 4 mmol) and acetic anhydride (306 mg, 3 mmol) were added to a stirred solution of *(2S,3R)*-1-*tert*-butyldimethylsilyloxy-3-methoxycarbonylamino-2-butanol **5** (554 mg, 2 mmol) in dry dichloromethane (10 ml) at room temperature. After being stirred for 12 h at room temperature the reaction mixture was treated with diethyl ether (50 ml), washed with 1M aqueous NH_4Cl and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography

(ether/hexane 1:1 as eluent) afforded 625 mg (98 % yield) of *(2R,3S)*-3-acetoxy-1-*tert*-butyldimethylsilyloxy-*N*-methoxycarbonyl-2-butylamine **6** as a colourless oil. $[\alpha]^{25}_D$ = + 2.4 (c, 1 in chloroform), IR (Nujol) 3342, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.02 (s, 6H). 0.86 (s, 9H), 1.13 (d, 3H, J = 6.9), 2.05 (s, 3H), 3.60-3.65 (m, 2H), 3.63 (s, 3H), 3.96-4.08 (m, 1H), 4.80-4.88 (m, 1H), 4.91 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ - 5.6, 18.1, 20.8, 25.7, 47.2, 52.0, 61.9, 75.8, 77.2, 156.5, 170.2 Anal. Calcd for $C_{14}H_{29}NO_5Si$: C, 52.64; H, 9.15; N, 4.38. Found: 52.78; H, 8.97; N, 4.51.

Hydrolysis of *(2R,3S)*-3-acetoxy-1-*tert*-butyldimethylsilyloxy-*N*-methoxycarbonyl-2-butylamine 6. Water (2 ml) was added to a stirred solution of *(2R,3S)*-3-acetoxy-1-*tert*-butyldimethylsilyloxy-*N*-methoxycarbonyl-2-butylamine **6** (480 mg, 1.5 mmol) in acetic acid (5 ml) at room temperature. After being stirred at room temperature for 24 h, the mixture was diluted with dichloromethane (30 ml). The organic solution was washed with saturated aqueous Na_2CO_3, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (ether/hexane 1:1 as eluent) afforded 275 mg (90 % yield) of a mixture of regioisomers which was used as such in the next step.

***(3R)*-1-Acetoxy-3-methoxycarbonylamino-2-butanone 8.** Small portions of $NaIO_4$ (856 mg, 4 mmol) were added to a stirred solution of the mixture of regioisomers obtained above (205 mg, 1 mmol) in 2:2:3 acetonitrile-ethyl acetate-water (10 ml). After being vigorously stirred for 5 min following completion of the addition the mixture was treated with $RuCl_3$ H_2O (4.5 mg, 0.022 mmol) and stirring was allowed to continue for 12h at room temperature. Ethyl acetate (40 ml) was then added, the organic phase was separated and the aqueous phase extracted with ethyl acetate (3 x 30 ml) . The organic extracts were dried over $MgSO_4$, concentrated *in vacuo* and the residue was dissolved in diethyl ether, washed with saturated aqueous Na_2CO_3, dried over $MgSO_4$ and concentrated *in vacuo* to afford 144 mg (71 % yield) of *(3R)*-1-acetoxy-3-methoxycarbonylamino-2-butanone **8**. ^1H NMR ($CDCl_3$, 300 MHz): δ 1.35 (d, 3H, J = 6.9), 2.13 (s, 3H), 3.64 (s, 3H), 4.37-4.45 (m, 1H), 4.74 (d, 1H, J = 17), 4.82 (d, 1H, J = 17), 5.38 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.4, 20.3, 52.4, 53.0, 65.9, 156.4, 170.1, 202.8. Anal. Calcd for $C_8H_{13}NO_5$: C, 47.29; H, 6.45; N, 6.89. Found: C, 47.18; H, 6.23; N, 7.07.

***(2R,3S)*-4-*tert*-Butyldimethylsilyloxy-*N*-methoxycarbonyl-3-methoxymethyloxy-2-butylamine 9.** Diisopropylethylamine (4.75 g, 30 mmol) and methoxymethylchloride (1.6 g, 20 mmol) were added to a stirred solution of *(2S,3R)*-1-*tert*-butyldimethylsilyloxy-3-methoxycarbonylamino-2-butanol **5** (1.4 g, 5 mmol) in dry dichloromethane (20 ml) was added . After being stirred under reflux conditions for 20 h, the mixture was diluted with ether (100 ml). The ethereal solution was washed with 1M aqueous NH_4Cl and brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (ether/hexane 1:1 as eluent) afforded 1.5 g (95 % yield) of *(2R,3S)*-4-*tert*-butyldimethylsilyloxy-*N*-methoxycarbonyl-3-methoxymethyloxy-2-butylamine **9** as a colourless oil. $[\alpha]^{25}_D$ = - 19.6 (c, 1 in chloroform), IR (Nujol) 3400, 1760 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.10 (s, 6H) 0.85 (s, 9H), 1.16 (d, 3H, J = 6.7), 3.35 (s, 3H), 3.40-3.63 (m, 3H), 3.61 (s, 3H), 3.84-3.95 (m, 1H), 4.61 (d, 1H, J = 6.7), 4.72 (d, 1H, J = 6.7), 5.12 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ - 5.6, 17.8, 18.1, 25.8, 47.4, 51.8, 55.7, 63.1, 79.7, 96.9, 156.5. Anal. Calcd for $C_{14}H_{31}NO_5Si$: C, 52.31; H, 9.72; N, 4.36. Found: C, 52.51; H, 9.57; N, 4.51.

***(2S,3R)*-3-Methoxycarbonylamino-2-methoxymethyloxy-1-butanol 10.** Water (6 ml) was added to a stirred solution of *(2R,3S)*-4-*tert*-butyldimethylsilyloxy-*N*-methoxycarbonyl-3-methoxymethyloxy-2-butylamine **9** (1,45 g, 4.5 mmol) in acetic acid (15 ml) at room temperature. After being stirred at room temperature for 24 h, the mixture was diluted with dichloromethane (100 ml). The organic solution was washed

with saturated aqueous Na_2CO_3, dried over $MgSO_4$ and concentrated *in vacuo*. Purification of the residue by flash chromatography (ether as eluent) afforded 866 mg (93 % yield) of *(2S,3R)*-3-methoxycarbonylamino-2-methoxymethyloxybutanol **10** as a colourless oil. $[\alpha]^{25}_D$ = + 41.2 (c, 1 in chloroform), IR (Nujol) 3360, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.19 (d, 3H, J = 6.9), 3.36 (s, 3H), 3.40-3.53 (m, 3H), 3.55-3.64 (brs, 1H), 3.64 (s, 3H), 3.95-4.02 (m, 1H), 4.61 (d, 1H, J = 6.8), 4.68 (d, 1H, J = 6.8), 4.86 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 18.0, 46.8, 52.3, 55.8, 62.1, 82.2, 97.3, 157.4. Anal. Calcd for $C_8H_{17}NO_5$: C, 46.37; H, 8.27; N, 6.76. Found: C, 46.49; H, 8.12; N, 6.66.

***(2S,3R)*-3-Methoxycarbonylamino-2-methoxymethyloxybutanoic acid 11.** A solution of DMSO (468 mg, 6 mmol) in dry dichloromethane (5 ml) was added to a stirred solution of oxalyl chloride (571 mg, 4.5 mmol) in dry dichloromethane (5 ml) at -78 °C. After stirring for 10 min at -78 °C a solution of *(2S,3R)*-3-methoxycarbonylamino-2-methoxymethyloxybutanol **10** (621 mg, 3 mmol) and triethylamine (909 mg, 9 mmol) in dry dichloromethane (5 ml) was added. The mixture was allowed to warm to room temperature, stirred for 2h at this temperature and then quenched with water (20 ml). The aqueous solution was then extracted with dichloromethane, dried over $MgSO_4$ and concentrated *in vacuo* to give the crude aldehyde which was dissolved in acetone (6 ml) at -15 °C and treated with Jones' reagent (0.6 ml). After being stirred at this temperature for 10 min, the mixture was diluted with water (10 ml) and extracted with dichloromethane (100 ml). The organic solution was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo to* afford 271 mg (41 % yield) of *(2S,3R)*-3-methoxycarbonylamino-2-methoxymethyloxybutanoic acid **11** as an oil. $[\alpha]^{25}_D$ = - 31.8 (c, 1.4 in chloroform), IR (Nujol) 3340, 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.23 (d, 3H, J = 6.8), 3.38 (s, 3H), 3.61 (s, 3H), 4.13-4.17 (m, 1H), 4.20-4.30 (m, 1H), 4.60 (d, 1H, J = 6.9), 4.73 (d, 1H, J = 6.9), 5.27 (d, 1H, J = 9.3), 5.85 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 17.7, 48.5, 52.1, 56.1, 76.2, 95.9, 156.6, 172.9 Anal. Calcd for $C_8H_{15}NO_6$: C, 43.44; H, 6.84; N, 6.33. Found: C, 43.26 H, 6.99 N, 6.36.

***(2S,3R)*-3-Amino-2-hydroxybutanoic acid 12.** A solution of *(2S,3R)*-3-methoxycarbonylamino-2-methoxymethyloxybutanoic acid **11** (221 mg, 1 mmol) in 10 % hydrochloric acid (25 ml) was heated at 100 °C for 5 h. The mixture was allowed to cool to room temperature and the aqueous solution was washed with dichloromethane and concentrated *in vacuo* to give the crude amino acid which was purified by ion-exchange chromatography (Dowex 50x8) to afford 100 mg (85 % yield) of *(2S,3R)*-3-amino-2-hydroxybutanoic acid **12** as a white solid. Further purification was performed by silica gel column chromatography (eluent water/acetonitrile 1:3). Mp > 225(decomp) °C; $[\alpha]^{25}_D$ = - 12.4 (c, 0.75 in water), ^1H NMR ($CDCl_3$, 300 MHz): δ 1.19 (d, 3H, J = 6.6), 3.35-3.43 (m, 1H), 3.85 (d, 1H, J = 4.5); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 13.0, 48.4, 71.1, 175.6 Anal. Calcd for $C_4H_9NO_3$: C, 40.33; H, 7.62; N, 11.76. Found: C, 40.46; H, 7.48; N, 11.87.

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