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Highly diastereoselective monoalkylation and Michael addition of *N*-(diphenylmethylene)glycinesultam under solid–liquid phase-transfer catalysis conditions using potassium carbonate as base

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Abstract

Treatment of a sultam-derived *N*-(diphenylmethylene)glycinate equivalent **1** with activated (allylic and propargylic) organic bromides and with Michael acceptors under solid–liquid phase-transfer catalysis conditions, using potassium carbonate as base, affords the monoalkylated compounds with high diastereoselectivity (>97% d.e.).

1. Introduction

Aldimines and ketimines of glycine esters are useful anionic equivalents for the preparation of amino acids.[1] O'Donnell has reported[2] that mono- and dialkylations of aldimines and monoalkylations (but not dialkylations) of ketimines can be carried out under several phase transfer catalysis (PTC) conditions.[3] The same author and others have described[4] asymmetric monoalkylations of the benzophenone imine of glycine esters under liquid–liquid or solid–liquid PTC conditions by using chiral catalysts based on cinchonine and cinchonidine alkaloids. Ketimines offer advantages over aldimines due to their superior stability and commercial availability. We have found[5] that not only monosubstituted but also disubstituted racemic amino acid derivatives can be obtained by alkylation (activated organic bromides) and Michael additions of *N*-(diphenylmethylene)glycinate under solid–liquid PTC conditions, potassium carbonate being required for the introduction of the first alkyl group on the α-position and potassium hydroxide or sodium ethoxide for the introduction of the second chain.

Several synthetic approaches have been reported in the literature to the asymmetric synthesis of substituted amino acids by α-alkylation of chiral glycine and alanine equivalents,[1,6] including Schöllkopf's bis(lactim) ether, Seebach's oxazolidinones and imidazolidinones, and Williams' diphenylox-

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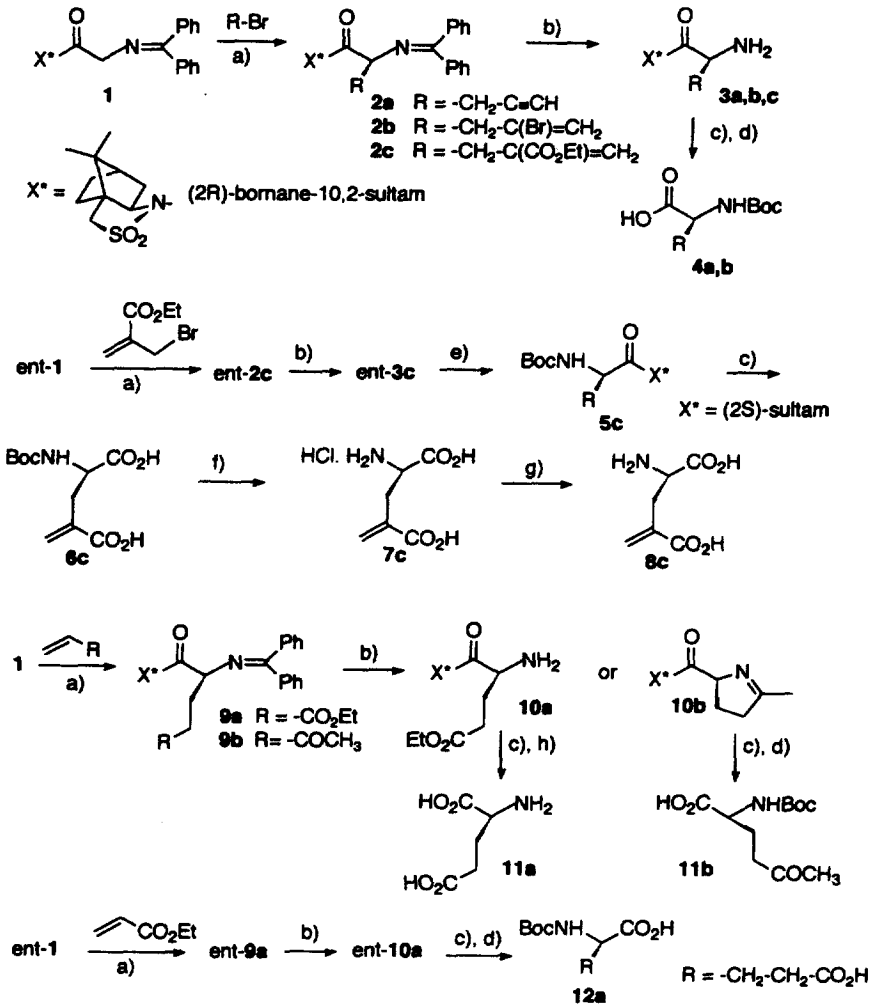
azinones as chiral building blocks. Very recently, Nájera[7] reported that a chiral alanine equivalent, 6-isopropyl-3-methyl-6-phenyl-2,3-dihydro-6*H*-1,4-oxazin-2-one, reacts with several electrophiles (activated halides and Michael acceptors) under PTC conditions. On the other hand, several ketone chiral auxiliaries have been used for the diastereoselective alkylation or Michael addition of chiral glycinate Schiff bases, i.e. 2-hydroxypinan-3-one,[1,8] camphor,[1] *N*-alkylcamphorsulfonamides,[9] *o*-[(*N*-benzylprolyl)amino]benzophenone (through the Ni(II) complex of the corresponding Schiff base)[10] and 4-formyl-5-hydroxy[2.2]paracyclophane.[11] Alternatively, chiral alcohols (i.e. binaphthol,[12] carbohydrate derivatives,[13] 8-phenylmenthyl[14]) and Oppolzer's bornane-10,2-sultam[15–17] have also been described as chiral auxiliaries for enolate alkylation of Schiff bases derived from glycine. In most of these cases, strong bases (*n*-BuLi, LDA) and low temperature conditions were used to deprotonate the glycine Schiff bases, only monoalkylations being described. Exceptionally, Chassaing[16] achieves the benzylation of 4-chlorobenzaldehyde aldimine of sultam-derived alanine under solid–liquid PTC conditions. Oppolzer[15b] also reports the reaction of a sultam-derived glycine ketimine with activated organohalides under ultrasound-assisted liquid–liquid PTC conditions (LiOH as base), hydrolysis of the *N*-acyl group being competitive without ultrasonication.

Here, we want to present the highly diastereoselective version of the PTC monoalkylation and Michael addition by use of Oppolzer's camphor sultam as chiral auxiliary. Our results are summarized in Scheme 1. Table 1 collects the yields of all synthesized compounds, their melting points and specific rotations, the configuration of Cα and some data from the literature when available.

2. Results and discussion

(2*R*)-Sultam glycine derivative **1**[17c] was reacted with propargyl bromide, 2,3-dibromopropene and ethyl 2-bromomethylpropenoate[18] under the solid–liquid PTC conditions indicated in Scheme 1 (K_2CO_3 as base) to afford the monoalkylated compounds **2a–c**. Subsequent mild hydrolysis of the imino group gave the amino derivatives **3a–c**. Compounds **3a,b** were converted into the *N*-Boc amino acid derivatives **4a,b** by removal of the sultam moiety (which was recovered quantitatively) and subsequent treatment with $(Boc)_2O$ under ultrasonic irradiation. Their melting points and specific rotations were concordant with those described in the literature[19,20] for pure *S* isomers. The differences in the specific rotations of **4b** may be due to errors in the measurement of a small α value. By analogous procedures, compounds ent-**2c** and ent-**3c** were obtained from ent-**1** (prepared from (2*S*)-bornane-10,2-sultam and ethyl *N*-(diphenylmethylene)glycinate). An X-ray diffraction analysis of the Schiff base ent-**2c** confirmed the presumed *R* configuration for the α carbon. Crystallographic details will be published elsewhere. The amino compound **3c** was converted to *N*-Boc derivative **5c**, from which *N*-*tert*-butoxycarbonyl-4-methyleneglutamic acid, **6c**, was obtained by selective removal of the chiral auxiliary and estersaponification. Treatment of **6c** with hydrogen chloride in ethyl acetate solution afforded the hydrochloride **7c**, which was reacted with propylene oxide to give the free amino acid **8c**. The experimental $[\alpha]_D$ of **8c** had the same value but opposite sign as for the described *S* isomer[21] (see Table 1).

On the other hand, Michael additions of **1** with ethyl acrylate and 3-buten-2-one were performed under the solid PTC conditions described in Scheme 1 (K_2CO_3 as base) to give diastereoselectively **9a** and **9b**. Hydrolysis of these Schiff bases with 15% citric acid afforded **10a** and **10b** respectively, an intramolecular imine formation taking place in the last case. Compound **10a** was converted to natural (*S*)-glutamic acid, **11a**,[22] by cleavage of sultam and ester groups with LiOH at 0°C in H_2O–THF, acidification and ion exchange chromatography. Imine **10b** was transformed into the amino acid derivative **11b** by removal of the auxiliary and N-protection (attempted purification of the amino acid hydrochloride



a) K_2CO_3, cat Bu_4NBr, CH_3CN, rt for **2c**, **9a-b** and reflux for **2a,b**. b) 1M HCl or 15% citric acid, H_2O/Et_2O, rt; then K_2CO_3. c) i) 2.5 M LiOH, H_2O/THF, 0° C; ii) 1M HCl or HBr, pH = 2. d) $(Boc)_2O$, $NaHCO_3$, EtOH,))). e) $(Boc)_2O$, refl $CHCl_3$. f) $HCl_{(g)}$, AcOEt, rt. g) propylene oxide, EtOH, rt. h) Dowex 50Wx8.

Scheme 1.

by ion exchange chromatography failed). A Michael addition between ent-**1** and ethyl acrylate was also achieved to give ent-**9a**, which was converted to (*R*)-*N*-(*tert*-butoxycarbonyl)glutamic acid, **12a**, through the aminoester ent-**10a**. Compound **12a** had the same specific rotation absolute value, but opposite sign, as the described *S* isomer[22] (see Table 1). In our monoalkylations and conjugate additions only one diastereoisomer was observed by ^1H NMR and TLC. When monoalkylated compounds were converted to known amino acid derivatives, the specific rotation indicated optical purities of ca 100%. A rationalization of the diastereoselectivity in PTC alkylations of a sultam-derived glycine equivalent has been proposed by Oppolzer.[15b]

Table 1
Some data for compounds **2–12**

Compd	% [a]	mp (C)	lit. mp	$[\alpha]_D$	lit. $[\alpha]_D$	Conf.
2a	82	84-85	----	-38.7 (c = 1.5, $CHCl_3$)	----	S
2b	80	193	----	-91.8 (c = 1.5, $CHCl_3$)	----	S
2c	83	150	----	-96.0 (c = 1.5, $CHCl_3$)	----	S
3a	84	153-154	----	-95.7 (c = 1.5, $CHCl_3$)	----	S
3b	73	97-98	----	-49.3 (c = 1.5, $CHCl_3$)	----	S
3c	84	119-120	----	-50.0 (c = 1.5, $CHCl_3$)	----	S
4a	76	84-85	84-85[b]	+23.6 (c = 1.95, CH_3OH)	+23.5 (c = 0.91, CH_3OH)[b]	S
4b	73	95	96[c]	+5.0 (c = 1.5, $CHCl_3$)[d]	+8.3 (c = 1.0, $CHCl_3$)[c]	S
ent-2c	81	150	----	+96.0 (c = 1.5, $CHCl_3$)	----	R[e]
ent-3c	85	119-120	----	+50.0 (c = 1.5, $CHCl_3$)	----	R
5c	95	oil	----	+50.7 (c = 1.5, $CHCl_3$)	----	R
6c	86	137	----	-24.8 (c = 0.94, $CHCl_3$)	----	R
7c	97	...[f]	---	-13.2 (c = 0.5, 5M HCl)	see **8c**	R
8c	92	192-194	192-194[g] 192-195[h]	-13.2 (c = 0.5, 5M HCl)	for S isomer: +12.8 (c = 0.53, 5M HCl)[g] +13.2 (c = 0.56, 5M HCl)[h]	R
9a	74	oil	----	-42.7 (c = 1.5, $CHCl_3$)	----	S
9b	90	146-147	----	-55.0 (c = 1.3, $CHCl_3$)	----	S
10a	69	oil	----	-72.0 (c = 0.5, CH_3OH)	----	S
10b	85	144-145	----	-70.2 (c = 0.85, $CHCl_3$)	----	S
11a	29	223-225	224-225[i]	+31.5 (c = 1.0, 6M HCl)	+31.4 (c = 1.0, 6M HCl)[i]	S
11b	69	oil	----	-14.0 (c = 1.15, $CHCl_3$)	----	S
ent-9a	82	oil	----	+42.7 (c = 1.5, $CHCl_3$)	----	R
ent-10a	72	oil	----	+72.0 (c = 0.5, CH_3OH)	----	R
12a	75	108-109	108-109[j]	+16.0 (c = 1.0, CH_3OH)	for S isomer: -16.1 (c = 1.0, CH_3OH)[j]	R

[a] Yield of isolated pure compound. [b] Lit. ref. 19. [c] Lit. ref. 20. [d] From o.r.d.: $[\alpha]_{217.6} = 102.7$; $[\alpha]_{222.6} = 95.7$, c = 0.5, CH_3OH. [e] Determined by X-Ray diffraction. [f] Hygroscopic solid. [g] Lit. ref. 21a. [h] Lit. ref. 21b. [i] Lit. ref. 22. [j] Lit ref. 23.

3. Experimental section

^1H NMR (^{13}C NMR) spectra were registered at 250 MHz (62.5 MHz) using tetramethylsilane as internal standard and data are given in δ units. Mass spectra were determined under electron impact at 70 eV unless otherwise stated. Melting points are uncorrected. (2*R*)- and (2*S*)-Bornane-10,2-sultam were purchased from Oxford Asymmetry and also prepared as described.[24] Glycine derivatives **1** and ent-**1** were synthesized according to the literature procedure.[17c] Ethyl α-hydroxymethylacrylate was prepared as reported.[18] Acetonitrile was distilled over P_2O_5.

3.1. (2R)-N-[(2S)-2-((Diphenylmethylidene)amino)-4-pentin-1-oyl]bornane-10,2-sultam **2a**

To a magnetically stirred mixture of potassium carbonate (4.1 g, 29.8 mmol) and tetrabutylammonium bromide (0.33 g, 0.99 mmol) in anhydrous acetonitrile (50 ml) was added a solution of **1** (4.30 g, 9.85 mmol) and propargyl bromide (2.40 g, 20.2 mmol) in anhydrous acetonitrile (50 ml). The mixture was heated under reflux for 5 h (TLC monitoring), then it was filtered and the solvent from the filtrate was evaporated, the residue redissolved in diethyl ether (100 ml) and washed with distilled water (3×75 ml). The organic layer was dried with anhydrous sodium sulfate and the solvent evaporated to yield a crude oil, which was chromatographed on silica gel under pressure, eluting with hexane:ethyl acetate mixtures of increasing polarity, from 9.5:0.5 to 7:3. The Schiff base **2a** was further purified by recrystallization from diethyl ether:hexane (3.84 g, 82%); m.p. 84–85°C; $[\alpha]_D^{20} = -38.7$ (c=1.5, $CHCl_3$); IR (KBr, cm^{-1}):

3282, 1700, 1614; ^{1}H NMR ($CDCl_3$): 0.94 (s, 3H), 1.06 (s, 3H), 1.18–1.36 (m, 2H), 1.66–1.85 (m, 3H), 1.99 (apparent t, J=2.5 Hz, 1H), 2.06–2.10 (m, 2H), 2.76 (ddd, J=16.1 Hz, 5.8 Hz, 2.9 Hz, 1H), 2.89 (ddd, J=16.1 Hz, 5.8 Hz, 2.2 Hz, 1H), 3.32 (d, J=13.2 Hz, 1H), 3.41 (d, J=13.2 Hz, 1H), 3.92 (dd, J=7.2 Hz, 5.4 Hz, 1H), 4.89 (t, J=5.8 Hz, 1H), 7.12–7.72 (m, 10H); ^{13}C NMR ($CDCl_3$): 19.8, 20.5, 25.1, 26.4, 32.6, 38.1, 44.4, 47.7, 48.4, 52.9, 63.7, 65.1, 71.0, 79.7, 127.8, 127.9, 128.4, 128.7, 129.0, 130.3, 135.6, 139.3, 170.7, 171.6; MS (m/z, %): 474 (M^+, 2), 473 (M−1, 6), 232 (100), 220 (12), 192 (27), 165 (19), 128 (13). Anal. calcd for $C_{28}H_{30}N_2SO_3$: C, 70.86; H, 6.38; N, 5.91; S, 6.74. Found: C, 70.72; H, 6.87; N, 5.50; S, 6.34.

3.2. (2R)-N-[(2S)-2-((Diphenylmethylidene)amino)-4-bromo-4-penten-1-oyl]bornane-10,2-sultam **2b**

Prepared as for **2a**. The crude solid residue was purified by digestion in diethyl ether to afford **2b** in 80% yield; m.p. 193°C; $[\alpha]_D^{20}$=−91.8 (c=1.5, $CHCl_3$); IR (KBr, cm^{-1}): 1708, 1630; ^{1}H NMR ($CDCl_3$): 0.93 (s, 3H), 1.11 (s, 3H), 1.25–1.46 (m, 2H), 1.78–2.13 (m, 5H), 2.86 (dd, J=13.9 Hz, 7.3 Hz, 1H), 3.29 (dd, J=13.9 Hz, 6.6 Hz, 1H), 3.34 (d, J=13.8 Hz, 1H), 3.41 (d, J=13.8 Hz, 1H), 3.93 (dd, J=7.3 Hz, 5.1 Hz, 1H), 5.11 (apparent t, J=6.9 Hz, 1H), 5.43 (d, J=1.5 Hz, 1H), 5.69 (broad s, 1H), 7.17–7.72 (m, 10H); ^{13}C NMR ($CDCl_3$): 19.8, 20.7, 26.4, 32.7, 38.3, 44.5, 46.3, 47.8, 48.5, 53.0, 63.7, 65.3, 120.3, 127.9, 128.2, 128.4, 128.6, 128.7, 130.0, 130.3, 135.7, 139.5, 171.3, 171.7. Anal. calcd for $C_{28}H_{31}N_2SO_3Br$: C, 60.64; H, 5.64; N; 5.05; S, 5.77; Br, 14.20. Found: C, 60.42; H, 5.61; N, 5.00; S, 5.62; Br, 14.35.

3.3. (2R)-N-[(2S)-2-((Diphenylmethylidene)amino)-4-ethoxycarbonyl-4-penten-1-oyl]bornane-10,2-sultam **2c**

Prepared as for **2a**, but the reaction was performed at room temperature for 6 h. The crude solid residue was recrystallized from diethyl ether to give **2c** in 83% yield; m.p. 150°C; $[\alpha]_D^{20}$=−96.0 (c=1.5, $CHCl_3$); IR (KBr, cm^{-1}): 1715, 1694, 1623; ^{1}H NMR ($CDCl_3$): 0.91 (s, 3H), 1.06 (s, 3H), 1.10 (t, J=6.9 Hz, 3H), 1.25–1.45 (m, 2H), 1.77–1.95 (m, 3H), 1.95–2.11 (m, 2H), 2.78 (dd, J=13.2 Hz, 7.3 Hz, 1H), 3.08 (dd, J=13.2 Hz, 6.6 Hz, 1H), 3.31 (d, J=13.5 Hz, 1H), 3.38 (d, J=13.5 Hz, 1H), 3.93 (t, J=5.1 Hz, 1H), 3.975 (m, 2H), 5.03 (apparent t, J=6.9 Hz, 1H), 5.58 (s, 1H), 6.19 (d, J=1.5 Hz, 1H), 7.15–7.68 (m, 10H); ^{13}C NMR ($CDCl_3$): 14.5, 20.4, 21.2, 26.9, 33.4, 37.7, 38.8, 45.1, 48.2, 48.9, 53.7, 61.2, 64.8, 65.9, 128.4, 128.7, 128.8, 129.0, 129.3, 130.7, 136.4, 136.8, 140.2, 166.8, 171.2, 172.3. Anal. calcd for $C_{31}H_{36}N_2O_5S$: C, 67.85; H, 6.62; N, 5.11; S, 5.83. Found: C, 67.68; H, 6.67; N, 5.06; S, 5.76.

3.4. (2R)-N-[(2S)-2-Amino-4-pentin-1-oyl]bornane-10,2-sultam **3a**

A vigorously magnetically stirred mixture of **2a** (1.10 g, 2.32 mmol) in diethyl ether (30 ml) and 1 M hydrochloric acid (30 ml, 28.3 mmol) was left at room temperature for 10 h (TLC monitoring). The two phases were separated, the aqueous layer was washed with diethyl ether (3×25 ml) to separate benzophenone, then it was basified with potassium carbonate and extracted with ethyl acetate (3×30 ml). The combined ethyl acetate extracts were dried with anhydrous sodium sulfate and the solvent was evaporated to give a solid residue which was recrystallized from diethyl ether, yielding **3a** (0.60 g, 84%); m.p. 153–154°C; $[\alpha]_D^{20}$=−95.7 (c=1.5, $CHCl_3$); IR (KBr, cm^{-1}): 3393, 3286, 1701; ^{1}H NMR ($CDCl_3$): 0.95 (s, 3H), 1.14 (s, 3H), 1.25–1.48 (m, 2H), 1.72 (broad s, 2H), 1.81–1.97 (m, 3H), 2.00 (t, J=2.8 Hz, 1H), 2.02–2.08 (m, 2H), 2.62 (ddd, J=16.8 Hz, 5.8 Hz, 2.8 Hz, 1H), 2.71 (ddd, J=16.8 Hz, 5.8 Hz, 2.8 Hz, 1H), 3.41 (d, J=13.9 Hz, 1H), 3.49 (d, J=13.9 Hz, 1H), 3.89 (t, J=6.2 Hz, 1H), 4.16 (t, J=5.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): 19.9, 20.6, 25.6, 26.5, 32.7, 38.1, 44.6, 47.8, 48.8, 53.0, 53.4, 65.1, 71.5, 79.0,

173.9; Anal. calcd for $C_{15}H_{22}N_2SO_3$: C, 58.04; H, 7.15; N, 9.03; S, 10.31. Found: C, 58.01; H, 7.27; N, 9.00; S, 10.35.

3.5. (2R)-N-[(2S)-2-Amino-4-bromo-4-penten-1-oyl]bornane-10,2-sultam 3b

Prepared as for **2b**, but the organic solvent for the reaction was a 4:1 mixture of diethyl ether:ethyl acetate. The acidic aqueous phase was extracted with ethyl acetate, and the basic one with chloroform. The crude solid residue was purified by digestion in diethyl ether to afford **3b** (73%); m.p. 97–98°C; $[\alpha]_D^{20}=-49.3$ (c=1.5, $CHCl_3$); IR (KBr, cm^{-1}): 3381, 3311, 1687, 1630; ^1H NMR ($CDCl_3$): 0.98 (s, 3H), 1.16 (s, 3H), 1.27–1.50 (m, 2H), 1.67 (broad s, 2H), 1.70–2.10 (m, 5H), 2.60 (dd, J=14.6 Hz, 7.3 Hz, 1H), 2.94 (dd, J=14.6 Hz, 6.2 Hz, 1H), 3.46 (d, J=13.9 Hz, 1H), 3.51 (d, J=13.9 Hz, 1H), 3.89 (apparent t, J=6.6 Hz, 1H), 4.38 (m, 1H), 5.54 (d, J=2.2 Hz, 1H), 5.67 (broad s, 1H); ^{13}C NMR ($CDCl_3$): 19.3, 20.2, 25.9, 32.3, 37.7, 44.2, 46.1, 47.3, 48.2, 52.5, 64.7, 119.7, 128.2, 173.9; MS (m/z, %): 392 (M^+, 0.1), 271 (14), 150 (100), 148 (99), 136 (14), 119 (14), 108 (14), 93 (17), 68 (12), 41 (19). Anal calcd for $C_{15}H_{23}N_2SO_3Br$: C, 46.04; H, 5.92; N, 7.16; S, 8.19; Br, 20.42. Found: C, 46.39; H, 6.12; N, 6.98; S, 7.83; Br, 19.77.

3.6. (2R)-N-[(2S)-2-Amino-4-ethoxycarbonyl-4-penten-1-oyl]bornane-10,2-sultam 3c

A 15% aqueous solution of citric acid (40 g, 30.6 mmol) was added to a solution of **2c** (1.40 g, 2.55 mmol) in diethyl ether (40 ml) and the vigorously magnetically stirred mixture was left at room temperature for 18 h (TLC monitoring). The phases were separated and the aqueous layer was washed with diethyl ether (3×50 ml) to remove benzophenone, then it was basified with potassium carbonate and extracted with chloroform (3×50 ml). The combined chloroformic extracts were dried with anhydrous sodium sulfate and the solvent was evaporated to give a residue, which was digested in diethyl ether to yield **3c** (0.82 g, 84%) as white crystals; m.p. 119–120°C; $[\alpha]_D^{20}=-50.0$ (c=1.5, $CHCl_3$); IR (KBr, cm^{-1}): 3374, 3304, 1722, 1680; ^1H NMR ($CDCl_3$): 0.94 (s, 3H), 1.12 (s, 3H), 1.28 (t, J=7.3 Hz, 3H), 1.27–1.43 (m, 2H), 1.60 (broad s, 2H), 1.80–1.94 (m, 3H), 1.94–2.08 (m, 2H), 2.68 (d, J=7.3 Hz, 2H), 3.40 (d, J=13.9 Hz, 1H), 3.49 (d, J=13.9 Hz, 1H), 3.87 (t, J=6.2 Hz, 1H), 4.16 (t, J=7.3 Hz, 1H), 4.23 (q, J=7.3 Hz, 2H), 5.61 (s, 1H), 6.20 (s, 1H); ^{13}C NMR ($CDCl_3$): 14.2, 20.0, 20.9, 26.6, 33.1, 37.6, 38.4, 45.0, 48.0, 48.9, 53.4, 54.0, 61.2, 65.6, 128.5, 137.4, 167.6, 176.6. Anal. calcd for $C_{18}H_{28}N_2O_5S$: C, 56.22; H, 7.35; N, 7.29; S, 8.32. Found: C, 56.09; H, 7.39; N, 7.25; S, 8.12.

3.7. (S)-2-tert-Butoxycarbonylamino-4-pentinoic acid 4a

A 2.5 M aqueous solution of lithium hydroxide (1.5 ml, 3.88 mmol) was added at 0°C to a magnetically stirred solution of **3a** (0.31 g, 0.97 mmol) in THF (2 ml). The stirred mixture was left at 0°C for 1 h. The THF was evaporated, the aqueous solution was acidified with 1 M hydrochloric acid until pH=2 and extracted with ethyl acetate (3×5 ml). The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated to recover the bornane-10,2-sultam quantitatively, which was recrystallized from ethanol. The aqueous phase was evaporated to dryness, giving a mixture of lithium chloride and the hydrochloride of (*S*)-2-amino-4-pentinoic acid [^1H NMR (CD_3OD): 2.51 (t, J=2.9 Hz, 1H), 2.80 (dd, J=5.1 Hz, 2.9 Hz, 2H), 4.04 (t, J=5.1 Hz, 1H)]. A mixture of this crude residue, di-*tert*-butyl dicarbonate (0.22 g, 1.01 mmol) and sodium hydrogenocarbonate (0.37 g, 4.40 mmol) in absolute ethanol (20 ml) was sonicated for 5 h. The mixture was filtered through Celite and the solvent from the filtrate was evaporated. The residue was redissolved in dichloromethane (25 ml) and washed with 1 M hydrochloric acid (3×25

ml). The organic layer was dried with anhydrous sodium sulfate and the solvent evaporated to give **4a** (0.16 g, 76% yield from **3a**), which was recrystallized from diethyl ether:hexane; m.p. 84–85°C (lit.[19] m.p. 84–85°C); $[\alpha]_D^{20}$=+23.6 (c=1.95, CH_3OH) (lit.[19] $[\alpha]_D$=+23.5, c=0.91, CH_3OH); IR (film, cm^{-1}): 3650–2200 (br), 1715 (br); ^1H NMR ($CDCl_3$): 1.40 (s, 9H), 2.07 (t, J=2.9 Hz, 1H), 2.65–2.81 (m, 2H), 4.42–4.56 (m, 1H), 5.32 (broad d, J=8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$): 22.5, 28.2, 51.8, 71.9, 78.3, 80.6, 155.4, 175.0.

3.8. (S)-4-Bromo-2-tert-butoxycarbonylamino-4-pentenoic acid 4b

Prepared as for **4a** in 73% overall yield. The crude solid was washed with diethyl ether and cold dichloromethane; m.p. 95°C (lit.[20] m.p. 96°C); $[\alpha]_D^{20}$=+5.0 (c=1.5, $CHCl_3$) (lit.[20] $[\alpha]_D$=+8.3, c=1.0, $CHCl_3$); IR (KBr, cm^{-1}): 3339, 1736, 1652; ^1H NMR ($CDCl_3$): 1.44 (s, 9H), 2.82–3.08 (m, 2H), 4.50 (m, 1H), 5.06 (m, 1H), 5.54 (s, 1H), 5.69 (s, 1H); ^{13}C NMR ($CDCl_3$): 28.2, 43.1, 44.7, 52.2, 52.9, 80.6, 82.2, 120.9, 127.8, 155.4, 156.7, 175.3, 175.6.

3.9. (2S)-N-[(2R)-2-(tert-Butoxycarbonylamino)-4-ethoxycarbonyl-4-penten-1-oyl]bornane-10,2-sultam 5c

A solution of ent-**3c** (0.26 g, 0.69 mmol) and di-*tert*-butyl dicarbonate (0.15 g, 0.71 mmol) in chloroform (20 ml) was heated under reflux for 1 h (TLC monitoring). The solution was washed with water (3×25 ml), the organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated. The residue was chromatographed on silica gel under pressure with hexane:ethyl acetate (8:2) as eluent, to afford **5c** (0.31 g, 95%) as an oil: $[\alpha]_D^{20}$=+50.7 (c=1.5, $CHCl_3$); IR (KBr, cm^{-1}): 3444, 3381, 1715 (br); ^1H NMR ($CDCl_3$): 0.91 (s, 3H), 1.15 (s, 3H), 1.29 (t, J=7.3 Hz, 3H), 1.38 (s, 9H), 1.5–2.15 (m, 5H), 2.61 (m, 1H), 2.84 (m, 1H), 3.41 (apparent s, 2H), 3.90 (m, 1H), 4.19 (q, J=7.3 Hz, 2H), 4.94 (m, 1H), 5.74 (s, 1H), 6.27 (s, 1H); ^{13}C NMR ($CDCl_3$): 14.6, 20.4, 21.3, 26.9, 27.9, 28.7, 33.4, 34.9, 38.6, 45.1, 48.3, 49.2, 53.4, 54.4, 61.5, 65.6, 68.4, 129.3, 136.1, 167.8, 171.8; MS (m/z, %): 429 ($M^+-C_4H_7$), 385 ($M^+-C_5H_7O_2$, 1), 271 (18), 167 (26), 149 (71), 142 (43), 91 (31), 71 (22), 57 (100). Anal. calcd for $C_{23}H_{36}N_2O_7S$: C, 57.01; H, 7.49; N, 5.78; S, 6.62. Found: C, 56.00; H, 7.56; N, 5.37; S, 5.95.

3.10. N-tert-Butoxycarbonyl-4-methylene-D-glutamic acid 6c

Prepared as described for **4a**. The crude solid residue was recrystallized from chloroform to give **6c** in 86% yield as a white powder, m.p. 137°C; $[\alpha]_D^{20}$=−24.8 (c=0.94, $CHCl_3$); IR (KBr, cm^{-1}): 3750–2250 (br), 1717 (br), 1633; ^1H NMR ($CDCl_3$): 1.39 (s, 9H), 2.55–2.95 (m, 2H), 4.45 (m, 1H), 5.37 (m, 1H), 5.76 (s, 1H), 6.37 (s, 1H); ^{13}C NMR ($CDCl_3$): 28.3, 34.5, 52.9, 80.4, 131.3, 134.7, 154.9, 171.9, 177.7; MS (m/z, %): 214 (M^+-CO_2H, 1), 114 (18), 96 (26), 86 (17), 74 (17), 59 (33), 57 (100). Anal. calcd for $C_{11}H_{17}NO_6$: C, 50.94; H, 6.61; N, 5.40. Found: C, 50.44; H, 6.64; N, 5.32.

3.11. Hydrochloride of 4-methylene-D-glutamic acid 7c

Dry hydrogen chloride was bubbled into a stirred solution of **6c** (0.040 g, 0.15 mmol) in ethyl acetate (5 ml). After 1 h, the solvent was evaporated and the residue was washed with diethyl ether affording **7c** (0.029 g, 97%) as a white hygroscopic solid; ^1H NMR (D_2O): 2.68 (dd, J=14.6 Hz, 8.0 Hz, 1H), 2.86 (dd, J=14.6 Hz, 5.8 Hz, 1H), 3.90–4.14 (m, 1H), 5.78 (s, 1H), 6.28 (s, 1H).

3.12. 4-Methylene-D-glutamic acid 8c

Propylene oxide (1 ml) was added to a solution of **7c** (0.029 g, 0.15 mmol) in absolute ethanol (1 ml) and the mixture was stirred at room temperature for one hour, a white solid being formed. The solution was centrifugated and the solid washed with absolute ethanol (1 ml) yielding **8c** (0.022 g, 93%); m.p. 192–194°C (lit.[21a] m.p. 192–194°C, lit.[21b] m.p. 192–195°C); $[\alpha]_D^{20}=-13.2$ (c=0.5, 5 M HCl) (lit.[21a] $[\alpha]_D$ for *S* isomer=+12.8, c=0.53, 5 M HCl; lit.[21b] $[\alpha]_D$ for *S* isomer=+13.2, c=0.56, 5 M HCl); IR (KBr, cm^{-1}): 3550–2200, 1687; ^1H NMR (D_2O–dioxane): 2.55 (dd, J=14.6 Hz, 8.2 Hz, 1H), 2.76 (dd, J=14.6 Hz, 5.0 Hz, 1H), 3.76 (dd, J=8.2 Hz, 5.0 Hz, 1H), 5.66 (broad s, 1H), 6.24 (br s, 1H); ^{13}C NMR (D_2O–dioxane): 34.35, 55.0, 131.8, 136.35, 171.7, 174.4.

3.13. (2R)-N-[(2S)-2-((Diphenylmethylidene)amino)-4-ethoxycarbonylbutan-1-oyl]bornane-10,2-sultam 9a

A solution of **1** (4.38 g, 10.0 mmol) and ethyl acrylate (2.02 g, 20.2 mmol) in anhydrous acetonitrile (50 ml) was added to a stirred mixture of potassium carbonate (4.17 g, 30.0 mmol), tetrabutylammonium bromide (0.33 g, 1.02 mmol) and anhydrous acetonitrile (50 ml). The stirred mixture was left at room temperature for 5 h (TLC monitoring), then it was filtered and the solvent from the filtrate was evaporated. The residue was redissolved in diethyl ether (200 ml) and washed with distilled water (3×150 ml). The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated to give an oil which was purified by column chromatography on silica gel under pressure, eluting with mixtures of hexane:diethyl ether of increasing polarity, from 9:1 to 7:3. The Schiff base **9a** was obtained as a colorless oil (3.97 g, 84%); $[\alpha]_D^{20}=-42.7$ (c=1.5, $CHCl_3$); IR (film, cm^{-1}): 1743, 1702, 1660; ^1H NMR ($CDCl_3$): 0.90 (s, 3H), 1.08 (s, 3H), 1.15 (t, J=7.1 Hz, 3H), 1.20–1.42 (m, 2H), 1.77–1.91 (m, 4H), 2.00 (m, 1H), 2.19–2.42 (m, 4H), 3.28 (d, J=13.5 Hz, 1H), 3.36 (d, J=13.5 Hz, 1H), 3.86 (apparent t, J=6.4 Hz, 1H), 4.02 (q, J=7.1 Hz, 2H), 4.69 (m, 1H), 7.09–7.81 (m, 10H); MS (CI, NH_3): 537 (M+1, 14), 373 (57), 327 (59), 315 (28), 233 (71), 216 (100), 183 (68).

3.14. (2R)-N-[(2S)-2-((Diphenylmethylidene)amino)-5-oxohexan-1-oyl]bornane-10,2-sultam 9b

Prepared as for **9a**. The crude solid residue was recrystallized from diethyl ether to afford **9b** in 90% yield; m.p. 146–147°C; $[\alpha]_D^{20}=-55.0$ (c=1.3, $CHCl_3$); IR (film, cm^{-1}): 1701, 1616; ^1H NMR ($CDCl_3$): 0.93 (s, 3H), 1.12 (s, 3H), 1.38 (m, 2H), 1.81–1.95 (m, 2H), 2.04 (m, 2H), 2.07 (s, 3H), 2.23 (m, 2H), 2.53 (m, 2H), 3.30 (d, J=13.9 Hz, 1H), 3.37 (d, J=13.9 Hz, 1H), 3.86 (dd, J=7.3 Hz, 5.1 Hz, 1H), 4.70 (t, J=5.8 Hz, 1H), 7.05–7.88 (m, 10H); ^{13}C NMR ($CDCl_3$): 19.8, 20.6, 26.4, 29.4, 29.8, 32.7, 38.3, 39.5, 44.5, 47.7, 48.4, 52.9, 64.1, 65.1, 127.8, 127.9, 128.5, 128.6, 128.9, 130.4, 136.0, 139.4, 171.0, 172.1, 207.7; MS (m/z, %): 507 (M+1, 1), 264 (100), 206 (30), 194 (16), 182 (12), 165 (17), 91 (15), 82 (23). Anal calcd for $C_{29}H_{34}N_2O_4S$: C, 68.74; H, 6.77; N, 5.53; S, 6.32. Found: C, 68.74; H, 6.88; N, 5.47; S, 6.35.

3.15. (2R)-N-[(2S)-2-Amino-4-ethoxycarbonylbutan-1-oyl]bornane-10,2-sultam 10a

A 15% aqueous solution of citric acid (12.0 g, 9.04 mmol) was added to a vigorously magnetically stirred solution of **9a** (0.40 g, 0.75 mmol) in diethyl ether (15 ml) and the stirred mixture left at room temperature for 24 h (TLC monitoring). The phases were separated, the aqueous layer was extracted with diethyl ether (2×25 ml) to remove benzophenone, and then basified with potassium

carbonate and extracted again with chloroform (3×25 ml). The combined chloroformic extracts were dried with anhydrous sodium sulfate and the solvent was evaporated to give an oil which was purified by column chromatography on silica gel under pressure, eluting with mixtures of increasing polarity, from hexane:ethyl acetate (7:3) to ethyl acetate. Compound **10a** was obtained as a colourless oil (0.19 g, 69%); $[\alpha]_D^{20}=-72$ (c=0.5, CH_3OH); IR (film, cm^{-1}): 3381–2959, 1729, 1694; ^1H NMR ($CDCl_3$): 0.98 (s, 3H), 1.15 (s, 3H), 1.25 (t, J=7.2 Hz, 3H), 1.30–1.50 (m, 2H), 1.58 (s, 2H), 1.75–1.97 (m, 4H), 1.98–2.11 (m, 3H), 2.41 (ddd, J=13.9 Hz, 9.5 Hz, 6.6 Hz, 1H), 2.53 (ddd, J=13.9 Hz, J=8.8 Hz, J=6.6 Hz, 1H), 3.43 (d, J=13.9 Hz, 1H), 3.52 (d, J=13.9 Hz, 1H), 3.90 (apparent t, J=6.6 Hz, 1H), 3.99 (dd, J=8.4 Hz, J=4.7 Hz, 1H), 4.12 (q, J=7.2 Hz, 2H); MS (CI, NH_3): 373 (M+1, 1), 327 (10), 233 (60), 216 (100), 176 (11).

3.16. (2R)-N-[(2S)-5-Methyl-3,4-dihydro-2H-2-pyrrolylcarbonyl]bornane-10,2-sultam ***10b***

Prepared as for **10a**. The crude solid residue was recrystallized from chloroform to afford **10b** in 85% yield; m.p. 144–145°C; $[\alpha]_D^{20}=-70.2$ (c=0.85, $CHCl_3$); IR (KBr, cm^{-1}): 1687, 1644; ^1H NMR ($CDCl_3$): 0.98 (s, 3H), 1.15 (s, 3H), 1.41 (m, 2H), 1.80–1.97 (m, 3H), 2.05–2.16 (m, 3H), 2.10 (s, 3H), 2.39 (m, 1H), 2.59 (m, 2H), 3.46 (d, J=13.1 Hz, 1H), 3.52 (d, J=13.1 Hz, 1H), 3.94 (t, J=6.6 Hz, 1H), 5.28 (m, 1H); ^{13}C NMR ($CDCl_3$): 19.7, 19.9, 20.8, 26.4, 28.6, 32.8, 38.2, 39.2, 44.6, 47.8, 48.6, 53.0, 65.1, 74.1, 172.2, 179.1; MS (m/z, %): 325 (M+1, 1), 150 (11), 135 (21), 93 (10), 82 (100). Anal calcd for $C_{16}H_{24}N_2O_3S$: C, 59.23; H, 7.46; N, 8.64; S, 9.86. Found: C, 58.74; H, 7.64; N, 8.39; S, 9.83.

3.17. (S)-Glutamic acid ***11a***

A 2.5 M aqueous solution of lithium hydroxide (1 ml, 2.62 mmol) is added at 0°C to a stirred solution of **10a** (0.24 g, 0.644 mmol) in THF (1 ml). The stirred mixture was left at 0°C for 1 h, then THF was evaporated, the remaining aqueous solution was acidified (pH 2) with 1 M hydrochloric acid and extracted with ethyl acetate (3×5 ml) to recover the Oppolzer sultam quantitatively. The aqueous layer was evaporated to dryness to give a mixture of lithium chloride and the hydrochloride of (*S*)-glutamic acid (^1H NMR (D_2O): 2.15 (m, 2H), 2.55 (m, 2H), 3.80 (t, J=6.5 Hz, 1H)), which was chromatographed through a sulfonic resin Dowex 50WX8, eluting with mixtures of water:pyridine from 10:0 to 9:1. (*S*)-Glutamic acid (0.028 g, 29%) was obtained as an oil which crystallized spontaneously; m.p. 223–225°C (lit.[22] m.p. 224–225°C); $[\alpha]_D^{20}=+31.5$ (c=1.0, 6 M HCl) (lit.[22] $[\alpha]_D=+31.4$, c=1.0, 6 M HCl); ^1H NMR (D_2O): 1.95–2.22 (m, 2H), 2.48 (apparent dt, J=16.5 Hz, 7.3 Hz, 1H), 2.5 (apparent dt, J=16.5 Hz, 7.3 Hz, 1H), 3.6 (dd, J=7.3 Hz, 4.4 Hz, 1H).

*3.18. (S)-2-*tert*-Butoxycarbonylamino-5-oxohexanoic acid* ***11b***

A 2.5 M aqueous solution of lithium hydroxide (4.3 ml, 10.7 mmol) was added at 0°C to a stirred solution of **10b** (0.87 g, 2.68 mmol) in THF (5 ml). The stirred mixture was left at 0°C for 2 h, then THF was evaporated, the remaining aqueous solution was acidified (pH 2) with 1 M hydrobromic acid and extracted with ethyl acetate (3×10 ml) to recover the Oppolzer sultam quantitatively. The aqueous layer was evaporated to dryness to give a mixture of lithium bromide and the hydrobromide of (*S*)-2-amino-5-oxohexanoic acid; ^1H NMR (D_2O): 2.25–2.44 (m, 1H), 2.52 (s, 3H), 2.57–2.75 (m, 1H), 3.20 (broad t, J=8.0 Hz, 2H), 5.12 (broad t, J=8.1 Hz, 1H); ^{13}C NMR (D_2O): 21.0, 26.6, 41.0, 69.4, 174.2, 200.9. A mixture of this crude residue, sodium hydrogencarbonate (1.02 g, 12.1 mmol) and di-*tert*-butyl dicarbonate (0.60 g, 2.75 mmol) in absolute ethanol (25 ml) was sonicated for 5 h. It was then filtered through Celite and the solvent from the filtrate was evaporated. The residue was redissolved in

dichloromethane (25 ml) and the organic solution was washed with 1 M hydrochloric acid (3×25 ml), it was dried with anhydrous sodium sulfate and the solvent was evaporated, affording **11b** (0.45 g, 69%) as an oil. Further purification was achieved by chromatography on a reversed phase C_{18} octadecil column, using methanol as eluent; $[\alpha]_D^{20}=-14.0$ (c=1.15, $CHCl_3$); IR (KBr, cm^{-1}): 3500–2800, 1714 (br); ^1H NMR ($CDCl_3$): 1.42 (s, 9H), 1.82–2.01 (m, 1H), 2.07–2.23 (m, 1H), 2.15 (s, 3H), 2.45–2.72 (m, 2H), 4.12–4.36 (m, 1H), 5.12–5.20 (m, 1H); ^{13}C NMR ($CDCl_3$): 21.0, 23.0, 24.7, 34.2, 47.6, 75.1, 150.6, 170.8, 203.2. Anal calcd for $C_{11}H_{19}NO_5 \cdot H_2O$: C, 50.18; H, 8.04; N, 5.32. Found: C, 50.23; H, 7.68; N, 5.32.

3.19. (R)-N-(tert-Butoxycarbonyl)glutamic acid 12a

A 2.5 M aqueous solution of lithium hydroxide (1.4 ml, 3.5 mmol) was added at 0°C to a stirred solution of ent-**10a** (0.32 g, 0.86 mmol) in THF (2 ml). The stirred mixture was left at 0°C for 1 h, then THF was evaporated and the remaining aqueous solution was acidified (pH 2) with 1 M hydrochloric acid and extracted with ethyl acetate (3×10 ml) to recover the Oppolzer sultam quantitatively. The aqueous layer was evaporated to dryness to give a mixture of lithium chloride and the hydrochloride of (*R*)-glutamic acid. A mixture of this crude residue, sodium hydrogencarbonate (0.13 g, 3.86 mmol) and di-*tert*-butyl dicarbonate (0.19 g, 0.86 mmol) in absolute ethanol (15 ml) was sonicated for 5 h. It was then filtered through Celite and the solvent from the filtrate was evaporated. The residue was redissolved in dichloromethane (20 ml) and the organic solution was washed with 10% aqueous citric acid (3×15 ml), then dried with anhydrous sodium sulfate and the solvent was evaporated to give an oil, which crystallized from chloroform to afford **12a** (0.16 g, 75%); m.p. 108–109°C (lit.[23] m.p. 108–109°C); $[\alpha]_D^{20}=+16.0$ (c=1.0, CH_3OH) (lit.[23] $[\alpha]_D=-16$, c=1.0, CH_3OH for the *S* enantiomer); ^1H NMR ($CDCl_3$): 1.44 (s, 9H), 1.85–2.07 (m, 1H), 2.07–2.30 (m, 1H), 2.32–2.50 (m, 2H), 4.20–4.38 (m, 1H), 5.20 (broad s, 1H).

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