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Enantioselective solution- and solid-phase synthesis of glutamic acid derivatives via Michael addition reactions

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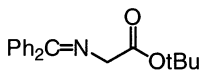
Abstract—The enantioselective conjugate addition of Schiff base ester derivatives to Michael acceptors either in solution (56–89% e.e.) or on solid-phase (34–82% e.e.) gave optically active unnatural α-amino acid derivatives. The reaction was conducted in the presence of chiral, non-racemic quaternary salts derived from the *cinchona* alkaloids using neutral, non-ionic phosphazene bases.

1. Introduction

The benzophenone imines of glycine alkyl esters (e.g. **1**) have been used for the synthesis of a variety of α-amino acid derivatives.[1,2] Reacting **1** with electrophiles, using asymmetric phase-transfer catalysts derived from the *cinchona* alkaloids, is a particularly attractive route to optically active α-amino acids because the chiral control element is inexpensive and is used in only a catalytic quantity.[3] Early studies in our laboratory using the *N*-alkyl *cinchona* quaternary ammonium salts[1f] were followed by the introduction of more effective catalysts, in which the free hydroxyl of the *cinchona* quat was replaced with an alkyl group.[1g,1h] In late 1997, independent publications from the Corey[4] and Lygo[5] groups introduced the 9-anthracenylmethyl group as a very effective nitrogen substituent in these catalysts. For example, the pseudoenantiomeric catalysts **3** and **4** gave high enantioselectivities in a variety of reactions.[6] A homogeneous, solution-phase enantioselective synthesis of α-amino acids from Schiff base ester **1**, which gave optically active derivatives of α-amino acids in 83–97% e.e., has also been reported recently.[1j]



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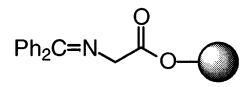

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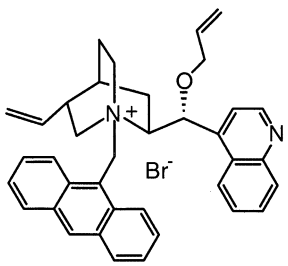
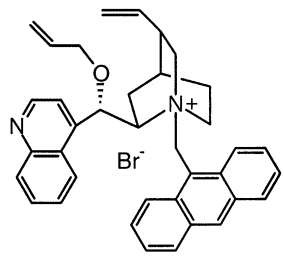


3 (from Cinchonidine)



4 (from Cinchonine)

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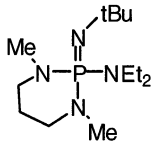
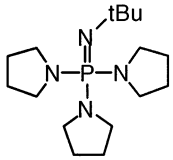
We began utilising resin-bound Schiff base esters **2** for the solid-phase synthesis of unnatural amino acids and peptides, termed 'unnatural peptide synthesis' (UPS), in 1995.[7,8] The methodology involves the introduction of an unnatural amino acid side chain during normal solid-phase peptide synthesis (SPPS). UPS chemistry has resulted in the preparation of mono-[7a,7c] and dialkylamino acid and peptide derivatives[7b,7d] by alkylations involving resin-bound anionic equivalents. In addition, glutamic acid derivatives were prepared by the corresponding Michael additions.[7e] The method was extended to the enantioselective solid-phase synthesis of α-amino acid derivatives, which were obtained in 51–89% e.e.[7f]

The key to both the solid-phase UPS methodology[7] and the homogeneous, solution-phase enantioselective synthesis[1j] was the use of the organic-soluble, non-ionic Schwesinger bases BEMP **5** or BTPP **6**.[9] These bases function in a manner similar to phase-transfer base systems since they do not react with alkyl halides[9b] and thus can be added simultaneously with the electrophile at the beginning of the reaction.



BEMP **5**



BTPP **6**

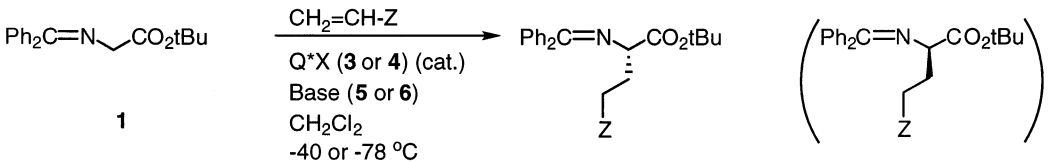
In this paper, we report our studies on an extension of this work to the enantioselective synthesis of glutamic acid derivatives both in solution- and solid-phase.[7e,10]

2. Results and discussion

Initial experiments in solution (Table 1) were carried out using methyl acrylate, a typical Michael acceptor. The phosphazene base BEMP **5** or BTPP **6** was added to a mixture of Schiff base **1**, Michael acceptor (CH_2=CH-Z, 5 equiv.), and a catalytic amount of the quaternary ammonium salt (**3** or **4**, 0.1 equiv.) in methylene chloride at −40 or −78°C. For methyl acrylate and the cinchonidine-derived catalyst **3**, the best results were obtained using BEMP at −78°C for 3 h, which afforded (*S*)-**7a** in 93% yield and 89% e.e. (e.r. = 94.5:5.5). Using the stronger base BTPP, either at −40 or −78°C, resulted in slightly poorer induction. The enantiomeric product (*R*)-**7a** was obtained by using the pseudoenantiomeric cinchonine-derived catalyst **4**, albeit with poorer enantioselectivity, with (*R*)-**7a** formed in 92% yield and 80% e.e. (e.r. = 90:10). Michael addition with BEMP as base and the reactive acceptors acrylonitrile, methyl vinyl ketone or ethyl vinyl ketone at −78°C over 3 h gave the corresponding Michael adducts (*S*)-**7b** in 84% e.e., (*S*)-**7c** in 89% e.e. and (*S*)-**7d** in 87% e.e. using catalyst **3**. In reactions with catalyst **4**, the enantiomeric (*R*)-products (*R*)-**7b** in 74% e.e., (*R*)-**7c** in 56% e.e., and (*R*)-**7d** in 61% e.e. were obtained.

With the less reactive phenyl vinyl sulfone the reaction was completed over 7 h and gave 76% e.e. for (*S*)-**7e** and 73% e.e. for (*R*)-**7e**. In all of the reactions examined, poorer enantioselectivities were observed using **4** as catalyst in comparison to reactions completed using catalyst **3**.

Table 1. Catalytic enantioselective Michael additions of **1** in solution

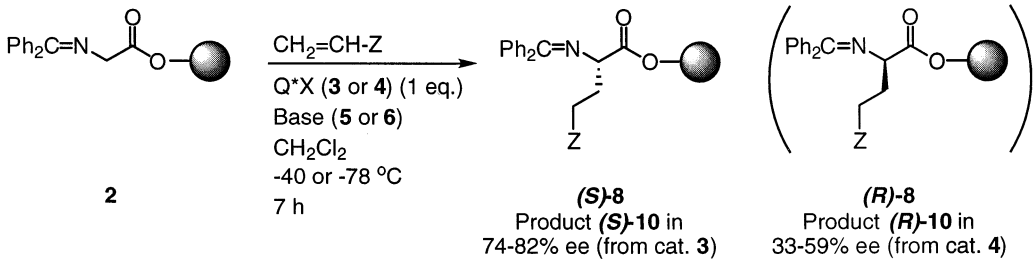


***(S)*-7**
76-89% ee (from cat. **3**)

***(R)*-7**
56-80% ee (from cat. ***4***)

Michael acceptor	Z	Q*X	Base	Temp. (°C)	Product	% Yield	% e.e.
Methyl acrylate	-CO_2Me	**3**	BEMP	−78	(*S*)-**7a**	93	**89**
Methyl acrylate	-CO_2Me	**3**	BTPP	−78	(*S*)-**7a**	92	86
Methyl acrylate	-CO_2Me	**3**	BTPP	−40	(*S*)-**7a**	87	87
Methyl acrylate	-CO_2Me	**4**	BEMP	−78	(*R*)-**7a**	92	**80**
Acrylonitrile	-CN	**3**	BEMP	−78	(*S*)-**7b**	83	**84**
Acrylonitrile	-CN	**3**	BTPP	−40	(*S*)-**7b**	83	67
Acrylonitrile	-CN	**4**	BEMP	−78	(*R*)-**7b**	81	**74**
Methyl vinyl ketone	-COMe	**3**	BEMP	−78	(*S*)-**7c**	82	**89**
Methyl vinyl ketone	-COMe	**3**	BTPP	−78	(*S*)-**7c**	80	66
Methyl vinyl ketone	-COMe	**3**	BTPP	−40	(*S*)-**7c**	81	65
Methyl vinyl ketone	-COMe	**4**	BEMP	−78	(*R*)-**7c**	80	**56**
Ethyl vinyl ketone	-COEt	**3**	BEMP	−78	(*S*)-**7d**	87	**87**
Ethyl vinyl ketone	-COEt	**4**	BEMP	−78	(*R*)-**7d**	85	**61**
Phenyl vinyl sulfone	-SO_2Ph	**3**	BEMP	−78	(*S*)-**7e**	91	**76**
Phenyl vinyl sulfone	-SO_2Ph	**4**	BEMP	−78	(*R*)-**7e**	90	**73**

Table 2. Enantioselective Michael additions of resin-bound benzophenone imine of glycinate **2**



Michael acceptor	Z	Q*X	Base	Temp. (°C)	Product	% Yield (wt)	% Prod. (HPLC)	% e.e.[a]
Methyl acrylate	$-CO_2Me$	**3**	BEMP	−78	(*S*)-**10a**	96	97	**74**
Methyl acrylate	$-CO_2Me$	**3**	BTPP	−40	(*S*)-**10a**	96	97	74
Methyl acrylate	$-CO_2Me$	**4**	BEMP	−78	(*R*)-**10a**	94	98	**33**
Acrylonitrile	-CN	**3**	BEMP	−78	(*S*)-**10b**	94	90	**82**
Acrylonitrile	-CN	**3**	BTPP	−40	(*S*)-**10b**	98	91	75
Acrylonitrile	-CN	**4**	BEMP	−78	(*R*)-**10b**	93	92	**59**
Methyl vinyl ketone	-COMe	**3**	BEMP	−78	(*S*)-**10c**	87	80	**74**
Methyl vinyl ketone	-COMe	**3**	BTPP	−40	(*S*)-**10c**	88	77	56
Methyl vinyl ketone	-COMe	**4**	BEMP	−78	(*R*)-**10c**	86	79	**34**
Ethyl vinyl ketone	-COEt	**3**	BEMP	−78	(*S*)-**10d**	89	81	**76**
Ethyl vinyl ketone	-COEt	**4**	BEMP	−78	(*R*)-**10d**	90	80	**34**
Phenyl vinyl sulfone	$-SO_2Ph$	**3**	BEMP	−78	(*S*)-**10e**	97	96	**81**
Phenyl vinyl sulfone	$-SO_2Ph$	**3**	BTPP	−40	(*S*)-**10e**	99	95	70
Phenyl vinyl sulfone	$-SO_2Ph$	**4**	BEMP	−78	(*R*)-**10e**	98	94	**49**

[a] % e.e. determined by derivatisation of amino acid to **11**; see text and Scheme 1.

Enantioselective Michael additions of the resin-bound glycinate **2** were also studied (Table 2). Optimal results were obtained when BEMP was used as the base in dichloromethane at −78°C. As in our earlier enantioselective alkylation studies[7f] on the resin-bound glycinate **1**, a full equivalent of the chiral quaternary ammonium salt **3** or **4** was used. Following alkylation, imine hydrolysis of the products **8** gave the resin-bound free amino glycinates **9**, which were analysed for yield and the level of stereoinduction (Scheme 1). Acylation of resin-bound **9** with quinaldic acid, followed by cleavage from the resin, yielded products **10**,[11] which were subjected to HPLC analysis to determine the purity of the products. The level of induction was determined by cleavage of the free amino glycinate **9** from the resin and then conversion to the GITC-derived diastereomers **11** for HPLC analysis.[7f,12] The (*S*)-enantiomers of the five Michael adducts were obtained in 74–82% e.e. (e.r. = 87:13–91:9) using catalyst **3**, while the corresponding (*R*)-enantiomers were obtained with considerably lower enantioselectivity with 33–59% e.e. (e.r. = 66:34–79:21).

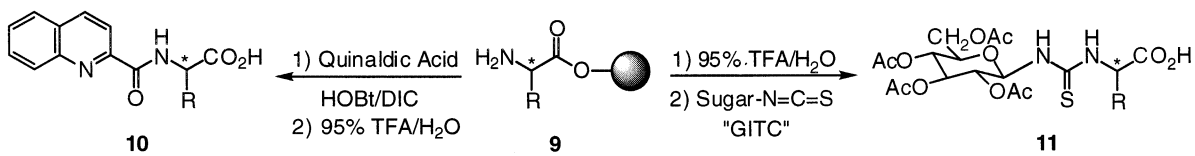
3. Conclusion

The enantioselective conjugate addition of Schiff base ester derivatives to Michael acceptors, either in solution or solid-phase, gave non-racemic unnatural α-amino acid derivatives. The reaction was conducted in the presence of chiral, non-racemic quaternary ammonium salts derived from the *cinchona* alkaloids using neutral, non-ionic phosphazene bases.

4. Experimental

4.1. General methods

NMR analyses were performed on a GE 300 MHz; δ is in ppm relative to TMS as internal standard in either $CDCl_3$, DMSO-d_6 or CD_3CN. Infrared spectra were recorded on a Perkin–Elmer Model 1600 FTIR. High resolution mass spectra (HRMS) were run in the FAB mode on a ZAB-2SE instrument.



Scheme 1. Analysis of reaction products from Michael additions on solid-phase.

4.2. General reaction procedure for the alkylation of Schiff base 1 in solution

All reactions were conducted under an argon atmosphere in oven-dried glassware. The Michael acceptor (0.43 mmol, 5 equiv.) was added to a mixture of the benzophenone imine of glycine *tert*-butyl ester **1** (25 mg, 0.085 mmol, 1.0 equiv.) and *O*-allyl-*N*-9-anthracenylmethyl cinchonidinium bromide[4a] (0.1 equiv.) in dry CH_2Cl_2 (0.5 mL). The reaction mixture was then cooled (−40 or −78°C) and the base BEMP **5**[9a] or BTPP **6**[9a] (5 equiv.) was added dropwise over a few seconds. The reaction mixture was then stirred at −40 or −78°C until the starting material **1** had been consumed (TLC). The solvent was evaporated in vacuo and the residue was purified by flash chromatography on silica gel to give product (*S*)-**7**. Products (*R*)-**7** were prepared using the above procedure with the pseudoenantiomeric catalyst, *O*-allyl-*N*-9-anthracenylmethyl cinchoninium bromide.[7f] Chiral HPLC analyses of products **7** were performed on a Varian 2010 system using the indicated column and conditions.

4.2.1. 1-(1,1-Dimethylethyl) 5-methyl *N*-(diphenylmethylene)-L-glutamate (*S*)-7a. (R = $CH_2CH_2CO_2CH_3$) 82% yield, e.e. = 89%; ^{1}H NMR ($CDCl_3$): 1.44 (s, 9H); 2.18–2.26 (m, 2H); 2.35–2.40 (m, 2H); 3.59 (s, 3H); 3.97 (t, 1H, J = 6.3 Hz); 7.16–7.19 (m, 2H); 7.29–7.46 (m, 6H); 7.62–7.65 (m, 2H); ^{13}C NMR ($CDCl_3$+DMSO-d_6): 28.0, 28.6, 30.5, 51.5, 64.7, 81.2, 127.7, 127.9, 128.3, 128.5, 128.7, 130.2, 136.3, 139.3, 170.6, 173.4; IR (KBr): 1736, 1624, 1150; HRMS m/z calcd for $C_{23}H_{28}NO_4$ 382.2018 for (M+H$^+$), found 382.2016. HPLC: column, Whelk-01; mobile phase, hexane:*iso*-propanol (95:5 v/v); flow rate 1.0 mL/min; retention times, (*R*) 10.09 and (*S*) 12.08 min.

4.2.2. 1,1-Dimethylethyl 4-cyano-(2*S*)-[(diphenylmethylene)amino]butanoate (*S*)-7b. (R = CH_2CH_2CN) 83% yield, e.e. = 84%; ^{1}H NMR ($CDCl_3$): 1.44 (s, 9H); 2.16–2.35 (m, 2H); 2.44–2.54 (m, 2H); 4.05 (dd, 1H, J = 7.4 and 4.4 Hz); 7.18–7.21 (m, 2H); 7.32–7.49 (m, 6H); 7.65 (d, 2H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$+DMSO-d_6): 13.9, 28.7, 29.5, 63.7, 81.8, 119.4, 127.6, 128.0, 128.5, 128.7, 130.6, 136.0, 139.0, 169.8, 172.0; IR (KBr): 2250, 1730, 1619, 1147; HRMS m/z calcd for $C_{22}H_{25}N_2O_2$ 349.1916 for (M+H$^+$), found 349.1929. HPLC: column, Chiracel OD, mobile phase, hexane:*iso*-propanol (95:5 v/v); flow rate 1.0 mL/min; retention times, (*R*) 15.26 and (*S*) 20.07 min.

4.2.3. 1,1-Dimethylethyl *N*-(diphenylmethylene)-5-oxo-nor-L-leucinate (*S*)-7c. (R = $CH_2CH_2COCH_3$) 93% yield, e.e. = 89%; ^{1}H NMR ($CDCl_3$): 1.43 (s, 9H); 2.07–2.18 (m, 5H); 2.52 (app. q, 2H, J = 7.4 Hz); 3.95 (t, 1H, J = 6.3 Hz); 7.16–7.17 (m, 2H); 7.30–7.44 (m, 6H); 7.64 (d, 2H, J = 7.4 Hz); HRMS m/z calcd for $C_{23}H_{28}NO_3$ 366.2069 for (M+H$^+$), found 366.2057. HPLC: column, Chiracel OD; mobile phase, hexane:*iso*-propanol (100:1 v/v); flow rate 1.0 mL/min; retention times, (*R*) 11.92 and (*S*) 15.28 min.

4.2.4. 1,1-Dimethylethyl (2*S*)-[(diphenylmethylene)-amino]-5-oxoheptanoate (*S*)-7d. (R = $CH_2CH_2COCH_2$-CH_3) 87% yield, e.e. = 87%; ^{1}H NMR ($CDCl_3$): 1.00 (t, 3H, J = 7.4 Hz); 1.43 (s, 9H); 2.14 (q, 2H, J = 7.4 Hz); 2.38–2.55 (m, 4H); 3.94 (t, 1H, J = 5.9 Hz); 7.14–7.19 (m, 2H); 7.29–7.44 (m, 6H); 7.61–7.64 (m, 2H); HRMS m/z calcd for $C_{24}H_{30}NO_3$ 380.2225 for (M+H$^+$), found 380.2205. HPLC: column, Chiracel OD; mobile phase, hexane:*iso*-propanol (100:1 v/v); flow rate 1.0 mL/min; retention times, (*R*) 9.78 and (*S*) 21.72 min.

4.2.5. 1,1-Dimethylethyl (2*S*)-[(diphenylmethylene)-amino]-4-(phenylsulfonyl)butanoate (*S*)-7e. (R = CH_2-CH_2SO_2Ph) 92% yield, e.e = 76%; ^{1}H NMR ($CDCl_3$): 1.38 (s, 9H); 2.12–2.29 (m, 2H); 3.15–3.45 (m, 2H); 4.00 (dd, 1H, J = 6.6 and 5.2 Hz); 7.11–7.14 (m, 2H); 7.29–7.45 (m, 6H); 7.53–7.67 (m, 5H); 7.88–7.91 (m, 2H); HRMS m/z calcd for $C_{27}H_{30}NO_4S$ 464.1895 for (M+H$^+$), found 464.1907. HPLC: column, Chiracel OD; mobile phase, hexane:*iso*-propanol (100:4 v/v); flow rate 0.5 mL/min; retention times, (*R*) 27.50 and (*S*) 31.59 min.

4.3. Preparation of the benzophenone imine of Gly-Wang-resin 2

Fmoc-Gly-Wang resin (2.0 g, 0.92 mmol, 0.46 mmol/g, Novabiochem) was wetted with CH_2Cl_2 (20 mL) and drained. Piperidine (20% in 1-methyl-2-pyrrolidinone (NMP), 20 mL) was added, briefly mixed and then drained. Fresh piperidine (20% in NMP, 20 mL) was added and the resulting slurry was mixed by rotation for 30 min. The resin was filtered and washed with NMP and CH_2Cl_2 (3×20 mL each). Benzophenone imine (1.54 mL, 9.2 mmol, 10 equiv.) in NMP (20 mL) was added to the resin followed by glacial acetic acid (0.475 mL, 8.28 mmol, 9 equiv.) and the suspension was mixed by rotation for 18 h at room temperature. The resin was filtered and washed with NMP, THF, THF:H_2O (3:1), THF and then CH_2Cl_2 (3×20 mL) and then dried in vacuo (room temperature, overnight) to give **2**.

4.4. Michael addition of the benzophenone imine of Gly-Wang-resin to give 8

Method A. The benzophenone imine of Wang resin **2** (50 μmol, 111 mg, substitution = 0.45 mmol/g) was weighed into a 3–4 mL capacity test tube. Dry CH_2Cl_2 (2 mL) was added, followed by the catalyst (30 mg, 50 μmol, 1 equiv.) and the Michael acceptor (0.25 mmol, 5 equiv.). The reaction mixture was cooled to −78°C, BEMP **5**[9a] (73 μL, 0.25 mmol, 5 equiv.) was added, and the reaction mixture was maintained at −78°C for 7 h with gentle stirring (slow magnetic stirring and manual agitation) under argon. The resin was then collected by filtration and washed with dichloromethane (6×1.5 mL).

Method B. The benzophenone imine of Wang resin **2** (50 μmol, 111 mg, substitution = 0.45 mmol/g) was weighed into a 3–4 mL capacity test tube. Dry dichloromethane (2 mL) was added, followed by the

catalyst (30 mg, 50 μmol, 1 equiv.) and the Michael acceptor (0.50 mmol, 10 equiv.). The reaction mixture was cooled to −40°C, BTPP **6**[9a] (153 μL, 0.50 mmol, 10 equiv.) was added, and the reaction mixture was maintained at −40°C for 7 h with gentle stirring (slow magnetic stirring and manual agitation) under argon. The resin was then collected by filtration and washed with dichloromethane (6×1.5 mL).

4.5. Hydrolysis of the imine

The resin-bound imine **8** (50 μmol) was washed with THF and then THF:H_2O (3:1) (3×1.5–2 mL each). 1N HCl:THF (1:2) (1.5–2 mL) was added to the resin and the suspension was mixed by rotation for 4 h at room temperature. The reaction mixture was filtered and washed with THF (3×1.5–2 mL) and then neutralised with 10% *N*,*N*-di-*iso*-propylethylamine (DIEA)/NMP (3×1.5–2 mL each). This was followed by washing with NMP, CH_2Cl_2 and then NMP (3×1.5–2 mL each) to give product **9**.

4.6. Acylation of monosubstituted amino acids of Wang resin

To the resin-bound amino acid **9** (50 μmol) was added NMP (1.50 mL) followed by a solution of quinaldic acid (1 M, 250 μL, 5 equiv.), 1 M solution of 1-hydroxybenzotriazole hydrate (HOBt·H_2O) (250 μL, 5 equiv.) and 1,3-diisopropylcarbodiimide (DIC) (39 μL, 5 equiv.). The suspension was mixed by rotation for 18 h at room temperature. The reaction was filtered and washed with NMP, THF, and then CH_2Cl_2 (3×1.5–2 mL).

4.7. Cleavage of the acylated product from the resin

To the resin-bound product (50 μmol), 95% trifluoroacetic acid (TFA)/H_2O (1.5–2 mL) was added and the reaction was mixed by rocking for 2 h at room temperature. The reaction mixture was filtered into a tared vial and the resin was washed with TFA/H_2O (3×1.5–2 mL) and then CH_2Cl_2 (3×1.5–2 mL). The solvents were evaporated under a stream of argon and the residue was dried in a vacuum oven at room temperature for several hours to give product **10**. The purity of compound **10** was determined by HPLC on a Varian 9010/9050 system using a Nova-Pak C18 column (150×3.9 mm) with mobile phases consisting of 0.1% (v/v) TFA/H_2O (A) and 0.08% (v/v) TFA/CH_3CN (B) with a gradient of 0–80% B in 20 min at a flow of 1 mL/min with detection at 220 nm.

4.8. GITC derivatisation and HPLC analysis procedure for products 11a–e

The crude amino acids (racemic or optically active reaction products) were obtained by cleavage with 95% TFA/H_2O from the resin-bound amino acid **9** as in the previous procedure. The crude amino acids were derivatised for HPLC analysis with GITC by the slightly modified method of Nimura et al.[12a] A 1 mg sample of the amino acid was dissolved in 50% (v/v) aqueous CH_3CN (1 mL) containing 0.4% (w/v) Et_3N (for the very hydrophobic amino acids, 90% aqueous CH_3CN containing 0.4% (w/v) of Et_3N was used). A 250 μL aliquot of this amino acid solution was mixed with 50 μL of a solution of 0.2% (w/v) 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiocyanate (GITC) in CH_3CN and the resulting mixture was allowed to stand at room temperature for 90 min.[12b] For the amino acids with aromatic side chains, a 0.25% (w/v) solution of ethanolamine in CH_3CN (0.100 mL) was added to scavenge excess GITC.[12c] After 10 min, 10–15 μL of TFA were added and a 5 μL aliquot was injected directly onto the HPLC column. A Varian 9010/9050 Series HPLC was used to analyse the GITC amino acid derivatives **11**. A Zorbax SB-C18 column (4.6×75 mm, 3.5 micron particle size) was eluted with CH_3CN/H_2O gradients containing 0.1% TFA at 1 mL/min. The products were detected at $\lambda = 250$ nm (gradient A = 0–25% CH_3CN 25 min; gradient B = 0–50% CH_3CN 25 min; gradient C = 15–25% CH_3CN 9 min, 25–50% CH_3CN 25 min).

4.9. Products 10 and GITC derivatives 11 from resin-bound amino acids 9

4.9.1. 5-Methyl hydrogen *N*-(2-quinolinylcarbonyl)-L-glutamate (*S*)-10a and GITC derivative 11a. (R = $CH_2CH_2CO_2CH_3$) 96% mass recovery, 97% purity (HPLC), e.e. = 74%; ^{1}H NMR ($CDCl_3$): 2.13–2.22 (m, 1H); 2.30–2.42 (m, 1H); 2.46–2.51 (m, 2H); 3.59 (s, 3H); 4.72 (td, 1H, J = 8.8 and 5.1 Hz); 7.73 (t, 1H, J = 7.4 Hz); 7.88 (t, 1H, J = 7.4 Hz); 8.04 (d, 1H, J = 8.1 Hz); 8.19 (t, 2H, J = 8.8 Hz); 8.53 (d, 1H, J = 8.1 Hz); 8.73 (d, 1H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$+DMSO-d_6): 27.5, 30.1, 51.4, 118.2, 127.2, 127.5, 128.8, 129.4, 129.6, 136.9, 145.9, 148.7, 163.8, 172.9, 174.1; IR (KBr): 1726, 1650; HRMS m/z calcd for $C_{16}H_{17}N_2O_5$ 317.1137 for (M+H$^+$), found 317.1129. HPLC of GITC derivative **11a**: gradient B; retention times, (*S*) 16.70 and (*R*) 17.26 min.

4.9.2. 4-Cyano-(2*S*)-[(2-quinolinylcarbonyl)amino]butanoic acid (*S*)-10b and GITC derivative 11b. (R = CH_2CH_2CN) 94% mass recovery, 90% purity (HPLC), e.e. = 82%; ^{1}H NMR ($CDCl_3$): 2.16–2.31 (m, 1H); 2.33–2.50 (m, 1H); 2.56 (t, 2H, J = 7.4 Hz); 4.75 (td, 1H, J = 8.8 and 5.2 Hz); 7.71 (t, 1H, J = 7.4 Hz); 7.87 (t, 1H, J = 7.4 Hz); 8.03 (d, 1H, J = 8.1 Hz); 8.16 (d, 1H, J = 8.1 Hz); 8.21 (d, 1H, J = 8.1 Hz); 8.49 (d, 1H, J = 8.8 Hz); 8.79 (d, 1H, J = 5.2 Hz); ^{13}C NMR ($CDCl_3$+DMSO-d_6): 12.9, 27.2, 50.2, 117.5, 126.7, 127.0, 127.1, 128.6, 129.2, 129.3, 136.5, 145.3, 148.1, 163.4, 173.2; IR (KBr): 2255, 1731, 1671; HRMS m/z calcd for $C_{15}H_{14}N_3O_3$ 284.1035 for (M+H$^+$), found 284.1031. HPLC of GITC derivative **11b**: gradient C; retention times, (*S*) 10.78 and (*R*) 11.92 min.

4.9.3. 5-Oxo-*N*-(2-quinolinylcarbonyl)-L-norleucine (*S*)-10c and GITC derivative 11c. (R = $CH_2CH_2COCH_3$) 87% mass recovery, 80% purity (HPLC), e.e. = 74%; ^{1}H NMR ($CDCl_3$): 2.21 (app. sept., 1H, J = 7.4 Hz); 2.18 (s, 3H); 2.41 (app. sept., 1H, J = 7.4 Hz); 2.63–2.86 (m, 2H); 4.82 (app. q, 1H, J = 8.1 Hz); 7.64 (t, 1H, J = 7.4 Hz); 7.79 (t, 1H, J = 7.4 Hz); 7.88 (d, 1H, J = 8.1 Hz);

8.17 (d, 1H, $J=8.1$ Hz); 8.25 (d, 1H, $J=8.8$ Hz); 8.33 (d, 1H, $J=8.8$ Hz); 8.90 (d, 1H, $J=7.4$ Hz); HRMS m/z calcd for $C_{16}H_{17}N_2O_4$ 301.1188 for ($M+H^+$), found 301.1188. HPLC of GITC derivative **11c**: gradient A; retention times, (*S*) 17.46 and (*R*) 18.03 min.

4.9.4. 5-Oxo-(2*S*)-[(2-quinolinylcarbonyl)amino]heptanoic acid (*S*)-10d and GITC derivative 11d. (R = $CH_2CH_2COCH_2CH_3$) 89% mass recovery, 81% purity (HPLC), e.e. = 76%; ^1H NMR ($CDCl_3$): 1.03 (t, 3H, $J=7.4$ Hz); 2.15–2.27 (m, 1H); 2.36–2.48 (m, 3H); 2.55–2.79 (m, 2H); 4.80 (td, 1H, $J=8.1$ and 7.4 Hz); 7.62 (t, 1H, $J=7.4$ Hz); 7.77 (t, 1H, $J=7.4$ Hz); 7.86 (d, 1H, $J=8.1$ Hz); 8.16 (d, 1H, $J=8.1$ Hz); 8.24 (d, 1H, $J=8.8$ Hz); 8.30 (d, 1H, $J=8.8$ Hz); 8.84 (d, 1H, $J=7.4$ Hz); HRMS m/z calcd for $C_{17}H_{19}N_2O_4$ 315.1345 for ($M+H^+$), found 315.1370. HPLC of GITC derivative **11d**: gradient B; retention times, (*S*) 15.72 and (*R*) 16.28 min.

4.9.5. 4-(Phenylsulfonyl)-(2*S*)-[(2-quinolinylcarbonyl)amino]butanoic acid (*S*)-10e and GITC derivative 11e. (R = $CH_2CH_2SO_2Ph$) 97% mass recovery, 96% purity (HPLC), e.e. = 81%; ^1H NMR ($CDCl_3$): 2.16–2.28 (m, 1H); 2.31–2.43 (m, 1H); 2.33 (app. td, 2H, $J=10.3$ and 5.9 Hz); 4.75 (td, 1H, $J=8.8$ and 5.2 Hz); 7.59 (t, 2H, $J=7.4$ Hz); 7.71 (q, 2H, $J=7.4$ Hz); 7.85–7.90 (m, 3H); 8.03 (d, 1H, $J=8.1$ Hz); 8.15 (d, 1H, $J=5.0$ Hz); 8.18 (d, 1H, $J=5.0$ Hz); 8.50 (d, 1H, $J=8.1$ Hz); 8.75 (d, 1H, $J=8.1$ Hz); ^{13}C NMR ($CDCl_3$+DMSO-d_6): 25.6, 50.3, 52.2, 118.0, 127.1, 127.3, 127.5, 128.7, 129.1, 129.6, 133.2, 138.0, 136.9, 145.7, 148.1, 163.7, 171.7; IR (KBr): 1654, 1301; HRMS m/z calcd for $C_{20}H_{19}N_2O_5S$ 399.1014 for ($M+H^+$), found 399.1016. HPLC of GITC derivative **11e**: gradient B; retention times, (*S*) 19.50 and (*R*) 20.00 min.

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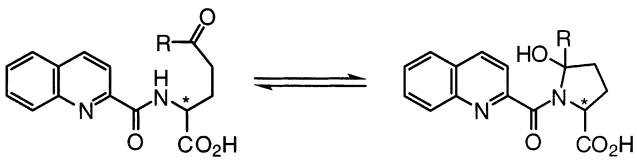
11. For the Michael addition of **2** with methyl or ethyl vinyl ketone, an equilibrium between the open ketoamide **10** and the cyclic form **12**, generated by intramolecular addition of the amide NH to the ketone carbonyl, was observed. This equilibrium depends on the solvent. In H_2O/CH_3CN, the solvent used for HPLC and LC/MS analyses, only the open form **10** was observed. However, in pure CD_3CN or $CDCl_3$, an equilibrium mixture approximately 1:1 of **10**/**12** was found by ^1H NMR of the crude product. Cyclised products **12** gave a clean triplet (no NH coupling) for the α-proton in $CDCl_3$ [**12c**, 4.75 (t, 1H, $J=8.8$ Hz); **12d**, 4.79 (t, 1H, $J=8.8$ Hz)]. It was not possible to isolate pure **12**, but an HRMS analysis of the crude mixtures of **10** and **12** ($-H_2O$) indicated the presence of both compounds. HRMS [M^+-H]; **10c**: calcd for $C_{16}H_{17}N_2O_4$ 301.1188, observed 301.1188: **12c**: calcd for $C_{16}H_{15}N_2O_3$ 283.1083, observed 283.1043. **10d**: calcd for $C_{17}H_{19}N_2O_4$ 315.1345, observed 315.1370. **12d**: calcd for $C_{17}H_{17}N_2O_3$ 297.1239, observed 297.1253.



10c (R=Me)
10d (R=Et)

12c (R=Me)
12d (R=Et)

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