A Novel Synthesis of *N*-But-3-enyl-α- and β-Amino Acids

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Abstract: *N*-But-3-enyl-α- and β-amino acids can be prepared by cleaving 1,3-oxazolidin-5-ones and 1,3-oxazinan-6-ones in the presence of allylsilanes and boron trifluoride etherate at room temperature in good to excellent yields.

Key words: 1,3-oxazolidin-5-ones, 1,3-oxazinan-6-ones, amino acids, allylations, Lewis acids

N-Substituted amino acids have been found in proteins, peptides, enzymes, hormones as well as other secondary metabolities.[1] These uncommon amino acids have received considerable attention from the scientific community because of their useful pharmacological properties, particularly when they are present in larger molecules.[2] Thus, they have become sub-targets in the synthesis of biologically active substances in medicinal chemistry. Both solution- and solid-phase synthesis of these compounds and their derivatives have been reported for the development of some leads in therapeutic peptide and peptidomimetic structures.

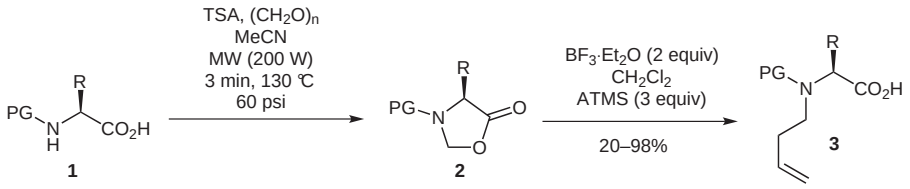
In previous publications,[3–5] we have reported the successful synthesis of N-methylated-α- and β-amino acids and some N-alkylated β-amino acids via reductive cleavage of 1,3-oxazolidin-5-ones and 1,3-oxazin-6-ones in the presence of triethylsilane and trifluoroacetic acid (TFA). These conditions have been modified to prepare analogues of N-alkenylated α- and β-amino acids. Both 1,3-oxazolidin-5-ones and 1,3-oxazin-6-ones were successfully cleaved using allyltrimethylsilane (ATMS) and boron trifluoride etherate ($BF_3{\cdot}OEt_2$) at room temperature to form *N*-but-3-enyl-α- and β-amino acids. A range of uncommon amino acids with different types of N-protecting groups were successfully made by this methodology. Optimization studies to improve the yields and purities of the intermediate 1,3-oxazolidin-5-ones and 1,3-oxazin-6-ones were also attempted.

N-But-3-enyl-α- and β-Amino Acids

Protected amino acids **1** were reacted with paraformaldehyde [$(CH_2O)_n$] in acetonitrile in the presence of *p*-toluenesulfonic acid (PTSA) as catalyst. This reaction was conducted in a microwave reactor at 130 °C for 3 minutes, as previously described by Govender and Arvidsson[6] to form 1,3-oxazolidin-5-ones **2** (Scheme 1). The intermediate **2** gave spectra identical to those of an authentic sample.[1,3,7,8]

Aurelio et al.[1,3,4,7,8] were successful in preparing N-protected N-methylated amino acids through the reductive opening of 1,3-oxazolidin-5-ones in the presence of triethylsilane and TFA or $BF_3{\cdot}OEt_2$. By similar methodology, *N*-but-3-enyl-α-amino acids **3** were successfully synthesized by cleaving intermediates **2** via treatment with ATMS and $BF_3{\cdot}OEt_2$ in dichloromethane at room temperature. A range of uncommon amino acids with different types of N-protecting groups were made by this methodology to form compounds **3** in good to excellent yields (Table 1). We also trialed the cleavage of 1,3-oxazolidin-5-ones through the use of ATMS and TFA, however, these conditions failed to form the expected *N*-but-3-enyl-α-amino acids.

It is worthwhile to emphasize that the use of $BF_3{\cdot}OEt_2$ catalyst in the reaction led to a rapid cleavage of acid sensitive side chain protecting groups as well as cleavage of Boc-protected 1,3-oxazolidin-5-ones and this led to purification problems via column chromatography.



PG = Cbz, Fmoc, Ts, Bz
R = H, Me, *i*-Pr, *s*-Bu, *i*-Bu, Ph, Bn, 4-$BnOC_6H_4CH_2$, $(CH_2)_2CO_2$(Troc), $(CH_2)_2CO_2$(DCHA), CH_2CO_2(Troc)

Scheme 1 Microwave formation of oxazolidin-5-ones **2** and their Lewis acid mediated cleavage to afford *N*-but-3-enyl-α-amino acids **3**

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Table 1 ATMS Cleavage of 1,3-Oxazolidinones **2** Using $BF_3{\cdot}OEt_2$ to *N*-But-3-enyl-α-amino Acids **3**

Residue	*N*-But-3-enyl-α-amino acid	Yield (%)	Residue	*N*-But-3-enyl-α-amino acid	Yield (%)
Cbz-L-Gly	**3a**	89	Bz-L-Leu	**3k**	60
Ts-L-Gly	**3b**	95	Cbz-L-Ile	**3l**	84
Cbz-L-Ala	**3c**	80	Cbz-L-Phg	**3m**	98
Cbz-D-Ala	**3d**	94	Cbz-L-Phe	**3n**	95
Fmoc-L-Ala	**3e**	82	Fmoc-L-Phe	**3o**	92
Troc-L-Ala	**3f**	76	Cbz-L-Tyr(OBn)	**3p**	20
Cbz-L-Val	**3g**	98	Cbz-L-Asp(DCHA)	**3q**	54
Fmoc-L-Val	**3h**	80	Cbz-L-Glu(DCHA)	**3r**	43
Cbz-L-Leu	**3i**	85	Fmoc-L-Glu(Troc)	**3s**	65
Fmoc-L-Leu	**3j**	98	Cbz-L-Glu(Troc)	**3t**	64

It is shown clearly from Table 1 that *N*-but-3-enyl-α-amino acids with simple aliphatic or aromatic side chains **3a**–**o** were obtained in good to excellent yields (60–98%). However, the five other compounds **3p**–**t** were obtained in lower yields (20–65%). It may be due to the complexity or reactivity of the side chains, resulting in unwanted side reactions that gave these lower yields. The dicyclohexylamine (DCHA) salt was also cleaved to give free side chains for compounds **3q** and **3r**.

Lewis Acids

Several Lewis acids were trialed in the cleavage of 1,3-oxazolidin-5-ones. It was shown from the study that $BF_3{\cdot}OEt_2$ is the best Lewis acid for the novel cleavage of **2** (Table 2). This is thought to be as a result of the stronger Lewis acidity of $BF_3{\cdot}OEt_2$ relative to the other Lewis acids tried though the use of $AlCl_3$ was uniformly unsuccessful.

Table 2 Yields of *N*-But-3-enyl-α-amino Acids Using Different Lewis acids

Residue	Lewis Acid	Product	Yield (%)
Cbz-L-Ala	$BF_3{\cdot}OEt_2$	**3c**	80
	$AlCl_3$		0
	$EtAlCl_2$		60
	Et_2AlCl		0
Fmoc-L-Phe	$BF_3{\cdot}OEt_2$	**3o**	92
	$AlCl_3$		0
	$EtAlCl_2$		65
	Et_2AlCl		0

Different Allyl-Substituted Silanes

Allyltriphenylsilane (ATPS) was also applied to cleave 1,3-oxazolidin-5-ones under the same reaction conditions as ATMS (see Scheme 1). Although results show the spectra for the product **3** to be identical, ATMS gave better yields than those obtained from the reaction of 1,3-oxazolidin-5-ones and ATPS (Table 3).

Table 3 Yields of *N*-But-3-enyl-α-amino Acids Using Different Allyl-Substituted Silanes

Residue	Allyl-substituted silane	*N*-But-3-enyl-α-amino acid	Yield (%)
Cbz-L-Ala	ATMS	**3c**	80
Cbz-L-Ala	ATPS	**3c**	55
Ts-L-Gly	ATMS	**3b**	95
Ts-L-Gly	ATPS	**3b**	60
Cbz-L-Phg	ATMS	**3m**	98
Cbz-L-Phg	ATPS	**3m**	55

N-But-3-enyl-β-amino Acids

The homologation of commercially available crystalline, optically pure α-amino acids to β-amino acids by the Arndt–Eistert method[9,10] has been accomplished employing α-amino acid derived diazoketones as the key intermediates.[11,12] These optically active substrates have been converted to the corresponding β-amino acids by Wolff rearrangement[13,14] in the presence of water, thermally,[15–18] photochemically,[10] by silver ion catalysis, and by using ultrasound.[19,20]

For the synthesis of N-alkylated-α- and β-amino acids, diazomethane is a well-known reagent for diazoketone formation, and is readily derived from *N*-nitroso-*p*-

toluenesulfonamide (Diazald).[21] However, Diazald was no longer commercially available to us.[7,22] Less hazardous trimethylsilyldiazomethane ($TMSCHN_2$) was reacted with protected amino acids **1** to produce diazoketones **4** in the presence of EtOCOCl and Et_3N under anhydrous conditions (Scheme 2).[23] The following Wolff rearrangement using silver benzoate catylyst[24] converted the diazoketones **4** to N-protected-β-amino acids **5**. The use of silver benzoate catalyst was based on previous work by Seebach et al.[25] with some modifications to avoid time consuming purification steps to remove benzoic acid as a by-product in the reaction mixture.[7] In addition, microwave irradiation was also employed to reduce the reaction time from 3–12 hours[18,25] (conventional method) to just 60 seconds at 110 °C and 200 W (Scheme 2). 1,3-Oxazinan-6-ones **6** were synthesized using the same method as for the synthesis of 1,3-oxazolidin-5-ones **2**.[6]

As an extension of the cleavage of 1,3-oxazolidin-5-ones **2** to *N*-but-3-enyl-α-amino acids **3**, *N*-but-3-enyl-β-amino acids **7** (Table 4) were successfully formed by the cleavage of 1,3-oxazinan-6-ones **6**. The same conditions were used as applied for the cleavage of 1,3-oxazolidin-5-ones; using ATMS and $BF_3{\cdot}OEt_2$ (Scheme 2).

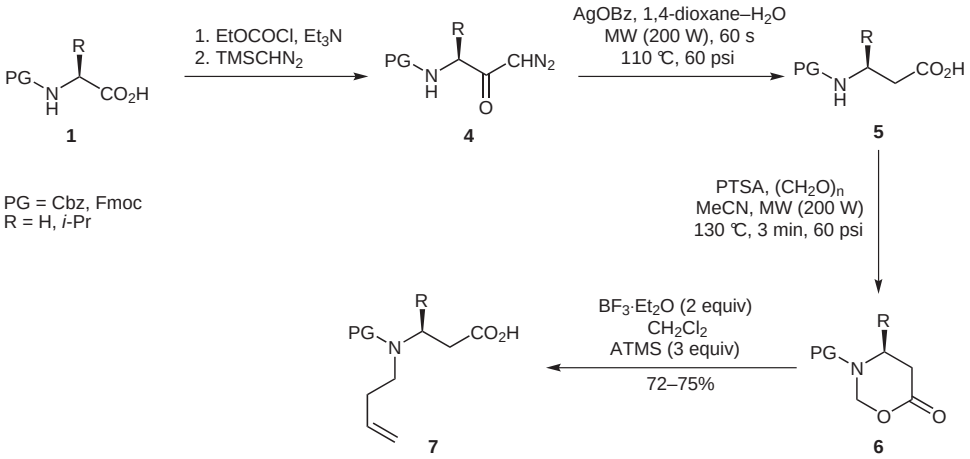
Table 4 Yields of *N*-But-3-enyl-β-amino acids

Residue	*N*-But-3-enyl-β-amino acid	Yield (%)
Cbz-L-Gly	**7a**	72
Fmoc-L-Val	**7b**	75

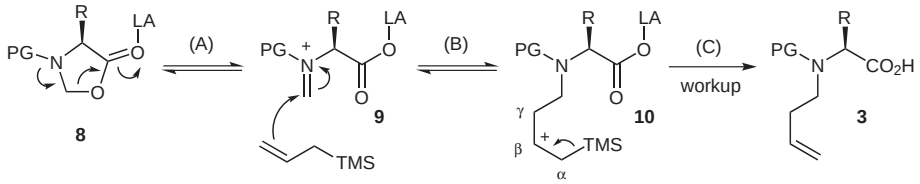
Mechanism

A mechanism for the cleavage of 1,3-oxazolidin-5-ones by ATMS/ATPS and $BF_3{\cdot}OEt_2/EtAlCl_2$ is shown in Scheme 3. The electrophilic C=O group in the ring is activated by a Lewis acid to form an iminium ion **9** (Step A). The nucleophilic double bond of ATMS/ATPS attacks the iminium cation to generate a stabilized carbocation β to the silicon atom (Step B). Subsequent loss of the silyl group from **10** results in the transposition of the double bond to form the *N*-but-3-enyl residue **3** (Step C).[26]

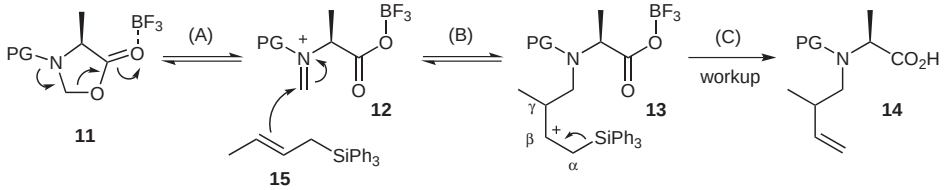
(2-Buten-1-yl)triphenylsilane (**15**) was also trialed to cleave (*S*)-3-benzyloxycarbonyl-4-methyl-5-oxazolidinone (**11**) (Scheme 4). The proposed reaction mechanism is the same as shown for the cleavage of 1,3-oxazolidin-5-ones by ATMS/ATPS. The Lewis acid $BF_3{\cdot}OEt_2$ activates



Scheme 2 Synthesis of *N*-but-3-enyl-β-amino acids



Scheme 3 Mechanism of the cleavage of 1,3-oxazolidinones using ATMS



Scheme 4 Mechanism of the cleavage of (*S*)-benzyloxycarbonyl-4-methyl-1,3-oxazoldin-5-one by (2-buten-1-yl)triphenylsilane

the ring in **11** to form an iminium cation **12** (Step A). Then the nucleophilic double bond of **15** attacks the electrophilic iminium ion to generate the intermediate **13** (Step B). Acidic workup provides compound **14**, as indicated by NMR and mass spectrometry.

We have presented a simple and convenient method for the cleavage of 1,3-oxazolidin-5-ones in the presence of ATMS and $BF_3{\cdot}OEt_2$ to form *N*-but-3-enyl-α-amino acids in good to excellent yields. Optimization of this reaction with different allyl-substituted silanes was tried and gave good yields. *N*-But-3-enyl-β-amino acids were also successfully synthesized through the cleavage of 1,3-oxazinan-6-ones using ATMS and $BF_3{\cdot}OEt_2$. A mechanism for this reaction has been proposed.

There are several extra carbons and one double bond in the N-protected-*N*-but-3-enyl-α- and β- amino acids as compared to the protected *N*-methylamino acids. There are numerous reactions that can be applied to these new modified amino acids, such as epoxidation, addition reactions and hydrogenation.

The bioactivities of *N*-but-3-enyl-α- and β-amino acids have not been researched yet, but we believe that they will have roles in peptidic natural products or peptidomimetic compounds.

Melting points are uncorrected and were recorded on a Reichert 'Thermopan' microscope hot-stage apparatus. IR spectra were recorded on a Bruker Vector 22 Fourier-Transform Spectrometer or a Perkin-Elmer 1720-X FT-IR Spectrometer using a diffuse reflectance accessory with KBr optics. Optical rotations were recorded on a Perkin-Elmer 141 Polarimeter. NMR spectroscopy was performed in $CDCl_3$ at 300 K, unless otherwise stated, on a Bruker Avance DRX-300 Spectrometer. Electrospray Ionization Mass Spectrometry (ESIMS) was carried out at the Mass Spectrometry & Proteomics Facility at La Trobe University on a Bruker Daltonics (Germany) Esquire 6000 ion trap mass spectrometer at 300 °C with scan rate 5500 *m*/z/sec and MeOH was used as the mobile phase. Low- and high-resolution mass spectra (LSIMS) were measured at the University of Tasmania by Dr. Noel Davies and co-workers on a Kratos Concept Mass Spectrometer at 70 eV; all using H_2O–MeOH–AcOH (0:99:1 or 50:50:1) mixtures as the mobile phase. Microanalyses were performed by E. Mocellin and co-workers from Chemical and Microanalytcial Services Pty Ltd in Belmont, Victoria. Flash chromatography was carried out using silica gel 60 particle size 0.040–0.063 μm (230–400 mesh ASTM) supplied by Merck Chemicals. EtOAc and hexane used for chromatography were distilled prior to use. CH_2Cl_2 was distilled and stored over Linde type 4 Å molecular sieves. TLC was performed on Merck Kieselgel 60 F_{254} plates and visualized with a UV lamp or by staining. Permanganate stain consists of $KMnO_4$ (1% v/w), K_2CO_3 (20% v/w), and NaOH (1% v/w) in H_2O. Molybdenum polyphosphoric acid stain consists of 10% molybdenum polyphosphoric acid in EtOH. All other reagents and solvents were purified or dried as described by Perrin and Armarego.[27]

1,3-Oxazolidin-5-ones 2; General Procedure

N-Protected α-amino acids **1** (2 mmol), paraformaldehyde (400 mg), and PTSA (40 mg) were suspended in MeCN (10 mL). The mixture was heated in a sealed microwave tube for 3 min at 130 °C, 200 W, and 60 psi. The mixture was hot-filtered through a glass frit, and the filtrate was concentrated in vacuo. The residue was taken up in EtOAc (20 mL), the organic phase was washed with sat. aq $NaHCO_3$ (3 × 15 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by column chromatography, eluting with 25–45% EtOAc–hexane to afford the title products **2**. Compounds **2a**–**t** have spectra identical in all respects with previously reported material.[1,7,8,28]

N-Protected *N*-But-3-enyl-α-amino Acids (3); General Procedure

1,3-Oxazolidin-5-ones **2** (1 mmol) were dissolved in CH_2Cl_2 (10 mL). $BF_3{\cdot}OEt_2$ (2 mmol) and ATMS (3 mmol) were added to the reaction mixture and the solution was stirred for 5 min–24 h with TLC monitoring. The reaction solution was taken up in Et_2O (20 mL) and extracted with sat. aq $NaHCO_3$ (3 × 15 mL). The aqueous layer was adjusted to pH 2 with dil. HCl (10%), and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residual oils were purified by silica gel column chromatography, eluting with 25–40% EtOAc–hexane to afford the title products **3**.

N-Benzyloxycarbonyl-2-aminobut-3-enylethanoic Acid (3a)

Yield: 243 mg (89%); light yellow oil; $[\alpha]_D^{18}$ –0.4 (*c* 1.43, CH_2Cl_2).

IR (KBr): 3067, 3010, 2920–2849, 1701, 1477, 1430, 1367, 1290, 1227, 1148, 996, 952, 916, 770, 736, 698 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ (rotamers) = 9.68 (br s, 1 H, OH), 7.34–7.24 (m, 5 H, ArH), 5.80–5.66 (m, 1 H, CH_2=C*H*), 5.16–5.10 (m, 2 H, ArCH_2), 5.04–5.00 (m, 2 H, CH_2CO_2H), 4.05 (d, *J* = 16.3 Hz, 2 H, CH_2=CH), 3.44–3.37 (m, 2 H, NCH_2CH_2), 2.34–2.24 (m, 2 H, NCH_2CH_2).

^{13}C NMR (75 MHz, $CDCl_3$, 315 K): δ (rotamers) = 174.2, 174.0, 156.4, 155.6 (C=O), 135.9 (aryl C), 134.4 (CH_2=*C*H), 128.1, 127.6, 127.4 (aryl CH), 116.7 (*C*H_2=CH), 67.4 (Ar*C*H_2), 48.8, 48.4 (*C*H_2CO_2H), 48.1, 47.6 (N*C*H_2CH_2), 32.5, 31.9 (NCH_2CH_2).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}NO_4$: 264.1230; found: 264.1242.

N-Toluenesulfonyl-2-aminobut-3-enylethanoic Acid (3b)

Yield: 268 mg (95%); white solid; mp 100–102 °C; $[\alpha]_D^{18}$ –1.2 (*c* 1.04, CH_2Cl_2).

IR (KBr): 3300–3250, 3010–2926, 1732, 1495, 1338, 1158, 1090, 938, 814, 757, 668, 629 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ (rotamers) = 9.58 (br s, 1 H, OH), 7.71–7.66 (m, 2 H, ArH), 7.28–7.23 (m, 2 H, ArH), 5.66–5.59 (m, 1 H, CH_2=C*H*), 5.05–4.97 (m, 2 H, CH_2=CH), 4.08–4.03 (m, 2 H, CH_2CO_2H), 3.29–3.24 (m, 2 H, NCH_2CH_2), 2.39 (s, 3 H, CH_3), 2.29–2.21 (m, 2 H, NCH_2CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ (rotamers) = 174.2 (C=O), 143.4, 136.1 (aryl C), 133.9 (CH_2=*C*H), 129.5, 129.3, 126.9 (aryl CH), 117.1 (*C*H_2=CH), 47.8 (*C*H_2CO_2H), 47.6 (N*C*H_2CH_2), 32.1 (NCH_2CH_2), 21.1 (CH_3).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}NO_4S$: 284.0950; found: 284.0949.

(2*S*)-*N*-Benzyloxycarbonyl-2-aminobut-3-enylpropanoic Acid (3c)

Yield: 221 mg (80%); light yellow oil; $[\alpha]_D^{18}$ –21.5 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3050, 3010, 3000–2943, 1704, 1683, 1652, 1475, 1422, 1368, 1293, 1199, 1157, 1066, 1015, 915, 771, 736, 697 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ (rotamers) = 10.80 (br s, 1 H, OH), 7.33–7.30 (m, 5 H, ArH), 5.79–5.68 (m, 1 H, CH_2=C*H*), 5.15 (s, 2 H, ArCH_2), 5.05–4.99 (m, 2 H, CH_2=CH), 4.50–4.29 (m, 1 H, C*H*CH_3), 3.46–3.13 (m, 2 H, NCH_2), 2.37–2.29 (m, 2 H, NCH_2CH_2), 1.49–1.45 (m, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 310 K): δ (rotamers) = 176.6, 156.1

(C=O), 135.9 (aryl C), 134.7 (CH_2=*C*H), 128.1, 127.6, 127.4 (aryl CH), 116.3 (*C*H_2=CH), 67.2 (Ar*C*H_2), 55.3 (*C*HCH$_3$), 46.6, 45.8 (NCH$_2$), 33.7, 32.9 (NCH$_2$*C*H$_2$), 15.5, 14.9 (CH$_3$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{19}NO_4$: 278.1387; found: 278.1385.

(2*R*)-*N*-Benzyloxycarbonyl-2-aminobut-3-enylpropanoic Acid (3d)

Yield: 259 mg (94%); light yellow oil; $[\alpha]_D^{18}$ +19.9 (*c* 1.15, CH_2Cl_2).

IR (KBr): 3050, 3010, 3000–2943, 1698, 1682, 1423, 1372, 1292, 1008, 915, 770, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (rotamers) = 10.00 (br s, 1 H, OH), 7.33–7.30 (m, 5 H, ArH), 5.76–5.65 (m, 1 H, CH_2=C*H*), 5.20 (s, 2 H, ArC*H*$_2$), 5.05–4.99 (m, 2 H, C*H*$_2$=CH), 4.50–4.29 (m, 1 H, C*H*CH$_3$), 3.46–3.44 (m, 1 H, NCH$_2$), 3.23–3.13 (m, 1 H, NCH$_2$), 2.37–2.29 (m, 2 H, NCH$_2$C*H*$_2$), 1.50–1.35 (m, 3 H, CH$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ (rotamers) = 176.8, 156.1, 155.4 (C=O), 135.9 (aryl C), 134.6 (CH_2=*C*H), 128.1, 127.7, 127.4 (aryl CH), 116.4 (*C*H_2=CH), 67.2 (Ar*C*H_2), 55.3 (*C*HCH$_3$), 46.7, 45.7 (NCH$_2$), 33.7, 32.9 (NCH$_2$*C*H$_2$), 15.5, 14.9 (CH$_3$).

(2*S*)-*N*-Fluorenylmethoxycarbonyl-2-aminobut-3-enylpropanoic Acid (3e)

Yield: 298 mg (82%); light yellow solid; mp 89 °C; $[\alpha]_D^{23}$ –17.7 (*c* 1.67, CH_2Cl_2).

IR (KBr): 3050, 3010, 3000–2946, 1703, 1450, 1350, 1292, 1189, 1071, 759, 740 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 310 K): δ (rotamers) = 10.09 (br s, 1 H, OH), 7.75–7.27 (m, 8 H, ArH), 5.56 (s, 1 H, CH_2=C*H*), 5.01 (d, *J* = 9.3 Hz, 2 H, C*H*$_2$=CH), 4.54–4.21 (m, 4 H, CHC*H*$_2$O, C*H*CH$_3$ and C*H*CH$_2$O), 3.40–3.02 (m, 2 H, NCH$_2$), 2.15–2.04 (m, 2 H, NCH$_2$C*H*$_2$), 1.43–1.23 (m, 3 H, CH$_3$).

^{13}C NMR (75 MHz, $CDCl_3$, 310 K): δ (rotamers) = 176.7, 156.0 (C=O), 143.6, 141.1 (aryl C), 134.5 (CH_2=*C*H), 127.3, 126.7, 124.4, 119.6 (aryl CH), 116.3 (*C*H$_2$=CH), 67.0 (CH*C*H$_2$O), 55.3, 54.7 (*C*HCH$_3$), 47.0 (*C*HCH$_2$O), 45.8 (NCH$_2$), 33.3 (NCH$_2$*C*H$_2$), 14.8 (CH$_3$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{23}NO_4$: 366.1699; found: 366.1699.

(2*S*)-*N*-Trichloroethoxycarbonyl-2-aminobut-3-enylpropanoic Acid (3f)

Yield: 29 mg (76%); light yellow oil.

IR (KBr): 3450–2900, 3050, 3010–2951, 1716, 1698, 1475, 1422, 1292, 1155, 1104, 919, 763, 718 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (rotamers) = 8.85 (br s, 1 H, OH), 5.80–5.74 (m, 1 H, CH_2=C*H*), 5.11–5.02 (m, 2 H, C*H*$_2$=CH), 4.80–4.70 (m, 2 H, CH$_2$O), 4.47–4.45 (m, 1 H, C*H*CH$_3$), 3.52–3.45 (m, 1 H, NCH$_2$), 3.21–3.16 (m, 1 H, NCH$_2$), 2.46–2.33 (m, 2 H, NCH$_2$C*H*$_2$), 1.57–1.50 (m, 3 H, CH$_3$).

^{13}C NMR (75 MHz, $CDCl_3$, 315 K): δ (rotamers) = 176.6, 176.4, 154.2, 153.5 (C=O), 134.3 (CH_2=*C*H), 116.7 (*C*H$_2$=CH), 95.0 (CCl$_3$), 75.0 (CH$_2$O), 55.6 (*C*HCH$_3$), 47.4, 46.2 (NCH$_2$), 33.6, 32.6 (NCH$_2$*C*H$_2$), 15.5, 14.7 (CH$_3$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{14}Cl_3NO_4$: 318.0061; found: 318.0059.

(2*S*)-*N*-Benzyloxycarbonyl-2-aminobut-3-enyl(3-methyl)butanoic Acid (3g)

Yield: 299 mg (98%); light yellow oil; $[\alpha]_D^{20}$ +5.1 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3450–2900, 3050, 3010, 2970–2800, 1738, 1703, 1699, 1682, 1651, 1538, 1455, 1290, 1229, 1151, 988, 916, 771, 752, 697, 668 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (rotamers) = 10.20 (br s, 1 H, OH), 7.33–7.16 (m, 5 H, ArH), 5.72–5.16 (m, 1 H, CH_2=C*H*), 5.17 (s, 2 H, ArC*H*$_2$), 5.08–4.96 (m, 2 H, C*H*$_2$=CH), 4.05–3.95 (m, 1 H, C*H*CO$_2$H), 3.48–3.18 (m, 2 H, NCH$_2$), 2.37–2.30 [m, 3 H, NCH$_2$C*H*$_2$ and C*H*(CH$_3$)$_2$], 1.02 (d, *J* = 6.0 Hz, 3 H, CH$_3$), 0.90 (d, *J* = 6.3 Hz, 3 H, CH$_3$).

^{13}C NMR (75 MHz, $CDCl_3$, 315 K): δ (rotamers) = 174.0, 157.0 (C=O), 135.8 (aryl C), 134.3 (CH_2=*C*H), 128.1, 127.8, 127.5 (aryl CH), 116.6 (*C*H$_2$=CH), 67.5 (*C*HCO$_2$H), 47.1 (NCH$_2$), 32.9 (NCH$_2$*C*H$_2$), 27.4 [*C*H(CH$_3$)$_2$], 19.5, 18.8 (CH$_3$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}NO_4$: 306.1699; found: 306.1702.

(2*S*)-*N*-Fluorenylmethoxycarbonyl-2-aminobut-3-enyl(3-methyl)butanoic Acid (3h)

Yield: 314 mg (80%); clear colorless oil; $[\alpha]_D^{23}$ +13.3 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3067, 2970–2850, 1702, 1473, 1451, 1423, 1291, 1230, 1153, 1108, 1000, 918, 760, 738, 622 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (rotamers) = 9.88 (br s, 1 H, OH), 7.75–7.25 (m, 8 H, ArH), 5.74–5.39 (s, 1 H, CH_2=C*H*), 5.07–4.87 (m, 2 H, C*H*$_2$=CH), 4.68–4.54 (m, 2 H, CHC*H*$_2$O), 4.22 (t, *J* = 5.4 Hz, 1 H, C*H*CH$_2$O), 3.88 (d, *J* = 10.3 Hz, 1 H, C*H*CO$_2$H), 3.28–3.13 (m, 1 H, NCH$_2$), 2.98–2.89 (m, 1 H, NCH$_2$), 2,34–2.31 [m, 1 H, C*H*(CH$_3$)$_2$], 2.08–2.01 (m, 2 H, NCH$_2$C*H*$_2$), 1.01–0.68 (m, 6 H, 2 × CH$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ (rotamers) = 174.2, 156.9 (C=O), 143.4, 143.2, 141.1 (aryl C), 134.1 (CH_2=*C*H), 127.4, 126.8, 124.3, 119.7 (aryl CH), 116.6 (*C*H$_2$=CH), 67.4, (*C*HCO$_2$H), 67.0 (CH*C*H$_2$O), 47.0 (*C*HCH$_2$O), 32.6 (NCH$_2$), 27.5, 27.2 (NCH$_2$*C*H$_2$), 25.5 [*C*H(CH$_3$)$_2$], 19.5, 18.8 (CH$_3$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{27}NO_4$: 394.2012; found: 394.2015.

(2*S*)-*N*-Benzyloxycarbonyl-2-aminobut-3-enyl(4-methyl)pentanoic Acid (3i)

Yield: 271 mg (85%); light yellow oil; $[\alpha]_D^{23}$ –19.9 (*c* 1.0, CH_2Cl_2).

IR (KBr): 3070, 3035, 2958–2870, 1739, 1705, 1499, 1456, 1388, 1369, 1264, 1154, 916, 771, 735, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 320 K): δ (rotamers) = 10.83 (br s, 1 H, CO$_2$H), 7.32–7.24 (m, 5 H, ArH), 5.72 (s, 1 H, CH_2=C*H*), 5.16 (s, 2 H, ArC*H*$_2$), 5.06–4.98 (m, 2 H, C*H*$_2$=CH), 4.56 (s, 1 H, C*H*CO$_2$H), 3.47 (s, 0.6 H, NCH$_2$), 3.17–3.07 (m, 0.4 H, NCH$_2$), 2.41–2.30 (m, 2 H, NCH$_2$C*H*$_2$), 1.77–1.62 [m, 3 H, C*H*$_2$C*H*(CH$_3$)$_2$], 0.94 (d, *J* = 5.7 Hz, 6 H, 2 × CH$_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ (rotamers) = 177.2, 156.8, 155.9 (C=O), 136.2 (aryl C), 135.1, 134.79 (CH_2=*C*H), 128.4, 127.9, 127.8, 127.6 (aryl CH), 116.6 (*C*H$_2$=CH), 67.5 (Ar*C*H$_2$), 58.3, 57.9 (*C*HCO$_2$H), 46.9, 46.1 (NCH$_2$), 38.7, 38.0 [*C*H$_2$CH(CH$_3$)$_2$], 33.8, 32.9 (NCH$_2$*C*H$_2$), 24.7 [*C*H(CH$_3$)$_2$], 22.9, 21.7 (CH$_3$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{25}NO_4$: 320.1856; found: 320.1849.

(2*S*)-*N*-Fluorenylmethoxycarbonyl-2-aminobut-3-enyl(4-methyl)pentanoic Acid (3j)

Yield: 398 mg (98%); clear glass; $[\alpha]_D^{22}$ –19.9 (*c* 1.02, CH_2Cl_2).

IR (KBr): 3090, 2960–2850, 1701, 1477, 1450, 1420, 1368, 1293, 1226, 1046, 917, 758, 738, 621 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (rotamers) = 9.78 (br s, 1 H, OH), 7.75–7.30 (m, 8 H, ArH), 5.54–5.48 (s, 1 H, CH_2=C*H*), 5.08–4.90

(m, 2 H, CH_2=CH), 4.61–4.60 (d, J = 5.2 Hz, 2 H, CHCH_2O), 4.54–4.51 (m, 1 H, CHCH$_2$O), 4.22 (d, J = 4.5 Hz, 1 H, CHCO$_2$H), 3.44–2.83 (m, 2 H, NCH$_2$), 2.38–2.05 (m, 2 H, NCH$_2$CH_2), 1.79–1.53 [m, 3 H, CH_2CH(CH$_3$)$_2$], 0.94–0.78 (m, 6 H, 2 × CH$_3$).

^{13}C NMR (75 MHz, CDCl$_3$): δ (rotamers) = 176.9, 156.5 (C=O), 143.5, 141.1 (aryl C), 134.8, 134.5 (CH$_2$=CH), 127.3, 126.7, 124.4, 119.6 (aryl CH), 116.3 (CH$_2$=CH), 66.8 (CHCH$_2$O), 58.1, 57.5 (CHCO$_2$H), 47.1 (CHCH$_2$O), 46.4, 45.8 (NCH$_2$), 38.1, 37.7 [CH$_2$CH(CH$_3$)$_2$], 33.1, 32.7 (NCH$_2$$CH_2$), 24.4 [$C$H(CH$_3$)$_2$], 22.6, 21.4 (CH$_3$).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{25}H_{29}NO_4$: 408.2169; found: 408.2178.

(2*S*)-*N*-Phenylcarbonyl-2-aminobut-3-enyl(4-methyl)pentanoic Acid (3k)

Yield: 173 mg (60%); light yellow oil; [α]$_D^{20}$ –3.2 (*c* 2.0, CH$_2$Cl$_2$).

IR (KBr): 3050, 2960–2850, 1733, 1594, 1446, 1350, 1250, 1234, 987, 700, 668 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ (rotamers) = 10.71 (br s, 1 H, OH), 7.42–7.33 (m, 5 H, ArH), 5.77–5.71 (m, 0.6 H, CH$_2$=CH), 5.42–5.40 (m, 0.4 H, CH$_2$=CH), 5.07–4.78 (m, 2 H, CH_2=CH), 4.52 (s, 0.4 H, CHCO$_2$H), 4.26 (s, 0.6 H, CHCO$_2$H), 3.45–3.13 (m, 2 H, NCH$_2$), 2.51–2.17 (m, 2 H, NCH$_2$CH_2), 1.98–1.43 [m, 3 H, CH_2CH(CH$_3$)$_2$], 0.97–0.52 (m, 6 H, 2 × CH$_3$).

^{13}C NMR (75 MHz, CDCl$_3$): δ (rotamers) = 173.4, 173.2 (C=O), 135.5, 135.2, 135.1 (aryl C), 133.4 (CH$_2$=CH), 130.4, 129.4, 128.2, 128.1, 127.5, 126.8, 126.4 (aryl CH), 117.2, 116.6 (CH$_2$=CH), 60.0 (CHCO$_2$H), 43.9, 43.5 (NCH$_2$), 38.2, 37.6, 36.9 [CH$_2$CH(CH$_3$)$_2$], 33.2, 32.0 (NCH$_2$$CH_2$), 24.8, 24.6 [$C$H(CH$_3$)$_2$], 21.7, 21.2 (CH$_3$).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{17}H_{23}NO_3$: 290.1750; found: 290.1751.

(2*S*,3*S*)-*N*-Benzyloxycarbonyl-2-aminobut-3-enyl(3-methyl)pentanoic Acid (3l)

Yield: 268 mg (84%); clear colorless oil; [α]$_D^{25}$ +6.1 (*c* 1.0, CH$_2$Cl$_2$).

IR (KBr): 3750–2850, 1699, 1683, 1456, 1418, 1292, 916, 748, 696, 668, 643, 612 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ (rotamers) = 10.5 (br s, 1 H, CO$_2$H), 7.33–7.14 (m, 5 H, ArH), 5.69–5.64 (m, 2 H, CH$_2$=CH), 5.17 (s, 2 H, ArCH_2), 4.99 (d, J = 10.1 Hz, 2 H, CH_2=CH), 4.17 (d, J = 9.7 Hz, 1 H, CHCO$_2$H), 3.49–3.19 (m, 2 H, NCH$_2$), 2.31–2.29 (m, 2 H, NCH$_2$CH_2), 2.14–2.00 (m, 1 H, C$_2$H$_5$CHCH$_3$), 1.45–1.35 (m, 1 H, CH_2CH$_3$), 0.99–0.85 (m, 7 H, CH_2CH$_3$ and 2 × CH$_3$).

^{13}C NMR (75 MHz, CDCl$_3$, 315 K): δ (rotamers) = 174.3, 157.0 (C=O), 135.8 (aryl C), 134.4 (CH$_2$=CH), 128.1, 127.8, 127.5 (aryl CH), 116.6 (CH$_2$=CH), 67.6 (CHCO$_2$H), 66.0 (ArCH$_2$), 46.5 NCH$_2$), 33.5, (C$_2$H$_5$$CHCH_3$), 33.0 (NCH$_2$$CH_2$), 24.9 ($CH_2CH_3$), 15.6 (CH$_3$), 11.3, 10.4 (CH$_2$$CH_3$).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{18}H_{25}NO_4$: 320.1856; found: 320.1869.

(2*S*)-*N*-Benzyloxycarbonyl-2-aminobut-3-enyl(2-phenyl)ethanoic Acid (3m)

Yield: 333 mg (98%); white solid; mp 75–77 °C; [α]$_D^{20}$ +85.2 (*c* 1.3, CH$_2$Cl$_2$).

IR (KBr): 3050, 3033, 3000–2900, 1743, 1696, 1479, 1455, 1416, 1366, 1291, 1187, 1144, 973, 917, 973, 917, 742, 698, 636 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ (rotamers) = 10.33 (br s, 1 H, CO$_2$H), 7.37–7.23 (m, 10 H, ArH), 5.96 (s, 1 H, CHCO$_2$H), 5.48–5.40 (m, 1 H, CH$_2$=CH), 5.24 (s, 2 H, ArCH_2), 4.88–4.76 (m, 2 H, CH_2=CH), 3.50–3.40 (m, 1 H, NCHH), 3.18–3.10 (m, 1 H, NCHH), 2.15 (s, 1 H, NCH$_2$CHH), 1.74 (s, 1 H, NCH$_2$CHH).

^{13}C NMR (75 MHz, CDCl$_3$): δ (rotamers) = 175.0, 156.9 (C=O), 135.8 (aryl C), 134.6 (CH$_2$=CH), 133.7 (aryl C), 129.2, 128.5, 128.2, 127.8, 127.5 (aryl CH), 116.0 (CH$_2$=CH), 67.6 (CHCO$_2$H), 63.0 (ArCH$_2$), 44.8 (NCH$_2$), 33.3, 32.7 (NCH$_2$$CH_2$).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{20}H_{21}NO_4$: 340.1543; found: 340.1544.

(2*S*)-*N*-Benzyloxycarbonyl-2-aminobut-3-enyl(3-phenyl)propanoic Acid (3n)

Yield: 336 mg (95%); colorless oil; [α]$_D^{24}$ –118.3 (*c* 1.0, CH$_2$Cl$_2$).

IR (KBr): 3050, 3030, 3000–2900, 1701, 1479, 1474, 1454, 1291, 1222, 1028, 916, 752, 698 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ (rotamers) = 9.53 (br s, 1 H, OH), 7.33–7.06 (m, 10 H, ArH), 5.67–5.51 (m, 1 H, CH$_2$=CH), 5.25–5.07 (m, 2 H, ArCH$_2$O), 5.00–4.88 (m, 2 H, CH_2=CH), 4.24–4.22 (m, 1 H, CHCO$_2$H), 3.34–3.07 (m, 3 H, ArCH_2CHCO$_2$H and NCH$_2$), 2.74–2.65 (m, 1 H, NCH$_2$), 2.14–2.04 (m, 2 H, NCH$_2$CH_2).

^{13}C NMR (75 MHz, CDCl$_3$, 315 K): δ (rotamers) = 174.8, 155.9 (C=O), 137.2, 136.0 (aryl C), 134.5 (CH$_2$=CH), 128.8, 128.2, 128.1, 127.7, 127.5, 126.4 (aryl CH), 116.2 (CH$_2$=CH), 67.2 (ArCH$_2$O), 63.3 (CHCO$_2$H), 48.6 (NCH$_2$), 34.7 (ArCH$_2$CHCO$_2$H), 32.6 (NCH$_2$$CH_2$).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{15}H_{19}NO_4$: 354.1699; found: 354.1706.

(2*S*)-*N*-Fluorenylmethoxycarbonyl-2-aminobut-3-enyl(3-phenyl)propanoic Acid (3o)

Yield: 405 mg (92%); clear glass; [α]$_D^{23}$ –79.6 (*c* 1.04, CH$_2$Cl$_2$).

IR (KBr): 3050, 3000–2900, 1701, 1478, 1450, 1423, 1223, 1001, 740, 701 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ (rotamers) = 9.47 (br s, 1 H, OH), 7.77–7.12 (m, 13 H, ArH), 5.63–5.39 (m, 1 H, CH$_2$=CH), 4.93–4.83 (m, 2 H, CH_2=CH), 4.68–4.62 (m, 1 H, CHCO$_2$H), 4.58–4.46 (m, 1 H, CHCH$_2$O), 4.27–4.10 (m, 2 H, CHCH_2O), 3.39–2.91 (m, 2 H, CH_2Ar), 2.65–2.42 (m, 2 H, NCH$_2$), 2.05–1.89 (m, 2 H, NCH$_2$CH_2).

^{13}C NMR (75 MHz, CDCl$_3$, 315 K): δ (rotamers) = 174.9, 155.8 (C=O), 143.5, 141.1, 137.3 (aryl C), 134.4 (CH$_2$=CH), 128.8, 128.2, 127.3, 126.8, 126.3, 124.4, 119.6 (aryl CH), 116.1 (CH$_2$=CH), 66.9 (CH$_2$O), 63.2 (CHCO$_2$H), 48.5 (NCH$_2$), 47.1 (CHCH$_2$O), 34.7 (CH$_2$Ar), 32.3 (NCH$_2$$CH_2$).

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{28}H_{27}NO_4$: 442.2018; found: 442.2015.

(2*S*)-*N*-Benzyloxycarbonyl-2-aminobut-3-enyl(3-benzyloxyphenyl)propanoic Acid (3p)

Yield: 48 mg (20%); clear colorless oil.

IR (KBr): 3400–2850, 3050, 3032, 1698, 1683, 1511, 1471, 1455, 1422, 1372, 1293, 1240, 1176, 1108, 1001, 917, 831, 736, 696, 668 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ (rotamers) = 8.78 (br s, 1 H, OH), 7.42–6.83 (m, 14 H, ArH), 5.68–5.53 (m, 1 H, CH$_2$=CH), 5.25–5.10 (m, 2 H, ArCH$_2$O), 5.02 (s, 2 H, ArCH$_2$OAr), 5.00–4.90 (m, 2 H, CH_2=CH), 4.17–4.12 (m, 2 H, CHCO$_2$H), 3.32–3.06 (m, 3 H, ArCH_2CHCO$_2$ and NCH$_2$), 2.74 (d, J = 7.2 Hz, 1 H, NCH$_2$), 2.18–2.05 (m, 2 H, NCH$_2$CH_2).

^{13}C NMR (75 MHz, CDCl$_3$, 315 K): δ (rotamers) = 175.1 (CO$_2$H), 157.3 (aryl COCH$_2$), 156.0 (C=O), 136.6, 136.0 (aryl CCH$_2$), 134.9 (aryl CCH$_2$CHCO$_2$H), 134.5 (CH$_2$=CH), 129.8, 129.4, 128.2, 128.1, 127.9, 127.8, 127.6, 127.5, 127.1 (aryl CH), 116.4, 116.2 (CH$_2$=CH), 114.7 (aryl CHCO), 69.7 (ArCH$_2$OAr), 67.2 (ArCH$_2$OCO), 63.5, 62.2 (CHCO$_2$H), 48.7 (NCH$_2$), 34.8, 33.7 (ArCH$_2$CHCO$_2$H), 32.6, 32.1 (NCH$_2$$CH_2$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{28}H_{29}NO_5$: 460.2118; found: 460.2133.

(2*S*)-*N*-Benzyloxycarbonyl-2-aminobut-3-enylbutanedioic Acid (3q)

Yield: 174 mg (54%); clear colorless oil; $[\alpha]_D^{20}$ –43.7 (*c* 1.68, CH_2Cl_2).

IR (KBr): 3500–2700, 3030, 1714, 1699, 1683, 1746, 1423, 1373, 1227, 1080, 1003, 914, 772, 735, 699, 624 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (rotamers) = 11.35 (br s, 2 H, 2 × OH), 7.33–7.16 (m, 5 H, ArH), 5.74–5.72 (m, 1 H, CH_2=C*H*), 5.14–5.02 (m, 2 H, Ar*CH*$_2$), 4.95–4.93 (m, 2 H, *CH*$_2$=CH), 4.46–4.41 (m, 1 H, *CH*CO_2H), 3.54–3.25 (m, 2 H, NCH_2), 2.37–2.35 (m, 1 H, *CH*$_2CO_2H$), 2.06–2.03 (m, 1 H, *CH*$_2CO_2H$), 1.27–1.22 (m, 2 H, NCH_2*CH*$_2$).

^{13}C NMR (75 MHz, $CDCl_3$, 315 K): δ (rotamers) = 176.1, 174.9, 169.5, 155.7 (C=O), 135.8 (aryl C), 134.6 (CH_2=*C*H), 128.5, 128.1, 127.8, 127.4 (aryl CH), 116.6, 116.5 (*C*H$_2$=CH), 67.3, 67.1 (ArCH_2), 57.7, 56.9 (*C*HCO_2H), 48.8 (NCH_2), 35.7 34.9 (*C*H$_2CO_2H$), 32.9, 32.3 (NCH_2*C*H$_2$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{19}NO_6$: 322.1295; found: 322.1285.

(2*S*)-*N*-Benzyloxycarbonyl-2-aminobut-3-enyl-5-oxo-5-(2,2,2-trichloroethoxy)pentanoic Acid (3r)

Yield: 296 mg (64%); clear colorless oil; $[\alpha]_D^{19}$ –43.7 (*c* 1.91, CH_2Cl_2).

IR (KBr): 3050, 3030, 3000–2850, 1747, 1704, 1474, 1422, 1371, 1223, 1143, 916, 722, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (rotamers) = 10.24 (br s, 1 H, OH), 7.33–7.28 (m, 5 H, ArH), 5.71–5.69 (m, 1 H, CH_2=C*H*), 5.14 (d, *J* = 11.4 Hz, 2 H, Ar*CH*$_2$), 5.04 (dd, *J* = 10.4, 7.1 Hz, 2 H, *CH*$_2$=CH), 4.74–4.67 (m, 2 H, *CH*$_2CCl_3$), 4.36–4.26 (m, 1 H, *CH*CO_2H), 3.56–3.46 (m, 1 H, NCH_2), 3.17–3.07 (m, 1 H, NCH_2), 2.59–2.15 (m, 6 H, NCH_2*CH*$_2$, CH*CH*$_2$CH$_2$, CHCH$_2$*CH*$_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ (rotamers) = 175.5, 170.9, 156.1, 155.4 (C=O), 135.8, 135.5 (aryl C), 134.4 (CH_2=*C*H), 128.2, 127.8, 127.7, 127.4 (aryl CH), 116.7 (*C*H$_2$=CH), 94.5 (CCl_3), 73.6 (CH_2CCl_3), 67.4 (Ar*CH*$_2$), 59.4, 58.9 (*C*HCO_2H), 48.2, 47.5 (NCH_2), 33.2, 32.4 (NCH_2*C*H$_2$), 30.0 (CH_2*C*H$_2CO_2$), 24.7, 24.1 (*C*H$_2CH_2CO_2$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{22}Cl_3NO_6$: 466.0585; found: 466.0583.

(2*S*)-*N*-Fluorenylmethoxycarbonyl-2-aminobut-3-enyl-5-oxo-5-(2,2,2-trichloroethoxy)pentanoic Acid (3s)

Yield: 360 mg (65%); clear colorless oil; $[\alpha]_D^{21}$ –25.2 (*c* 1.98, CH_2Cl_2).

IR (KBr): 3068, 3000–2900, 1749, 1703, 1698, 1478, 1450, 1422, 1372, 1289, 1223, 1142, 1047, 912, 799, 759, 740, 621 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ (rotamers) = 10.12 (br s, 1 H, OH), 7.77–7.23 (m, 8 H, ArH), 5.70–5.46 (m, 1 H, C*H*=CH$_2$), 5.05–4.82 (m, 2 H, *CH*$_2$=CH), 4.73 (s, 2 H, CH_2CCl_3), 4.60 (d, *J* = 5.0 Hz, 2 H, CH_2O), 4.21–4.01 (m, 2 H, *CH*CH_2O and *CH*CO_2H), 3.44–2.87 (m, 2 H, NCH_2), 2.46–2.02 (m, 6 H, NCH_2*CH*$_2$, *CH*$_2CH_2CO_2$, and CH_2*CH*$_2CO_2$).

^{13}C NMR (75 MHz, $CDCl_3$): δ (rotamers) = 175.4, 170.9, 156.0 (C=O), 143.4, 141.1 (aryl C), 134.5, 134.3 (CH_2=*C*H), 127.4, 126.8, 124.4, 119.6 (aryl CH), 116.5 (*C*H$_2$=CH), 94.5 (CCl_3), 73.7 (CH_2CCl_3), 66.7 (CH*C*H$_2$O), 60.2, 59.4, 58.7 (*C*HCO_2H), 47.9 (*C*HCO_2H), 47.4, 47.0 (NCH_2), 32.8, 32.4 (NCH_2*C*H$_2$), 29.9 (CH_2*C*H$_2CO_2$), 24.3, 23.9 (*C*H$_2CH_2CO_2$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{26}H_{26}Cl_3NO_6$: 554.0898; found: 554.0892.

(2*S*)-*N*-Benzyloxycarbonyl-2-aminobut-3-enylpentanedioic Acid (3t)

Yield: 146 mg (43%); clear colorless oil; $[\alpha]_D^{20}$ –60.4 (*c* 1.46, CH_2Cl_2).

IR (KBr): 3450–2800, 3069, 1712, 1498, 1475, 1423, 1371, 1225, 1001, 915, 772, 735, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 315 K): δ (rotamers) = 11.53 (br s, 2 H, 2 × OH), 7.31 (s, 5 H, ArH), 5.73 (s, 1 H, CH_2=C*H*), 5.14 (s, 2 H, Ar*CH*$_2$), 5.09–4.98 (m, 2 H, *CH*$_2$=CH), 4.40–4.20 (m, 1 H, *CH*CO_2H), 3.51 (s, 1 H, NCH_2), 3.20–3.11 (m, 1 H, NCH_2), 2.59–2.02 (m, 6 H, CH_2*CH*$_2CO_2H$, NCH_2*CH*$_2$, *CH*$_2CH_2CO_2H$).

^{13}C NMR (75 MHz, $CDCl_3$): δ (rotamers) = 178.6, 176.3, 156.2, 155.5 (C=O), 135.8, 135.5 (aryl C), 134.5 (CH_2=*C*H), 128.2, 127.8, 127.4 (aryl CH), 116.6 (*C*H$_2$=CH), 67.4 (Ar*CH*$_2$), 59.4, 59.1 (*C*HCO$_2$H), 48.2, 47.4 (NCH_2), 33.2, 32.4 (*C*H$_2CO_2H$), 30.1 (NCH_2*C*H$_2$), 24.7, 24.0 (*C*H$_2CH_2CO_2H$).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{22}NO_6$: 336.1441; found: 336.1448.

Diazoketones 4; General Procedure

Ethyl chloroformate (3.1 mmol) in anhyd THF (5 mL) was added to a solution of PG-*N*-α-amino acid (3 mmol) and Et_3N (3.1 mmol) in THF (15 mL) at –15 °C and the mixture was stirred for 30 min at –5 °C under argon. The precipitated $Et_3NH^+Cl^-$ was filtered off. MeCN (10 mL) and $TMSCHN_2$ (6 mmol) were added to the filtrate and the mixture was stirred for 48 h at 4 °C. After that, Et_2O (30 mL) was added and the mixture was extracted sequentially with 10% aq citric acid (30 mL), sat. aq $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was separated and then dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was purified by chromatography (EtOAc–hexane, 1:3) to afford the title compound. Products **4a** and **4b** had spectra identical with those of an authentic sample.[7,14,29–31]

N-Protected β-Amino Acids 5; General Procedure

A mixture of *N*-α-aminoacyldiazomethane **4** (1 mmol), silver benzoate (2 mg, 0.08 mmol) in 1,4-dioxane (8 mL) and H_2O (2 mL) was prepared in a closed vessel. The reaction was performed for 60 sec at 110 °C, 200 W, and 60 psi. The remaining solvent was filtered off and evaporated under reduced pressure. The resulting residue was redissolved in 10% aq $NaHCO_3$ (20 mL). The aqueous layer was washed with Et_2O (2 × 20 mL) and acidified to pH 2 with aq 10% HCl and then extracted using EtOAc (3 × 20 mL). The combined organic layers were washed with H_2O (2 × 15 mL), dried (Na_2SO_4), and evaporated to obtain the title products **5**. Products **5a** and **5b** had spectra identical in all respects with the previously reported material.[4]

1,3-Oxazinan-6-ones 6; General Procedure

The method applied to synthesize 1,3-oxazinan-6-ones was the same as the method for synthesizing 1,3-oxazolidin-5-ones. Products **6a** and **6b** have spectra identical in all respects with the previously reported material.[7]

N-Protected *N*-But-3-enyl-β-amino Acids 7; General Procedure

The procedure for synthesizing *N*-but-3-enyl-β-amino acids **7** was the same procedure as for the preparation of *N*-but-3-enyl-α-amino acids **3**.

***N*-Benzyloxycarbonyl-3-aminobut-3-enylpropanoic Acid (7a)**

Yield: 20 mg (72%); light yellow oil.

IR (KBr): 3067, 3000–2900, 1730, 1704, 1480, 1423, 1368, 1291, 1218, 1189, 1138, 1028, 997, 916 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ (rotamers) = 9.58 (br s, 1 H, OH), 7.31–7.15 (m, 5 H, ArH), 5.70 (br s, 1 H, CH_2=C*H*), 5.11–5.08 (m, 2 H, ArCH_2), 5.01 (d, *J* = 9.8 Hz, 2 H, CH_2=CH), 3.55–3.45 (m, 2 H, C$H_2CH_2CO_2H$), 3.36–3.32 (m, 2 H, NCH_2), 2.71–2.59 (m, 2 H, CH_2CO_2H), 2.34–2.27 (m, 2 H, NCH_2CH_2).

^{13}C NMR (75 MHz, $CDCl_3$): δ (rotamers) = 175.8, 156.2 (C=O), 136.2 (aryl C), 134.6 (CH_2=*C*H) 128.1, 127.9, 127.8, 127.5, (aryl CH), 116.7 (*C*H_2=CH), 66.9 (Ar*C*H_2), 47.3 (NCH_2), 44.5 (*C*$H_2CH_2CO_2H$), 32.9 (CH_2*C*H_2CO_2H), 29.7 (NCH_2*C*H_2).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{18}NO_4$: 278.1392; found: 278.1397.

(2*S*)-*N*-Fluorenylmethoxycarbonyl-3-aminobut-3-enyl(4-methyl)pentanoic Acid (7b)

Yield: 23 mg (75%); amorphous solid.

IR (KBr): 3160, 3068, 3043, 3020, 3000–2850, 1698, 1667, 1463, 1450, 1388, 1291, 1149, 1000, 912 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ (rotamers) = 9.71 (br s, 1 H, OH), 7.73–7.25 (m, 8 H, ArH), 5.73–5.40 (m, 1 H, CH_2=C*H*), 5.01–4.85 (m, 2 H, CH_2=CH), 4.61–4.55 (m, 2 H, CHCH_2O), 4.19–4.12 (m, 1 H, C*H*CH_2O), 3.20 (m, 1 H, NCH_2), 2.66–2.63 (m, 1 H, C*H*CH_2CO_2H), 2.20–1.69 (m, 4 H, CHCH_2CO_2H, NCH_2CH_2), 1.26–1.10 [m, 1 H, C*H*$(CH_3)_2$], 0.92–0.75 (m, 3 H, CH_3), 0.57–0.46 (m, 3 H, CH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ (rotamers) = 177.1, 176.7, 155.7 (C=O), 143.8, 141.1 (aryl C), 135.0, 134.7 (CH_2=*C*H), 128.0, 127.2, 126.8, 126.7, 125.6, 124.4, 124.1, 119.5 (aryl CH), 116.1 (*C*H_2=CH), 66.0 (CH*C*H_2O), 61.8 (*C*HCH_2CO_2H), 47.2, 47.0 (*C*HCH_2O), 46.4 (NCH_2), 36.8, 36.4 (*C*H_2CO_2), 33.2, 32.5, 31.5 [*C*H$(CH_3)_2$], 30.9, 30.5 (NCH_2*C*H_2), 19.6, 19.3 (2 × CH_3).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{30}NO_4$: 408.2169; found: 408.2175.

(2*S*)-*N*-Benzyloxycarbonyl-2-aminobut-2-methyl-3-enylpropanoic Acid (14)

(*S*)-3-Benzyloxycarbonyl-4-methyl-1,3-oxazolidin-5-one (**11**; 0.15 mmol) was dissolved in CH_2Cl_2 (5 mL). $BF_3{\cdot}OEt_2$ (0.3 mmol) and ATMS (0.45 mmol) were added to the reaction mixture and the solution was stirred for 18 h with TLC monitoring. The reaction solution was taken up in Et_2O (10 mL) and extracted with aq sat. $NaHCO_3$ (3 × 10 mL). The aqueous layer was adjusted to pH 2 with 10% dil. HCl, and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residual oils were purified via silica gel column chromatography, eluting with 30% EtOAc–hexane to afford the title product; yield: 17.5 mg (40%); light yellow oil.

IR (KBr): 3400–2900, 3068, 3033, 2980–2900, 1694, 1668, 1470, 1446, 1429, 1255, 1207, 1172, 1101, 1080, 1014, 917 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ (rotamers) = 7.62–7.51 (m, 5 H, ArH), 5.66 (br s, 1 H, CH_2=C*H*), 5.12 (s, 2 H, ArCH_2), 4.96 (br s, 2 H, CH_2=CH), 4.13 (br s, 1 H, CH_3CHCO_2H), 3.34–3.09 (m, 2 H, NCH_2), 2.47 (br s, 1 H, NCH_2CHCH_3), 1.69–1.32 (m, 3 H, CH_3CHCO_2H) 0.98–0.82 (m, 3 H, NCH_2CHCH_3).

^{13}C NMR (75 MHz, $CDCl_3$): δ (rotamers) = 175.8, 156.4, 155.7 (C=O), 140.7 (aryl C), 135.8, 135.5, 135.3 (CH_2=*C*H), 129.4, 128.6, 128.1, 127.7, 127.6 (aryl CH), 114.5 (*C*H_2=CH), 67.2 (Ar*C*H_2), 57.0, 56.5 (CH_3CHCO_2H), 53.2, 52.8 (NCH_2), 37.6, 37.4 (NCH_2CHCH_3), 17.1, 17.0 (NCH_2CHCH_3), 15.5, 14.8, 13.9 (CH_3CHCO_2H).

MS (ESI, 3000V): *m*/*z* (%) = 314 (100, [M + Na]), 292 (20, [M + H]).

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