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A new constrained proline analogue with an 8-azabicyclo[3.2.1]octane skeleton

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Abstract

A straightforward synthesis of 8-azabicyclo[3.2.1]octane-1-carboxylic acid, a new proline analogue with a bicyclic structure, is described. The procedure makes use of readily available starting materials and involves simple, high-yielding transformations.

Keywords

constrained amino acid; quaternary amino acid; proline analogue; bicyclic proline; ring-closing metathesis

1. Introduction

The introduction of rigidity into bioactive peptides has proven to be a very useful tool to study the conformational requirements for biological activity. One of the most efficient strategies to limit peptide flexibility is the incorporation of conformationally restricted amino acids.^{1,2} Among such non-proteinogenic residues, α -tetrasubstituted (also called *quaternary*) amino acids are known to induce dramatic changes in the peptide structure, drastically reducing the conformational space available.^{1a–d,2} The great potential of constrained amino acids in peptide design has led to the synthesis of a wide variety of conformationally restricted analogues of proteinogenic residues.^{1d,e,3}

One of the proteinogenic amino acids that has attracted particular attention in this context is proline. The high significance of proline in peptide conformation and biology,⁴ together with the more recently recognized utility in organocatalysis,^{5,6} has stimulated the work of many organic chemists in the search for new proline analogues endowed with tailored properties. In particular, a great deal of effort has been directed in recent years towards the preparation of α -tetrasubstituted prolines.^{3c,7} A peculiar family of quaternary prolines is generated when the α -carbon (position 2 of the pyrrolidine moiety) and another position (n) of the five-membered ring are connected through an alkylidene bridge. Such a modification gives rise to bicyclic systems – which can be named as 2,n-alkaneprolines – and is expected to strongly influence the properties of the parent amino acid.

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Among this series of constrained proline analogues, we have focused our attention on the 2,5-alkaneproline family (Figure 1), in which the α (2) and δ (5) carbons of the pyrrolidine ring are bridged. This modification reduces simultaneously the conformational freedom of the proline backbone and side-chain and may have an impact on the *cis-trans* isomerization of the amide bond involving the proline nitrogen. We^{8,9} and other authors¹⁰ have reported the synthesis of the ethane derivative characterized by a 7-azabicyclo[2.2.1]heptane skeleton (Figure 1, a). This proline analogue has been incorporated into different peptides in order to study its biological¹¹ and conformational¹² properties. Interest in this amino acid certainly stems from the presence of the 7-azabicyclo[2.2.1]heptane system in epibatidine,¹³ a highly potent non-opioid analgesic.

In sharp contrast, other members of the 2,5-alkaneproline family have received little attention. To the best of our knowledge, a procedure has yet to be reported for the synthesis of the 2,5-propano derivative, 8-azabicyclo[3.2.1]octane-1-carboxylic acid, (Figure 1, b). Only a precursor of this amino acid has been obtained¹⁴ as the minor product in the radical cyclization of α -allyl protected prolines, where the isomeric 3-methyl-7-azabicyclo[2.2.1]heptane derivative was the major product. An analogous radical process involving a protected α -allyl pipercolic acid has led to the formation of a *gem*-dimethylated derivative.¹⁵ We report here the first synthesis of the novel bicyclic proline analogue 2,5-propanoproline in racemic form.

2. Results and discussion

The target amino acid has a bicyclic structure including both a seven- and a five-membered ring (Figure 1, b). A retrosynthetic analysis of this compound (Scheme 1) shows that the pyrrolidine ring could be formed by intramolecular cyclization of a cycloheptane system bearing the appropriate substituents, with the amino moiety acting as a nucleophile. Thus, besides the adequately protected amino and carboxylic acid functions, such a cycloheptane derivative should incorporate a leaving group at carbon 4 in a *trans* relative disposition with respect to the nucleophile. This leaving group could be introduced on a double bond, which in turn could be obtained by Grubbs cyclization of a symmetric bis-homoallylic compound.

On the basis of the analysis outlined above, our synthetic route to 2,5-propanoproline started with the bis-homoallylation of a glycine precursor. Ethyl isocyanoacetate was used for this purpose and was reacted with excess 4-bromo-1-butene as previously reported by Kotha, *i.e.*, using NaH as a base in a mixture of diethyl ether and dimethyl sulfoxide.¹⁶ Under these conditions, the bis-homoallylated compound **1** was isolated in good yield (Scheme 2).

We next addressed the formation of the seven-membered ring through a metathesis reaction. This procedure involves the use of ruthenium carbene complexes to produce bond reorganization in which olefins are transformed into other alkylidene moieties.¹⁷ Prior to the metathesis, in order to avoid undesired reactions, the isonitrile moiety in **1** was hydrolyzed by stirring in ethanol containing a small amount of concentrated HCl and the resulting amino hydrochloride was reacted with di-*tert*-butyl dicarbonate to give the *N*-Boc protected derivative **2** (Scheme 2). Treatment of this compound with the Grubbs' ruthenium catalyst in anhydrous toluene afforded the cyclized product **3** in good yield.

At this stage, our efforts focused on the introduction of a leaving group with the appropriate stereochemistry to carry out an intramolecular nucleophilic substitution in the next step. The introduction of a halogen atom or an oxygen-based group on a double bond is a straightforward task. Moreover, given the symmetrical structure of compound **3**, such a group could be incorporated on either of the two olefinic carbons in the molecule. In this case, however, the difficulty lies in the requirement that the leaving group has a *trans* relative disposition with

respect to the amino moiety so that the subsequent intramolecular nucleophilic substitution can be accomplished.

Bearing in mind that the incorporation of a substituent in the 4 position of the seven-membered ring in **3** would most probably lead to the formation of *cis/trans* mixtures, with the *cis* stereoisomer being unsuitable for the next step, we considered the possibility of carrying out dibromination of the double bond. As the two vicinal bromine atoms are introduced in an *anti* disposition, this ensures that one of them has the appropriate *trans* stereochemistry with respect to the amino group. The well-known debromination reaction would subsequently be necessary to eliminate the additional bromine atom.

Transformation of alkene **3** into the dibrominated derivative **4** was accomplished in excellent yield by treatment with trimethylphenylammonium tribromide and tetraethylammonium bromide¹⁸ (Scheme 2). This tribromide was preferred to liquid molecular bromine as the bromine source due to ease of handling.

The next step in our synthetic route to 2,5-propanoprolinone involved intramolecular cyclization to build the pyrrolidine ring and, concomitantly, the bicyclic moiety. Similar intramolecular nucleophilic substitutions have been used to form a pyrrolidine ring from 4-substituted cyclohexylamines, yielding bicyclic systems of the 7-azanorbornane type.^{8,9d,18,19} Bearing this idea in mind, Boc protection in **4** was removed under acidic conditions and the resulting amino hydrochloride was heated in chloroform in the presence of potassium carbonate to afford the desired azabicyclic derivative **5** in quantitative yield.

Removal of the remaining bromine atom was then carried out. Among the different methodologies that can be applied for this purpose,²⁰ procedures involving radical dehalogenation are well established. However, direct debromination of compound **5** by treatment with tributyltin hydride and 2,2'-azobis(isobutyronitrile) (AIBN) as a radical initiator provided a very complex mixture of products, from which the desired compound could not be isolated. In an attempt to minimize side-reactions, the amino group in **5** was protected by reaction with benzoyl chloride, and debromination of the resulting benzamide (**6**) proceeded satisfactorily (Scheme 2). The structure of the compound thus obtained (**7**) was confirmed by single crystal X-ray diffraction analysis (Figure 2).

Finally, the amidoester **7** was subjected to hydrolysis by heating under reflux in 6N aqueous HCl to afford quantitatively the amino acid hydrochloride **8**. This route gave the desired proline analogue in 41% global yield from ethyl isocyanoacetate.

3. Conclusion

We have developed an efficient methodology for the synthesis of 8-azabicyclo[3.2.1]octane-1-carboxylic acid, a new proline analogue of interest in peptide design. Starting from readily available substrates and using simple transformations, significant amounts of this amino acid have been isolated in good overall yield. The procedure is suitable for scale-up. The extension of this methodology to the preparation of enantiomerically pure compounds is underway.

4. Experimental

4.1. General

Thin layer chromatography was performed on Merck 60 F₂₄₀ precoated silica gel polyester plates and products were visualized under UV light (254 nm), iodine vapour, anisaldehyde or phosphomolybdic acid reaction, as appropriate. Column chromatography was performed using silica gel (Kieselgel 60). Solvents were dried, when necessary, by standard methods. Melting

points were determined on a Gallenkamp apparatus and were not corrected. IR spectra were registered on a Mattson Genesis FTIR spectrophotometer; $\nu_{\max}$ is given for the main absorption bands. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-400 instrument at room temperature in CDCl_3 or D_2O , using the residual solvent signal as the internal standard; chemical shifts (δ) are expressed in ppm and coupling constants (J) in Hertz. Elemental analyses were carried out on a Perkin-Elmer 200 C,H,N,S analyzer.

4.2. X-ray diffraction

Colourless single crystals of **7** were obtained by slow evaporation from a dichloromethane/diethyl ether solution. The X-ray diffraction data were collected at room temperature on an Oxford Diffraction Xcalibur diffractometer provided with a Sapphire CCD detector, using graphite-monochromated Mo- $K\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$). The structure was solved by direct methods using SHELXS-97^{21a} and refinement was performed using SHELXL-97^{21b} by the full-matrix least-squares technique with anisotropic thermal factors for heavy atoms. Hydrogen atoms were located by calculation and affected by an isotropic thermal factor fixed to 1.2 times the U_{eq} of the carrier atom (1.5 for the methyl protons). Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 637425. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Crystallographic data: monoclinic, space group $P2_1/c$; $a = 7.4288(9) \text{ \AA}$, $b = 19.4183(4) \text{ \AA}$, $c = 11.0531(3) \text{ \AA}$, $\beta = 111.739(3)^\circ$; $Z = 4$; $d_{\text{calcd}} = 1.289 \text{ g} \cdot \text{cm}^{-3}$; 18767 reflections collected, 3234 unique ($R_{\text{int}} = 0.0327$); data/parameters: 3234/190; final R indices ($I > 2\sigma I$): $R_1 = 0.0323$, $wR_2 = 0.0752$; final R indices (all data): $R_1 = 0.0636$, $wR_2 = 0.0805$. Highest residual electron density: $0.16 \text{ e}^- \text{ \AA}^{-3}$.

4.3. Ethyl 2-(but-3-enyl)-2-isocyanohept-5-enoate (1)

To a solution of ethyl isocyanoacetate (5.0 g, 44.25 mmol) in dry diethyl ether (100 mL) and dry dimethyl sulfoxide (10 mL) at 0°C under argon was added NaH (mineral suspension) (2.12 g, 88.50 mmol) in small portions. A few minutes later, 4-bromo-1-butene (9.88 mL, 97.34 mmol) was added and the system was allowed to warm up to room temperature. After 24 h, the reaction was treated with a further portion of NaH (531 mg, 22.12 mmol) and 4-bromo-1-butene (2.25 mL, 22.12 mmol) and stirring was continued for an additional 24 h. Water (80 mL) was added and, after separation of the two phases, the aqueous layer was extracted thoroughly with diethyl ether. The ethereal solutions were combined, washed with brine, dried, and filtered. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (eluent: hexanes/ethyl acetate 10/1) to afford pure **1** as a colourless liquid (8.05 g, 36.41 mmol, 82% yield). IR (neat): 2136, 1750 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 1.29 (t, $J = 7.1 \text{ Hz}$, 3H), 1.78–1.90 (m, 2H), 1.94–2.08 (m, 4H), 2.23–2.36 (m, 2H), 4.22 (q, $J = 7.1 \text{ Hz}$, 2H), 4.95–5.07 (m, 4H), 5.72 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 13.92, 28.22, 38.22, 62.44, 67.54, 115.92, 135.84, 159.47, 168.33.

4.4. Ethyl 2-(but-3-enyl)-2-(*N*-tert-butoxycarbonylamino)hex-5-enoate (2)

Isonitrile **1** (7.89 g, 35.70 mmol) was dissolved in ethanol (40 mL) containing 12N aqueous HCl (1.50 mL) and the resulting solution was stirred at room temperature for ca. 24 h, until the starting material had been consumed (TLC monitoring, eluent: hexanes/ethyl acetate 9/1). The solvent was removed under reduced pressure and the remaining oil was taken up in chloroform (100 mL). Triethylamine (7.41 mL, 53.55 mmol) was added dropwise, followed by di-*tert*-butyl dicarbonate (11.67 g, 53.55 mmol), and the reaction mixture was stirred at 50°C for 5 days. It was then cooled, washed with 5% aqueous KHSO_4 ($2 \times 70 \text{ mL}$), dried and filtered. The solvent was removed and the residue was chromatographed (eluent: hexanes/ethyl acetate

9/1) to give **2** as a colourless oil (8.32 g, 26.75 mmol, 75% yield). IR (neat): 3427, 1717 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 1.25 (t, $J = 7.1$ Hz, 3H), 1.40 (s, 9H), 1.68–1.84 (m, 4H), 1.95–2.08 (m, 2H), 2.30–2.47 (m, 2H), 4.17 (q, $J = 7.1$ Hz, 2H), 4.85–4.98 (m, 4H), 5.55 (br s, 1H), 5.71 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 14.07, 27.31, 28.28, 34.64, 61.65, 63.02, 85.00, 114.78, 137.52, 146.65, 153.55, 173.62.

4.5. Ethyl 1-(*N*-*tert*-butoxycarbonylamino)cyclohept-4-ene-1-carboxylate (**3**)

A solution of benzylidenebis(tricyclohexylphosphine)-dichlororuthenium (2.10 g, 2.55 mmol) in dry toluene (50 mL) under argon was added by cannula to a solution of compound **2** (7.94 g, 25.53 mmol) in dry toluene (8 mL) under argon. The reaction mixture was stirred at 70 °C for 24 h. The solvent was evaporated and the residue was purified by column chromatography (eluent: hexanes/ethyl acetate 8/2) to give **3** as a colourless oil (5.94 g, 20.99 mmol, 82% yield). IR (neat): 3369, 1711 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 1.22 (t, $J = 7.1$ Hz, 3H), 1.40 (s, 9H), 1.94–2.07 (m, 2H), 2.08–2.20 (m, 6H), 4.14 (q, $J = 7.1$ Hz, 2H), 4.83 (br s, 1H), 5.65 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ 14.07, 23.18, 28.19, 34.13, 60.97, 62.29, 79.65, 130.85, 154.61, 174.26.

4.6. Ethyl *c*-4,*t*-5-dibromo-1-(*N*-*tert*-butoxycarbonylamino)cycloheptane-*r*-1-carboxylate (**4**)

A solution of **3** (4.0 g, 14.13 mmol) and tetraethylammonium bromide (29.67 g, 141.3 mmol) in dichloromethane (60 mL) was cooled to –78 °C and treated with trimethylphenylammonium tribromide (10.73 g, 28.26 mmol). After 1 h the mixture was allowed to warm up to room temperature and stirring was continued for 20 h. Saturated aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (60 mL) was then added and the reaction mixture was stirred until the brown colour had disappeared. The organic layer was separated and the aqueous phase was extracted with diethyl ether (2 $\times$ 50 mL). The combined organic phases were dried over MgSO_4 , filtered and evaporated to dryness. The residue was purified by column chromatography (eluent: hexanes/ethyl acetate 8/2) to afford **4** as a white solid (5.78 g, 13.05 mmol, 92% yield). Mp 106–107 °C. IR (nujol): 3348, 1724, 1700 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 1.24 (t, $J = 7.1$ Hz, 3H), 1.40 (s, 9H), 1.86–2.00 (m, 3H), 2.06–2.17 (m, 1H), 2.22–2.39 (m, 3H), 2.52–2.64 (m, 1H), 4.16 (q, $J = 7.1$ Hz, 2H), 4.62 (m, 2H), 4.94 (br s, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 14.01, 27.27, 27.85, 28.14, 58.95, 59.43, 61.30, 79.96, 154.73, 174.06. Anal. Calcd for $\text{C}_{15}\text{H}_{25}\text{Br}_2\text{NO}_4$: C, 40.65; H, 5.69; N, 3.16. Found: C, 40.39; H, 5.73; N, 3.31.

4.7. Ethyl 4-*exo*-bromo-8-azabicyclo[3.2.1]octane-1-carboxylate (**5**)

A 3N solution of HCl in ethyl acetate (5 mL) was added to compound **4** (5.32 g, 12.0 mmol) and the reaction mixture was stirred at room temperature for 1 h. After evaporation of the solvent, chloroform (50 mL) and K_2CO_3 (3.31 g, 24.0 mmol) were added and the resulting suspension was heated under reflux for 3 h. Saturated aqueous NaHCO_3 (40 mL) was then added. The organic layer was separated and the aqueous phase was further extracted with dichloromethane (3 $\times$ 40 mL). The combined organic extracts were dried and the solvent removed to give **5** as a colourless oil (3.08 g, 11.76 mmol, 98% yield). IR (neat): 1737 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 1.16 (t, $J = 7.1$ Hz, 3H), 1.54 (m, 1H), 1.64 (m, 1H), 1.76 (m, 1H), 1.86–2.12 (m, 4H), 2.22 (m, 1H), 2.82 (br s, 1H), 3.58 (m, 1H), 4.07 (q, $J = 7.1$ Hz, 2H), 4.12 (m, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ 13.88, 27.15, 28.12, 30.06, 30.53, 54.87, 60.61, 60.69, 64.40, 173.61.

4.8. Ethyl *N*-benzoyl-4-*exo*-bromo-8-azabicyclo[3.2.1]octane-1-carboxylate (**6**)

N,N-diisopropylethylamine (2.40 mL, 13.80 mmol) and benzoyl chloride (1.61 mL, 13.80 mmol) were added dropwise to a solution of **5** (3.01 g, 11.50 mmol) in anhydrous dichloromethane (50 mL) under an argon atmosphere. The reaction mixture was stirred at room temperature for 24 h, after which it was washed successively with 5% aqueous solutions of

KHSO₄ (30 mL) and NaHCO₃ (30 mL). The organic phase was dried and filtered and the solvent was removed. The residue was purified by chromatography (eluent: hexanes/ethyl acetate 6/4) to give **6** as a white solid (3.96 g, 10.82 mmol, 94% yield). Mp 108–109 °C. IR (nujol): 1722, 1631 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 1.25 (t, *J* = 7.1 Hz, 3H), 1.81 (m, 1H), 1.92 (m, 1H), 1.98–2.05 (m, 1H), 2.09 (m, 1H), 2.32–2.56 (m, 3H), 2.70 (m, 1H), 4.13 (m, 1H), 4.18 (dq, *J* = 7.1, 10.8 Hz, 1H), 4.26 (dq, *J* = 7.1, 10.8 Hz, 1H), 4.54 (m, 1H), 7.34–7.45 (m, 3H), 7.56–7.60 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 13.82, 25.56, 27.72, 28.23, 32.41, 53.61, 61.01, 63.97, 64.06, 127.95, 128.62, 130.25, 135.74, 169.75, 170.96. Anal. Calcd for C₁₇H₂₀BrNO₃: C, 55.75; H, 5.50; N, 3.82. Found: C, 55.98; H, 5.63; N, 3.61.

4.9. Ethyl *N*-benzoyl-8-azabicyclo[3.2.1]octane-1-carboxylate (**7**)

Bromide **6** (3.9 g, 10.66 mmol) and 2,2'-azobis(isobutyronitrile) (1.78 g, 10.66 mmol) were dissolved in anhydrous toluene (50 mL) under argon. Tributyltin hydride (8.48 mL, 31.98 mmol) was added by syringe and the resulting mixture was heated at 80 °C for 3 h. The solvent was removed and the residue was purified by column chromatography (eluent: hexanes/ethyl acetate 7/3) to afford **7** as a white solid (2.98 g, 10.38 mmol, 97% yield). Mp 102–103 °C. IR (nujol): 1730, 1629 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ 1.19 (t, *J* = 7.1 Hz, 3H), 1.23–1.30 (m, 1H), 1.37 (m, 1H), 1.60–1.80 (m, 3H), 1.84–1.92 (m, 1H), 1.97 (m, 1H), 2.20–2.34 (m, 3H), 4.12 (dq, *J* = 7.1, 10.8 Hz, 1H), 4.17 (dq, *J* = 7.1, 10.8 Hz, 1H), 4.24 (m, 1H), 7.30–7.40 (m, 3H), 7.46–7.51 (m, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 14.03, 17.15, 27.62, 29.68, 32.15, 33.73, 59.64, 60.95, 65.01, 127.55, 128.35, 130.32, 136.07, 169.91, 172.00. Anal. Calcd for C₁₇H₂₁NO₃: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.82; H, 7.44; N, 5.02.

4.10. 8-Azabicyclo[3.2.1]octane-1-carboxylic acid hydrochloride (**8**)

A suspension of **7** (2.44 g, 8.50 mmol) in 6N aqueous HCl (120 mL) was heated under reflux for 12 h. The solvent was evaporated to dryness and the residue partitioned between diethyl ether (50 mL) and water (100 mL). The organic layer was discarded and the aqueous phase was washed with an additional portion of diethyl ether (30 mL). The aqueous solution was concentrated and lyophilized to provide **8** as a white solid (1.62 g, 8.44 mmol, 99% yield). Mp 292–295 °C (dec.). IR (nujol): 3150–2100, 1728 cm⁻¹. ¹H NMR (400 MHz, D₂O): δ 1.66–2.30 (m, 10H), 4.09 (m, 1H). ¹³C NMR (100 MHz, D₂O): δ 15.21, 25.79, 27.17, 29.19, 31.18, 56.15, 68.11, 173.63. Anal. Calcd for C₈H₁₄ClNO₂: C, 50.13; H, 7.36; N, 7.31. Found: C, 50.46; H, 7.25; N, 7.18.

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Figure 1. Structure of proline and its bicyclic analogues obtained by linking positions 2 and 5 of the pyrrolidine ring: (a) 2,5-ethanoproline, (b) 2,5-propanoproline.

Figure 2. X-ray crystal structure of compound **7** (one enantiomer is shown). The N and O atoms are shown as thermal ellipsoids. Hydrogens have been omitted for clarity.

Scheme 1.

Retrosynthetic analysis for 2,5-propanoprolino (LG: leaving group).

Scheme 2.

Synthetic route to 2,5-propanoproline. Reagents and conditions: (i) NaH, Et₂O/DMSO; (ii) a. HCl/EtOH; b. (Boc)₂O, Et₃N, CHCl₃, 50 °C; (iii) Grubbs' catalyst, toluene, 70 °C; (iv) PhMe₃NBr₃, Et₄NBr, CH₂Cl₂, -78 °C → rt; (v) a. 3N HCl/AcOEt; b. K₂CO₃, CHCl₃, reflux; (vi) PhCOCl, *i*Pr₂EtN, CH₂Cl₂; (vii) Bu₃SnH, AIBN, toluene, 80 °C; (viii) aq. 6N HCl, reflux.