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Synthesis of enantiomerically enriched β,γ-unsaturated-α-amino acids

Nicholas G. W. Rose, Mark A. Blaskovich, Alex Wong and Gilles A. Lajoie*

Department of Chemistry, University of Waterloo, Waterloo, Ontario, Canada N2L 3G1

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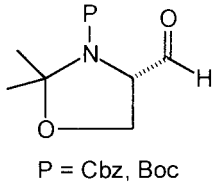
Abstract—A variety of enantiomerically enriched β,γ-unsaturated-α-amino acids are synthesized by olefination of a Cbz-protected serine aldehyde equivalent, readily prepared from serine. A cyclic *ortho* ester protecting group is employed to minimize racemization. The deprotected amino acids are obtained in good yield, ranging from 70–95% ee, with double-bond geometry determined by the type of Wittig reagent used. Isotopically labeled side chains are readily introduced by this procedure, and free γ-^{13}C-vinylglycine was prepared in 44% yield from the protected serine aldehyde synthon.

1. Introduction

β,γ-Unsaturated-α-amino acids **1**, otherwise known as the vinylglycines, have been isolated from a variety of natural sources.[1] There is considerable interest in their biological activity, in particular their ability to act as suicide substrates or mechanistic probes of pyridoxal phosphate (PLP) dependent enzymes.[2] These enzymes are a vital link in many biosynthetic pathways as they are involved in catalyzing chemical changes at the α-, β-, or γ-carbons of amino acids. In addition, β,γ-unsaturated-α-amino acids sometimes possess antimicrobial activity,[3] can be useful synthetic intermediates,[4] and can serve as conformationally restricted analogs of common amino acids for structure-activity relationship studies.

The β,γ-unsaturated-α-amino acids pose a synthetic challenge, primarily due to the tendency of these compounds to isomerize to the conjugated α,β-unsaturated derivatives. A number of routes to racemic β,γ-unsaturated-α-amino acids have been reported.[2j,5] Racemic vinylglycine itself was first synthesized in 1974 by a Strecker synthesis,[6] while a number of efficient syntheses of optically active vinylglycine have been published since 1980.[7] However, most procedures rely upon the degradation of an amino acid, so isotopic labeling is difficult, and no ^{13}C-labeled compounds have been reported. More versatile procedures for preparing a number of β,γ-unsaturated-α-amino acids have also appeared.[8] Probably the most effective synthetic route makes use of a Wittig olefination of the serine derived Garner aldehyde **2** to generate a β,γ-unsaturated amino alcohol.[9a] An oxidation step is then required to generate the amino acid, limiting the type of side chain functional groups which can be present.[9b–d] A variation of this strategy employs a cysteine derived *N*-acylthiazolidinone as the cyclic aldehyde; much milder oxidation conditions are required to regenerate the acid moiety.[10]

1



P = Cbz, Boc

2

We have recently described the development of a new strategy for the synthesis of a variety of classes of amino acids, based upon the elaboration of an optically active serine-derived aldehyde in which the optical integrity is maintained by a cyclic ortho ester carboxyl protecting group.[11–14] These syntheses have previously utilized the 9-fluorenylmethoxycarbonyl (Fmoc) group for amine protection. While this base sensitive moiety is stable to the reaction of the serine aldehyde with stabilized ylides,[11] it is quickly cleaved during attempts at reaction with unstabilized reagents. We now report the olefination of the corresponding benzyloxycarbonyl (Cbz) protected serine derived aldehyde with a number of Wittig-type reagents and under both Nozaki[15] and Peterson[16] conditions.

2. Results

Cbz-L-serine **4** was readily converted to the Cbz protected 4-methyl-2,6,7-trioxabicyclo[2.2.2] ortho (OBO) ester **6** and oxidized to the aldehyde **7** under conditions identical

Keywords: vinylglycines; olefination; α-amino acid.

* Corresponding author. Tel.: +519-888-4620; fax: +519-746-0435; e-mail: glajoie@uwaterloo.ca

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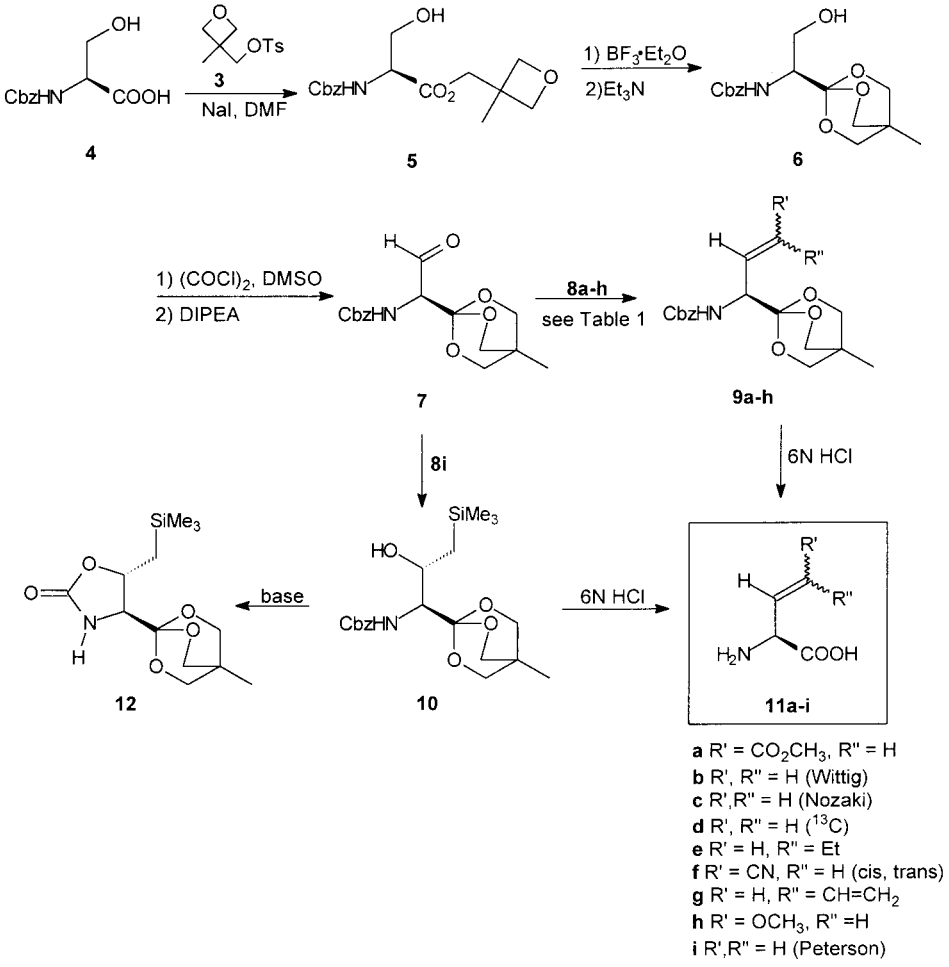

Scheme 1.

to those employed for the analogous Fmoc-protected compounds (Scheme 1).[11,13] The Cbz-protected alcohol **6** and aldehyde **7** crystallize more easily than the corresponding Fmoc compound and is obtained in high ee (>95%).[11] The Boc-protected compounds were also prepared, but were obtained in reduced yields and as oils.[13]

Reaction of the Cbz aldehyde **7** with the stabilized ylide $Ph_3P{=}CH{-}CO_2CH_3$ gave the desired olefin **9a** in 77% yield from **6**, with a ratio better than 95:5 *E*:*Z* geometry. Unfortunately, deprotection to give the highly unstable[9a,17] free β,γ-unsaturated glutamic acid was unsuccessful. Attempts to react the aldehyde **7** with unstablized ylides initially focussed on the simplest reagent, methylenetriphenylphosphorane, which leads to protected vinylglycine **9b**. A variety of ylide generation conditions were explored ($NaNH_2$/DMSO, $NaNH_2$/THF, NaH/DMSO, *n*-BuLi/DMSO, *n*-BuLi/THF), with minimal success. However, KO*t*-Bu/Et_2O, recommended as the best base to methylenate sterically hindered ketones with triphenylmethylphosphorane,[18] gave good yields (71%) of the alkene adduct **9b**. Both the Boc and Fmoc-protected aldehydes could be olefinated under these conditions, albeit with reduced yields (54% and 6%, respectively).

Table 1. Olefination reactions with protected aldehyde **7**

Entry	Reagent	Product	*E*:*Z*	Yield (%)	ee (%)[a]
1	**8a** $Ph_3P{=}CHCO_2CH_3$	**9a**–CH=$CHCO_2CH_3$	>95:<5	77[b]	>95
2	**8b** $Ph_3P^+{-}CH_3Br^-$	**9b**–CH=CH_2	–	71[b]	77
3	**8c** $AlMe_3/CH_2I_2/Zn$	**9c**–CH=CH_2	–	76[b]	86
4	**8d** $Ph_3P^+{-}{}^{13}CH_3Br^-$	**9d**–CH=$^{13}CH_2$	–	71[b]	72
5	**8e** $Ph_3P^+{-}CH_2EtBr^-$	**9e**–CH=CH–Et	17:83	64[b]	72
6	**8f** $(EtO)_2P(O){-}CH_2CN$	**9f**–CH=CH–CN	78:22	71[b]	–
7	**8g** $Ph_3P^+{-}CH_2CH{=}CH_2Br^-$	**9g**–CH=CH–CH=CH_2	92:8	55[b]	–
8	**8h** $Ph_3P^+{-}CH_2OCH_3$	**9h**–CH=CH_2–OCH_3	63:37	35[b]	–
9	**8i** $TMSCH_2MgCl$	**11i**–CH=CH_2	–	53[c]	>95

[a] %ee determined after deprotection.
[b] Yields after two steps.
[c] Yields after three steps.

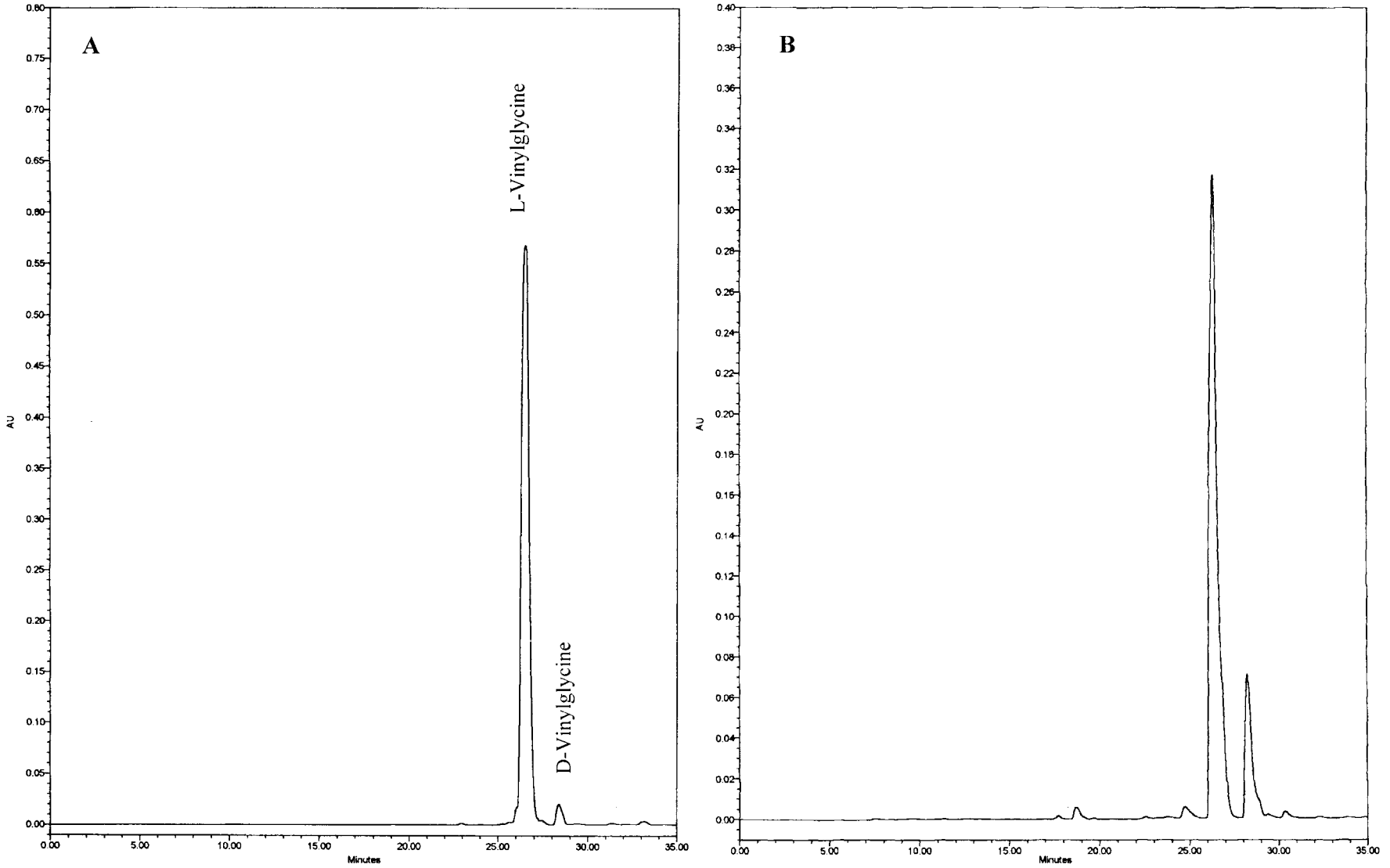

Figure 1. Assessment of enantiomeric purity of L-vinylglycine obtained after deprotection of (A) Cbz-L-Ser(CH_2TMS)–OBO ester **10** after ion exchange purification (B) Cbz-L-Gly(–CH═CH_2)–OBO ester **9b** after ion exchange purification. Amino acid samples were prepared as described in Section 5.

The KO*t*Bu/Et_2O conditions were employed to generate a number of other unstabilized and semistabilized ylides, including ^{13}C-labeled methylenetriphenylphosphorane (Table 1). Reaction with the Cbz-protected aldehyde produced the alkenes **9e–h** in 35–71% yield from **6**, with the double bond geometry corresponding to that expected for the nature of the reagent: unstabilized ylides adding with *cis* stereoselectivity (entry 5) while semistabilized reagents produced predominantly *trans* isomers (entries 6–8). In most cases the two isomers were readily separable by flash chromatography with *cis* possessing a lower R_f than the *trans* isomer.

Methylenation of the Cbz protected serine aldehyde **7** under Nozaki conditions ($AlMe_3/CH_2I_2/Zn$)[15] gave protected vinylglycine **9b** in both good yield (76%) and ee (86%) as determined by derivatization and subsequent HPLC analysis described previously.[11]

Formation of the terminal alkene **9b** under Peterson olefination conditions was also investigated. The β-hydroxyalkylsilane **10** was generated by Grignard reaction of trimethylsilylmethylene magnesium chloride with serine aldehyde **7** and proceeded in quantitative yield with *threo* stereochemistry as previously reported.[11,13a] Base mediated elimination failed to afford the desired olefin **9b** giving instead oxazolidinone **12** as a single diastereomer in high yield regardless of base used, temperature or length of reaction. On the other hand, acid promoted elimination and simultaneous deprotection of β-hydroxyalkylsilane **10** gave vinylglycine **11i** ($R'=R''=H$) in good yield (74%) with little epimerization (>95% ee) providing a route to isotopically labeled vinylglycine by incorporating the label in trimethylsilylmethylene magnesium chloride.

2.1. Deprotection

Removal of the protecting groups from **9b** with TMSI, under conditions successfully used to deprotect Fmoc/OBO ester protected serine[11] (neat TMSI, 80°C, 20 h, aqueous NaOH workup, cation exchange column), led to nearly quantitative conversion to α-aminobutyric acid. This was identified by comparison to authentic material by TLC, HPLC and ^1H and ^{13}C NMR. The α-aminobutyric acid was racemic as determined by both chiral HPLC analysis of the derivatized amino acid and by optical rotation. A variety of modified conditions were explored, including fewer equivalents of TMSI, dilution with CH_2Cl_2, reduced reaction temperature, and in situ generated TMSI. The optimum conditions (7 equiv. of TMSI diluted in CH_2Cl_2 at room temperature) produced the desired vinylglycine **11** ($R'=R''=H$), but still resulted in 10% α-aminobutyric acid contamination. Derivatization with *o*-phthalaldehyde and *N*-*i*-Bu-L-cysteine followed by HPLC analysis[20] showed that the α-aminobutyric acid was racemic, but the vinylglycine possessed approximately 70% ee (Fig. 1).[21]

Acid hydrolysis with refluxing 6N HCl has previously been used to deprotect Cbz protected methyl[7a] or isopropyl esters[7e] of vinylglycine in good yield. When the same conditions were applied to Cbz-vinylglycine-OBO ester **9b** the free amino acid **11** ($R'=R''=H$) was obtained in 72% yield with 71% ee when derived through Wittig olefination and 76% yield with 86% ee via Nozaki olefination. Unfortunately, recrystallization of the protected intermediate **9b** does not result in enrichment of optical purity, in contrast to the resolution achieved by recrystallizing partially racemic Cbz-vinylglycine benzyl ester.[7h] A similar optical purity was observed with the deprotected substituted γ-ethylvinylglycine.

Since Cbz cleavage is quantitative, purification on an anion exchange column instead of a cation exchange column allows for the easy separation of any non-hydrolyzed ester. The anion exchange column also has the advantage that the only exposure of the deprotected vinylglycine to base is during the very brief neutralization while the sample is loaded onto the column.

3. Discussion

The partial racemization observed with unstabilized ylides occurs during carbonyl addition, as the aldehyde is known to be enantiomerically pure and the deprotection and derivatization reactions have been shown to cause minimal racemization.[11]

Nevertheless, this procedure has certain advantages over use of the Garner aldehyde, in that no oxidation step is required following alkene formation. The side chain must only be resistant to acid hydrolysis. It should be noted that the Garner aldehyde does not always lead to enantiomerically pure products; in fact with methylenetriphenylphosphorane generated by *n*-BuLi/THF, the alkene is obtained in 27% yield and 69% ee;[9a] with KH/benzene, racemic material is obtained.[22] It is unclear why the propyltriphenylphosphorane derived ylide gives a product with 70% ee when reacted with the Cbz/OBO ester protected aldehyde, while giving a product with a reported >95% ee when reacted with the Garner aldehyde. Nozaki conditions give the protected vinylglycine in good yield but partial racemization is observed.

Attempts at base mediated Peterson olefination consistently resulted in formation oxazolidinone **12** in high yield regardless of base used. This may be explained by the requirement of the β-hydroxysilane to adopt the *syn* confirmation which is not easily achieved due to steric considerations whereas oxazolidinone formation does not suffer from this constraint. This is in contrast to the recently reported synthesis of (*S*)-2-amino-(*Z*)-3,5-hexadecanoic acid in which conjugation is installed through base-mediated elimination of the Peterson olefination addition product.[19] In this case the diene system does not suffer from this limitation.

The production of α-aminobutyric acid during attempts at deprotection of Cbz-vinylglycine-OBO ester with TMSI appears to be due to the presence of trace amounts of HI, which may add to the isomerized α,β-unsaturated alkene bond following OBO ester ring-opening. However, the use of 6N HCl to remove both the OBO and Cbz protecting groups proved to be very successful in giving excellent yield of vinylglycines.

4. Conclusions

We have demonstrated the ability of the serine derived aldehyde OBO ester synthon to provide entry to another class of amino acids, the vinylglycines, through olefination with a variety of reagents. Partial racemization (10–15%) with Wittig-type reagents occurs during the alkene formation, but this disadvantage is balanced by the possibilities of being able to readily synthesize a variety of unusual highly functionalized molecules, including isotopically labeled compounds that are of immense interest in mechanistic enzymology. With the Peterson olefination conditions, vinylglycine can be obtained in excellent yield and optical purity.

5. Experimental

5.1. General methods

Cbz-L-Serine was purchased from Advanced Chemtech and most other reagents from Aldrich Chemical Company and were used without further purification with the following exceptions. Zn dust was washed several times with 5% hydrochloric acid, washed with copious amounts of water, followed by methanol, then ether and dried under high vacuum. CH_2Cl_2, DMSO, and DIPEA were distilled from CaH_2; THF and Et_2O from Na/benzophenone. Reactions were carried out under Ar in glassware dried overnight at 120°C or flame dried before use.

NMR spectra were recorded in $CDCl_3$ (referenced to TMS at 0.00 ppm for ^1H, to $CDCl_3$ at 77.00 ppm for ^{13}C) or D_2O (referenced to 2,2,3,3-d_4-3-(trimethylsilyl)propionic acid at 0.00 ppm for both ^1H and ^{13}C) on a Bruker AC-200, AM-250 or AM-300 spectrometer. $CDCl_3$ used for NMR samples containing an ortho ester was prefiltered through basic alumina to remove traces of acid. IR spectra were recorded on a Bomem MB-100 FT–IR spectrophotometer. Optical rotations were measured on a Jasco DIP-360 digital polarimeter. Melting points were determined on a Mel-Temp apparatus in an open capillary tube and are uncorrected. Low and high-resolution mass spectral analyses were carried out by Gaston Boulay at the Université de Sherbrooke. For deprotected amino acids, a low resolution mass was obtained on a Kratos MALDI 3 matrix assisted laser desorption time of flight mass spectrometer. Samples were prepared using 1 μL of a 1 nmol/μL solution, mixed on the sample slide with sinapinic acid. The sodium (M^+=23), potassium (M^+=39), and sinapinic acid (MH^+=225, MH^+-18=207) peaks were used as internal mass calibrants. Standard positive ion mode was used for most samples for maximum sensitivity; for those compounds with molecular weights close to matrix peaks reflectron mode was used to increase resolution. Elemental analyses were determined by M-H-W Laboratories in Phoenix, Arizona. HPLC analyses were performed using a Waters 600E System Controller with Waters 600 Multi-solvent Delivery System, Model 481 or 486 Variable Wavelength UV/Vis Detector, and Waters 745 Data Module. TLC was carried out on Merck aluminum backed silica gel 60 F_{254}, with visualization by UV, ninhydrin solution (2% in EtOH), or I_2. TLC solvent systems commonly used: A, 1:1 EtOAc/hex; B, 3:1 EtOAc/hex; C, 1:1:1:1 H_2O/EtOAc/*n*-BuOH/MeOH.

5.1.1. 3-Methyl-3-(toluenesulfonyloxymethyl)oxetane, oxetane tosylate, 3. A dry, 1 L round-bottomed flask was charged with toluene-4-sulfonyl chloride (57.20 g, 0.3 mol) to which pyridine (250 mL) was added whilst stirring under nitrogen. The reaction flask was placed inside a container to which an ice/water mixture could be added in the event that the reaction became too exothermic. 3-Methyl-3-oxetane-methanol (20.4 g, 0.2 mol) was then added slowly and the mixture stirred for 1.5 h. The mixture was then slowly added to a vigorously stirring mixture of de-ionized water (700 mL) and crushed ice (700 g) in a 2 L Erlenmeyer flask and allowed to stir for an additional 0.5 h. The white precipitate was then collected on Whatman filter paper #1 and washed with cold H_2O. The product was dried under high vacuum and/or P_2O_5 to obtain the white powder of oxetane tosylate **3** (49.11 g, 92%). Mp 49.5–51°C. TLC (3:2, Hex/EtOAc) R_f=0.42; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.81 (d, J=8.2 Hz, 2H), 7.37 (d, J=8.2 Hz, 2H), 4.37 (m, 4H), 4.11 (s, 2H), 2.46 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 145.1, 132.8, 129.9, 127.9, 78.9, 74.2, 39.3, 21.6, 20.6. HRMS (FAB) calcd for ($M+H^+$) $C_{12}H_{16}O_4S$ 256.0769, found 256.0774. Anal. Calcd for $C_{12}H_{16}O_4S$: C, 56.23; H, 6.29. Found: C, 56.33; H, 6.44.

5.1.2. *N*-(Benzyloxycarbonyl)-L-serine-3-methyl-3-hydroxymethyl-oxetane ester, Cbz-L-Ser-oxetane ester, 5. Cbz-L-Ser **4** (11.36 g, 0.047 mol) and Cs_2CO_3 (9.19 g, 0.028 mol) were combined and dissolved in H_2O (100 mL). The water was then removed in vacuo and the resulting oil was lyophilized for 12 h to give a white foam. To this foam was added oxetane tosylate (12.65 g, 0.049 mol) and NaI (1.41 g, 9.8 mmol) which was then taken up in DMF (400 mL) and allowed to stir under Ar for 48 h. The DMF was then removed in vacuo and the resulting solid dissolved in EtOAc (600 mL) and H_2O (200 mL) and extracted with 10% $NaHCO_3$ (2×100 mL), saturated NaCl (100 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield a yellow oil which was recrystallized from ethyl acetate and hexanes to yield colourless rod-like crystals in 78% yield (11.85 g). Mp 70–70.5°C; $[\alpha]^{20}_D$=+76.1 (c=0.5, H_2O); TLC (Solvent A), R_f=0.34; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.35 (s, 5H), 5.89 (d, J=7.4 Hz, 1H), 5.12 (s, 2H), 4.55–4.39 (m, 6H), 4.14–4.06 (m, 1H), 4.11 (d, J=11.2 Hz, 1H), 3.92–3.78 (m, 1H), 3.12 (t, J=6.0 Hz, 1H), 1.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 170.6, 156.2, 136.1, 128.5, 128.2, 128.1, 79.4, 69.0, 67.1, 63.3, 56.4, 39.6, 20.7; IR (cast from CH_2Cl_2) 3371 (br m), 3064 (vw), 3034 (vw), 2956 (m), 2879 (m), 1723 (s), 1525 (m), 1457 (w), 1339 (m), 1214 (m), 1195 (m), 1061 (m), 978 (w), 834 (w), 744 (w), 699 (w) cm^{-1}; MS (CI, CH_4) m/z 324 (MH^+, 100), 306 (MH^+-18, 76), 293 (MH^+-31, 65), 280 (MH^+-44, 29); HRMS (CI, CH_4) Calcd for $C_{16}H_{22}O_6N$: 324.1447. Found: 324.1454 (MH^+); Anal. Calcd for $C_{16}H_{21}O_6N$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.51; H, 6.57; N, 4.36.

5.1.3. 1-[*N*-(Benzyloxycarbonyl)-(1*S*)-1-amino-2-ethanol]-4-methyl-2,6,7-trioxa-bicyclo[2.2.2]octane, Cbz-L-Ser-OBO ester, 6. Cbz-Ser oxetane ester **5** (15.0 g,

46.2 mmol) was dissolved in dry CH_2Cl_2 (450 mL) and cooled to 0°C under Ar. $BF_3{\cdot}Et_2O$ (0.11 mL, 0.93 mmol) was diluted in CH_2Cl_2 (5.0 mL) and added to the reaction flask after which the reaction was allowed to warm up to room temperature. After 6 h, Et_3N (1.29 mL, 9.25 mmol) was added and the reaction was stirred for an additional 30 min before being concentrated to a thick oil. The crude product was redissolved in EtOAc (400 mL) and washed with 3% NH_4Cl (2×250 mL), 10% $NaHCO_3$ (100 mL), saturated NaCl (250 mL), dried ($MgSO_4$), and evaporated to dryness. The reaction yielded a colourless thick oil in 95% (14.2 g) yield was crystallized from EtOAc to give rod-like shiny crystals in 93% (13.6 g) yield. Mp=103.5–105.0°C; $[\alpha]^{20}_D=-24.8$ (c=1.00, EtOAc); TLC (3:1 EtOAc/hexane), R_f=0.37; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.36–7.31 (m, 5H), 5.34 (br d, J=8.8 Hz, 1H), 5.17–5.11 (m, 2H), 3.94–3.83 (m, 2H), 3.91 (s, 6H), 3.71–3.67 (m, 1H), 2.60 (br s, 1H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 156.3, 136.4, 128.4, 128.0, 127.9, 108.0, 72.7, 66.9, 61.9, 55.3, 30.5, 14.2; IR (cast from CH_2Cl_2) 3407 (br m), 3063 (vw), 3033 (vw), 2948 (m), 2883 (m), 1716 (s), 1607 (vw), 1586 (vw), 1527 (m), 1399 (m), 1352 (m), 1237 (m), 1048 (s), 1010 (s), 990 (m), 885 (w), 773 (w), 743 (w), 699 (w) cm^{-1}; MS (CI, CH_4) m/z 324 (MH^+, 100), 316 (MH^+-8, 73); HRMS (CI, CH_4) Calcd for $C_{16}H_{22}O_6N$: 324.1447. Found: 324.1435 (MH^+); Anal. Calcd for $C_{16}H_{21}O_6N$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.43; H, 6.64; N, 4.34.

5.1.4. 1-[*N*-(Benzyloxycarbonyl)-(1*S*)-1-amino-2-oxoethyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane, Cbz-L-Ser(ald)-OBO ester, 7. Cbz-Ser OBO ester **6** (9.04 g, 27.86 mmol) was dissolved in freshly distilled CH_2Cl_2 (80 mL) under Ar and cooled to −78°C in flask 1. Oxalyl chloride (3.89 mL, 44.58 mmol, 1.60 equiv.) was added to CH_2Cl_2 (120 mL) in a separate round bottom flask (flask 2) under Ar, and cooled to −78°C. Dry DMSO (7.03 mL, 91.94 mmol, 3.30 equiv.) was added quickly to the oxalyl chloride solution (flask 2) and the mixture was stirred at −78°C for 15 min. The alcohol solution was transferred slowly by cannula to flask 2 over a period of 45 min and then rinsed with CH_2Cl_2 (50 mL). The resulting cloudy, white mixture was stirred for 1.5 h at −78°C. DIPEA (24.27 mL, 0.14 mol) was added and the solution stirred for 30 min at −78°C and 10 min at 0°C. Ice-cold CH_2Cl_2 (250 mL) was added and the solution was washed with ice-cold 3% NH_4Cl (3×250 mL), 10% $NaHCO_3$ (100 mL), saturated NaCl (250 mL), dried ($MgSO_4$), and evaporated to dryness. The reaction yielded a slightly yellowish solid in 96% (8.68 g) yield. The enantiomeric purity of Cbz-Ser(ald) OBO ester was determined by chiral shift ^{1}H NMR studies. Cbz-Ser(ald) OBO ester **6** (10 mg) was dissolved in benzene-d_6. Eu(hfc)$_3$ (100 μL, 50 mg/mL in benzene-d_6) was added to obtain the ^{1}H NMR spectrum at 250 MHz. The purity was observed to be 97–99% ee. Recrystallization was possible from EtOAc/hexane. Mp 139.5–141.5°C; $[\alpha]^{20}_D=-99.3$ (c=1.03, EtOAc); TLC (3:1 EtOAc/hex), R_f=0.60; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.69 (s, 1H), 7.38–7.30 (m, 5H), 5.34 (d, J=9.2 Hz, 1H), 5.15–5.10 (m, 2H), 4.61 (d, J=8.9 Hz, 1H), 3.94 (s, 6H), 0.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 63 MHz); δ 195.6, 156.1, 136.1, 128.4, 128.1, 107.1, 72.8, 67.1, 63.2, 30.8, 14.2; IR (cast from CH_2Cl_2) 3353 (br m), 3063 (vw), 3033 (vw), 2947 (w), 2884 (w), 1723 (s br), 1599 (vw), 1521 (m), 1355 (m), 1234 (m), 1192 (w), 1071 (m), 1046 (s), 1012 (m), 990 (w), 946 (w), 895 (w), 747 (w), 699 (w) cm^{-1}; HRMS (FAB) calculated for ($M+H^+$) $C_{16}H_{20}O_6N$: 322.12906; observed: 322.12854. Anal. Calcd for $C_{16}H_{20}O_6N$: C, 59.81; H, 5.96; N, 4.36. Found: C, 59.72; H, 6.12; N, 4.33.

5.2. General procedure for Wittig addition to the protected aldehyde

The ylide was prepared by suspending potassium *tert*-butoxide (2.1 equiv.) in freshly distilled Et_2O (2–4 mL) under N_2. The phosphine salt or phosphine oxide (2.3 equiv.) was then added, and the resulting brightly colored suspension was refluxed for 15 min. The Et_2O was then evaporated with a stream of N_2 until a thick slurry was obtained, at which point a solution of crude Cbz-Ser(ald)-OBO ester **7** (1 equiv., 0.8–1.6 mmol assuming 100% yield of the aldehyde from the oxidation) in freshly distilled THF (2–3 mL) was added. After 5–10 min at 50°C, the reaction was poured into H_2O (20 mL) and CH_2Cl_2 (20 mL). The layers were separated, the H_2O washed with CH_2Cl_2 (50 mL), and the organic fractions were then combined, washed with H_2O (1×100 mL), dried ($MgSO_4$), and evaporated to dryness. The residue was purified by flash column chromatography (1:1 EtOAc/hexane, loaded in CH_2Cl_2).

5.2.1. Wittig addition of $Ph_3P{=}CH{-}CO_2CH_3$ to Cbz-L-Ser(ald)-OBO ester 7: 1-[methyl-*N*-(benzyloxycarbonyl)-(1*S*)-1-amino-(*E*)-2-butenoate]-4-methyl-2,6,7-trioxabicyclo-[2.2.2]-octane, Cbz-L-trans-β,γ-dehydro-Glu (OCH_3)–OBO ester, 9a. Cbz-L-Ser(ald)-OBO ester **7** (0.099 g, 0.31 mmol assuming 100% yield in the oxidation), $Ph_3P{=}CH{-}CO_2CH_3$ (0.120 g, 0.359 mmol, 1.2 equiv.), and dry CH_2Cl_2 (6 mL) were added to a flask and stirred at room temperature for 20 min. The reaction was washed with 3% NH_4Cl (3×10 mL), dried ($MgSO_4$), and evaporated to dryness. Purification by flash column chromatography (1:1 EtOAc/hexane), yielded 0.089 g of white solid (77% from **6**), with a >95:<5 *E*/*Z* ratio (as determined by NMR integration of the alkene protons). The oil crystallized upon standing. Mp 106–108°C; $[\alpha]^{20}_D=-33.2$ (c=1.16, EtOAc); TLC (Solvent B) R_f 0.37 (*E*); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.35 (s, 5H), 6.99 (dd, J=15.8, 5.0 Hz, 1H), 6.01 (dd, J=15.8, 1.6 Hz, 1H), 5.20 (d, J=9.3 Hz, 1H), 5.12 (s, 2H), 4.57 (ddd, J=8.4, 4.3, 1.4 Hz, 1H), 3.89 (s, 6H), 3.72 (s, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 166.4, 155.8, 143.2, 136.2, 128.4, 128.1, 122.4, 107.6, 72.8, 67.0, 56.0, 51.5, 30.7, 14.1; IR (Nujol mull) 3347 (br w), 3063 (vw), 3033 (vw), 2949 (w), 2883 (w), 1720 (s), 1663 (w), 1606 (vw), 1587 (vw), 1518 (m), 1456 (w), 1436 (w), 1309 (m), 1275 (m), 1247 (m), 1196 (m), 1172 (w), 1049 (s), 1013 (m), 887 (w), 862 (w), 750 (w), 699 (w) cm^{-1}; MS (EI, 70 eV) m/z 377 (M^+, 81), 335 (M^+-42, 6), 302 (M^+-75, 18), 270 (M^+-107, 43), 242 (M^+-135, 1008); HRMS (EI, 70 eV) Calcd for $C_{19}H_{23}O_7N$: 377.1474. Found: 377.1474±0.0011 (M^+); Anal. Calcd for $C_{19}H_{23}O_7N$: C, 60.47; H, 6.16; N, 3.71. Found: C, 60.43; H, 5.91; N, 3.73.

5.2.2. Wittig addition of $Ph_3P{=}CH_2$ to Cbz-L-Ser(ald)-OBO ester 4: 1-[*N*-(benzyl-oxycarbonyl)-(1*S*)-1-amino-2-propene]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane, Cbz-L-Gly(-CH=CH_2)–OBO ester, 9b. Crude Cbz-Ser(ald)-OBO ester **7** (0.524 g, 1.63 mmol assuming 100% yield of

the aldehyde from the oxidation) was reacted with the yellow ylide generated from $MeP^+Ph_3Br^-$ according to the general procedure. Purification gave 0.368 g (71% from **6**) of a thick oil ($[\alpha]^{20}_D=-61.9$ (c=1.00, EtOAc)); 75% ee by HPLC analysis). The oil could be crystallized from Et_2O/hexane to give colourless crystals: mp 73–74°C; $[\alpha]^{20}_D=-68.5$ (c=1.12, EtOAc); TLC (Solvent A) R_f 0.48; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.34–7.25 (m, 5H), 5.92 (ddd, J=17.2, 10.5, 5.5 Hz, 1H), 5.31–5.06 (m, 3H), 5.12 (s, 2H), 4.43 (br t, J=6.9 Hz, 1H), 3.89 (s, 6H), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 156.0, 136.5, 133.2, 128.4, 128.0, 116.7, 108.0, 72.8, 67.8, 57.1, 30.7, 14.3; IR (cast from CH_2Cl_2) 3371 (br w), 3064 (vw), 3033 (vw), 2944 (w), 2881 (m), 1722 (s br), 1646 (vw), 1515 (m), 1397 (w), 1336 (m), 1223 (m), 1053 (s), 995 (s), 932 (w), 748 (w), 699 (w) cm^{-1}; MS (EI, 70 eV) m/z 319 (M^+, 13), 246 (M^+-73, 100), 236 (M^+-83, 13), 228 (M^+-91, 22), 218 (M^+-101, 23); HRMS (EI, 70 eV) Calcd for $C_{17}H_{21}O_5N$: 319.1420. Found: 319.1427 (MH^+); Anal. Calcd for $C_{17}H_{21}O_5N$: C, 63.94; H, 6.64; N, 4.39. Found: C, 64.09; H, 6.73; N, 4.36.

5.2.3. Nozaki olefination of Cbz-L-Ser(ald)-OBO ester 7: 1-[*N*-(benzyl-oxycarbonyl)-(1*S*)-1-amino-2-propene]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane, Cbz-L-Gly(-CH=CH$_2$)–OBO ester, 9b. Crude Cbz-Ser(ald)-OBO ester **7** (0.50 g, 1.56 mmol assuming 100% yield of the aldehyde from the oxidation) was dissolved in dry THF (10 mL) then added via cannula to a stirring mixture of zinc dust (0.918 g, 14.04 mmol), freshly distilled diiodomethane (0.376 g, 4.67 mmol) and trimethylaluminum (0.47 mL, 0.94 mmol, 2.0 M in hexanes) in dry THF (10 mL) under Ar. The mixture was stirred at room temperature for 4 h before cold 3% NH_4Cl (10 mL) was added. The resulting aluminum salt was filtered off and the filtrate extracted with EtOAc (3×40 mL). The organic layers were pooled and extracted with 3% NH_4Cl (2×25 mL), 10% $NaHCO_3$ (25 mL), saturated NaCl (25 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting slightly yellow oil purified by flash chromatography (EtOAc/hex 1:1) to give a clear oil which was crystallized from Et_2O/hexanes to give 0.35 g of **9c** (76% yield). Mp 73–74°C; $[\alpha]^{20}_D=-66.5$ (c=0.9, EtOAc) 86% ee by HPLC analysis.

5.2.4. Grignard addition of trimethylsilylmethylmagnesium chloride to Cbz-L-Ser(ald)-OBO ester 7: 1-[*N*-(benzyloxycarbonyl)-(1*S*)-1-amino-2-hydroxy-3-(1,1,1-trimethylsilyl)propyl]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane, Cbz-L-Ser(CH$_2$TMS)–OBO ester, 10. Crude Cbz-Ser(ald)-OBO ester **7** (0.40 g, 1.25 mmol assuming 100% yield of the aldehyde from the oxidation) was dissolved in dry THF (40 mL) to which trimethylsilylmethylmagnesium chloride (5.0 mL, 5.0 mmol, 1.0 M in Et_2O) was added by syringe. The mixture was refluxed under Ar for 6 h before 3% NH_4Cl (20 mL) was added and then extracted with EtOAc (3×50 mL). The organic fractions were pooled and then extracted with 3% NH_4Cl (2×25 mL), 10% $NaHCO_3$ (25 mL), saturated NaCl (25 mL) and dried over $MgSO_4$. The solvent was removed in vacuo and the resulting oil purified by flash chromatography to give 1.42 g (72% yield) of a colorless oil. TLC (Solvent A) R_f 0.58; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.40–7.26 (m, 5H), 5.32 (d, J=10.3 Hz, 1H), 5.12 (s, 2H), 4.31 (dd, J=4.8, 9.7 Hz, 1H), 3.89 (s, 6H), 3.68 (d, J=10.3 Hz, 1H), 0.85 (dd, J=9.6, 14.7 Hz, 1H), 0.78 (s, 3H), 0.60 (dd, J=4.7, 14.7 Hz, 1H), 0.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.2, 136.7, 128.6, 128.5, 128.2, 108.9, 72.8, 67.1, 60.5, 59.1, 30.7, 21.5, 14.3, −0.8; IR (cast from CH_2Cl_2) 3389 (br w), 3064 (vw), 3033 (vw), 2944 (w), 2881 (m), 1719 (s br), 1510 (m), 1387 (w), 1336 (m), 1223 (m), 1053 (s), 995 (s), cm^{-1}; Anal. Calcd for $C_{20}H_{31}NO_6Si$: C, 58.65; H, 7.63; N, 3.42. Found: C, 58.56; H, 7.85; N, 3.21.

5.2.5. Deprotection of Cbz-L-Gly(-CH=CH$_2$)–OBO ester 9b: L-vinylglycine, 11b.

(*a*) *TMSI.* Cbz-L-Gly(–CH=CH$_2$)–OBO ester **9b** (0.230 g, 0.720 mmol) was treated with TMSI (1.5 mL, 10.5 mmol, 15 equiv.) at 80°C for 20 h. After cooling, Et_2O (3 mL) was carefully added, followed by the dropwise addition of 0.5N NaOH (5 mL). The organic layer was removed and washed with 0.5N NaOH (2×4 mL). The aqueous fractions were combined, washed (2×5 mL Et_2O), acidified to pH<3 with 2N HCl and purified on a cation exchange column (loaded on a Bio-Rad AG 50W-X8 100–200 mesh, hydrogen form, 1×12 cm, washed with 0.01N HCl and H_2O, then eluted with 5% Et_3N in H_2O, or, alternately, a 1 M NH_4OH solution). The eluate was evaporated to dryness under vacuum gave 0.0681 g (92%) of a colorless solid, which NMR and ES–MS analysis revealed to be predominantly α-aminobutyric acid: $[\alpha]^{25}_D=0.2$ (c=0.47, AcOH); ^1H NMR (D_2O, 250 MHz) δ 4.27 (d, J=7.6 Hz, 1H), 1.90 (quintet, J=7.1 Hz, 2H), 0.98 (t, J=7.5 Hz, 3H); ^{13}C NMR (D_2O, 62.7 MHz) δ 177.7, 58.7, 26.5, 11.3; MS (ES) m/z 104 (MH^+). Derivatisation with *o*-phthaladehyde and *N*-isobutyryl-L-cysteine, and analysis by HPLC, with comparison to commercial α-aminobutyric acid and vinylglycine standards, indicated a 50:50 ratio of L- and D-isomers (Waters 125, 8×100 mm μ-Bondapak C_{18} Radial-Pak™ cartridge column, 1 mL/min; 100% 30 mM sodium acetate buffer, pH 6.5; linear gradient over 35 min to 50:50 buffer/MeOH; detection at 338 nm; diastereomers formed by L-α-aminobutyric acid at 28.9 min, by D-α-aminobutyric acid at 31.1 min, by L-vinylglycine at 26.6 min, and by D-vinylglycine at 28.5 min). The reaction time, temperature, source of TMSI and equivalents of TMSI were all varied in attempts to produce the desired vinylglycine. Ratios of α-aminobutyric acid and vinylglycine were determined by both ^1H NMR and HPLC, as outlined above. For monitoring the reactions over time, an aliquot (5–50 μL) was removed, added to 0.5N NaOH (100–300 μL), and extracted with Et_2O (1 mL). A portion of the aqueous fraction (10–40 μL) was then derivatized and analyzed as outlined above. For the in situ generation of TMSI, NaI (10 equiv.) and the alkene were dissolved in CH_3CN, and TMSCl (10 equiv.) was added.

(*b*) *Acid hydrolysis of **9b** with 6N HCl.* Cbz-L-Gly(–CH=CH$_2$)–OBO ester **9b** (0.230 g, 0.720 mmol) was mixed with 6N HCl (2.0 mL) and refluxed for 1 h. The solution was cooled, neutralized with a saturated solution of $NaHCO_3$ (approx. 50 mL), then loaded on an anion exchange column (Bio-Rad AG 1-X4 100–200 mesh, chloride form, converted to hydroxide form by prewashing with 4N NaOH). The column was washed with H_2O, and eluted with 1N AcOH, then lyopholized to give 0.0109 g (79%) of a colorless powder. Recrystallization (H_2O/acetone) gave

0.0100 g (72%) of solid. Derivatisation with *o*-phthalaldehyde and *N*-isobutyryl-L-cysteine, and analysis by HPLC indicated 77% ee (conditions as outlined above): mp 178–180°C (dec); TLC (Solvent C) R_f 0.46; ^{1}H NMR (D_2O, 200 MHz) δ 5.85 (ddd, J=17.4, 10.1, 7.4 Hz, 1H), 5.38 (d, J=17.2 Hz, 1H), 5.38 (d, J=10.4 Hz, 1H), 4.27 (d, J=7.3 Hz, 1H); ^{13}C NMR (D_2O, 50.3 MHz): δ 174.7, 132.0, 124.8, 59.1; MS (LD, sinapinic acid) m/z 102 (MH^+).

(*c*) *Acid hydrolysis of* ***10*** *with 6N HCl.* Cbz-L-Ser-(CH_2TMS)–OBO ester **10** (0.140 g, 0.34 mmol) was mixed with 6N HCl (10.0 mL) and refluxed for 3 h. The solution was cooled extracted twice with ether (2×5 mL), neutralized with a saturated solution of $NaHCO_3$ (approx. 50 mL), then loaded on an anion exchange column (Bio-Rad AG 1-X4 100–200 mesh, chloride form, converted to hydroxide form by prewashing with 4N NaOH). The column was washed with H_2O, and eluted with 1N AcOH, then lyopholized to give 0.028 g (81%) of a colorless powder. Recrystallization (H_2O/acetone) gave 0.025 g (74%) of solid. Derivatisation with *o*-phthaladehyde and *N*-isobutyryl-L-cysteine, and analysis by HPLC indicated 95% ee (conditions as outlined above): mp 177–180°C (dec); TLC (Solvent C) R_f 0.46.

5.2.6. 1-[*N*-(Benzyloxycarbonyl)-(1S)-1-amino-3-^{13}C-2-propene]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane, Cbz-L-Gly(–CH=^{13}CH$_2$)–OBO ester, 9d. Crude Cbz-Ser(ald)-OBO ester **7** (0.395 g, 1.19 mmol assuming 100% yield of the aldehyde from the oxidation) was reacted with the ylide generated from $(^{13}CH_3)_3P^+Ph_3I^-$ according to the general procedure. Purification gave 0.237 g (62% from **6**) of a thick oil. The oil could be crystallized from Et_2O/hexane to give 0.082 g (21%) of a first crop of colourless plate crystals. The filtrate ($[\alpha]^{25}_D$=−33.2, (c=0.62, EtOAc) was deprotected without further purification. The deprotected amino acid was determined to have 72% ee, the same as the unlabeled analog prepared by the same procedure, despite the unlabeled protected vinylglycine having substantially better optical rotation. $[\alpha]^{25}_D$=−4.7 (c=1.16, EtOAc); TLC (Solvent A) R_f 0.46; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.34–7.25 (m, 5H), 5.92 (ddd, J=16.7, 10.6, 5.8 Hz, 1H), 5.27 (dd, J=17.9, 15.8 Hz, 1H), 5.21 (dd, J=15.9, 10.4 Hz, 1H), 5.15–5.06 (m, 1H), 5.12 (s, 2H), 4.49–4.35 (br m, 1H), 3.90 (s, 6H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 155.9, 136.5, 133.2, 128.3, 127.9, 116.6 (s, superimposed on d, J=71.6 Hz, relative intensity s:d 172:1: CH=^{13}CH$_2$), 107.9, 72.8, 67.7, 57.1, 30.6, 14.2; IR (cast from CH_2Cl_2) 3369 (br w), 3066 (vw), 3031 (vw), 2943 (w), 2880 (m), 1722 (s br), 1622 (vw), 1587 (vw), 1514 (m), 1456 (w), 1397 (w), 1335 (m), 1222 (m), 1052 (s), 994 (s), 922 (w), 882 (w), 773 (w), 748 (w), 698 (w) cm^{-1}; MS (EI, 70 eV) m/z 320 (M^+, 100), 245 (M^+−75, 8), 229 (M^+−91, 14), 220 (M^+−100, 12), 213 (M^+−107, 25); HRMS (EI, 70 eV) Calcd for $C_{16}{}^{13}CH_{21}O_5N$: 320.1453. Found: 320.1445 (M^+).

5.2.7. Deprotection of Cbz-L-Gly(–CH=^{13}CH$_2$)–OBO ester 9d: γ-^{13}C-vinylglycine 11d. Cbz-L-Gly(–CH=^{13}CH$_2$)–OBO ester **9d** (0.121 g, 0.376 mmol) was deprotected with 6N HCl (3.0 mL) and purified by anion exchange chromatography as outlined above to give 0.028 g (71%) of a colorless powder. Recrystallization (H_2O/acetone) gave 0.023 g (60%) of solid. Derivatization with *o*-phthaladehyde and *N*-isobutyryl-L-cysteine, and analysis by HPLC indicated 72.2% ee (conditions as outlined above): mp 178–181°C (dec); TLC (Solvent C) R_f 0.46; ^{1}H NMR (D_2O, 250 MHz) δ 5.92–5.72 (m, 1H), 5.36 (ddd, J=154.9, 17.0, 0.6 Hz, 1H), 5.36 (ddd, J=161.1, 10.2, 0.7 Hz, 1H), 4.13 (td, J=6.5, 0.7 Hz, 1H); ^{13}C NMR (D_2O, 62.7 MHz): δ 174.7, 132.9 (d, J=70.1 Hz, CH=^{13}CH$_2$), 124.0 (s, superimposed on d, J=69.8 Hz, relative intensity 180:1, CH=^{13}CH$_2$), 59.8; MS (LD, sinapinic acid) m/z 103 (MH^+); Anal. Calcd for $C_3{}^{13}CH_7O_2N$: H, 6.91; N, 13.72. Found: H, 7.06; N, 13.55.

5.2.8. 1-[*N*-(Benzyloxycarbonyl)-(1*S*)-1-amino-(*Z*)-2-pentene]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane, Cbz-L-cis-Gly(–CH=CH–Et)–OBO ester, 9e. Crude Cbz-Ser(ald)-OBO ester **7** (0.241 g, 0.739 mmol assuming 100% yield of the aldehyde from the oxidation) was reacted with the orange–yellow ylide generated from $Ph_3P^+CH_2CH_2CH_3Br^-$ according to the general procedure. Purification gave 0.164 g (64% from **6**) of an 83:17 *Z*/*E* mixture as an oil. Crystallization from Et_2O/hexane gave a colorless solid with the same *Z*:*E* ratio: mp 98–99.5°C; $[\alpha]^{25}_D$=−0.3 (c=1.26, EtOAc); TLC (Solvent A) R_f 0.72; ^{1}H NMR ($CDCl_3$, 250 MHz) *Z*/*E* 83:17: δ 7.35–7.28 (m, 5H), 5.62 (br dt, J=10.0, 7.6 Hz, 1H, *cis*+*trans* CH=C*H*–CH_2), 5.46 (dd, J=15.6, 6.1 Hz, 0.17H, *trans* C*H*=CH–CH_2), 5.31 (br t, J=10.0 Hz, 0.83H, *cis* C*H*=CH–CH_2), 5.10 (br s, 3H), 4.67 (br t, J=9.1 Hz, 1H), 3.90 (s, 6H), 2.20–2.00 (br m, 2H), 0.97 (br t, J=7.3 Hz, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 155.6, 136.6 (*cis* *C*H=CH–Et), 136.4, 135.1 (w, *trans* *C*H=CH–Et), 128.4, 128.0, 127.9, 124.0 (*cis* CH=*C*H–Et), 123.9 (w, *trans* CH=*C*H–Et), 108.4, 72.8, 66.7, 52.1, 30.7, 25.3 (w, *trans* =CH–*C*H$_2$–CH$_3$), 21.1 (*cis* =CH–*C*H$_2$–CH$_3$), 14.2, 14.0 (*cis* =CH–CH$_2$–*C*H$_3$), 13.2 (w, *trans* =CH–CH$_2$–*C*H$_3$); IR (cast from CH_2Cl_2) 3451 (br w), 3360 (br w), 3063 (vw), 3029 (vw), 2962 (m), 2934 (w), 2879 (m), 1722 (s), 1608 (vw), 1587 (vw), 1511 (m), 1456 (w), 1397 (w), 1334 (m), 1219 (m), 1049 (s), 1008 (s), 995 (s), 890 (w), 811 (w), 754 (w), 699 (w) cm^{-1}; MS (EI, 70 eV) m/z 347 (M^+, 100), 256 (M^+−91, 20), 218 (M^+−129, 41); HRMS (EI, 70 eV) Calcd for $C_{19}H_{25}O_5N$: 347.1733. Found: 347.1729 (M^+); Anal. Calcd for $C_{19}H_{25}O_5N$: C, 65.69; H, 7.27; N, 4.03. Found: C, 65.72; H, 7.00; N, 4.04.

5.2.9. Deprotection of Cbz-L-Gly(–CH=CH$_2$–Et)–OBO ester 9e: *Z*-ethylvinylglycine, 11d. Cbz-L-Gly(–CH=CH$_2$–Et)–OBO ester **9d** (0.071 g, 0.210 mmol) was deprotected with 6N HCl (2.0 mL) and purified by anion exchange column as described above to give 0.022 g (83%) of a colorless powder, with 83:17 *Z*/*E* ratio by ^{1}H NMR. Derivatization with *o*-phthaladehyde and *N*-isobutyryl-L-cysteine, and analysis by HPLC indicated 72% ee (Waters 125 μ 8×100 mm μ-Bondapak C_{18} Radial-Pak™ cartridge column, 2 mL/min; 100% 30 mM sodium acetate buffer, pH 6.5; linear gradient over 60 min to 20:80 buffer/MeOH; detection at 338 nm; diastereomers formed by L-ethylvinylglycine at 38.0 min, and by D-ethylvinylglycine at 39.9 min. The *E* and *Z* isomers were not resolved): TLC (Solvent C) R_f 0.58; ^{1}H NMR (D_2O, 250 MHz) *cis* isomer: δ 5.82 (dt, J=10.2, 8.3 Hz, 0.85H), 5.29 (dd, J=10.2, 0.5 Hz, 0.85H), 4.45 (dd, J=10.2, 0.5 Hz, 0.85H), 2.10 (m, 1.7H), 0.90 (t, J=7.5 Hz, 2.55H) *trans* isomer: δ 5.93 (dt, J=15.3, 6.0 Hz,

0.15H), 5.43 (dd, J=15.3, 8.3 Hz, 0.15H), 4.10 (d, J=8.3 Hz, 0.15H), 2.00 (m, 0.3H), 0.89 (m, 0.45H); ^{13}C NMR (D_2O, 62.7 MHz): *cis* isomer: δ 176.5, 143.9, 122.9, 54.6, 23.4, 15.8, *trans* isomer: 176.5, 144.1, 123.3, 59.5, 27.6, 14.9.

5.2.10. 1-[*N*-(Benzyloxycarbonyl)-(1*S*)-1-amino-3-cyano-(*E*)-2-propene]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane, Cbz-L-*trans*-Gly(−CH=CH−CN)−OBO ester, 9f. Crude Cbz-Ser(ald)-OBO ester **7** (0.507 g, 1.54 mmol assuming 100% yield of the aldehyde from the oxidation) was reacted with the yellow ylide generated from $(EtO)_2PO(CH_2–CN)$ according to the general procedure. Purification gave 0.294 g (55% from **6**) of the *trans* isomer and 0.084 g (16%) of the *cis* isomer as well separated compounds (71%, 78:22 *E*/*Z* overall). The *trans* isomer could be recrystallized from Et_2O/hexane; the *cis* from CH_2Cl_2/Et_2O.

trans Isomer. Mp 106–107.5°C; $[\alpha]^{25}_D$=−0.7 (c=1.37, EtOAc); TLC (Solvent A) R_f 0.44; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.36 (s, 5H), 6.77 (dd, J=16.4, 4.8 Hz, 1H), 5.53 (dd, J=16.3, 1.1 Hz, 1H), 5.18–5.11 (m, 3H), 4.56–4.51 (m, 1H), 3.90 (s, 6H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 155.8, 149.7, 136.0, 128.5, 128.3, 128.1, 116.9, 107.4, 101.5, 72.9, 67.3, 56.6, 30.8, 14.1; IR (cast from CH_2Cl_2) 3339 (br w), 3064 (vw), 3035 (vw), 2948 (w), 2884 (w), 2226 (w), 1720 (s), 1640 (vw), 1587 (vw), 1517 (m), 1332 (w), 1253 (m), 1226 (m), 1049 (s), 1018 (s), 966 (m), 736 (w), 699 (w) cm^{-1}; MS (EI, 70 eV) m/z 344 (M^+, 100), 253 (M^+−91, 20), 237 (M^+−107, 53); HRMS (EI, 70 eV) Calcd for $C_{18}H_{20}O_5N_2$: 344.1372. Found: 344.1370 (M^+); Anal. Calcd for $C_{18}H_{20}O_5N_2$: C, 62.78; H, 5.87; N, 8.14. Found: C, 62.64; H, 6.00; N, 8.03.

cis Isomer. Mp 161.5–162.5°C; $[\alpha]^{25}_D$=+0.9 (c=0.80, EtOAc); TLC (Solvent A) R_f 0.35; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.38–7.32 (m, 5H), 6.35 (br dd, J=10.7, 8.1 Hz, 1H), 5.49 (br d, J=11.2 Hz, 1H), 5.35 (br d, J=7.3 Hz, 1H), 5.13 (s, 2H), 4.74 (br t, J=7.9 Hz, 1H), 3.91 (s, 6H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 155.5, 147.8, 136.1, 128.4, 128.2, 128.1, 115.2, 107.4, 102.1, 72.9, 67.2, 56.0, 30.7, 14.1; IR (cast from CH_2Cl_2) 3355 (br w), 3062 (vw), 2949 (w), 2884 (w), 2223 (w), 1722 (s), 1652 (vw), 1634 (vw), 1512 (m), 1397 (w), 1327 (m), 1256 (m), 1223 (m), 1049 (s), 1016 (s), 1003 (s), 912 (w), 883 (w), 811 (w), 759 (w), 738 (w), 699 (w) cm^{-1}; MS (EI, 70 eV) m/z 344 (M^+, 67), 300 (M^+−44, 8), 253 (M^+−91, 18), 237 (M^+−107, 42), 224 (M^+−120, 100); HRMS (EI, 70 eV) Calcd for $C_{18}H_{20}O_5N_2$: 344.1372. Found: 344.1370 (M^+); Anal. Calcd for $C_{18}H_{20}O_5N_2$: C, 62.78; H, 5.87; N, 8.14. Found: C, 62.74; H, 6.00; N, 8.01.

5.2.11. 1-[*N*-(Benzyloxycarbonyl)-(1*S*)-1-amino-(*Z*)-2-pentene]-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane, Cbz-L-*cis*-Gly(−CH=CH−CH=CH_2)-OBO ester, 9g. Crude Cbz-Ser(ald)-OBO ester **7** (0.257 g, 0.778 mmol assuming 100% yield of the aldehyde from the oxidation) was reacted with the orange–red ylide generated from $Ph_3P^+CH_2CH{=}CH_2Br^-$ according to the general procedure. Purification gave 0.152 g (55% from **6**) of predominantly *trans* isomer (approximately 92:8 *E*/*Z* as estimated from ^{13}C NMR) as an oil. Recrystallization attempts resulted in a clear gel which was insoluble in most solvents: $[\alpha]^{25}_D$=−33.0 (c=1.56, EtOAc); TLC (Solvent A) R_f 0.62; ^{1}H NMR ($CDCl_3$, 250 MHz) *E*/*Z* 90:10: δ 7.34–7.26 (m, 5H), 6.34 (ddd, J=16.4, 10.1, 10.1 Hz, 1H, *trans*+*cis* –CH_B=CH_C–CH_D=CH_EH_F), 6.33–6.18 (br m, *cis*+*trans* 1H, –CH_B=CH_C–CH_D=CH_EH_F), 5.73 (dd, J=14.6, 6.1 Hz, 0.9H, *trans* –CH_B=CH_C–CH_D=CH_EH_F), 5.39 (br t, J=9.9 Hz, 0.1H, *cis* –CH_B=CH_C–CH_D=CH_EH_F), 5.17 (br d, J=17.1 Hz, 1H, *trans*+*cis* –CH_B=CH_C–CH_D=CH_EH_F), 5.20–5.05 (m, 3H, N*H*, Cbz CH_2O), 5.07 (br d, J=10.0 Hz, 1H, *trans*+*cis* –CH_B=CH_C–CH_D=CH_EH_F), 4.46 (br t, J=7.2 Hz, 1H, α-C*H*), 3.89 (s, 6H, 3 OBO ester CH_2–O), 0.78 (s, 3H, OBO ester CH_3): from decoupling experiments for *trans* isomer J_{AG}=8.0, J_{AB}=6.1 Hz, J_{BC}=14.6, J_{CD}=10.3, J_{DE}=16.4, J_{DF}=10.1; ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 155.8, 136.5, 136.2 (*trans* –CH=CH–*C*H=CH_2), 132.7, 128.8 (*trans* –*C*H=*C*H–CH=CH_2), 128.4, 128.0, 127.9, 117.5, 108.0, 72.8, 66.8, 56.5, 30.6, 14.2: observe weak peaks from *cis* isomer at δ 132.1, 126.1, 119.6; IR (cast from CH_2Cl_2) 3373 (br w), 3086 (vw), 3063 (vw), 3034 (w), 2946 (m), 2880 (m), 1721 (s), 1655 (vw), 1604 (vw), 1515 (s), 1456 (w), 1396 (w), 1332 (m), 1224 (m), 1049 (s), 1009 (s), 910 (w), 887 (w), 850 (w), 773 (w), 742(w), 699 (w) cm^{-1}; MS (EI, 70 eV) m/z 345 (M^+, 100), 254 (M^+−91, 21); HRMS (EI, 70 eV) Calcd for $C_{19}H_{31}O_5N$: 345.1576. Found: 345.1570 (M^+).

5.2.12. 1-[*N*-(Benzyloxycarbonyl)-(1*S*)-1-amino-3-methoxy-(*E*)-2-propene]-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane, Cbz-L-*trans*-Gly(−CH=CH−OMe)−OBO ester, 9h. Crude Cbz-Ser(ald)-OBO ester **7** (0.262 g, 0.802 mmol assuming 100% yield of the aldehyde from the oxidation) was reacted with the orange ylide generated from $Ph_3P^+CH_2OCH_3Cl^-$ according to the general procedure. Purification gave 0.063 g (22% from **6**) of the *trans* isomer and 0.038 g (13%) of the *cis* isomer as well-separated compounds (35%, 63:37 *E*/*Z* overall). Both the *trans* and *cis* isomers could be recrystallized from Et_2O/hexane.

trans Isomer. Mp 117–118.5°C; $[\alpha]^{25}_D$=−3.9 (c=0.90, EtOAc); TLC (Solvent A) R_f 0.36; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.36–7.29 (m, 5H), 6.52 (d, J=12.4 Hz, 1H), 5.10 (br s, 3H), 4.73 (dd, J=12.7, 8.3 Hz, 1H), 4.29 (t, J=8.6 Hz, 1H), 3.90 (s, 6H), 3.53 (s, 3H), 0.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 155.7, 150.8, 136.6, 128.4, 128.1, 128.0, 108.2, 99.1, 72.8, 66.7, 56.2, 54.6, 30.7, 14.3; IR (cast from CH_2Cl_2) 3359 (br w), 3064 (vw), 3032 (vw), 2943 (m), 2880 (m), 2835 (vw), 1721 (s), 1659 (m), 1586 (vw), 1514 (s), 1456 (w), 1397 (w), 1333 (m), 1278 (m), 1217 (s), 1164 (m), 1049 (s), 1009 (s), 937 (w), 888 (w), 822 (w), 773 (w), 742 (w), 700 (w) cm^{-1}; MS (EI, 70 eV) m/z 349 (M^+, 100), 274 (M^+−75, 4), 258 (M^+−91, 5), 220 (M^+−129, 54), 214 (M^+−135, 38); HRMS (EI, 70 eV) Calcd for $C_{18}H_{23}O_6N$: 349.1525. Found: 349.1519 (M^+); Anal. Calcd for $C_{18}H_{23}O_6N$: C, 61.88; H, 6.65; N, 4.01. Found: C, 61.83; H, 6.60; N, 4.03.

cis Isomer. Mp 112–114°C; $[\alpha]^{25}_D$=+1.3 (c=0.96, EtOAc); TLC (Solvent A) R_f 0.25; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.37–7.28 (m, 5H), 6.06 (d, J=6.1 Hz, 1H), 5.12 (br s, 3H), 4.87 (t, J=9.2 Hz, 1H), 4.41 (dd, J=9.1, 6.2 Hz, 1H), 3.91 (s, 6H), 3.61 (very br s, 3H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 155.7, 149.1, 136.7, 128.3,

128.1, 127.8, 108.4, 101.8, 72.8, 66.6, 60.1, 50.3, 30.7, 14.3; IR (cast from CH_2Cl_2) 3373 (br w), 2939 (w), 2879 (m), 1722 (s), 1669 (w), 1514 (m), 1456 (w), 1396 (w), 1332 (w), 1238 (m), 1090 (m), 1049 (s), 1008 (s), 942 (w), 885 (w), 803 (w), 751 (w), 738 (w), 698 (w) cm^{-1}; MS (EI, 70 eV) *m/z* 349 (M^+, 100), 274 (M^+-75, 5), 258 (M^+-91, 6), 220 (M^+-129, 71), 214 (M^+-135, 65); HRMS (EI, 70 eV) Calcd for $C_{18}H_{23}O_6N$: 349.1525. Found: 349.1519 (M^+); Anal. Calcd for $C_{18}H_{23}O_6N$: C, 61.88; H, 6.65; N, 4.01. Found: C, 61.65; H, 6.63; N, 3.96.

5.2.13. Attempted base-mediated Peterson olefination of Cbz-L-Ser(CH_2TMS)–OBO ester, 10. (5*S*)-4-(4-methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)-5-[(1,1,1-trimethylsilyl)-methyl]-1,3-oxazolan-2-one, 12. Cbz-L-Ser(CH_2TMS)–OBO ester **10** (0.210 g, 0.52 mmol) was dissolved in dry THF (20 mL) and rapidly transferred to a flask containing KH (0.063 g, 0.55 mmol, washed with Et_2O) suspended in THF (10 mL) at −10°C under Ar. One hour later a TLC indicated total conversion to **12**. TLC (1:2 EtOAc/hexane), R_f=0.41; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.38 (s, 1H), 4.66 (ddd, *J*=7.8, 6.8, 3.4 Hz, 1H), 3.85 (s, 6H), 3.30 (d, *J*=3.4 Hz, 1H), 1.06 (dd, *J*=14.5, 7.8 Hz, 1H), 0.95 (dd, *J*=14.5, 6.8 1H), 0.76 (s, 3H), 0.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 158.9, 107.4, 76.3, 72.7, 62.8, 30.8, 24.7, 14.1, −1.1; Anal. Calcd for $C_{16}H_{21}O_6N$: C, 51.80; H, 7.69; N, 4.65. Found: C, 52.09; H, 7.96; N, 4.34.

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