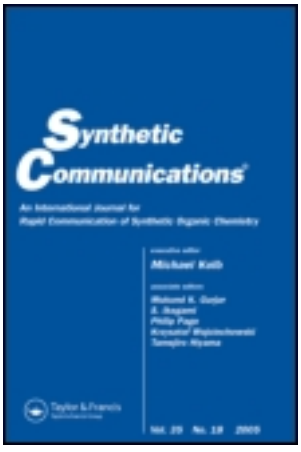

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Regioselective Reduction of β-Enaminoesters

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Regioselective Reduction of β-Enaminoesters

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Abstract: The regioselective reduction of β-enaminoesters derived from pyroglutamic acid can be readily achieved under mild conditions.

Keywords: Regioselective reduction, pyroglutamic, enaminoesters

The 2,5-disubstituted pyrrolidine ring occurs in many medicinally important compounds. Examples of bioactive 2,5-disubstituted pyrrolidines include cocaine,[1] the antitumor carzinophilin,[2] the novel glutamate receptor antagonist kaitocephalin,[3] the antibiotic lemonomycin,[4] and the analgesic epibatidine.[5] Our interest has been concerned with the development of methodology to access 2,5-disubstituted pyrrolidines from the readily available pyroglutamic acid, and to this end, we recently reported that regio- and stereoselective reduction of enaminoesters derived from pyroglutamic acid to give either *trans*- or *cis*- 2,5-disubstituted pyrrolidines, depending on the nature of the nitrogen-protecting group, is possible, and that these intermediates can be in turn regio- and stereoselectively alkylated.[6,7] At about the same time, Elliott and Long reported efficient regioselective reduction of the C-2 ester function of a related β-enaminodiester with $NaBH_4$.[8,9] This paper describes the development of reliable chemistry for the regioselective ester

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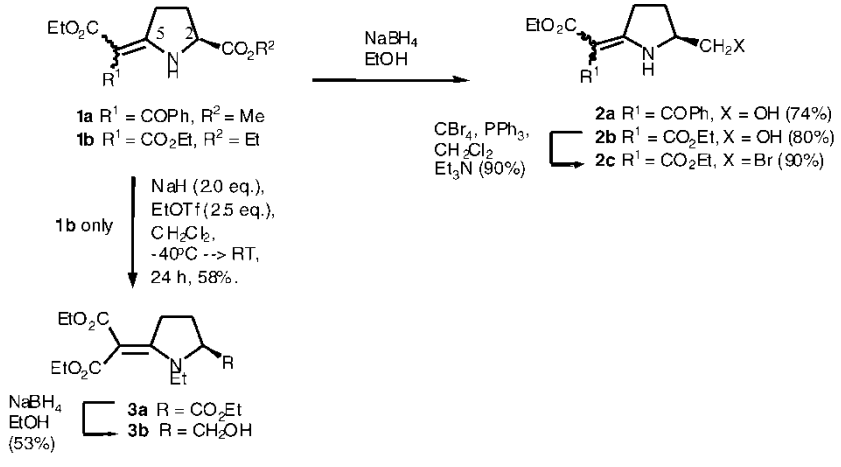
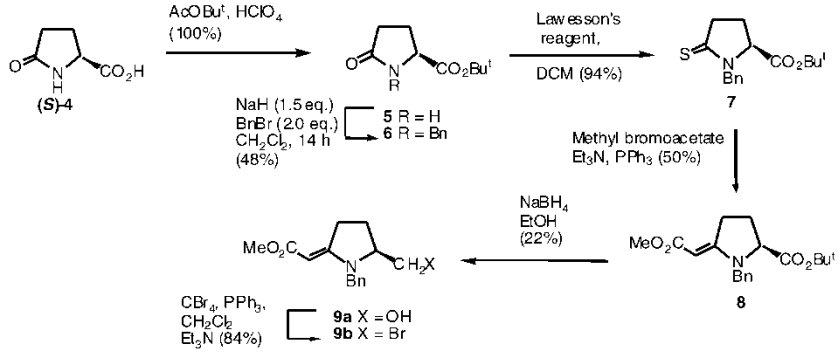
reduction of several 5-methylene-pyrrolidine-2-carboxylic esters derived from pyroglutamic acid.

We had earlier found that the C-2 ester of pyrrolidines **1a,b**, readily available as described,[6] could be selectively reduced to the corresponding alcohol by $NaBH_4$ (Scheme 1),[6] and subsequent optimization of this reaction improved the reported yield of alcohol **2a** from 50% to 74% (1:5 mixture of diastereomers); noteworthy is the unreactivity of other carbonyl functionality conjugated with the enamine function. Similarly, alcohol **2b** could be obtained in quantitative yield (^{1}H NMR) although chromatographic purification gave an 80% recovered yield.

Extension of this methodology to *N*-alkyl-protected analogues was also examined: these materials were available either by alkylation of the enamine function of **1b** to give pyrrolidine **3a**, a reaction that required forcing conditions as a result of the low reactivity of that nitrogen, or by elaboration from pyroglutamic acid according to Scheme 2. The required *N*-benzyl-*t*-butylpyroglutamate **6** was prepared by *tert*-butyl esterification of (*S*)-pyroglutamic acid **4** to give ester **5**; several conditions for this reaction were tried, including *t*-butyl 2,2,2-trichloroacetimidate,[10] which gave an inseparable mixture, and other common methods all gave low yields [$(Boc)_2O$, DMAP, CH_3CN, 41 h, 22%;[11] *t*-BuOH $(COCl)_2$, py, *t*-BuOH, DMF, CH_3CN, 24 h, $<10\%$;[12] and *tert*-butyl acetate AcO*t*-Bu (20 eq.), H_2SO_4 (conc.) (3 eq.), 19 h, NaOH quench, 28%,[13] $NaHCO_3$ quench 44%]. It was necessary to use perchloric acid and excess of *tert*-butyl acetate [AcO*t*-Bu (20 eq.), $HClO_4$ (0.35 eq.), 18 h, 100%][14] with a modification in workup procedure to get complete conversion to ester which was then



Scheme 1.



Scheme 2.

N-benzylated using standard methodology in good yield. Thiolactam (*S*)-**7** was obtained from *N*-benzyl-*t*-butylpyroglutamate **6** using our optimized conditions for thionation in excellent yield and without purification difficulties,[7] and this was converted to enamine **8** by an Eschenmoser coupling reaction using Et_3N as base in 50% yield.[12]

Regioselective C-2 ester reduction was then attempted on pyrrolidines **3a** and **8**. Reaction of **3a** with $NaBH_4$ ($NaBH_4$, EtOH, 7 h) gave 53% yield of alcohol **3b**, whereas reaction of the t-butyl ester **8** ($NaBH_4$, EtOH, 28 h) gave alcohol **9a** in 22% yield along with 48% recovery of starting material (46% yield based on recovered starting material). That this reaction is regioselective reflects the extensive delocalization and therefore deactivation of the enamine ester system, but the reactivity of the C-2 ester is obviously subject to steric effects also, as shown by the lower reactivity of ester **8**.

That these alcohols **2b** and **9a** could be valuable synthetic intermediates was demonstrated by their conversion into bromides **2c** and **9b** in excellent yields. Bromide **2c** has been previously synthesized in nine steps for the synthesis of carzinophilin analogues,[2] but by using our regioselective reduction it can be obtained in only five steps starting from (*S*)-pyroglutamic acid.

Preparation of (2S)-tert-Butyl-pyroglutamate 5

To a stirred suspension of (*S*)-(−)-pyroglutamic acid (13 gm, 0.10 mol) in AcOBu*t* (200 mL, 1.48 mol), was added dropwise 70% aqueous $HClO_4$ (3.0 mL, 0.035 mol), and the solution was stirred for 18 h at room temperature. It was carefully poured into a saturated solution of $NaHCO_3$ and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water and brine. It was dried with $MgSO_4$ and evaporated to give tert-butyl-pyroglutamate **5** (18.5 g, 100%) as white crystals.

Typical Procedure for the Reduction β-Enaminoester

To a solution of β-enaminoester (10 mmol) in absolute ethanol (150 mL) was added sodium borohydride (40 mmol) and stirring continued for 30 min at 0°C, then at room temperature for 6 h. Galacial acetic acid was then carefully added to the mixture with stirring and cooling in an ice bath until pH 5.0 was reached. The mixture was partitioned between CH_2Cl_2 and water. The CH_2Cl_2 layer was washed with a saturated solution of $NaHCO_3$, water, and brine; dried over $MgSO_4$; and evaporated. Silica-gel chromatography gave the corresponding alcohol. Data for the reduction products are as follows:

2-(2-Hydroxymethyl-pyrrolidin-5-ylidene)-3-oxo-3-phenyl-propionic acid ethyl ester 2a. Obtained as an inseparable mixture of diastereomers. $\mathbf{R_f} = 0.36$ (EtOAc); $\nu_{\mathbf{max}}/\mathrm{cm}^{-1}$(neat) 3340, 3044, 1659, 1589, 1476; $\delta_{\mathbf{H}}$ (400 MHz, $CDCl_3$) (major) 0.71 (3H, t, *J* 7.0, $OCH_2C\underline{H}_3$), 1.67–1.75 (1H, m, C(3)$\underline{H}$H), 2.03–2.13 (1H, m, C(3)H$\underline{H}$), 3.08–3.18 (2H, m, C(4)$\underline{H}_2$), 3.31 (1H, dd, *J* 11.4, 6.9, C$\underline{H}$HOH), 3.64–3.86 (3H, m, CH$\underline{H}$OH, $OC\underline{H}_2CH_3$), 4.04–4.51 (1H, m, C(2)$\underline{H}$), 7.25–7.60 (5H, m, $C_6\underline{H}_5$), 11.01 (1H, br, N$\underline{H}$); $\delta_{\mathbf{C}}$ (100 MHz, $CDCl_3$) 13.5 ($OCH_2\underline{C}H_3$), 22.8 ($\underline{C}$(3)), 33.0 ($\underline{C}$(4)), 59.5 ($OC\underline{H}_2CH_3$), 62.5 ($\underline{C}$(2)), 64.6 ($\underline{C}H_2OH$), 98.1 (NC$\underline{C}$), 125.6, 127.6, 129.4 (Ar$\underline{C}$), 143.5 (quaternary Ar$\underline{C}$), 169.13, 173.0 ($\underline{C}$(5), $\underline{C}OOC_2H_5$), 195.2 ($C_6H_5\underline{C}O$); $\boldsymbol{m/z}$ (APCI$^+$) 290 ($M + H^+$, 4%), 244 (100%). $\delta_{\mathbf{H}}$ (400 MHz, $CDCl_3$) (minor) 1.24 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$), 1.67–1.75 (1H, m, C(3)$\underline{H}$H), 2.03–2.13 (1H, m, C(3)H$\underline{H}$), 2.59–2.61 (2H, m, C(4)$\underline{H}_2$), 3.42–3.58 (2H, m, $C\underline{H}_2OH$), 3.64–3.86 (1H, m, C(2)$\underline{H}$), 4.04–4.51 (2H, m, $OC\underline{H}_2CH_3$), 7.25–7.6 (5H, m, $C_6\underline{H}_5$), 9.47 (1H, br, N$\underline{H}$); $\delta_{\mathbf{C}}$ (100 MHz, $CDCl_3$) 14.6 ($OCH_2\underline{C}H_3$), 23.8 ($\underline{C}$(3)), 31.7 ($\underline{C}$(4)), 59.1 ($OC\underline{H}_2CH_3$), 61.6 ($\underline{C}$(2)), 65.1 ($\underline{C}H_2OH$), 95.6 (NC$\underline{C}$), 125.6, 128.4, 131.7 (Ar$\underline{C}$), 142.9 (quaternary Ar$\underline{C}$), 170.1, 170.8 ($\underline{C}$(5), $\underline{C}O_2C_2H_5$), 195.4 ($C_6H_5\underline{C}O$).

2-(2-Hydroxymethyl-pyrrolidin-5-ylidene)-malonic acid diethyl ester 2b. $\mathbf{R_f} = 0.26$ (3:7 Petrol (40/60): EtOAc); $[\alpha]_{\mathbf{D}}^{\mathbf{22}} = +19.3$ (c = 0.14, $CHCl_3$); $\nu_{\mathbf{max}}/\mathrm{cm}^{-1}$ (neat) 3416, 1644, 1567; $\delta_{\mathbf{H}}$ (400 MHz, $CDCl_3$) 1.27 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$), 1.28 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$), 1.73–1.8 (1H, m, C(3)$\underline{H}$H), 2.05–2.15 (1H, m, C(3)H$\underline{H}$), 2.78 (1H, s, O$\underline{H}$), 3.02–3.2 (2H, m, C(4)$\underline{H}_2$), 3.52 (1H, dd, *J* 11, 6.7, C$\underline{H}$HOH), 3.71 (1H, dd, *J* 11, 4.0, CH$\underline{H}$OH), 3.98–4.01 (1H, m, C(2)$\underline{H}$), 4.14–4.28 (4H, m, 2 × $OC\underline{H}_2CH_3$), 9.59 (1H, br, N$\underline{H}$); $\delta_{\mathbf{C}}$ (50 MHz, $CDCl_3$) 14.3 (2 × $OCH_2\underline{C}H_3$), 23.8 ($\underline{C}$(3)), 33.8 ($\underline{C}$(4)), 59.6 (2 × $OC\underline{H}_2CH_3$), 60.4 ($\underline{C}$(2)), 66.1 ($\underline{C}H_2OH$), 87.3 (NC$\underline{C}$), 167.8, 169.7, 172.7 ($\underline{C}$(5), 2 × $\underline{C}O_2C_2H_5$); $\boldsymbol{m/z}$ (APCI$^+$) 258 ($M + H^+$, 8%), 212 (100%); **HRMS** ($M + H^+$) 258.1340, $C_{12}H_{20}NO_5$ requires 258.1341.

***N*-Ethyl-2-(2-Hydroxymethyl-pyrrolidin-5-ylidene)-malonic acid diethyl ester 3b.** $\mathbf{R_f} = 0.5$ (95:5 EtOAc: MeOH); $\nu_{\mathbf{max}}/\mathrm{cm}^{-1}$ (neat) 3440, 1683, 1560; $\delta_{\mathbf{H}}$ (400 MHz, $CDCl_3$) 1.07–1.16 (3H, m, $NCH_2C\underline{H}_3$), 1.22–1.30

(6H, 2 × $OCH_2C\underline{H}_3$), 1.77–1.86 (1H, m, C(3)$\underline{H}$H), 1.95–2.03 (1H, m, C(3)H$\underline{H}$), 2.92–3.02 (1H, m, C(4)$\underline{H}$H), 3.16–3.36 (3H, m, C(4)H$\underline{H}$, $NC\underline{H}_2CH_3$), 3.51 (1H, d, *J* 11.5, C$\underline{H}$HOH), 3.72 (1H, d, *J* 11.5, CH$\underline{H}$OH), 3.85 (1H, br, C(2)$\underline{H}$), 4.07–4.28 (4H, m, 2 × $OC\underline{H}_2CH_3$); $\delta_{\mathbf{C}}$ (100 MHz, $CDCl_3$) 12.2 ($NCH_2\underline{C}H_3$), 14.2 (2 × $OCH_2\underline{C}H_3$), 25.7 (C(3)), 34.3 (C(4)), 42.0 ($N\underline{C}H_2CH_3$), 60.1 (2 × $OC\underline{H}_2CH_3$), 62.7 ($\underline{C}H_2OH$), 64.9 (C(2)), 89.7 (NCC), 163.6, 167.3, 168.5 (C(5), 2 × $\underline{C}O_2C_2H_5$); ***m/z*** (ES^+) 308 (M + Na, 100%), 286 ($M + H^+$, 30%), 240 (58%); **HRMS** ($M + H^+$) 308.1474, $C_{14}H_{23}NO_5Na$ requires 308.1474.

N*-Benzyl-(*E*)-2-(2-Hydroxymethyl-pyrrolidin-5-ylidene)-ethanoic acid methyl ester 9a.** $\mathbf{R_f} = 0.11$ (3:2 Petrol (40/60): EtOAc); $\mathbf{[\alpha]_D^{26}} = +36$ (c = 0.18, CH_2Cl_2); $\nu_{\mathbf{max}}/cm^{-1}$ (neat) 3419, 1732, 1662; $\delta_{\mathbf{H}}$ (500 MHz, $CDCl_3$) 1.93–1.98 (1H, m, C(3)$\underline{H}$H), 2.06–2.11 (1H, m, C(3)H$\underline{H}$), 3.21–3.29 (2H, m, C(4)$\underline{H}_2$), 3.57–3.71 (3H, m, C(2)$\underline{H}$, $C\underline{H}_2OH$), 3.60 (3H, s, $OC\underline{H}_3$), 4.44 (1H, d, *J* 16.4, C$\underline{H}$HC_6H_5), 4.49 (1H, d, *J* 16.4, CH$\underline{H}$$C_6H_5$), 4.68 (1H, s, NCC$\underline{H}$), 7.19–7.21 (2H, m, Ar$\underline{H}$), 7.26–7.28 (1H, m, Ar$\underline{H}$), 7.31–7.34 (2H, m, Ar$\underline{H}$); $\delta_{\mathbf{C}}$ (125 MHz, $CDCl_3$) 24.1 (C(3)), 31.1 (C(4)), 48.7 ($\underline{C}H_2C_6H_5$), 49.9 ($CO_2\underline{C}H_3$), 63.2 ($\underline{C}H_2OH$), 64.9 (C(2)), 78.9 (NC$\underline{C}$H), 126.5, 127.3, 128.7 (Ar$\underline{C}$), 136.4 (quaternary Ar$\underline{C}$), 166.3 (C(5)), 169.8 ($\underline{C}O_2CH_3$); ***m/z (ES^+) 262 ($M + H^+$, 100%), **HRMS** ($M + H^+$) 262.1440, $C_{15}H_{20}NO_3$ requires 262.1443.

Typical Procedure for the bromination of alcohols

To a stirred solution of the alcohol (2 mmol) in CH_2Cl_2 (30 mL) was added CBr_4 (3 mmol) at 0°C under noninert conditions. After all CBr_4 had dissolved, PPh_3 (3 mmol) in CH_2Cl_2 (5 ml) was added dropwise. The resulting mixture was allowed to come to room temperature and stir for 20 h. To this solution, triethylamine (2 mmol) was added and stirred for 2.5 h. Solvent was removed and the residue was chromatographed to give the product.

2-(2-Bromomethyl-pyrrolidin-5-ylidene)-malonic acid diethyl ester 2c. **mp** 74–76°C; $\mathbf{R_f} = 0.54$ (3:2 Petrol (40/60): EtOAc); $\mathbf{[\alpha]_D^{25}} = -18.9$ (c = 0.28, $CHCl_3$); $\nu_{\mathbf{max}}/cm^{-1}$ (neat) 3300, 1690, 1648, 1570, 799; $\delta_{\mathbf{H}}$ (400 MHz, $CDCl_3$) 1.18 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$), 1.19 (3H, t, *J* 7.1, $OCH_2C\underline{H}_3$), 1.68–1.77 (1H, m, C(3)$\underline{H}$H), 2.10–2.19 (1H, m, C(3)H$\underline{H}$), 2.96–3.04 (1H, m, C(4)$\underline{H}$H), 3.08–3.17 (1H, m, C(4)H$\underline{H}$), 3.28 (1H, dd, *J* 10.3, 6.8, C$\underline{H}$HBr), 3.36 (1H, dd, *J* 10.3, 5.3, CH$\underline{H}$Br), 4.04–4.12 (5H, m, C(2)$\underline{H}$, 2 × $OC\underline{H}_2CH_3$), 9.55 (1H, br, N$\underline{H}$); $\delta_{\mathbf{C}}$ (100 MHz, $CDCl_3$) 14.3 (2 × $OCH_2\underline{C}H_3$), 26.6 (C(3)), 33.4 (C(4)), 35.6 ($\underline{C}H_2Br$), 59.5, 59.6 (2 × $OC\underline{H}_2CH_3$), 60.5 (C(2)), 88.1 (NC$\underline{C}$), 167.3, 169.4, 171.7 (C(5), 2 × $\underline{C}O_2C_2H_5$); ***m/z*** (ES^+) 342 (M + Na, 100%), 344 (M + 2 + Na, 98%); **HRMS** (M + Na) 342.0307, $C_{12}H_{18}NO_4BrNa$ requires 342.0317.

N*-Benzyl-(E)-2-(Bromomethyl-pyrrolidin-5-ylidene)-ethanoic acid methyl ester 9b.** $R_f = 0.57$ (3:2 Petrol (40/60): EtOAc); $[\alpha]_D^{25} = +19.5$ (c = 0.38, CH_2Cl_2); ν_{max}/cm^{-1} (neat) 1732, 1687, 1595; δ_H (400 MHz, $CDCl_3$) 1.99–2.07 (1H, m, C(3)HH), 2.16–2.25 (1H, m, C(3)HH), 3.17–3.26 (1H, m, C(4)HH), 3.29–3.42 (3H, m, C(4)HH, CH_2Br), 3.61 (3H, s, OCH_3), 3.84–3.99 (1H, m, C(2)H), 4.30 (1H, d, *J* 16.4, $CHHC_6H_5$), 4.52 (1H, d, *J* 16.4, $CHHC_6H_5$), 4.70 (1H, s, NCCH), 7.17–7.26 (2H, m, ArH), 7.27–7.36 (3H, m, ArH); δ_C (100 MHz, $CDCl_3$) 26.3 (C(3)), 30.5 (C(4)), 34.0 (CH_2Br), 48.3 ($CH_2C_6H_5$), 50.1 (CO_2CH_3), 63.4 (C(2)), 79.9 (NCCH), 126.8, 127.6, 128.8 (ArC), 135.7 (quaternary ArC), 165.3, 169.6 (C(5), CO_2CH_3); ***m/z (ES^+) 326 (M + 2 + H, 100%), 324 (M + H, 78%); **HRMS** (M + H) 324.0603, $C_{15}H_{19}NO_2Br$ requires 324.0599.

In summary, we have found mild conditions for the regioselective reduction of β-enaminoesters, giving intermediates suitable for a variety of synthetic applications.

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