Studies on Pyrrolidones. An Improved Synthesis of *N*-Arylmethyl Pyroglutamic Acids

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Low solubility of the aromatic aldehyde in a water/ethanol medium can prevent the sodium borohydride reductive alkylation of the sodium salt of glutamic acid. In that case, the reductive alkylation can be realized in methanol by using a triethylammonium salt. The uses of 2 molar equivalent of triethylammonium salt of glutamic acid for one molar equivalent of aldehyde strongly raise the yields. Cyclization of the N-substituted glutamic acids obtained gives then N-arylmethyl pyroglutamic acids in good yields.

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Within the framework of a program aimed at the synthesis of condensed hexahydroindolizine diones **1** [1] we needed a convenient supply of pyroglutamic acids **2a-d** in high yield (Figure 1). The reaction of benzyl chlorides or bromides with activated forms of pyroglutamic esters such as an N-sodium salt [2], an N-silyl derivative [3] or an iminoether [4] was described in the literature. It is also possible to synthesize an open form of the lactam ring which is subsequently cyclized. In that way the reaction of dimethyl bromoglutarate with a benzyl amine [5] or of diisopropyl glutamate with a benzyl halide [6] yields good results, but there is a high risk of dialkylation of the amine. A more interesting method is the reductive alkylation of dimethyl [7a] or diisopropyl [7b] glutamate that is versatile and gives good yields.

All these reactions can be used for our purpose but are at least two or three steps away from glutamic acid. They also suffer from the handling of large amounts of sodium hydride, or of the need to synthesize intermediates such as iminoethers, silyl derivatives or diisopropyl esters. Another method, the reductive amination of the dialkaline salt of glutamic acid in methanol [8a] or in water [8b], has been reported in the past. Decroix described a considerable improvement of this synthesis [9a]: equimolar amounts of the disodium salt of glutamic acid and of an aromatic aldehyde were dissolved in an 85/15 water/ethanol mixture then cooled. A sodium borohydride reduction [9b] of this solution was performed; more aldehyde (0.2 eq.) in ethanol was then added. After a second reduction step, also performed under cooling, ethanol was removed by evaporation. Excess aldehyde and the benzylic alcohol by-product were removed by a diethyl ether extraction. Acidification of the aqueous phase then led to a precipitate of *N*-arylmethyl glutamic acid which readily cyclizes in refluxing ethanol. By using this method we obtained, as described [9], a 90 % yield of acid **2e** (Ar = Ph) (Scheme 1).

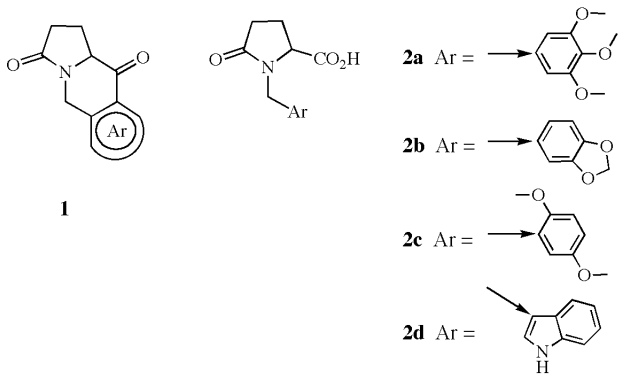
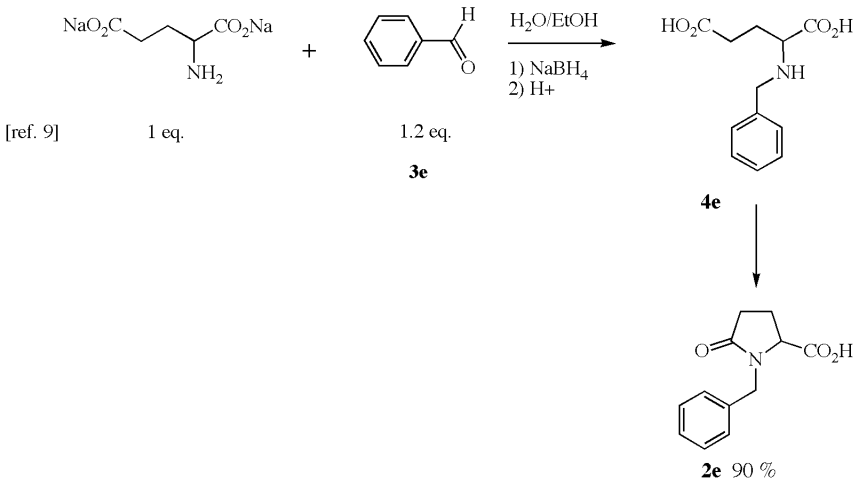


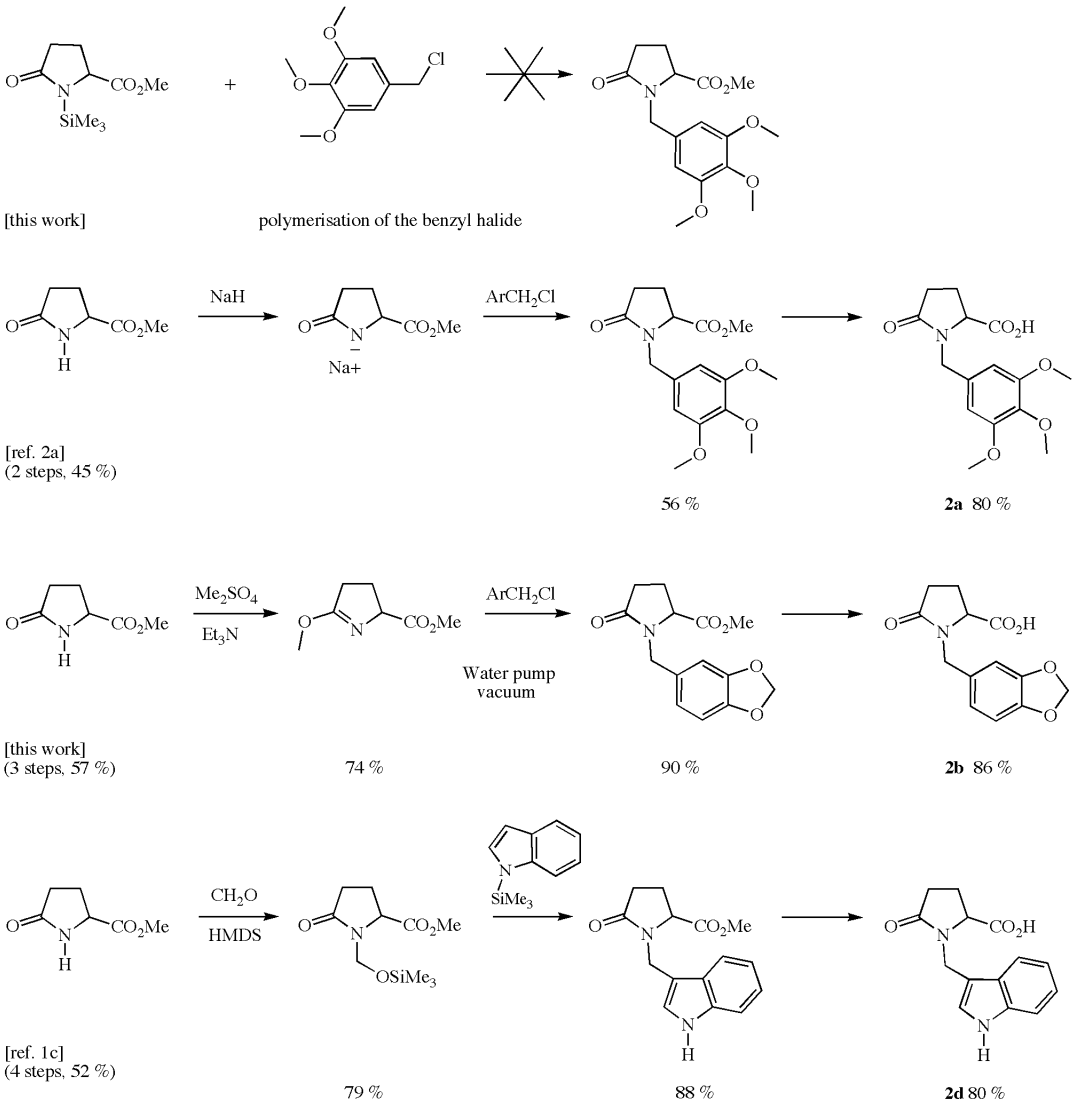
Figure 1

It is possible to obtain acids **2a-d** by using the procedures previously described and some of these results have already been published [1c,2a] (Scheme 2). When we tried Decroix's method, poor results were obtained with aldehydes **3a-d,** probably because of the low solubility of theses aldehydes in the 85/15 water/ethanol solvent. These aldehydes can be dissolved by using a larger ethanol content (water/ethanol: 35/65) but this leads to a biphasic medium with only a small improvement in the yield. In this case slightly better results are also obtained by adding a phase transfer agent. It was then thought that a homogeneous reaction mixture could be obtained by solubilizing the aldehyde, and the bis triethylammonium salt of glutamic

Scheme 1



Scheme 2



acid, in methanol. To our delight this was indeed the case, and the sodium borohydride reduction of this homogeneous mixture readily led to acids **4**. Another improvement to Decroix's method is the use of two equivalents of glutamic acid, which is an inexpensive starting material compared to many of the aromatic aldehydes. All of the aldehyde was thus used to form the aminal **5**, and the yield in **4** was better (Scheme 3).

Also noteworthy is the fact that the *N*-indolylmethylpyroglutamic acid **2d** thus obtained is very easy to purify, whereas the best previous method (Scheme 2) leads to compounds whose the purification is rather difficult [1c].

The yields obtained by using these different reactions are reported in Table 1. We consider that this new reductive alkylation of the triethylammonium salt of glutamic acid in methanol is generally applicable, and will give good results in all cases where the low solubility of the aromatic aldehyde in a water/ethanol medium prevent the use of Decroix's [9] method.

EXPERIMENTAL

Melting points are uncorrected. The infrared spectra were recorded in the ATR mode on a "Tensor 27" Bruker spectrometer and the nmr spectra on a Varian 'Gemini 2000' at 200 MHz using tetramethylsilane as an internal reference. Elemental analyses were performed by the «Service Central de Microanalyses» (CNRS, Vernaison, France). Known compounds were not analyzed.

Scheme 3

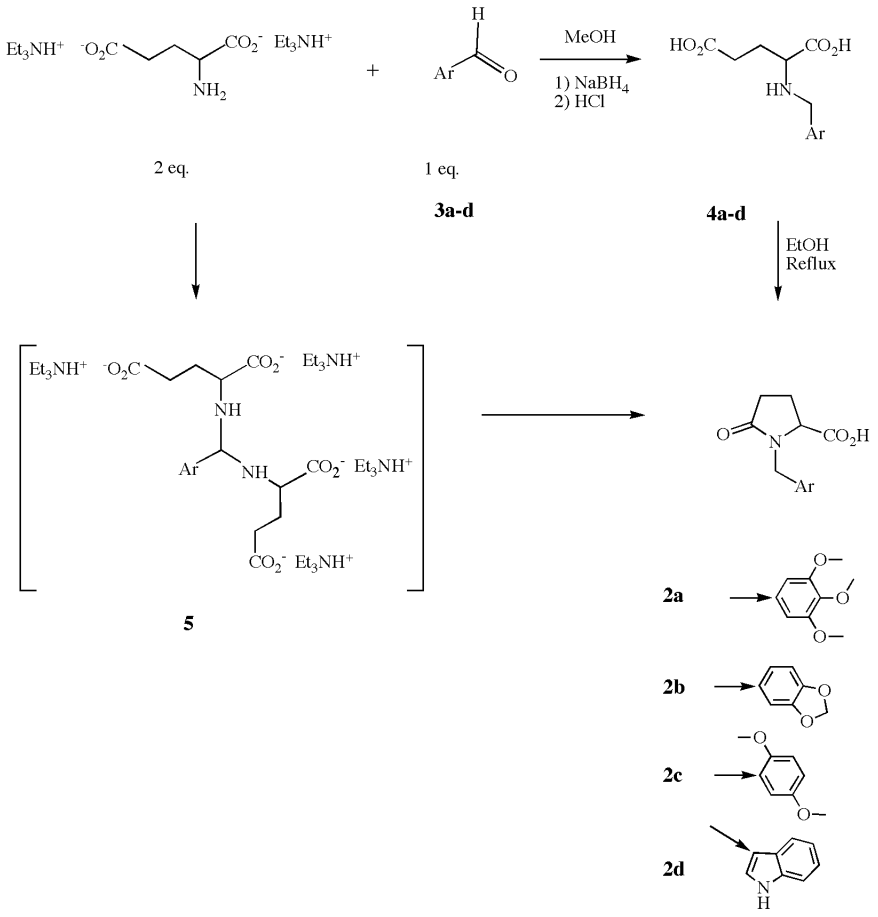


Table 1

Reductive Amination of Glutamic Salts

	This work: triethylammonium salt in methanol Yields %	Decroix method: sodium salt in ethanol/water Yields %
2a	90	56
2b	82	27
2c	81	30
2d	61	22

Triethylammonium Salt Method.

N-(3,4,5-Trimethoxybenzyl)glutamic Acid (**4a**) and *N*-(3,4,5-Trimethoxybenzyl)pyroglutamic Acid (**2a**).

Trimethoxybenzaldehyde (98 g, 0.5 mol) was added to well stirred solution of glutamic acid (147 g, 1 mol) in methanol (2250

ml) and triethylamine (218 g, 2.16 mol). The solution was cooled below 0 °C then sodium borohydride (4.75 g, 125 mmol) was added slowly while keeping the temperature of the reaction mixture below 0 °C. The solution was stirred at room temperature for 90 min, then the pH was adjusted to 3 with 37 % hydrochloric acid. The precipitate of diacid **4a** was washed with cold water then dried, mp 148-149 °C (H_2O); IR: 3490, 1720, 1625, 1595, 1575, 1510, 1460, 1125 cm^{-1}; ^1H NMR (D_2O/NaOD): δ 1.7-1.9 (m, 2H), 2.15 (t, J = 6.7 Hz, 2H), 3.04 (dd, J = 7.8, 6.2 Hz, 1 H), 3.54 (d, J = 12.8 Hz, 1H), 3.72 (d, J = 12.8 Hz, 1H), 3.77 (s, 3H), 3.87 (s, 6H), 6.73 (s, 2H). ^{13}C NMR (D_2O/NaOD): δ 23.4, 31.3, 47.5, 53.3, 58.1, 58.9, 104.6, 124.6, 134.5, 150.0, 170.8, 178.5.

Anal. Calcd. For $C_{15}H_{21}NO_7$, H_2O: C, 52.17; H, 6.71; N, 4.06; O, 37.06. Found: C, 52.06; H, 6.47; N, 4.15; O, 36.69.

The crude compound **4a** was refluxed for 5 hours in a 95/5 ethanol/water solution (4000 ml). After cooling at room temperature the mixture was filtered in order to remove unreacted pyroglutamic acid. The filtrate was evaporated then partitioned between water and dichloromethane. The pH of the aqueous phase was adjusted to 1 with 37 % hydrochloric acid; this phase then was extracted with dichloromethane. The organic phase was dried, then evaporated, leading to 90 % of acid **2a**, mp 160-161 °C (EtOH); IR: 3305, 1710, 1605, 1550, 1495, 1460, 1150 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.11-2.47 (m, 2H), 2.47-2.75 (m, 2H), 3.83 (s, 3H), 3.84 (s, 6H), 3.95 (d, J = 14.7 Hz, 1H), 4.07 (dd, J = 9, 3.3 Hz, 1H) 5.04 (d, J = 14.7 Hz, 1H), 6.46 (s, 2H), 6.68 (bs, D_2O exchangeable, 1H); ^{13}C NMR ($CDCl_3$): δ 22.9, 29.6, 46.0, 56.1, 58.6, 60.7, 105.5, 130.6, 137.2, 153.1, 174.0, 176.0.

N-(1,3-Benzodioxol-5-ylmethyl)glutamic Acid (**4b**) and *N*-(1,3-Benzodioxol-5-ylmethyl)-5-pyroglutamic Acid (**2b**).

These compounds were obtained in the same way as for **2a** and **4a**. Acid **4b**: mp 172-3 °C (H_2O); IR: 1710, 1615, 1505, 1480, 1445, 1040 cm^{-1}; ^1H NMR (D_2O/NaOD): δ 1.64-1.90 (m, 2H), 2.15 (t, J = 8.8 Hz, 2H), 3.04 (dd, J = 7.7, 5.8 Hz, 1 H), 3.48 (d, J = 12.5 Hz, 1H), 3.65 (d, J = 12.5 Hz, 1H), 5.98 (s, 2H), 6.79-6.90 (m, 3H).

Anal. Calcd. For $C_{13}H_{15}NO_6$: C, 55.51; H, 5.38; N, 4.98; O, 34.13. Found: C, 55.15; H, 5.35; N, 5.34; O, 34.43.

Acid **2b** was obtained in 82 % yield, mp 138-9 (AcOEt); IR: 1715, 1635, 1500, 1470, 1450, 1040 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.06-2.45 (m, 2H), 2.45-2.73 (m, 2H), 3.90 (d, J = 15 Hz, 1H), 4.04 (dd, J = 8.9, 3.2 Hz, 1H), 5.04 (d, J = 15 Hz, 1H), 5.95 (s, 2H), 6.68 (dd, J = 7.8, 1.5 Hz, 1H), 6.73 (d, J = 1.5 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 7.88 (bs, D_2O exchangeable, 1H); ^{13}C NMR ($CDCl_3$): δ 22.9, 29.6, 45.4, 58.3, 101.0, 108.1, 108.7, 121.9, 128.8, 147.1, 147.8, 174.7, 175.7.

Anal. Calcd. For $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32; O, 30.39. Found: C, 59.58; H, 4.97; N, 5.45; O, 30.39.

N-(2,5-Dimethoxybenzyl)glutamic Acid (**4c**) and *N*-(2,5-Dimethoxybenzyl)pyroglutamic Acid (**2c**).

These compounds were obtained in the same way as for **2a** and **4a**. Acid **4c**: mp 164-5 °C (H_2O); IR: 1715, 1575, 1505, 1455, 1045 cm^{-1}; ^1H NMR (D_2O/NaOD): δ 1.68-1.94 (m, 2H), 2.18 (t, J = 8.5 Hz, 2H), 3.04 (dd, J = 7.4, 6.2 Hz, 1 H), 3.58 (d, J = 13.1 Hz, 1H), 3.71 (d, J = 13.1 Hz, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 6.91 (d, J = 9.2 Hz, 1H), 6.93 (s, 1H), 7.0 (d, J = 9.2 Hz, 1H).

Anal. Calcd. For $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71; O, 32.29. Found: C, 56.73; H, 6.67; N, 4.50; O, 31.91.

Acid **2c** was obtained in 81 % yield, mp 151-2 (AcOEt); IR: 1740, 1635, 1505, 1460, 1040 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.01-2.23 (m, 1H), 2.23-2.4 (m, 1H), 2.40-2.67 (m, 2H), 3.75 (s, 3H), 3.76 (s, 3H), 4.7 (bs, D_2O exchangeable, 1H), 4.11 (dd, J = 9, 4 Hz, 1H), 4.20 (d, J = 14.5 Hz, 1H), 4.90 (d, J = 14.5 Hz, 1H), 6.79 (d, J = 2.0 Hz, 2H), 6.84 (d, J = 2Hz, 1H).

Anal. Calcd. For $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02; O, 28.64. Found: C, 60.49; H, 6.47; N, 5.39; O, 28.33.

N-(1*H*-Indol-3-ylmethyl)glutamic Acid (**4d**) and 1-(1*H*-Indol-3-ylmethyl)-5-pyroglutamic Acid (**2d**).

Indole-3-carbaldehyde (50 g, 344 mmol) was added to a well stirred solution of glutamic acid (105 g, 714 mmol) in methanol (600 ml) and triethylamine (200 ml, 145 g, 1434 mmol). The solution was cooled below -5 °C then sodium borohydride (5 g, 104 mmol) was added slowly while keeping the temperature of the reaction mixture between -5 and 0 °C. The solution was stirred at room temperature for 90 min then the solvents were evaporated. Water (1000 ml) was added and the solution was extracted 3 times with ethyl acetate. The pH was adjusted to 3 by a very slow addition of 1 *N* hydrochloric acid. The precipitate of diacid **4d** was washed with cold water then dried, mp 195-200 °C (H_2O); IR: 3420, 1705, 1615, 1585, 1550, 1455, 1175 cm^{-1}; ^1H NMR (D_2O/NaOD): δ 1.63-1.99 (m, 2H), 2.19 (t, J = 8.4 Hz, 2H), 3.16 (dd, J = 7.7, 5.9 Hz, 1 H), 3.79 (d, J = 13.1 Hz, 1H), 3.94 (d, J = 13.1 Hz, 1H), 7.18 (t, J = 6.7 Hz, 1H), 7.26 (t, J = 6.7 Hz, 1H),7.33 (s, 1H), 7.52 (d, J = 7.4 Hz, 1H), 7.94 (d, J = 7.4 Hz, 1H); ^{13}C NMR (D_2O/NaOD): δ 29.7, 34.1, 41.6, 62.9, 111.6, 112.1, 118.3, 119.1, 121.7, 124.3, 126.6, 135.9, 182.0, 182.5.

Anal. Calcd. For $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14; O, 23.16. Found: C, 60.49; H, 5.93; N, 5.48; O, 22.85.

The crude compound **4d** was refluxed for 5 hours in ethanol (1000 ml). After cooling at room temperature the mixture was filtered in order to remove unreacted pyroglutamic acid. The filtrate was evaporated then dried, leading to 61 % of acid **2d**, mp 176-2 (EtOH); IR: 1720, 1620, 1500 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.79-1.97 (m, 1H), 2.04-2.29 (m, 1H), 2.27-2.69 (m, 2H), 3.74 (dd, J = 9.2, 5.2 Hz, 1H), 4.18 (d, J = 15.2 Hz, 1H), 5.15 (d, J = 15.2 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.26 (t, J = 7.5 Hz, 1H), 7.33 (s, 1H), 7.53 (d, J = 5.8 Hz, 1H), 7.56 (d, J = 5.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 22.5, 30.0, 37.4, 58.0, 109.2, 111.7, 118.7, 119.3, 121.7, 125.0, 126.7, 136.7, 174.0, 174.8.

Iminoether Method.

5-(Chloromethyl)-1,3-benzodioxole.

A mixture of piperonyl alcohol (100 g, 0.66 mol) and 37 % HCl was strongly stirred for 20 min, then the product was extracted with dichloromethane. After drying the chloride was obtained in 98 % yield. ^1H NMR ($CDCl_3$): δ 4.51 (s, 2H), 5.94 (s, 2H), 6.74 (dd, J = 7.8, 0.5 Hz, 1H), 6.83 (dd, J = 7.8, 1.8 Hz, 1H), 6.86 (dd, J = 1.8, 0.5 Hz, 1H).

Methyl 1-(1,3-Benzodioxol-5-ylmethyl)pyroglutamate.

A 1000 ml round bottom flask equipped with a high surface Graham condenser connected to a water pump was charged with a mixture of 5-(chloromethyl)-1,3-benzodioxole (167 g, 0.98 mol) and methyl 5-methoxy-3,4-dihydro-2*H*-pyrrole-2-carboxylate [10] (183 g, 1.16 mol). A good magnetic stirring was applied, then the water pump vacuum was applied (in order to remove all the methyl chloride formed during the reaction) and the solution was refluxed for 8 hours, yielding 90 % in methyl 1-(1,3-benzodioxol-5-ylmethyl)pyroglutamate, mp 94-7 °C (AcOEt); IR: 1735, 1680, 1495, 1445, 1035 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.98-

2.19 (m, 1H), 2.19-2.37 (m, 1H), 2.37-2.69 (m, 2H), 3.71 (s, 3H), 3.88 (d, J = 14.7 Hz, 1H), 3.99 (dd, J = 8.7, 3.3 Hz, 1H), 4.94 (d, J = 14.7 Hz, 1H), 5.95 (s, 2H), 6.65 (dd, J = 7.8, 1.7 Hz, 1H), 6.71 (d, J = 1.7Hz, 1H), 6.74 (dd, J = 7.8, 0.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 22.7, 29.5, 45.2, 52.3, 58.4, 100.9, 108.0, 108.6, 121.7, 129.2, 146.9, 147.6, 171.8, 174.6.

Anal. Calcd. For $C_{14}H_{15}NO_5$: C, 60.65; H, 5.45; N, 5.05; O, 28.85. Found: C, 60.54; H, 5.51; N, 5.15; O, 28.67.

N-(1,3-Benzodioxol-5-ylmethyl)pyroglutamic Acid (**2b**).

A stirred mixture of methyl 1-(1,3-benzodioxol-5-ylmethyl)-pyroglutamate (150 g, 0.54 mol) in water 500 ml and sodium hydroxide (60 g, 1.5 mol) was heated at 80 °C for 1 hour. The solution was washed with dichloromethane, then acidified with 37 % HCl. The solid obtained was washed with water then dissolved in acetone and dried. The compound obtained after evaporation was recrystallized from ethyl acetate yielding 86 % of acid **2b** identical to the product obtained by reductive alkylation.

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