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A Convenient Synthesis of 5-Oxo-L-pipecolic Acid Derivative from L-Glutamic Acid

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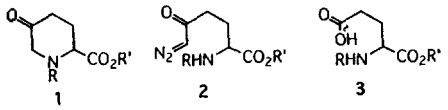
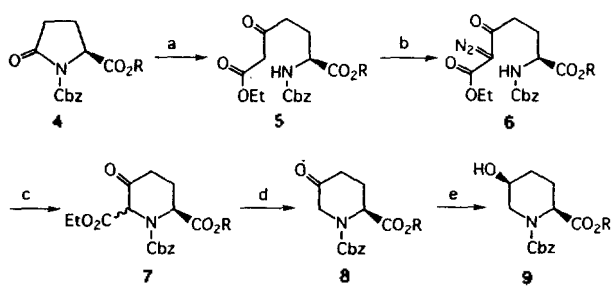
2-Pipecolic acid derivatives are currently drawing interest since they can serve as starting materials for potential enzyme (*e.g.* protein kinase C) inhibitors,[1] synthetic drugs and natural products such as the immunosuppressant FK506,[2] the antifungal antibiotics demethoxyrapamycin[3] and mycotoxic alkaloid verruculotoxin.[4] Therefore many synthetic efforts have been devoted to the preparation of 2-pipecolic acid derivatives.[5] Previously, we reported that 5-oxo-L-pipecolic acid derivatives **1** can be prepared by rhodium(II) acetate catalyzed cyclization of diazoketones **2** derived from L-glutamic acids **3**.[5c] However, one drawback of this approach lies in the use of explosive and toxic diazomethane for the conversion of **3** to **2**, which is not suitable for scale-up. We thought that α-diazo β-keto ester **6**, prepared by the diazo transfer reaction of β-keto ester **5**, can be used as an alternative substrate for the rhodium-catalyzed cyclization, as shown in Scheme 1.[6] In this note we report that this approach can be successfully utilized for the preparation of **1**.



The β-keto ester **5** prepared by the known reaction[7] of lithium enolate of ethyl acetate with pyroglutamate **4** was treated with *p*-acetamidobenzenesulfonyl azide[8] in the presence of Et_3N to give the corresponding α-diazo β-keto ester **6**. Cyclization of diazo compound **6** using the Rapoport protocol (refluxing benzene, 5% rhodium acetate, 30 min)[9] gave the crude cyclized product **7**, whose IR spectrum lacked the characteristic diazo peak at 2140 cm^{-1}. Without further purification the dealkoxycarbonylation[10] of **7** with LiOH hydrate in THF gave the 5-oxo-L-pipecolic acid derivative **8**. $NaBH_4$ reduction of **8** gave cis alcohol **9**,[11] which showed a complex NMR spectrum due to the presence of several rotamers. However, mass spectrum showed the correct molecular ion at m/e 335.

Scheme 1 (R = *t*-Bu)



a: CH_3CO_2Et, $LiN(SiMe_3)_2$, THF, -78 °C, 67%. b: p-$AcNHC_6H_4SO_2N_3$, Et_3N, CH_3CN, 86%. c: 5% $Rh_2(OAc)_4$, benzene, reflux. d: $LiOH{\cdot}H_2O$, THF, 58%. e: $NaBH_4$, EtOH, 93%.

In summary, we have achieved a short, straightforward synthesis of **8** from L-glutamic acid, which is amenable to scale-up and adaptable for the synthesis of pipecolic acids protected with other groups.

Experimental Section

t-Butyl L-*N*-Benzyloxycarbonylpyroglutamate (4). was prepared according to the known procedure[12] from L-*N*-benzyloxycarbonylglutamic acid in 64% yield, mp 48-50 °C (lit.[12] mp 48-52 °C); R_f=0.67 (hexane : ethyl acetate=1 : 1); $[\alpha]_D$= −39.4 (c=2.21, CH_2Cl_2) [lit.[12] $[\alpha]_D$= −36.9 (c=4.5, CH_2Cl_2); ^1H NMR (200 MHz, $CDCl_3$) δ 7.4-7.3 (m, 5H), 5.29, 5.26 (AB q, 2H, J=12 Hz), 4.55 (dd, 1H, J=3, 9 Hz), 2.7-2.5 (m, 2H), 2.45-2.25 (m, 1H), 2.1-2.0 (m, 1H), 1.39 (s, 9H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 173.0 (CO_2-*t*-Bu), 169.9, 150.7 ($NHCO_2Bn$), 134.9, 128.4, 128.2, 128.0, 82.3 (CO_2CMe_3), 68.0 (OCH_2Ph), 59.2, 30.8, 27.6, 21.7.

1-*t*-Butyl 7-ethyl 2-L-(benzyloxycarbonyl)amino-5-oxopimelate (5). A solution of ethyl acetate (2.11 g, 24 mmol) in dry THF (40 mL) was treated with 1 M lithium bis(trimethylsilyl)amide in THF (24 mL, 24 mmol) at −78 °C. After stirring for 30 min a solution of pyroglutamate **4** (2.55 g, 8.0 mmol) in THF (10 mL) was added dropwise to the above solution and the whole mixture was stirred for 30 min. TLC showed the absence of starting material. The reaction mixture was quenched with sat NH_4Cl (3 mL) at

−78 ℃ and extracted with ethyl acetate (2×50 mL). The organic layer was dried (Na_2SO_4) and concentrated *in vacuo*, and the resulting residue was chromatographed (hexane : ethyl acetate = 5 : 1) to give **5** (2.19 g, 67% yield) as a colorless oil: R_f = 0.50 (hexane : ethyl acetate = 2 : 1), for the starting material R_f = 0.30; $[\alpha]_D$ = +5.7 (c = 1.50, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35 (s, 5H), 5.37 (bd, 1H, *J* = 8 Hz, N*H*), 5.10 (s, 2H, CO_2CH_2Ph), 4.3-4.1 (m, 3H, C-2 and OCH_2CH_3), 3.43 (s, 2H, C-6), 2.7-2.6 (m, 2H, C-4), 2.25-2.1 (m, 1H), 2.0-1.75 (m, 1H), 1.45 (s, 9H), 1.28 (t, 3H, *J* = 7 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 201.5 (C5), 170.9, 166.9, 155.9 ($NHCO_2Bn$), 136.1, 128.3, 127.98, 127.93, 82.2 (CO_2CMe_3), 66.8 (OCH_2Ph), 61.2 (CO_2CH_2), 53.5 (C2), 49.1 (C6), 38.5 (C4), 27.8 ($C(CH_3)_3$), 26.3 (C3), 13.9 ($CO_2CH_2CH_3$); IR (neat) cm^{-1} 3360 (m), 2990 (s), 2940 (s), 1720 (s), 1530 (s), 1460 (m), 1380 (m), 1160 (s), 1055 (s), and others.

1-*t*-Butyl 7-ethyl 2-L-(benzyloxycarbonyl)amino-6-diazo-5-oxopimelate (6). A solution of β-keto ester **5** (3.85 g, 9.45 mmol) in CH_3CN (50 mL) was treated with *p*-acetamidobenzenesulfonyl azide (2.47 g, 9.46 mmol) and Et_3N (2.87 g, 28.4 mmol) at rt and the mixture was stirred for 3 h. The precipitated solid was filtered and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in ethyl acetate (100 mL) and the organic solution was washed with dil HCl, dried (Na_2SO_4) and concentrated to give a residue, which was chromatographed (hexane : ethyl acetate = 5 : 1) to give **6** (3.51 g, 86% yield) as a yellow oil: R_f = 0.62 (hexane : ethyl acetate = 2 : 1) for the starting material, R_f = 0.55; $[\alpha]_D$ = +11.3 (c = 1.58, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36 (s, 5H), 5.46 (bd, 1H, *J* = 8 Hz, N*H*), 5.10 (s, 2H), 4.28 (q, 2H, *J* = 7 Hz), 4.2 (m, 1H, C-2), 3.0-2.9 (m, 2H, C-4), 2.3-1.9 (m, 2H, C-3), 1.46 (s, 9H), 1.32 (t, 3H, *J* = 7 Hz); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 191.5, 170.9, 160.9, 155.8 ($NHCO_2Bn$), 136.3, 128.3, 127.9, 82.0 (CO_2CMe_3), 66.6 (OCH_2Ph), 61.3 (CO_2CH_2), 53.7 (C2), 35.9 (C4), 27.7 ($C(CH_3)_3$), 26.8 (C3), 14.1 ($CO_2CH_2CH_3$); IR (neat) cm^{-1} 3370 (m). 2990 (s), 2140 (s), 1730 (s), 1660 (s), 1525 (s), 1460 (m), 1305 (s), 1230 (s), 1160 (s), 1045 (s), and others.

5-Oxo-*N*-benzyloxycarbonyl-L-pipecolic acid *t*-butyl ester (8). A heated (80 ℃) solution of diazo compound **6** (560 mg, 1.29 mmol) in benzene (26 mL, 0.05 M solution) was treated with $Rh_2(OAc)_4$ (43 mg, 5%) and the mixture was refluxed for 30 min. TLC showed the absence of the starting material (R_f = 0.62 in hexane : ethyl acetate = 2 : 1) and the appearance of new products (major: R_f = 0.52; minors: R_f = 0.43, 0.29, 0.17). When charred with ninhydrin on TLC, the products were yellow and the starting diazo compounds were dark brown. The benzene solution was diluted with ethyl acetate (100 mL), washed with brine and concentrated *in vacuo* to give 520 mg of the crude cyclized product **7**. This crude product was dissolved in THF (20 mL) and treated with $LiOH \cdot H_2O$ (160 mg, 3.8 mmol, 3 equiv). After stirring for 3 hr at rt, the solution was acidified with dil HCl and extracted with ethyl acetate (3×30 mL). The organic solution was dried (Na_2SO_4) and concentrated *in vacuo* to give a residue, which was chromatographed (hexane : ethyl acetate = 3 : 1) to give **8** (250 mg, 58% yield) as an oil: $[\alpha]_D$ ≐ +11.8 (c = 1.62, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33 (s, 5H), 5.4-5.0 (m, 2H), 4.7 (m, 1H, C-2), 4.3-4.0 (m, 2H, C-6), 2.6-2.3 (m, 2H, C-4), 1.45 (s, *t*-Bu, a rotamer), 1.33 (s, *t*-Bu, a rotamer); ^{13}C NMR (50.3 MHz, $CDCl_3$) for the major rotamer δ 198.3 (C5), 170.4, 155.8, 135.6, 128.3, 128.0, 82.4, 68.0, 62.4, 54.9, 33.2, 27.8, 21.8, 13.8; IR (neat) cm^{-1} 1737 and others.

***cis*-5-Hydroxy-*N*-benzyloxycarbonyl-L-pipecolic acid *t*-butyl ester (9).**[12] A cooled (0 ℃) solution of ketone **8** (160 mg, 0.48 mmol) in EtOH (20 mL) was treated with $NaBH_4$ (18 mg, 0.48 mmol). After being stirred for 1 h, the reaction mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate (20 mL). The organic solution was washed with dil HCl and brine, dried (Na_2SO_4) and concentrated. The resulting residue was chromatographed (hexane : ethyl acetate = 3 : 1) to give **9** (150 mg, 93% yield) as an oil: R_f = 0.21 (hexane : ethyl acetate = 3 : 1) for the starting ketone, R_f = 0.52; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.32 (s, 5H), 5.3-5.1 (m, 2H), 4.7-4.5 (m, 1H), 4.3-4.2 (m, 1H), 2.4-1.1 (m, 4H), and others; ^{13}C NMR (50.3 MHz, $CDCl_3$) for the major rotamer δ 169.6, 155.7, 136.0, 128.2, 127.9, 81.4, 67.7, 60.8, 55.4, 52.6, 27.7, 24.8, 13.7; IR (neat) cm^{-1} 1737, 1716, and others; MS m/z (relative intensity) 335 (M^+, 0.08), 334 (M-H, 1.3), 290 (4.5), 262 (5.0), 172 (9.5), 91 (benzyl, 100), 57 (*t*-Bu, 60).

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