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ASYMMETRIC SYNTHESIS OF BOTH ENANTIOMERS OF 2-TRIFLUOROMETHYL-4-AMINOBUTYRIC ACID

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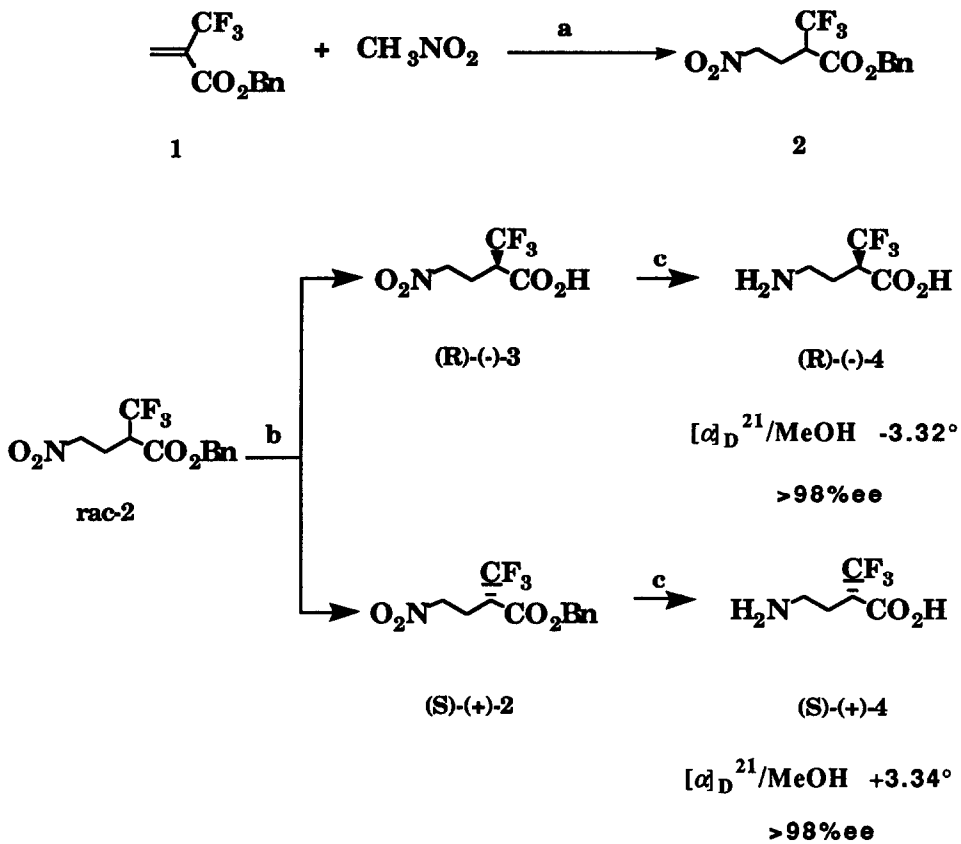
Abstract. The preparation of both enantiomers of 2-trifluoromethyl-4-aminobutyric acid based on the enzymatic resolution of benzyl 2-trifluoromethyl-4-nitrobutyrate was described.

The utility of amino acids, as chemotherapeutic agents, has resulted extensive attention in recent years.[1-5] It is well established that the strongly electronegative nature of fluorine sometimes interferes with or alters the course of reactions when compared to the analogous reactions involving non fluorinated reactants. This has been one of the most significant factors in preventing the development of stereoselective procedures in the fluorine chemistry.[6-9]

In this paper, we describe the synthesis of both enantiomers of 2-trifluoromethyl-4-aminobutyric acid. The synthetic strategy show in Scheme 1 is based upon the reaction of benzyl 2-(trifluoromethyl)propenate **1** with nitromethane as a very convenient way of preparing benzyl 2-trifluoromethyl-4-nitrobutyrate **2**; a useful precursor for 2-trifluoromethyl-4-aminobutyric acid. The asymmetric hydrolysis of benzyl 2-trifluoromethyl-4-nitrobutyrate with lipase P (*Pseudomonas sp.*: Amano Seiyaku Co. Ltd.) produces the optically active (R)-(-)-2-trifluoromethyl-4-nitrobutyric acid, (-)-**3**.[10] The ee of (R)-(-)-2-trifluoromethyl-4-nitrobutyric acid obtained at 49% conversion was >98 %ee, $[\alpha]_D^{21}$ -5.58° (c 1.14, MeOH).

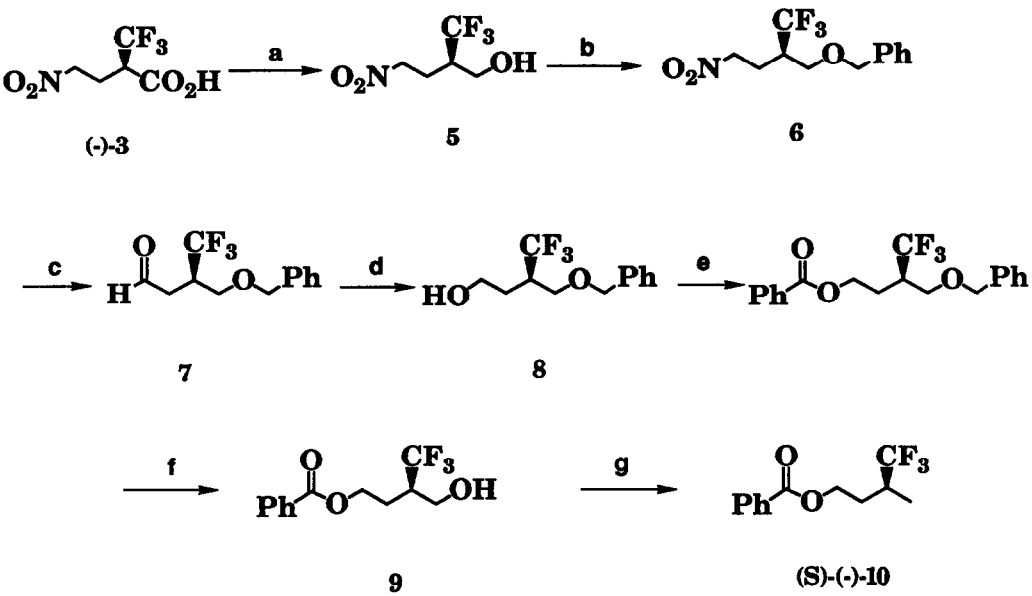
The desired (R)-(-)-2-trifluoromethyl-4-aminobutyric acid,[11] (-)-**4** [>98 %ee, $[\alpha]_D^{21}$ -3.32° (c 0.83, MeOH)], was obtained from the reduction of (R)-(-)-2-trifluoromethyl-4-nitrobutyric acid using Pd-C/H_2. The residual (S)-(+)-benzyl 2-trifluoromethyl-4-nitrobutyrate from the hydrolysis reaction [>98 %ee, $[\alpha]_D^{21}$ +13.32° (c 1.05, MeOH)], was also converted to the (S)-enantiomer [(S)-(+)-**4**: $[\alpha]_D^{21}$ +3.34° (c 0.42, MeOH)], using Pd-C/H_2.



a)0.3M aq.K_2CO_3/reflux/20h b)lipase P Amano c)10%Pd-C/H_2/EtOH

Scheme 1

We investigated the absolute configuration of optically pure 2-trifluoromethyl-4-aminobutyric acid **4** as shown in Scheme **2**. (-)-2-Trifluoromethyl-4-nitrobutyric acid [(-)-**3**; >95 %ee, $[\alpha]_D^{21}$ -5.51° (c 1.03, MeOH)], was reduced with diborane to give the corresponding ω-nitro alcohol **5**. After protection of the ω-nitro alcohol as the benzyl ether **6**, it was reacted with titanium trichloride to give the corresponding aldehyde **7**. Reduction of this aldehyde with sodium borohydride gave the alcohol **8**, and then the alcohol was converted to the ω-hydroxy ester **9**. Treatment of **9** with $Me(PhO)_3PI$ and then $NaBH_3CN$ gave (S)-(-)-3-(trifluoromethyl)butylbenzoate **10** with known absolute configuration, $[\alpha]_D^{21}$ -20.7° (c 1.02, $CHCl_3$), >95 %ee [lit.[12] : $[\alpha]_D^{21}$ -21.2° (c 1.02, $CHCl_3$), >98 %ee. These results establish that absolute configuration of (-)-2-trrifluoromethyl-4-aminobutyric acid, (-)-**4** is (R)-enantiomer.



a)B_2H_6,THF,-20°C → rt,78% b)$PhCH_2OC(=NH)CCl_3$,$TfOH$, CH_2Cl_2-cyclohexane,rt,77% c)Ti(III)Cl_3aq., dimethoxyethane,rt,quant. f)H_2/Pd-C,EtOH,rt,quant. g)$Me(PhO)_3PI$,$NaBH_3CN$,HMPT,70°C,59%

Scheme 2

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10. ^{19}F NMR ($CDCl_3$; from ext. CF_3CO_2H): δ 10.4 (d, $J_{F,H}$ = 8.7 Hz) ppm. ; ^{1}H NMR ($CDCl_3$) : δ 2.47 (2H, q, $J_{H,H}$ = 7.1 Hz), 3.43 (1H, m), 4.67 (2H, t) 10.4 (1H, s). IR (cm^{-1}) 1730 (C=O).
High-resolution mass calcd: 201.100, Found: 201.274.
11. ^{19}F NMR ($CDCl_3$; from ext. CF_3CO_2H): δ 8.70 (d, $J_{F,H}$ = 7.5 Hz) ppm. ; ^{1}H NMR ($CDCl_3$) : δ 2.07 (2H, m), 2.92-3.22 (3H, m), 7.45 (2H, br) 10.4 (1H, s). IR (cm^{-1}) 3450 (NH_2), 1730 (C=O).
Anal. Found: C, 35.14; H, 4.47; N, 7.95. Calcd for $C_5H_8NO_2F_3$: C, 35.10; H, 4.71; N, 8.19.
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