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A straightforward synthesis of both enantiomers of α-vinylalanine and α-ethynylalanine

Alberto Avenoza,[a,*] Carlos Cativiela,[b,*] Jesús M. Peregrina,[a] David Sucunza [a] and María M. Zurbano [a]

[a]*Departamento de Química, Universidad de La Rioja, Grupo de Síntesis Química de la Rioja, U.A.-C.S.I.C., 26001 Logroño, Spain*

[b]*Departmento de Química Orgánica, Instituto de Ciencia de Materiales de Aragón, Universidad de Zaragoza-C.S.I.C., 50009 Zaragoza, Spain*

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Abstract

This report describes the synthesis of enantiomerically pure (*S*)- and (*R*)-α-vinylalanines and (*S*)- and (*R*)-α-ethynylalanines, four quaternary α-amino acids, using a straightforward synthetic route and starting from (*S*)- and (*R*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinals.

1. Introduction

The α-alkyl α-amino acids are an important class of non-proteinogenic amino acids used to increase conformational restrictions in peptides and thereby change their biological activity and stability.[1] They have attracted a great deal of research interest and a number of interesting approaches have been developed.[2] In this context, one of us recently published a review that covers the literature related to the synthesis of α-substituted quaternary α-amino acids with an acyclic backbone.[3]

β,γ-Unsaturated amino acid derivatives have received special attention since they are important enzyme inhibitors,[4] for example, α-vinyl amino acids are known to inhibit pyridoxal phosphate-dependent enzymes, and in particular, amino acid decarboxylases.[5] They are also potential precursors to new α-branched α-amino acids as building blocks for de novo peptide design.[6] Moreover, α-ethynyl amino acids are of interest as potential suicide inhibitors of glutamic acid decarboxylase; in particular, ethynylglycine (FR-900130) is a well-known natural antibiotic, and is a suicide substrate for alanine racemase.[7]

Given this background, we have focused our attention on the synthesis of β,γ-unsaturated α-methyl α-amino acids, particularly α-vinylalanine and α-ethynylalanine. To the best of our knowledge, there

* Corresponding authors. E-mail: alberto.avenoza@dq.unirioja.es

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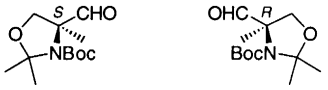
are three methods in the literature for the synthesis of racemic α-vinylalanine[8] and four strategies for the preparation of its enantiomerically pure forms,[9] while the asymmetric synthesis of (*S*)-ethynylalanine was only reported by Hegedus.[9c] The asymmetric synthesis of (*R*)-vinylalanine and (*R*)-ethynylalanine methyl esters was described by Schöllkopf using the well-known bis-lactim ether method.[10]

In this context and as a part of our research program on the synthesis of new conformationally constrained α-amino acids,[11] we have recently reported the synthesis of (*S*)- and (*R*)-2-amino-2-methylbutanoic acids starting from both enantiomers of *N*-Boc-*N,O*-isopropylidene-α-methylserinal (**1** and **2**) (Fig. 1).[12]



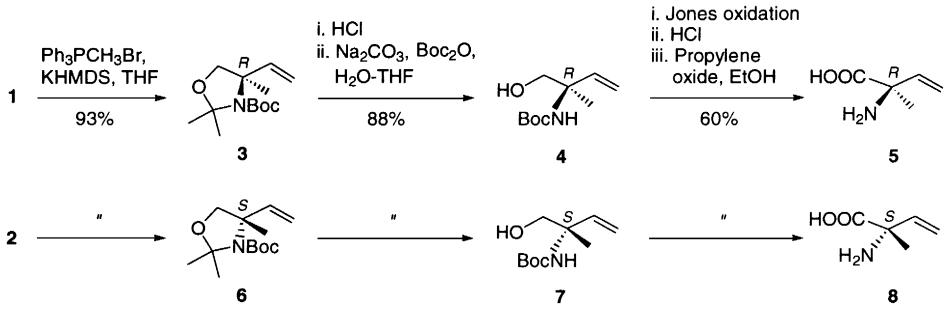
1 **2**

Fig. 1. (*S*)- and (*R*)-*N*-Boc-*N,O*-isopropylidene-α-methylserinals **1** and **2**

In this paper, in order to demonstrate the synthetic utility of both compounds **1** and **2** as chiral building blocks in the synthesis of enantiomerically pure α-substituted alanines, we now describe a more convenient synthesis of (*R*)- and (*S*)-α-vinylalanines **5** and **8** and (*R*)- and (*S*)-α-ethynylalanines **11** and **14**.

2. Results and discussion

Starting from (*S*)- and (*R*)-*N*-Boc-α-methylserinal acetonides **1** and **2**, and using six steps, we obtained both enantiomers of α-vinylalanine with an excellent overall yield (49%) (Scheme 1).



Scheme 1. Synthesis of both enantiomers of α-vinylalanine (**5** and **8**)

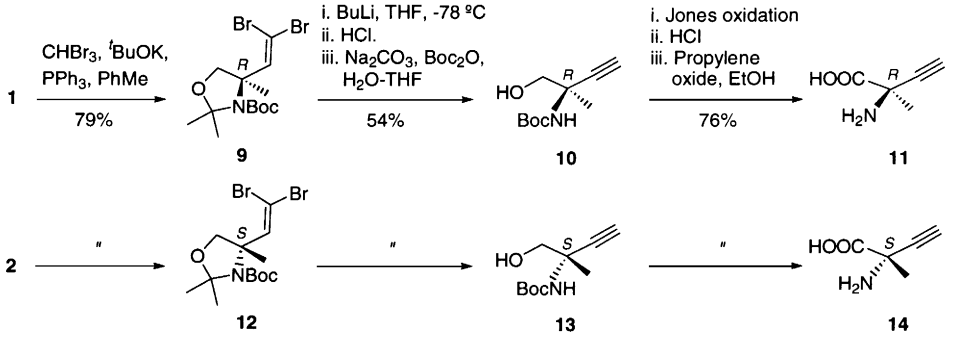
The initial step involved Wittig methylenation of (*S*)-α-methylserinal **1** and was carried out under salt-free Wittig conditions[13] using methyltriphenylphosphonium bromide and potassium bis(trimethylsilyl)amide (KHMDS) as the base, obtaining olefin **3** in 93% yield. Starting from this compound, several attempts to carry out the selective deprotection of the acetonide moiety of **3** failed (*p*-TsOH, $BF_3 \cdot AcOH$[14]). However, using $Sc(OTf)_3$ (10 mol%) as a Lewis acid catalyst[15] we obtained compound **4** in a 25% yield. All attempts to improve the yield by increasing the temperature were unsuccessful, since at 40°C we observed partial deprotection of the *N*-Boc group.

Since we could not obtain an acceptable yield via the selective cleavage of the acetonide moiety of **3**, we decided to try acid hydrolysis using hydrochloride acid. After 2 h at 25°C, the cleavage of the acetonide moiety and the hydrolysis of the *N*-Boc group took place in almost quantitative yield. The corresponding aminoalcohol hydrochloride was then protected with Boc_2O in the presence of sodium carbonate to give **4** (88% from **3**).

In order to transform this compound into the required quaternary amino acid **5**, it was oxidized with Jones' reagent,[16] hydrolyzed using a mixture of concentrated HCl and THF at room temperature and finally treated with propylene oxide in ethanol at reflux to give (*R*)-α-vinylalanine **5** in a 60% yield. The spectral data and optical activity of this compound proved to be identical to those previously reported[9c] (Scheme 1).

The enantiomer (*S*)-α-vinylalanine **8** was obtained using the same strategy but starting from (*R*)-α-methylserinal **2**. The spectral data of compound **8** were identical to those previously obtained for amino acid **5**, but with an optical rotation of opposite sign (Scheme 1).

The syntheses of (*R*)- and (*S*)-α-ethynylalanines **11** and **14** also start from (*S*)- and (*R*)-methylserinals **1** and **2**, respectively, and involve seven steps with an overall yield of 32% (Scheme 2).



Scheme 2. Synthesis of both enantiomers of α-ethynylalanine **11** and **14**

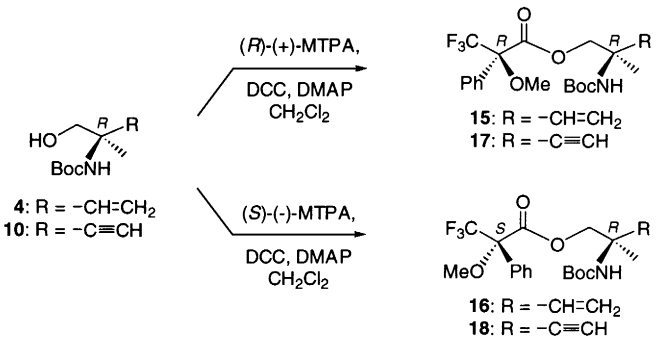
The aldehyde-to-acetylene conversion protocol can be undertaken using either of two strategies: in one step by ethynylation of the aldehyde with dimethyl-1-diazo-2-oxopropyl phosphonate[17] or in two steps using a dibromovinyl intermediate (the Corey–Fuchs strategy).[18] The literature reports that when this transformation was carried out on *N*-protected serinal acetonides, the second method gave better results.[19] We, therefore, decided to obtain the α-alkynyl-α-methylamino acids **11** and **14** by using the Corey–Fuchs transformation. In this way, (*R*)- and (*S*)-methylserinals **1** and **2** were converted into the corresponding alkynes **10** and **13**, using the vinyl intermediates **9** and **12** (Scheme 2).

Initially, we attempted the olefination of aldehyde **1** using a recently reported modification of the Corey–Fuchs method, involving the presence of Et_3N at low temperature (CBr_4, PPh_3, Et_3N, 14 h, 10°C).[20] Unfortunately, this method provided dibromoolefin **9** only in a 49% yield. We attempted the olefination using the original Corey–Fuchs conditions (CBr_4, PPh_3, Zn, 14 h, rt), obtaining dibromoolefin **9** in a 57% yield. However, the best result was obtained by preparation of the dibromomethyl phosphorane using bromoform with ^{t}BuOK in the presence of PPh_3,[21] followed by addition of aldehyde **1** at rt in toluene, giving a 79% yield of **9** and recovering a 15% yield of **1** (Scheme 2).

Treatment of dibromoolefin **9** with two equivalents of *n*-BuLi at −78°C gave the corresponding acetylene derivative, which was hydrolyzed, without purification, by the action of concentrated HCl, obtaining the 1,2-aminoalcohol hydrochloride. Protection of this compound with Boc_2O in the presence of sodium carbonate gave **10** (54% from **9**). The conversion of compound **10** into the desired (*R*)-ethynylalanine **11** was achieved in the same way as described above for the preparation of amino acid **5** from alcohol **4** (Scheme 2).

The synthesis of (*S*)-ethynylalanine **14** was performed using the same strategy described for its enantiomer **11**, but starting from aldehyde **2** (Scheme 2).

The enantiomeric purity of the intermediates in the synthesis of the four quaternary amino acids was examined by preparation of the Mosher esters of alcohols **4** and **10** (Scheme 3).



Scheme 3. Determination of enantiomeric purity of **4** and **10**

In accordance with the protocol described in the literature,[22] alcohol **4** was coupled with (*R*)-(+)- and (*S*)-(−)-methoxytrifluorophenylacetic acid [(*R*)-(+)- and (*S*)-(−)-MTPA] in the presence of DCC and DMAP to give Mosher esters **15** and **16**, respectively. Analysis of the NMR spectra of esters **15** and **16** showed that the enantiomeric purity of compound **4** was at least 96% (only one isomer was observed in the ^{1}H and ^{19}F NMR spectra). Similarly, the synthesis of Mosher esters **17** and **18** was carried out using the same methodology, but now starting from alcohol **10** (Scheme 3).

In conclusion, we have developed a methodology that offers a straightforward route to the synthesis of β,γ-unsaturated α-methyl α-amino acids. In this way, we have achieved the synthesis of four interesting quaternary α-amino acids in enantiomerically pure form: (*R*)- and (*S*)-vinylalanines **5** and **8** and (*R*)- and (*S*)-ethynylalanines **11** and **14**, thus demonstrating that (*S*)- and (*R*)-*N*-Boc-α-methylserinal acetonides **1** and **2** are valuable chiral building blocks in the enantioselective synthesis of α-methyl α-amino acids.

3. Experimental

Solvents were purified according to standard procedures. Analytical TLC was performed using Polychrom SI F_{254} plates. Column chromatography was performed using silica gel 60 (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX-300 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard and in CD_3OD with TMS as the external standard using a coaxial microtube (chemical shifts are reported in ppm on the δ scale, coupling constants in Hz). The assignment of all separate signals in the ^{1}H NMR spectra was made on the basis of coupling constants, selective proton–proton homonuclear decoupling experiments, proton–proton COSY experiments and proton–carbon HETCOR experiments. Melting points were determined on a Büchi SMP-20 melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 341 polarimeter in 1 and 0.5 dm cells of 1 and 3.4 mL capacity, respectively. Microanalyses were carried out on a CE Instruments EA-1110 analyser and are in good agreement with the calculated values. IR spectra were recorded on a Perkin–Elmer FT-IR Spectrum 1000 spectrometer.

*3.1. (R)-2-((*tert*-Butoxycarbonyl)amino)-2-methyl-3-buten-1-ol **4***

Concentrated HCl (10 mL) was added to (*R*)-*N*-(*tert*-butoxycarbonyl)-4-vinyl-2,2,4-trimethyl-3-oxazolidine **3** (274 mg, 1.13 mmol), which was previously obtained according to the procedure described by us in the literature,[12] and the solution was stirred, at rt, for 2 h. The HCl was then removed to give the corresponding 1,2-aminoalcohol as an orange oil. This compound was dissolved in (1:5) H_2O:THF (6 mL) and then $Na_2CO_3 \cdot 10H_2O$ (812 mg, 2.83 mmol) and Boc_2O (306 mg, 1.36 mmol) were added.

The mixture was stirred at rt for 14 h and the reaction was quenched with saturated NH_4Cl (10 mL) and extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by flash silica gel chromatography (hexane:ethyl acetate, 8:2) to give compound **4** (200 mg, 88%) as a white solid. Mp: 41–43°C. $[\alpha]_D^{25}$=+10.9 (*c* 1.13, MeOH); ^{1}H NMR ($CDCl_3$): δ 1.29 (s, 3H, CH_3), 1.40 (s, 9H, $(CH_3)_3C$), 3.52 (d, 1H, *J*=11.4 Hz, CH_2O), 3.59 (d, 1H, *J*=11.4 Hz, CH_2O), 4.97 (br s, 1H, NHCO), 5.12 (d, 1H, *J*=6.6 Hz, C*H*$_2$=CH), 5.17 (s, 1H, C*H*$_2$=CH), 5.85 (dd, 1H, *J*=17.1 Hz, *J*=11.1 Hz, CH_2=C*H*); ^{13}C NMR ($CDCl_3$): δ 22.8 (CH_3), 28.2 ((*C*H_3)$_3$C), 58.3 (*C*(CH$_3$)NH), 69.3 (*C*H_2O), 79.8 ((CH$_3$)$_3$*C*), 113.9 (*C*H_2=CH), 140.4 (CH_2=*C*H), 155.9 (OCON); ESI$^+$ (*m/z*)=202.3. Anal. calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 58.91; H, 10.01; N, 6.92.

*3.2. (*R*)-2-Amino-2-methyl-3-butenoic acid **5***

To a solution of compound **4** (165 mg, 0.82 mmol) in acetone (10 mL) at 0°C was added a 1.5-fold excess of Jones' reagent, drop by drop over 5 min. The mixture was stirred at 0°C for 3 h and then at rt for a further 3 h. The excess of Jones' reagent was destroyed with 2-propanol. The mixture was then diluted with water (10 mL) and extracted with ethyl acetate (4×20 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residual yellow oil (150 mg) was dissolved in THF (15 mL) and was treated with concentrated HCl (2 mL). The mixture was stirred at rt for 6 h. The solvent was removed and the residual oil partitioned between water (10 mL) and ethyl acetate (10 mL). The aqueous phase was concentrated in vacuo to give (*R*)-α-vinylalanine hydrochloride as a white solid (103 mg, 83%). This compound was dissolved in (3:1) EtOH:propylene oxide (4 mL) and the mixture heated under reflux for 2 h, after which time the amino acid partially precipitated as a white solid (35 mg). The filtrate was concentrated and the residue dissolved in distilled water and eluted through a C_{18} reverse-phase Sep-Pak cartridge to give, after removal of the water, 21 mg of (*R*)-α-vinylalanine **5** as a white solid. Total amount: 56 mg (72%, 60% from **4**). $[\alpha]_D^{25}$=−27.4 (*c* 0.62, H_2O); ESI$^-$ (*m/z*)=116.2. Anal. calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.21; H, 7.33; N, 12.20. Spectral data were identical to those reported in the literature (Ref. 9c).

*3.3. (*S*)-2-((*tert*-Butoxycarbonyl)amino)-2-methyl-3-buten-1-ol **7***

In a similar way to that described for its enantiomer **4**, compound **7** (202 mg, 88%) was obtained from oxazolidine **6** (272 mg, 1.13 mmol). $[\alpha]_D^{25}$=−10.5 (*c* 1.08, MeOH). Anal. calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96. Found: C, 59.00; H, 9.97; N, 7.01.

*3.4. (*S*)-2-Amino-2-methyl-3-butenoic acid **8***

In a similar way to that described for its enantiomer **5**, (*S*)-α-vinylalanine **8** (54 mg, 58%) was obtained from alcohol **7** (160 mg, 0.82 mmol). $[\alpha]_D^{25}$=+27.3 (*c* 0.63, H_2O). Anal. calcd for $C_5H_9NO_2$: C, 52.16; H, 7.88; N, 12.17. Found: C, 52.33; H, 7.21; N, 12.17.

*3.5. (*R*)-*N*-(tert-Butoxycarbonyl)-4-(2′,2′-dibromoethenyl)-2,2,4-trimethyl-3-oxazolidine **9***

$CHBr_3$ (2.57 g, 9.88 mmol) was rapidly added dropwise to a 1 M solution of ^{t}BuOK in THF (10 mL, 10.00 mmol) and PPh_3 (2.62 g, 9.88 mmol) in toluene (30 mL) at −20°C, followed after 15 min by aldehyde (*S*)-*N*-(*tert*-butoxycarbonyl)-4-formyl-2,2,4-trimethyl-3-oxazolidine **1** (600 mg, 2.47 mmol) in

toluene (15 mL). After 15 min, the cooling bath was removed and the reaction mixture was allowed to warm to rt. After 17 h, the reaction mixture was diluted with ethyl ether (50 mL), filtered and concentrated in vacuo. The crude product was purified by silica gel chromatography (hexane:ethyl acetate, 19:1) to give the required compound **9** (780 mg, 79%) as a colourless oil. $[\alpha]_D^{25}=-95.1$ (*c* 1.18, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.48–1.69 (m, 18H, $(CH_3)_3C$, CH_3, $(CH_3)_2C$), 3.92, 4.03 (2d, 1H, *J*=8.7 Hz, *J*=8.7 Hz, CH_2O), 4.15, 4.16 (2d, 1H, *J*=8.7 Hz, *J*=8.7 Hz, CH_2O), 6.83, 7.11 (2s, 1H, $CH{=}CBr_2$); ^{13}C NMR ($CDCl_3$): δ 22.0, 23.8, 24.8, 25.6, 26.2, 27.3 (CH_3, $(CH_3)_2C$), 28.4 ($(CH_3)_3C$), 64.2, 65.1 ($C(CH_3)N$), 72.6, 72.8 (CH_2O), 80.3, 80.5 ($(CH_3)_3C$), 86.7, 86.8 ($CH{=}CBr_2$), 94.4, 95.5 ($(CH_3)_2C$), 142.1, 142.3 ($CH{=}CBr_2$), 151.0, 151.3 (OCON); ESI^+ (*m/z*)=400.1. Anal. calcd for $C_{13}H_{21}Br_2NO_3$: C, 39.12; H, 5.30; N, 3.51. Found: C, 39.22; H, 5.28; N, 3.48.

3.6. (R)-2-((tert-Butoxycarbonyl)amino)-2-methyl-3-butyn-1-ol **10**

A solution of oxazolidine **9** (304 mg, 0.76 mmol) in THF (15 mL) was cooled at −78°C and a 2 M solution of *n*-BuLi in hexane (0.8 mL, 1.60 mmol) was added dropwise. After 3.5 h, the cooling bath was removed, the mixture was quenched with saturated NH_4Cl (10 mL) and extracted with ethyl acetate (2×20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Concentrated HCl (10 mL) was added to this mixture and the solution was stirred, at rt, for 2 h. The HCl was then removed to give the corresponding aminoalcohol (orange oil). This compound was dissolved in (1:5) H_2O:THF (6 mL) and then $Na_2CO_3\cdot 10H_2O$ (545 mg, 1.90 mmol) and Boc_2O (206 mg, 0.91 mmol) were added to the solution. The mixture was stirred at rt for 14 h. The reaction was quenched with saturated NH_4Cl (10 mL) and extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by flash silica gel chromatography (hexane:ethyl acetate, 7:3) to give compound **10** (82 mg, 54%) as a yellow oil. $[\alpha]_D^{25}=-9.4$ (*c* 1.05, MeOH); ^1H NMR ($CDCl_3$): δ 1.42 (s, 9H, $(CH_3)_3C$), 1.51 (s, 3H, CH_3), 2.37 (s, 1H, C≡CH), 3.50 (br s, 1H, OH), 3.63 (d, 1H, *J*=10.8 Hz, CH_2O), 3.74 (d, 1H, *J*=10.8 Hz, CH_2O), 5.12 (br s, 1H, NHCO); ^{13}C NMR ($CDCl_3$): δ 24.2 (CH_3), 28.3 ($(CH_3)_3C$), 52.2 ($C(CH_3)NH$), 69.4 (CH_2O), 71.3 (C≡CH), 80.4 ($(CH_3)_3C$), 84.4 (C≡CH), 155.2 (OCON); ESI^+ (*m/z*)=200.2. Anal. calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.39; H, 8.88; N, 7.13.

3.7. (R)-2-Amino-2-methyl-3-butynoic acid **11**

To a solution of alcohol **10** (95 mg, 0.48 mmol) in acetone (10 mL) at 0°C a 1.5-fold excess of Jones' reagent was added, drop by drop, over 5 min. The mixture was stirred at 0°C for 3 h and then at rt for a further 3 h. The excess of Jones' reagent was destroyed with 2-propanol. The mixture was then diluted with water (10 mL) and extracted with ethyl acetate (4×20 mL). The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated in vacuo. The residual yellow oil (82 mg) was dissolved in THF (15 mL) and was treated with concentrated HCl (2 mL). The mixture was stirred at rt for 6 h. The solvent was removed and the residual oil partitioned between water (10 mL) and ethyl acetate (10 mL). The aqueous phase was concentrated in vacuo to give (*R*)-α-ethynylalanine hydrochloride as a white solid (57 mg). This compound was dissolved in (3:1) EtOH:propylene oxide (4 mL) and the mixture heated under reflux for 2 h after which time the amino acid partially precipitated as a white solid (15 mg). The filtrate was concentrated, the residue dissolved in distilled water and eluted through a C_{18} reverse-phase Sep-Pak cartridge to give, after removal of the water, 26 mg of (*R*)-α-ethynylalanine **11** as a white solid. Total amount: 41 mg (76%). $[\alpha]_D^{25}=-43.1$ (*c* 0.74, H_2O); ESI^- (*m/z*)=114.2. Anal.

calcd for $C_5H_7NO_2$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.44; H, 7.05; N, 13.09. Spectral data were identical to those reported in the literature (Ref. 9c).

*3.8. (*S*)-*N*-(*tert*-Butoxycarbonyl)-4-(2′,2′-dibromoethenyl)-2,2,4-trimethyl-3-oxazolidine* ***12***

In a similar way to that described for its enantiomer **9**, compound **12** (783 mg, 79%) was obtained from aldehyde **2** (602 mg, 2.47 mmol). $[\alpha]_D^{25}$=+96.0 (*c* 1.06, $CHCl_3$). Anal. calcd for $C_{13}H_{21}Br_2NO_3$: C, 39.12; H, 5.30; N, 3.51. Found: C, 39.25; H, 5.39; N, 3.55.

*3.9. (*S*)-2-((*tert*-Butoxycarbonyl)amino)-2-methyl-3-butyn-1-ol* ***13***

In a similar way to that described for its enantiomer **10**, compound **13** (80 mg, 54%) was obtained from oxazolidine **12** (303 mg, 0.76 mmol). $[\alpha]_D^{25}$=+10.0 (*c* 1.05, MeOH). Anal. calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.36; H, 8.90; N, 7.10.

*3.10. (*S*)-2-Amino-2-methyl-3-butynoic acid* ***14***

In a similar way to that described for its enantiomer **11**, (*S*)-α-ethynylalanine **14** (39 mg, 73%) was obtained from alcohol **13** (94 mg, 0.48 mmol). $[\alpha]_D^{25}$=+43.4 (*c* 0.78, H_2O). Anal. calcd for $C_5H_7NO_2$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.53; H, 6.96; N, 12.98.

*3.11. (2*R*,2′*R*)-2′-((*tert*-Butoxycarbonyl)amino)-2′-methyl-3′-butenyl 2-methoxy-2-(trifluoromethyl)-2-phenylacetate* ***15***

To a solution of alcohol **4** (20 mg, 0.20 mmol), DCC (41 mg, 0.20 mmol) and DMAP (2.5 mg, 0.02 mmol) in dry CH_2Cl_2 (6 mL) was added a solution of (*R*)-(+)-MTPA (52 mg, 0.22 mmol) in dry CH_2Cl_2 (4 mL). After stirring the mixture at rt for 6 h, the resulting white suspension was filtered to remove the *N*,*N*′-dicyclohexylurea. The filtrate was concentrated in vacuo to give a white slurry, to which Et_2O was added. The resulting suspension was filtered to remove the acylurea and the solvent was evaporated. The residue was purified by column chromatography (hexane:ethyl acetate, 7:3) to give **15** (51 mg, 65%) as an oil. $[\alpha]_D^{25}$=+31.0 (*c* 1.43, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 3H, CH_3), 1.40 (s, 9H, $(CH_3)_3C$), 3.53 (s, 3H, OCH_3), 4.44 (d, 1H, *J*=10.8 Hz, CH_2O), 4.59 (d, 1H, *J*=10.8 Hz, CH_2O), 4.60 (br s, 1H, NHCO), 5.14 (d, 1H, *J*=7.2 Hz, C*H*$_2$=CH), 5.18 (br s, 1H, C*H*$_2$=CH), 5.90 (dd, 1H, *J*=17.4 Hz, *J*=10.8 Hz, CH_2=C*H*), 7.40 (m, 3H, Ph), 7.51 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$): δ 22.8 (CH_3), 28.3 ((*C*H_3)$_3$C), 55.4 (*C*(CH_3)NH), 55.5 (OCH_3), 68.9 (CH_2O), 79.7 ((CH$_3$)$_3$*C*), 114.7 (*C*H_2=CH), 121.3 (*C*(CF_3)), 125.2 (CF_3), 127.4, 128.4, 129.6, 132.0 (Ph), 139.4 (CH_2=*C*H), 154.2 (OCON), 166.1 (*C*CO_2CH_2); ^{19}F NMR ($CDCl_3$): δ −71.8; ESI$^+$ (*m/z*)=418.3. Anal. calcd for $C_{20}H_{26}F_3NO_5$: C, 57.55; H, 6.28; N, 3.36. Found: C, 56.92; H, 6.62; N, 3.43.

*3.12. (2*S*,2′*R*)-2′-((*tert*-Butoxycarbonyl)amino)-2′-methyl-3′-butenyl 2-methoxy-2-(trifluoromethyl)-2-phenylacetate* ***16***

In a similar way to that described for compound **15**, Mosher ester **16** (54 mg, 69%) was obtained from alcohol **4** (22 mg, 0.20 mmol) and (*S*)-(−)-MTPA (52 mg, 0.22 mmol). $[\alpha]_D^{25}$=−22.2 (*c* 0.82, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 3H, CH_3), 1.40 (s, 9H, $(CH_3)_3C$), 3.53 (s, 3H, OCH_3), 4.39 (d, 1H, *J*=10.8 Hz, CH_2O), 4.58 (br s, 1H, NHCO), 4.63 (d, 1H, *J*=10.8 Hz, CH_2O), 5.13 (d, 1H, *J*=5.4 Hz,

C*H*$_2$=CH), 5.18 (d, 1H, *J*=1.5 Hz, C*H*$_2$=CH), 5.91 (dd, 1H, *J*=17.4 Hz, *J*=10.8 Hz, CH$_2$=CH), 7.40 (m, 3H, Ph), 7.51 (m, 2H, Ph); ^{13}C NMR (CDCl$_3$): δ 22.7 (CH$_3$), 28.3 ((*C*H$_3$)$_3$C), 55.4 (*C*(CH$_3$)NH), 55.5 (OCH$_3$), 69.0 (CH$_2$O), 79.7 ((CH$_3$)$_3$*C*), 114.7 (*C*H$_2$=CH), 121.3 (*C*(CF$_3$)), 125.2 (CF$_3$), 127.4, 128.4, 129.6, 132.0 (Ph), 139.4 (CH$_2$=*C*H), 154.2 (OCON), 166.1 (*C*CO$_2$CH$_2$); ^{19}F NMR (CDCl$_3$): δ −71.8; ESI$^+$ (*m/z*)=418.3. Anal. calcd for $C_{20}H_{26}F_3NO_5$: C, 57.55; H, 6.28; N, 3.36. Found: C, 56.90; H, 6.57; N, 3.49.

*3.13. (2*R*,2′*R*)-2′-((*tert*-Butoxycarbonyl)amino)-2′-methyl-3′-butynyl 2-methoxy-2-(trifluoromethyl)-2-phenylacetate **17***

In a similar way to that described for compound **15**, Mosher ester **17** (51 mg, 61%) was obtained from alcohol **10** (19 mg, 0.20 mmol) and (*R*)-(+)-MTPA (51 mg, 0.22 mmol). $[\alpha]_D^{25}$=+32.2 (*c* 0.95, CHCl$_3$); ^{1}H NMR (CDCl$_3$): δ 1.42 (s, 9H, (CH$_3$)$_3$C), 1.54 (s, 3H, CH$_3$), 2.37 (s, 1H, C≡CH), 3.55 (s, 3H, OCH$_3$), 4.50 (d, 1H, *J*=10.8 Hz, CH$_2$O), 4.69 (d, 1H, *J*=10.8 Hz, CH$_2$O), 4.70 (br s, 1H, NHCO), 7.41 (m, 3H, Ph), 7.53 (m, 2H, Ph); ^{13}C NMR (CDCl$_3$): δ 24.6 (CH$_3$), 28.2 ((*C*H$_3$)$_3$C), 49.7 (*C*(CH$_3$)NH), 55.4 (OCH$_3$), 68.5 (CH$_2$O), 71.8 (C≡*C*H), 80.4 ((CH$_3$)$_3$*C*), 82.9 (*C*≡CH), 121.3 (*C*(CF$_3$)), 125.1 (CF$_3$), 127.4, 128.4, 129.7, 132.0 (Ph), 153.7 (OCON), 165.9 (*C*CO$_2$CH$_2$); ^{19}F NMR (CDCl$_3$): δ −71.9; ESI$^+$ (*m/z*)=416.2. Anal. calcd for $C_{20}H_{24}F_3NO_5$: C, 57.83; H, 5.82; N, 3.37. Found: C, 57.02; H, 6.10; N, 3.48.

*3.14. (2*S*,2′*R*)-2′-((*tert*-Butoxycarbonyl)amino)-2′-methyl-3′-butynyl 2-methoxy-2-(trifluoromethyl)-2-phenylacetate **18***

In a similar way to that described for compound **16**, Mosher ester **18** (46 mg, 55%) was obtained from alcohol **10** (20 mg, 0.20 mmol) and (*S*)-MTPA (50 mg, 0.22 mmol). $[\alpha]_D^{25}$=−28.0 (*c* 1.18, CHCl$_3$); ^{1}H NMR (CDCl$_3$): δ 1.43 (s, 9H, (CH$_3$)$_3$C), 1.52 (s, 3H, CH$_3$), 2.37 (s, 1H, C≡CH), 3.55 (s, 3H, OCH$_3$), 4.50 (d, 1H, *J*=10.8 Hz, CH$_2$O), 4.67 (br s, 1H, NHCO), 4.71 (d, 1H, *J*=10.8 Hz, CH$_2$O), 7.41 (m, 3H, Ph), 7.53 (m, 2H, Ph); ^{13}C NMR (CDCl$_3$): δ 24.6 (CH$_3$), 28.2 ((*C*H$_3$)$_3$C), 49.8 (*C*(CH$_3$)NH), 55.5 (OCH$_3$), 68.5 (CH$_2$O), 71.8 (C≡*C*H), 80.4 ((CH$_3$)$_3$*C*), 82.9 (*C*≡CH), 121.3 (*C*(CF$_3$)), 125.1 (CF$_3$), 127.4, 128.4, 129.7, 132.0 (Ph), 153.7 (OCON), 165.8 (*C*CO$_2$CH$_2$); ^{19}F NMR (CDCl$_3$): δ −71.9; ESI$^+$ (*m/z*)=416.2. Anal. calcd for $C_{20}H_{24}F_3NO_5$: C, 57.83; H, 5.82; N, 3.37. Found: C, 57.21; H, 6.06; N, 3.50.

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