Tetrahedron 65 (2009) 128–133

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of non-proteinogenic amino acids using Michael addition to unsaturated orthopyroglutamate derivative

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ARTICLE INFO

Article history:
Received 3 October 2008
Received in revised form 24 October 2008
Accepted 29 October 2008
Available online 6 November 2008

Keywords:
Amino acids
Pyroglutaminol
Michael addition
ABO ester

ABSTRACT

Stereoselective synthesis of non-proteinogenic amino acids via Michael addition to 3,4-didehydropyroglutamate derivative in which the carboxyl function is protected as a 2,7,8-trioxabicyclo[3.2.1]octane (ABO ester) group is described. The obtained 3-substituted pyroglutamic ABO ester was directly converted to 3-substituted glutamic acids such as chlorpheg by acidic hydrolysis, whereas 3-substituted proline derivatives were obtained by chemoselective reduction of the lactam carbonyl group. A formal total synthesis of baclofen, a γ-aminobutyric acid (GABA) analogue, is also described.

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1. Introduction

Non-proteinogenic amino acids are compounds of interest as biologically active substrates, chiral building blocks, and components of oligopeptides and proteins.[1] For the preparation of such amino acids, L-pyroglutamic acid is often employed as a starting material.[2,3] Among a wide variety of synthons derived from L-pyroglutamic acid, unsaturated pyroglutaminol derivatives are well suited as versatile chiral templates because the olefin functionality can be easily modified by conjugate addition, dihydroxylation, cyclopropanation, epoxidation, cycloaddition and so on.[4] However, the procedure requires reduction of the carboxyl group in order to perform the above transformations without affecting the integrity of chirality. After the required modifications have been completed, the carboxyl group must be regenerated if necessary.

Recently, we have reported the synthesis of a novel unsaturated pyroglutamate derivative **1** in which the carboxyl function was protected as a 5-methyl-2,7,8-trioxabicyclo[3.2.1]octane[5] (ABO ester).[6,7] The unsaturated orthopyroglutamate **1** was found to be an excellent substrate for the synthesis of non-proteinogenic amino acids where redox treatment of the carboxyl group, as described above, was unnecessary. During the course of our previous investigation, Herdeis and co-workers employed Corey's OBO ester[8–12] (4-methyl-2,6,7-trioxabicyclo[2.2.2]octane) as a carboxyl protecting group of unsaturated pyroglutamate, and demonstrated its utility as a Michael acceptor.[13]

We herein describe the stereoselective synthesis of some non-proteinogenic amino acids via Michael addition to the unsaturated ABO ester **1**. As shown in Figure 1, hydrolysis of the Michael adduct directly yields 3-substituted glutamic acids, whereas 3-substituted prolines can be obtained by chemoselective reduction of the lactam carbonyl group. Construction of the 3-substituted γ-aminobutyric acid (GABA) framework is also feasible by a decarboxylation reaction. In this work, a formal total synthesis of baclofen is demonstrated.

2. Results and discussion

First, we examined the stereoselective introduction of substituents at the β-position of the pyroglutamate skeleton by a Michael-type conjugate addition of nucleophiles. The results are listed in Table 1.

Treatment of Michael acceptor **1** with a Gilman reagent, prepared from MeLi and CuI, at −80 °C gave methylated derivative **2a** in 90% yield (entry 1). Similar reactions with Grignard-cuprates containing phenyl and 4-chlorophenyl groups proceeded smoothly to produce the 1,4-adducts **2b** and **2c** in 71 and 68% yields, respectively (entries 2 and 3). In these cuprate additions, higher yields were obtained in comparison with the Herdeis' work.[13] The addition of sodium diethyl malonate also afforded Michael adduct **2d** in quantitative yield (entry 4).

The ^{1}H NMR spectra of the ABO derivatives **2a–d** were too complex to be analyzed properly. In all cases, the stereochemistry

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doi:10.1016/j.tet.2008.10.092

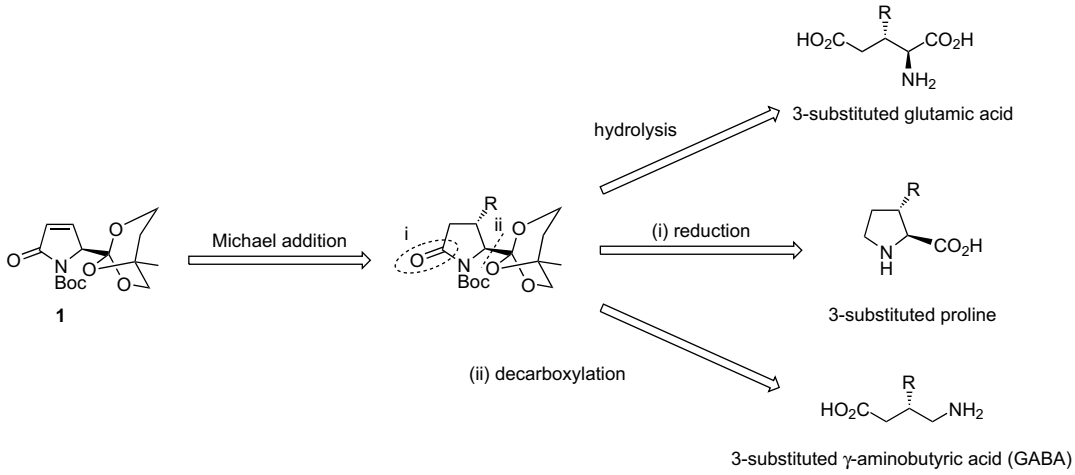
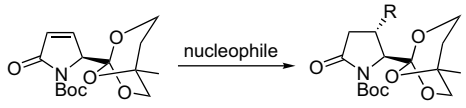


Figure 1. Synthetic course of non-proteinogenic amino acids.

Table 1
Michael addition to unsaturated orthopyroglutamate **1**

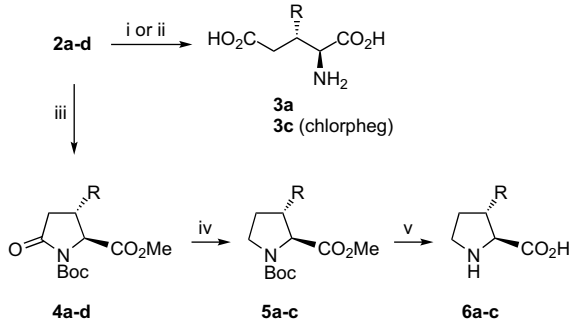


1 **2a-d**

Entry	Reagent	R	Yield[a] (%)
1	Me_2CuLi	Me (**2a**)	90
2	$Ph_2CuMgBr$	Ph (**2b**)	71
3	$(4\text{-}ClC_6H_4)_2CuMgBr$	$4\text{-}ClC_6H_4$ (**2c**)	68
4	$NaCH(CO_2Et)_2$	$CH(CO_2Et)_2$ (**2d**)	Quant

[a] Isolated yield.

of the β-position was tentatively assigned on the basis of addition from the less-hindered face. In order to determine the stereochemical course of the addition reactions, the ABO ester was converted to the corresponding methyl ester by HCl-promoted methanolysis. Subsequent reprotection of the amido proton liberated during the alcoholysis by a Boc group furnished methyl pyroglutamate derivatives **4a**–**d** in good yields (Scheme 1). By comparing the observed vicinal coupling constants (J=3–4 Hz) between the α- and β-protons with those of related systems (J=3.4–3.9 Hz),[14,15] the relative configuration was assigned to be trans.

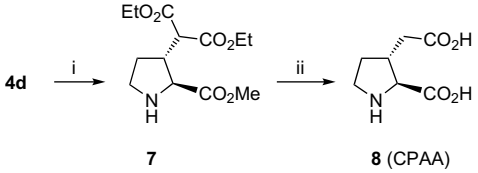


a: R = Me, **b:** R = Ph, **c:** R = $4\text{-}ClC_6H_4$,
d: R = $CH(CO_2Et)_2$

Scheme 1. Synthesis of 3-substituted glutamic acids and prolines. *Reagents and conditions*: (i) 6 M HCl, then propylene oxide, EtOH, **3a**: 50%; (ii) 6 M HCl, then DOWEX 50WX8, **3c**: 63%; (iii) HCl, MeOH, then $(t\text{-}BuOCO)_2O$, DMAP, MeCN, **4a**: 83%; **4b**: 62%; **4c**: 66%; **4d**: 87%; (iv) BH_3–THF, **5a**: 94%; **5b**: 69%; **5c**: 51%; (v) 1 M HCl, then DOWEX 50WX8, **6a**: 90%; **6b**: 70%; **6c**: 78%.

The structure of the Michael adducts **2** was also confirmed after converting to 3-substituted glutamic acids. A closely related work has been reported by Herdeis and co-workers,[13] where 3-substituted glutamic acids were obtained from the corresponding OBO ester in a three-step sequence. When a mixture of ABO ester **2a** and 6 M HCl was refluxed overnight, deprotection of the Boc group, ring opening and hydrolysis of the ABO group took place simultaneously to produce 3-methylglutamic acid hydrochloride, which led to a free amino acid **3a** in 50% yield upon treatment with propylene oxide. Its physical and spectral data are in accordance with those of the reported (2*S*,3*S*)-isomer,[13] suggesting exclusive addition of the Gilman reagent towards the Michael acceptor **1** anti to the resident ABO moiety. This result prompted us to examine concise preparation of 3-(4-chlorophenyl)glutamic acid (chlorpheg),[16–18] which has shown to be a selective L-homocysteate uptake inhibitor. As expected, chlorpheg **3c** could be obtained in 63% yield by simply refluxing the adduct **2c** in 6 M HCl.

Further modification of the pyroglutamate **4a**–**d** to produce the 3-substituted proline was accomplished by chemoselective reduction of the lactam carbonyl group. As shown in Scheme 1, treatment of pyroglutamate **4a** with 3 equiv of borane–THF at room temperature effected a smooth reduction, giving 3-methylprolinate **5a** in 94% yield. Deprotection of **5a** in refluxing 1 M HCl followed by an ion exchange treatment with DOWEX 50WX8 resin furnished (2*S*,3*S*)-3-methylproline **6a** in 90% yield. Similar treatments of **4b** and **4c** led to 3-arylprolines **6b** and **6c**, the conformationally restricted analogues of phenylalanine and chlorpheg, respectively, in good yields. However, exposure of **4d** to borane–THF resulted in the formation of a complex mixture. Therefore, a two-step sequence was adopted to reduce the lactam carbonyl moiety of **4d** (Scheme 2).

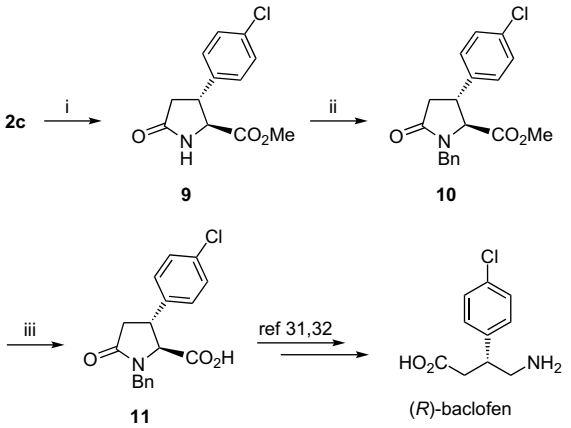


Scheme 2. Preparation of (2*S*,3*R*)-2-carboxypyrrolidine-3-acetic acid (**8**, CPAA). *Reagents and conditions*: (i) DIBAL-H, then Et_3SiH, BF_3–OEt_2; (ii) 1 M HCl, then DOWEX 50WX8, 53% (3 steps).

Despite the presence of five carbonyl functions in **4d**, we found that treatment with DIBAL-H followed by triethylsilane in the presence of boron trifluoride allowed selective reduction of the lactam carbonyl group,[19,20] yielding the prolinate **7**, which was then submitted to deprotection and decarboxylation procedure to

produce (2*S*,3*R*)-2-carboxypyrrolidine-3-acetic acid (**8**, CPAA), an NMDA receptor agonist,[21] in 53% yield (3 steps) based on the pyroglutamate **4d**.

As an extension of the present protocol to the preparation of 3-substituted γ-aminobutyric acid (GABA) derivatives, we have demonstrated here a formal total synthesis of (*R*)-baclofen, which is known as a muscle relaxer and an antispastic agent.[22] Although baclofen has been commercialized in its racemic form, its biological activity resides exclusively in the (*R*)-enantiomer.[23] Many chemical syntheses of baclofen have already been described.[24–30] As outlined in Scheme 3, after methanolysis of the ABO function of **2c**, installation of benzyl protective group into the lactam nitrogen followed by LiOH-promoted hydrolysis of the methyl ester yielded pyroglutamic acid **11**, which was spectroscopically identical to that previously reported.[31,32] The acid **11** can be converted to baclofen as described by Chang and co-workers.[31,32]



Scheme 3. Formal total synthesis of (*R*)-baclofen. *Reagents and conditions*: (i) HCl, MeOH, 75%; (ii) $PhCH_2Br$, NaH, THF, 55%; (iii) 1 M LiOH, THF, 98%.

3. Conclusion

We have developed a simple method for the stereoselective preparation of 3-substituted glutamic acids and prolines using Michael addition to the unsaturated pyroglutamic ABO ester **1** where it was not necessary to change the oxidation state of the carboxyl function. The utility of the present protocol is demonstrated by the concise synthesis of some biologically active non-proteinogenic amino acids such as chlorpheg and CPAA. As an application of this methodology, a formal total synthesis of baclofen was also demonstrated.

4. Experimental

4.1. General

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were measured at 400 and 100 MHz, respectively. All chemical shifts are reported as δ values (ppm) relative to residual chloroform (δ_H 7.26), HDO (δ_H 4.65) or the central peak of deuteriochloroform (δ_C 77.0). High-resolution mass spectra (HRMS) were determined using perfluorokerosene as an internal standard. Optical rotations were measured on a HORIBA SEPA-200 polarimeter. Solvents and reagents were of commercial grade and purified if necessary.

*4.1.1. (4S,5S)-1-tert-Butoxycarbonyl-4-methyl-5-(5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl)-2-pyrrolidone (**2a**)*

MeLi in ether (1.20 M, 25.0 mL, 30.0 mmol) was added to a stirred suspension of CuI (2.86 g, 15.0 mmol) in ether (40 mL) at −15 °C under an argon atmosphere, and the mixture was stirred for 10 min. A solution of the olefin **1** (1.56 g, 5.01 mmol) in ether (40 mL) was added to the resulting solution at −80 °C. After 4 h, saturated aqueous NH_4Cl was added and the reaction mixture was warmed to room temperature. The organic layer was separated, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (hexanes/ethyl acetate=50:50) to yield the title compound **2a** (1.48 g, 90%) as colourless crystals, mp 130–132 °C. ^1H NMR ($CDCl_3$): δ=1.12 and 1.13 (2d, *J*=7 Hz, 3H), 1.34 and 1.35 (2s, 3H), 1.43–1.48 (m, 1H), 1.51 (s, 9H), 1.94 (d, *J*=17 Hz, 1H), 2.04 (m, 1H), 2.52 (m, 1H), 3.00 (m, 1H), 3.46 (m, 1H), 3.88 (m, 1H), 3.96–4.11 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$): δ=21.29 and 21.43, 21.78, 26.89 and 27.37, 27.79 and 27.83, 33.73 and 33.77, 40.15, 59.32 and 59.40, 65.48 and 65.91, 73.54 and 73.77, 78.97 and 79.07, 82.51, 119.98 and 120.09, 150.21 and 150.29, 174.93 ppm. HRMS (EI, 30 eV): *m*/*z* 327.1642 (M^+, calcd for $C_{16}H_{25}NO_6$ 327.1682).

*4.1.2. (4R,5S)-1-tert-Butoxycarbonyl-4-phenyl-5-(5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl)-2-pyrrolidone (**2b**)*

A solution of phenylmagnesium bromide, prepared from bromobenzene (5.30 g, 33.8 mmol) and magnesium (822 mg, 33.8 mmol) in ether (50 mL), was added to a stirred suspension of CuBr–SMe_2 (3.47 g, 16.9 mmol) in ether (50 mL) at −40 °C under an argon atmosphere, and the mixture was stirred for 30 min. A solution of the olefin **1** (1.05 g, 3.37 mmol) and chlorotrimethylsilane (1.17 g, 10.8 mmol) in ether (50 mL) was added to the resulting solution at −80 °C. After 1 h, saturated aqueous NH_4Cl was added and the reaction mixture was warmed to room temperature. The organic layer was separated, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (hexanes/ethyl acetate=50:50) to yield the title compound **2b** (933 mg, 71%) as a pale yellow oil. ^1H NMR ($CDCl_3$): δ=1.35 and 1.37 (2s, 3H), 1.48 (m, 1H), 1.48 (s, 9H), 2.07 (m, 1H), 2.43 (m, 1H), 3.27 (m, 1H), 3.50 (m, 1H), 3.63 (m, 1H), 3.92 (m, 1H), 4.03 (m, 1H), 4.11 (m, 1H), 4.42 and 4.46 (2s, 1H), 7.17–7.32 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$): δ=21.78, 27.73 and 27.78, 33.71 and 33.76, 37.11 and 37.59, 39.56 and 39.60, 59.42 and 59.51, 65.54 and 65.96, 73.58 and 73.87, 79.10 and 79.28, 82.67, 119.85 and 119.98, 126.17, 126.94, 128.93, 143.92 and 143.98, 149.67 and 149.75, 174.62 ppm. HRMS (EI, 70 eV): *m*/*z* 390.1951 [$(M+H)^+$, calcd for $C_{21}H_{28}NO_6$ 390.1917].

*4.1.3. (4R,5S)-1-tert-Butoxycarbonyl-4-(4-chlorophenyl)-5-(5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl)-2-pyrrolidone (**2c**)*

A solution of 4-chlorophenylmagnesium bromide, prepared from 4-bromochlorobenzene (15.3 g, 79.9 mmol) and magnesium (1.95 g, 80.2 mmol) in ether (80 mL), was added to a stirred suspension of CuBr–SMe_2 (8.22 g, 40.0 mmol) in ether (80 mL) at −40 °C under an argon atmosphere, and the mixture was stirred for 30 min. A solution of the olefin **1** (2.49 g, 8.00 mmol) and chlorotrimethylsilane (2.76 g, 25.4 mmol) in ether (80 mL) was added to the resulting solution at −80 °C. After 1 h, saturated aqueous NH_4Cl was added and the reaction mixture was warmed to room temperature. The organic layer was separated, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (hexanes/ethyl acetate=50:50) to yield the title compound **2c** (2.30 g, 68%) as a pale yellow oil. ^1H NMR ($CDCl_3$): δ=1.36 and 1.38 (2s, 3H), 1.49 (m, 1H), 1.49 (s, 9H), 2.08 (m, 1H), 2.40 (m, 1H), 3.28 (m, 1H), 3.51 (m, 1H), 3.61 (m, 1H), 3.93 (m, 1H), 4.04 (m, 1H), 4.11 (m, 1H), 4.35 and 4.39 (2s, 1H), 7.12 and 7.13 (2d, *J*=8 Hz, 2H), 7.28 and 7.29 (2d, *J*=8 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ=21.80, 27.75 and 27.80, 33.72 and 33.78, 36.62 and 37.11, 39.32 and 39.36, 59.47 and 59.57, 65.55 and 65.96, 73.63 and 73.91, 79.21 and 79.37, 82.90, 119.74 and 119.87, 127.62, 129.08, 132.79 and 132.81, 142.35 and 142.41, 149.59 and 149.67, 174.24 ppm. HRMS (EI, 70 eV): *m*/*z* 423.1485 (M^+, calcd for $C_{21}H_{26}NO_6Cl$ 423.1449).

4.1.4. (4R,5S)-1-tert-Butoxycarbonyl-4-(bis(ethoxycarbonyl)methyl)-5-(5-methyl-2,7,8-trioxabicyclo[3.2.1]oct-1-yl)-2-pyrrolidone (**2d**)

Diethyl malonate (4.80 g, 30.0 mmol) was added dropwise to a stirred suspension of sodium hydride (60% dispersion in mineral oil, 1.20 g, 30.0 mmol) in THF (40 mL) at 0 °C under an argon atmosphere, and the mixture was stirred for 30 min. A solution of the olefin **1** (1.87 g, 6.01 mmol) and Me_3SiCl (1.30 g, 12.0 mmol) in THF (40 mL) was added to the resulting mixture and the reaction mixture was stirred at room temperature overnight. The reaction was quenched with saturated aqueous NH_4Cl and the organic layer was separated, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel (hexanes/ethyl acetate=50:50) to produce quantitative yield of the title compound **2d** (2.83 g) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ=1.247 and 1.249 (2t, J=7 Hz, 3H), 1.26 (t, J=7 Hz, 3H), 1.33 and 1.34 (2s, 3H), 1.42–1.47 (m, 1H), 1.50 (s, 9H), 2.04 (m, 1H), 2.32 (m, 1H), 3.03–3.18 (m, 2H), 3.45–3.49 (m, 2H), 3.88 (m, 1H), 3.99 (m, 1H), 4.06 (m, 1H), 4.18 (m, 4H), 4.38 and 4.43 (2s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ=13.93, 13.97, 21.77, 27.77 and 27.80, 32.07 and 32.54, 33.71 and 33.74, 36.49, 55.10 and 55.15, 59.44 and 59.52, 61.32, 61.35, 61.82, 73.64 and 73.92, 79.12 and 79.33, 82.59, 119.75 and 119.88, 149.46 and 149.53, 167.59, 167.61, 173.63 ppm. HRMS (EI, 70 eV): m/z 471.2134 (M^+, calcd for $C_{22}H_{33}NO_{10}$ 471.2104).

4.1.5. (2S,3S)-3-Methylglutamic acid (**3a**)[13,33]

A mixture of compound **2a** (1.47 g, 4.49 mmol) and 6 M HCl (10 mL) was heated to reflux overnight. The cooled solution was washed with chloroform and concentrated to dryness. The residue was then dissolved in a mixture of propylene oxide (4 mL) and ethanol (12 mL) and the solution was refluxed for 1 h. The precipitated solids were collected by filtration to yield the title compound **3a** (362 mg, 50%) as colourless crystals, mp 177–178 °C (lit. mp 182–184 °C[13]; mp 171–173 °C[33]). $[\alpha]_D^{23}$ +41.0 (c 1.00, 6 M HCl) (lit. $[\alpha]_D^{20}$ +41.9 (c 0.82, 6 M HCl)[13]; $[\alpha]_D^{25}$ +42.0 (c 0.9, 6 M HCl)[33]). ^{1}H NMR (NaOD–D_2O): δ=0.76 (d, J=7 Hz, 3H), 1.77 (dd, J=13 and 11 Hz, 1H), 1.91 (m, 1H), 2.22 (dd, J=13 and 3 Hz, 1H), 2.89 (d, J=6 Hz, 1H) ppm.

4.1.6. (2S,3R)-3-(4-Chlorophenyl)glutamic acid (chlorpheg) (**3c**)[16]

A mixture of compound **2c** (552 mg, 1.30 mmol) and 6 M HCl (10 mL) was heated to reflux overnight. The cooled solution was washed with chloroform and concentrated to dryness. The residue was submitted to ion-exchange column chromatography on DOWEX 50WX8 and elution with 1 M NH_4OH to yield the ammonium salt of compound **3c**. The salt was then dissolved in water and the solution was acidified to pH 3 with 1 M HCl. The precipitated solids were collected by filtration to yield the title compound **3c** (210 mg, 63%) as colourless crystals, mp 188–190 °C (lit.[16] mp 194.7–194.9 °C). $[\alpha]_D^{24}$ +21.0 (c 0.10, 1 M NaOH) (lit.[16] $[\alpha]_D^{20}$ +21.5 (c 0.39, 1 M NaOH)). ^{1}H NMR (NaOD–D_2O): δ=2.41 (dd, J=15 and 12 Hz, 1H), 2.54 (dd, J=15 and 4 Hz, 1H), 3.07 (ddd, J=12, 7 and 4 Hz, 1H), 3.18 (d, J=7 Hz, 1H), 7.07 (d, J=8 Hz, 2H), 7.17 (d, J=8 Hz, 2H) ppm.

4.1.7. Methyl (2S,3S)-N-tert-butoxycarbonyl-3-methylpyroglutamate (**4a**)

A solution of compound **2a** (1.17 g, 3.57 mmol) in methanol (60 mL) was cooled in an ice bath and a slow stream of HCl was introduced with stirring to saturation. After being stirred at room temperature for 3 h, the solution was concentrated and the residue was extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated to yield crude methyl 3-methylpyroglutamate (550 mg, 98%).

The obtained pyroglutamate was treated with di-*tert*-butyl dicarbonate (915 mg, 4.19 mmol) and DMAP (427 mg, 3.50 mmol) in acetonitrile (5 mL) at room temperature for 1.5 h. After removal of the solvent, the residue was extracted with ethyl acetate. The organic layer was washed successively with aqueous $KHSO_4$ and brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel (hexanes/ethyl acetate=50:50) to yield the title compound **4a** (761 mg, 83%, 2 steps) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ=1.23 (d, J=7 Hz, 3H), 1.47 (s, 9H), 2.14 (dd, J=17 and 5 Hz, 1H), 2.36 (m, 1H), 2.77 (dd, J=17 and 8 Hz, 1H), 3.76 (s, 3H), 4.17 (d, J=4 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ=20.37, 27.80, 29.62, 39.39, 52.46, 65.87, 83.60, 149.29, 171.36, 172.73 ppm. HRMS (EI, 70 eV): m/z 258.1359 [$(M+H)^+$, calcd for $C_{12}H_{19}NO_5$ 258.1341].

4.1.8. Methyl (2S,3R)-N-tert-butoxycarbonyl-3-phenylpyroglutamate (**4b**)

According to the procedure described for the synthesis of compound **4a**, methanolysis of the compound **2b** (738 mg, 1.90 mmol) with hydrogen chloride in methanol (50 mL) followed by protection with di-*tert*-butyl dicarbonate (497 mg, 2.28 mmol) and DMAP (232 mg, 1.90 mmol) in acetonitrile (20 mL) yielded the title compound **4b** (378 mg, 62%, 2 steps) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ=1.48 (s, 9H), 2.69 (dd, J=17 and 5 Hz, 1H), 3.07 (dd, J=17 and 9 Hz, 1H), 3.46 (ddd, J=17, 5 and 4 Hz, 1H), 3.80 (s, 3H), 4.56 (d, J=4 Hz, 1H), 7.23–7.40 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$): δ=27.82, 38.82, 39.68, 52.65, 66.24, 83.93, 126.47, 127.85, 129.21, 141.03, 149.05, 171.15, 172.40 ppm. HRMS (EI, 70 eV): m/z 319.1440 (M^+, calcd for $C_{17}H_{21}NO_5$ 319.1420).

4.1.9. Methyl (2S,3R)-N-tert-butoxycarbonyl-3-(4-chlorophenyl)pyroglutamate (**4c**)

According to the procedure described for the synthesis of compound **4a**, methanolysis of the compound **2c** (1.28 g, 3.02 mmol) with hydrogen chloride in methanol (60 mL) followed by protection with di-*tert*-butyl dicarbonate (793 mg, 3.63 mmol) and DMAP (370 mg, 3.03 mmol) in acetonitrile (20 mL) yielded the title compound **4c** (703 mg, 66%, 2 steps) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ=1.48 (s, 9H), 2.63 (dd, J=17 and 5 Hz, 1H), 3.06 (dd, J=17 and 9 Hz, 1H), 3.44 (ddd, J=9, 5 and 4 Hz, 1H), 3.80 (s, 3H), 4.51 (d, J=4 Hz, 1H), 7.17 (d, J=9 Hz, 2H), 7.34 (d, J=9 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ=27.83, 38.72, 39.18, 52.75, 66.10, 84.13, 127.90, 129.40, 133.81, 139.40, 148.99, 170.91, 171.97 ppm. HRMS (EI, 70 eV): m/z 353.1059 (M^+, calcd for $C_{17}H_{20}NO_5Cl$ 353.1030).

4.1.10. Methyl (2S,3R)-N-tert-butoxycarbonyl-3-(bis(ethoxycarbonyl)methyl)pyroglutamate (**4d**)

According to the procedure described for the synthesis of compound **4a**, methanolysis of the compound **2d** (9.18 g, 19.5 mmol) with hydrogen chloride in methanol (200 mL) followed by protection with di-*tert*-butyl dicarbonate (4.58 g, 21.0 mmol) and DMAP (2.44 g, 20.0 mmol) in acetonitrile (30 mL) yielded the title compound **4d** (6.79 g, 87%, 2 steps) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ=1.27 (t, J=7 Hz, 3H), 1.28 (t, J=7 Hz, 3H), 1.48 (s, 9H), 2.48 (dd, J=17 and 3 Hz, 1H), 2.85–2.98 (m, 2H), 3.54 (d, J=7 Hz, 1H), 3.79 (s, 3H), 4.23 (m, 4H), 4.54 (d, J=3 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ=13.92, 13.94, 27.84, 33.61, 35.50, 52.78, 54.42, 61.71, 62.20, 62.26, 83.97, 149.02, 167.08, 167.15, 170.91, 171.45 ppm. HRMS (EI, 70 eV): m/z 402.1740 [$(M+H)^+$, calcd for $C_{18}H_{28}NO_9$ 402.1764].

4.1.11. Methyl (2S,3S)-N-tert-butoxycarbonyl-3-methylprolinate (**5a**)

A solution of borane in THF (1 M, 9 mL, 9 mmol) was added to a solution of compound **4a** (761 mg, 2.96 mmol) in THF (3 mL) under an argon atmosphere, and the mixture was stirred at room temperature overnight. The reaction was quenched by addition of methanol, and after being stirred for 1 h, the mixture was diluted with dichloromethane. The organic layer was then dried over $MgSO_4$ and concentrated. The crude product was purified by flash

column chromatography on silica gel (hexanes/ethyl acetate=50:50) to produce the title compound **5a** (678 mg, 94%) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ=1.13 and 1.14 (2d, J=7 Hz, 3H), 1.38 and 1.44 (2s, 9H), 1.51 (m, 1H), 2.02 (m, 1H), 2.29 (m, 1H), 3.40–3.61 (m, 2H), 3.71 and 3.72 (2s, 3H), 3.73 and 3.84 (2d, J=6 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ=18.23 and 18.44, 28.22 and 28.35, 32.08 and 32.48, 38.36 and 39.49, 45.68 and 45.84, 51.83 and 52.02, 65.62 and 66.12, 79.72 and 79.82, 153.71 and 154.37, 173.22 and 173.45 ppm. HRMS (EI, 70 eV): m/z 243.1501 (M^+, calcd for $C_{12}H_{21}NO_4$ 243.1471).

4.1.12. Methyl (2S,3R)-N-tert-butoxycarbonyl-3-phenylprolinate (**5b**)

According to the procedure described for the synthesis of compound **5a**, treatment of the compound **4b** (378 mg, 1.18 mmol) in THF (10 mL) with an 1 M solution of borane in THF (3.6 mL, 3.6 mmol) yielded the title compound **5b** (248 mg, 69%) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ=1.41 and 1.48 (2s, 9H), 2.03 (m, 1H), 2.30 (m, 1H), 3.44 (m, 1H), 3.61 and 3.76 (2m, 2H), 3.70 and 3.71 (2s, 3H), 4.24 and 4.38 (2d, J=7 Hz, 1H), 7.22–7.36 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$): δ=28.23 and 28.39, 32.24 and 32.96, 45.95 and 46.11, 48.71 and 49.91, 51.95 and 52.17, 65.09 and 65.78, 80.08 and 80.19, 126.88 and 126.93, 127.11 and 127.24, 128.72 and 128.75, 140.50 and 140.86, 153.58 and 154.22, 173.05 and 173.19 ppm. HRMS (EI, 70 eV): m/z 305.1675 (M^+, calcd for $C_{17}H_{23}NO_4$ 305.1627).

4.1.13. Methyl (2S,3R)-N-tert-butoxycarbonyl-3-(4-chlorophenyl)prolinate (**5c**)

According to the procedure described for the synthesis of compound **5a**, treatment of the compound **4c** (703 mg, 1.99 mmol) in THF (15 mL) with an 1 M solution of borane in THF (6.0 mL, 6.0 mmol) yielded the title compound **5c** (345 mg, 51%) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ=1.41 and 1.48 (2s, 9H), 1.98 (m, 1H), 2.30 (m, 1H), 3.40 (m, 1H), 3.60 and 3.74 (2m, 2H), 3.70 and 3.71 (2s, 3H), 4.19 and 4.32 (2d, J=7 Hz, 1H), 7.16 (d, J=9 Hz, 2H), 7.30 (d, J=9 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ=28.22 and 28.38, 32.25 and 32.98, 45.89 and 46.04, 48.13 and 49.32, 52.04 and 52.26, 65.04 and 65.70, 80.23 and 80.34, 128.28 and 128.34, 128.88 and 128.92, 132.91 and 133.04, 138.92 and 139.29, 153.50 and 154.19, 172.79 and 172.96 ppm. HRMS (EI, 70 eV): m/z 339.1196 (M^+, calcd for $C_{17}H_{22}NO_4Cl$ 339.1237).

4.1.14. (2S,3S)-3-Methylproline (**6a**)[34]

A mixture of compound **5a** (276 mg, 1.13 mmol) and 1 M HCl (20 mL) was heated to reflux for 3 h. The cooled solution was washed with chloroform and concentrated to dryness. The residue was submitted to ion-exchange column chromatography on DOWEX 50WX8 and elution with 1 M NH_4OH to yield the title compound **6a** (132 mg, 90%) as colourless crystals, mp 240–242 °C (lit.[34] mp 245 °C). $[\alpha]_D^{22}$ −28.0 (c 1.00, H_2O) (lit.[34] $[\alpha]_D^{20}$ −30.0 (c 0.27, H_2O)). ^{1}H NMR (D_2O): δ=1.06 (d, J=7 Hz, 3H), 1.51 (m, 1H), 2.03 (m, 1H), 2.22 (m, 1H), 3.21 (m, 2H), 3.43 (d, J=8 Hz, 1H) ppm.

4.1.15. (2S,3R)-3-Phenylproline (**6b**)[34]

According to the procedure described for the synthesis of compound **6a**, deprotection of the compound **5b** (248 mg, 0.812 mmol) in refluxing 1 M HCl (15 mL) followed by ion exchange chromatography on DOWEX 50WX8 produced the title compound **6b** (108 mg, 70%) as colourless crystals, mp 247–249 °C (lit.[34] mp >250 °C). $[\alpha]_D^{25}$ +65.0 (c 0.2, H_2O) (lit.[34] $[\alpha]_D^{20}$ +65.0 (c 0.2, 1 M HCl)). ^{1}H NMR (D_2O): δ=2.05 (m, 1H), 2.31 (m, 1H), 3.29–3.38 (m, 2H), 3.44 (m, 1H), 3.94 (d, J=9 Hz, 1H), 7.17–7.29 (m, 5H) ppm.

4.1.16. (2S,3R)-3-(4-Chlorophenyl)proline (**6c**)

According to the procedure described for the synthesis of compound **6a**, deprotection of the compound **5c** (345 mg, 1.02 mmol) in refluxing 1 M HCl (15 mL) followed by ion exchange chromatography on DOWEX 50WX8 produced the title compound **6c** (179 mg, 78%) as colourless crystals, mp 240–242 °C. $[\alpha]_D^{21}$ +68.0 (c 0.1, H_2O). ^{1}H NMR (D_2O): δ=2.03 (m, 1H), 2.31 (m, 1H), 3.32 (m, 2H), 3.44 (m, 1H), 3.90 (d, J=9 Hz, 1H), 7.19 (d, J=9 Hz, 2H), 7.26 (d, J=9 Hz, 2H) ppm. ^{13}C NMR (D_2O): δ=33.05, 45.96, 47.33, 64.58, 129.04, 129.20, 133.07, 136.77, 170.51 ppm. HRMS (EI, 70 eV): m/z 225.0582 (M^+, calcd for $C_{11}H_{12}NO_2Cl$ 225.0557).

4.1.17. (2S,3R)-3-Carboxymethylproline (**8**)[35]

A solution of DIBAL-H in toluene (1 M, 5.00 mL, 5.00 mmol) was added to a solution of the pyroglutamate **4d** (674 mg, 1.68 mmol) in THF (10 mL) at −80 °C under an argon atmosphere, and the reaction mixture was stirred for 1 h. Then, the mixture was quenched with methanol and warmed up to room temperature. After addition of saturated aqueous potassium tartarate (17 mL) and ethyl acetate (17 mL), the mixture was stirred for an additional 15 min. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated, and the residue was dissolved in dichloromethane (10 mL). Et_3SiH (390 mg, 3.35 mmol) and boron trifluoride diethyl etherate (477 mg, 3.36 mmol) were added to the solution at 0 °C under an argon atmosphere, and the resulting solution was stirred for 2 h. Then the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and the organic layer was dried over $MgSO_4$ and concentrated to produce crude methyl (2*S*,3*R*)-3-(bis(ethoxycarbonyl)methyl)prolinate (**7**). Although the obtained prolinate **7** could be used in the next step without further purification, a small aliquot obtained from a separate run was purified by column chromatography on silica gel (chloroform/ethanol=85:15) for the structural elucidation. ^{1}H NMR ($CDCl_3$): δ=1.251 (t, J=7 Hz, 3H), 1.254 (t, J=7 Hz, 3H), 1.62 (m, 1H), 2.06 (m, 1H), 2.20 (br s, 1H), 2.90 (m, 1H), 3.00 (m, 2H), 3.51 (d, J=9 Hz, 1H), 3.68 (d, J=6 Hz, 1H), 3.71 (s, 3H), 4.18 (m, 4H) ppm. ^{13}C NMR ($CDCl_3$): δ=13.96, 14.02, 30.48, 42.61, 46.16, 52.20, 54.93, 61.46, 61.53, 63.05, 168.19, 168.36, 174.62 ppm. HRMS (EI, 70 eV): m/z 287.1383 (M^+, calcd for $C_{13}H_{21}NO_6$ 287.1369).

Deprotection of the crude prolinate **7** was carried out in refluxing 1 M HCl (18 mL) overnight. The cooled solution was washed with chloroform and concentrated to dryness. The residue was submitted to ion-exchange column chromatography on DOWEX 50WX8 and elution with 1 M NH_4OH to produce the ammonium salt of the title compound. The salt was then dissolved in water and the solution was acidified to pH 3 with 1 M HCl. The precipitated solids were collected by filtration and recrystallized from water/acetone to yield the title compound **8** (153 mg, 53%, 3 steps) as colourless crystals, mp 236–239 °C (lit.[35] mp 242–244 °C). $[\alpha]_D^{22}$ +19.0 (c 0.5, H_2O) (lit.[35] $[\alpha]_D^{25}$ +20.0 (c 0.1, H_2O)). ^{1}H NMR (D_2O): δ=1.64 (m, 1H), 2.15 (m, 1H), 2.39 (dd, J=16 and 9 Hz, 1H), 2.55 (m, 1H), 2.68 (dd, J=16 and 5 Hz, 1H), 3.27 (m, 2H), 3.65 (d, J=8 Hz, 1H) ppm.

4.1.18. Methyl (2S,3R)-3-(4-chlorophenyl)pyroglutamate (**9**)

A solution of compound **2c** (4.99 g, 11.8 mmol) in methanol (200 mL) was cooled in an ice bath, and a slow stream of HCl was introduced with stirring to saturation. After being stirred at room temperature for 3 h, the solution was concentrated and the residue was extracted with ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel and elution with ethyl acetate yielded the title compound **9** as a colourless oil (2.24 g, 75%). ^{1}H NMR ($CDCl_3$): δ=2.48 (dd, J=17 and 7 Hz, 1H), 2.86 (dd, J=17 and 9 Hz, 1H), 3.72 (ddd, J=9, 7 and 5 Hz, 1H), 3.77 (s, 3H), 4.20 (d, J=5 Hz, 1H), 6.08 (br s, 1H), 7.23 (d, J=8 Hz, 2H), 7.34 (d, J=8 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ=37.71, 43.17, 52.78, 62.61, 128.23, 129.19, 133.42, 140.18, 171.50, 176.38 ppm. HRMS (EI, 70 eV): m/z 253.0503 (M^+, calcd for $C_{12}H_{12}NO_3Cl$ 253.0506).

4.1.19. Methyl (2S,3R)-N-benzyl-3-(4-chlorophenyl)-pyroglutamate (**10**)

Sodium hydride (60% dispersion in mineral oil, 48.0 mg, 2.00 mmol) was added to a solution of **9** (253 mg, 0.997 mmol) and benzyl bromide (205 mg, 1.20 mmol) in THF (10 mL) and the reaction mixture was refluxed for 1 h. After cooling, the mixture was diluted with ether and washed successively with saturated aqueous NH_4Cl and water. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel, and elution with a mixture of hexane and ethyl acetate (70:30) yielded the title compound **10** (188 mg, 55%) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ=2.50 (dd, J=17 and 4 Hz, 1H), 3.03 (dd, J=17 and 9 Hz, 1H), 3.50 (ddd, J=9, 4 and 3 Hz, 1H), 3.69 (s, 3H), 3.88 (d, J=3 Hz, 1H), 4.03 (d, J=15 Hz, 1H), 5.06 (d, J=15 Hz, 1H), 6.98 (d, J=8 Hz, 2H), 7.17–7.23 (m, 2H), 7.21 (d, J=8 Hz, 2H), 7.27–7.31 (m, 3H) ppm. ^{13}C NMR ($CDCl_3$): δ=37.76, 40.51, 45.81, 52.59, 66.13, 127.75, 127.99, 128.68, 128.73, 129.08, 133.30, 135.25, 140.70, 171.24, 173.64 ppm. HRMS (EI, 70 eV): m/z 343.0963 (M^+, calcd for $C_{19}H_{18}NO_3Cl$ 343.0975).

4.1.20. (2S,3R)-N-Benzyl-3-(4-chlorophenyl)pyroglutamic acid (**11**)[31,32]

LiOH (1 M, 9 mL) was added to a solution of **10** (441 mg, 1.28 mmol) in THF (15 mL), and the reaction mixture was stirred for 2 h. After removal of the solvent, the residue was diluted with water and washed with ether. The aqueous layer was then acidified to pH 3 with 1 M HCl. The precipitated solids were collected by filtration to yield the title compound **11** (411 mg, 98%) as colourless crystals, mp 155–158 °C (lit.[31,32] mp 168–169 °C). The structure was also confirmed by comparison of their spectral data with those reported in the literature.[31,32] ^{1}H NMR ($CDCl_3$): δ=2.56 (dd, J=17 and 4 Hz, 1H), 3.08 (dd, J=17 and 10 Hz, 1H), 3.59 (ddd, J=10, 4, and 3 Hz, 1H), 3.92 (d, J=3 Hz, 1H), 3.99 (d, J=15 Hz, 1H), 5.21 (d, J=15 Hz, 1H), 6.98 (d, J=8 Hz, 2H), 7.19–7.23 (m, 2H), 7.22 (d, J=8 Hz, 2H), 7.27–7.30 (m, 3H) ppm.

References and notes

1. Reviews: (a) Haldar, D. *Curr. Org. Synth.* **2008**, *5*, 61–80; (b) Perdih, A.; Dolenc, M. S. *Curr. Org. Chem.* **2007**, *11*, 801–832; (c) Galeazzi, R.; Mobbili, G.; Orena, M. *Curr. Org. Chem.* **2004**, *8*, 1799–1829.
2. Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis. Construction of Chiral Molecule Using Amino Acids*; John Wiley: New York, NY, 1987.
3. Reviews: (a) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825–1872; (b) Nájera, C.; Yus, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2245–2303.
4. Recent examples: (a) Flemer, S.; Wurthmann, A.; Mamai, A.; Madalengoitia, J. S. *J. Org. Chem.* **2008**, *73*, 7593–7602; (b) Einsiedel, J.; Lanig, H.; Waibel, R.; Gmeiner, P. *J. Org. Chem.* **2007**, *72*, 9102–9113; (c) Spiess, S.; Berthold, C.; Weihofen, R.; Helmchen, G. *Org. Biomol. Chem.* **2007**, *5*, 2357–2360; (d) Alvarez de Cienfuegos, L.; Langlois, N. *Tetrahedron: Asymmetry* **2006**, *17*, 1863–1866; (e) Milne, C.; Powell, A.; Jim, J.; Al Nakeeb, M.; Smith, C. P.; Micklefield, J. *J. Am. Chem. Soc.* **2006**, *128*, 11250–11259; (f) Hanessian, S.; Gauchet, C.; Charron, G.; Marin, J.; Nakache, P. *J. Org. Chem.* **2006**, *71*, 2760–2778.
5. Wipf, P.; Xu, W.; Kim, H.; Takahashi, H. *Tetrahedron* **1997**, *53*, 16575–16596.
6. Oba, M.; Nishiyama, N.; Nishiyama, K. *Chem. Commun.* **2003**, 776–777.
7. Oba, M.; Nishiyama, N.; Nishiyama, K. *Tetrahedron* **2005**, *61*, 8456–8464.
8. Corey, E. J.; Raju, N. *Tetrahedron Lett.* **1983**, *24*, 5571–5574.
9. Blaskovich, M. A.; Lajoie, G. A. *J. Am. Chem. Soc.* **1993**, *115*, 5021–5030.
10. Rose, N. G. W.; Blaskovich, M. A.; Evindar, G.; Wilkinson, S.; Luo, Y.; Fishlock, D.; Reid, C.; Lajoie, G. A. *Org. Synth.* **2003**, *79*, 216–227.
11. Hansen, D. B.; Wan, X.; Carroll, P. J.; Joullié, M. M. *J. Org. Chem.* **2005**, *70*, 3120–3126.
12. Hansen, D. B.; Lewis, A. S.; Gavalas, S. J.; Joullie, M. M. *Tetrahedron: Asymmetry* **2006**, *17*, 15–21.
13. Herdeis, C.; Kelm, B. *Tetrahedron* **2003**, *59*, 217–229.
14. Hara, S.; Makino, K.; Hamada, Y. *Tetrahedron* **2004**, *60*, 8031–8035.
15. Soloshonok, V. A.; Ueki, H.; Tiwari, R.; Cai, C.; Hruby, V. J. *J. Org. Chem.* **2004**, *69*, 4984–4990.
16. Jane, D. E.; Chalmers, D. J.; Howard, J. A. K.; Kilpatrick, I. C.; Sunter, D. C.; Thompson, G. A.; Udvarhelyi, P. M.; Wilson, C.; Watkins, J. C. *J. Med. Chem.* **1996**, *39*, 4738–4743.
17. Davies, J.; Francis, A. A.; Oakes, D. J.; Sheardown, M. J.; Watkins, J. C. *Neuropharmacology* **1985**, *24*, 177–180.
18. Zeise, M. L.; Knöpfel, T.; Zieglgänsberger, W. *Brain Res.* **1988**, *443*, 373–376.
19. Collado, I.; Ezquerra, J.; Mateo, A. I.; Rubio, A. *J. Org. Chem.* **1998**, *63*, 1995–2001.
20. Pedregal, C.; Ezquerra, J.; Escribano, A.; Carreño, M. C.; García Ruano, J. L. *Tetrahedron Lett.* **1994**, *35*, 2053–2056.
21. Tsai, C.; Schnider, J. A.; Lehmann, J. *Neurosci. Lett.* **1988**, *92*, 298–302.
22. Mann, A.; Boulanger, T.; Brandau, B.; Durant, F.; Evrard, G.; Haeulme, M.; Desaulles, E.; Wermuth, C. G. *J. Med. Chem.* **1991**, *4*, 1307–1313.
23. Olpe, H. P.; Demikeville, H.; Baltzer, W. L.; Koella, W. P.; Wolf, P.; Haas, H. L. *Eur. J. Pharmacol.* **1978**, *52*, 133–136.
24. Deng, J.; Duan, Z.-C.; Huang, J.-D.; Hu, X.-P.; Wang, D.-Y.; Yu, S.-B.; Xu, X.-F.; Zheng, Z. *Org. Lett.* **2007**, *9*, 4825–4828.
25. Nemoto, T.; Jin, L.; Nakamura, H.; Hamada, Y. *Tetrahedron Lett.* **2006**, *47*, 6577–6581.
26. Armstrong, A.; Convine, N. J.; Popkin, M. E. *Synlett* **2006**, 1589–1591.
27. Paraskar, A. S.; Sudalai, A. *Tetrahedron* **2006**, *62*, 4907–4916.
28. Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119–125.
29. Becht, J.-M.; Meyer, O.; Helmchen, G. *Synthesis* **2003**, *18*, 2805–2810.
30. Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **2000**, *2*, 4257–4259.
31. Chang, M.-Y.; Sun, P.-P.; Chen, S.-T.; Chang, N.-C. *Tetrahedron Lett.* **2003**, *44*, 5271–5273.
32. Chang, M.-Y.; Chen, C.-Y.; Tasi, M.-R.; Tseng, T.-W.; Chang, N.-C. *Synthesis* **2004**, 840–846.
33. Xian, M.; Alaux, S.; Sagot, E.; Gefflaut, T. *J. Org. Chem.* **2007**, *72*, 7560–7566.
34. Herdeis, C.; Hubmann, H. P.; Lotter, H. *Tetrahedron: Asymmetry* **1994**, *5*, 351–354.
35. Karoyan, P.; Chassaing, G. *Tetrahedron Lett.* **2002**, *43*, 253–255.