Practical and Efficient Route to (*S*)-γ-Fluoroleucine

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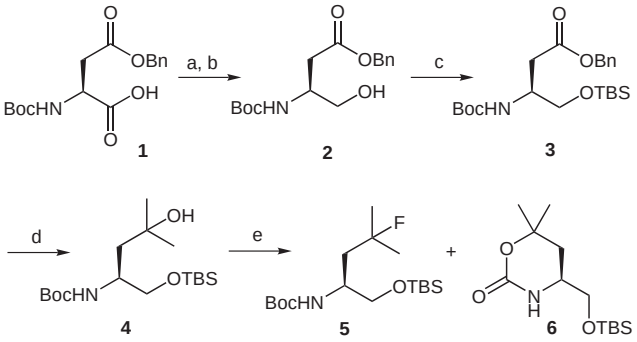
Received 18 January 2005

Abstract: A practical and efficient route to (*S*)-γ-fluoroleucine was developed via compound **9**. Introduction of the fluorine was achieved using *N*,*N*-diethylaminosulfur trifluoride (DAST) treatment on a tertiary alcohol **8**.

Key words: (*S*)-γ-fluoroleucine, methylmagnesium bromide, *N*,*N*-diethylaminosulfur trifluoride, oxazolidinone, continuous liquid-liquid extraction

Fluorinated amino acids have recently received much attention because of their potential use in a wide variety of bioactive agents[1] and the challenge associated with their preparations. A number of research groups have successfully achieved the synthesis of some chiral fluorinated amino acids.[2] For example, a lipase-catalyzed dynamic ring-opening of an azlactone provided a highly efficient chemo-enzymatic approach to (*S*)-γ-fluoroleucine ethyl ester.[3] In addition, Papageorgiou et al.[1d] reported an enantioselective chemical synthesis of (*S*)-γ-fluoroleucine ethyl ester using bis-lactim ether methodology. However, this route is limited by the high cost of the bis-lactim ether precursor and a low yield of the key diastereoselective alkylation step. The requirement for (*S*)-γ-fluoroleucine in one of our medicinal chemistry programs and the lack of a practical chemical approach to this derivative prompted us to develop the efficient route reported herein.

The reaction sequence is shown in Scheme 1. Selective reduction of the *N*-(*tert*-butoxycarbonyl)-L-aspartic acid 4-benzyl ester **1**, via an activated mixed anhydride,[4] afforded the desired alcohol **2** which was then protected as the silyl ether **3**. Treatment of **3** with 4 equivalents of methylmagnesium bromide converted the benzyl ester to the tertiary alcohol **4**. This alcohol was then reacted with *N*,*N*-diethylaminosulfur trifluoride[5] in anhydrous dichloromethane to afford the fluorinated intermediate **5** in low yield (42%). Significant amount of the oxazolidinone **6**, resulting from undesired participation of *tert*-butyl carbamate functional group, was also isolated. Similar observations were reported by Zhao and co-workers.[6] They found that treatment of *N*-*tert*-butoxycarbonyl derivatives of β-amino primary alcohols with DAST undergo intramolecular cyclizations to give oxazolidinones in good yields.



1 **2** **3** **4** **5** **6**

Scheme 1 *Reagents and conditions*: a) NMM (1 equiv), *i*-BuOC(O)Cl (1 equiv), DME, –15 °C, 30 min; b) $NaBH_4$, H_2O, –50 °C to –15 °C, 85% (last two steps); c) TBSCl (1.2 equiv), Et_3N, DMAP, CH_2Cl_2, r.t. 90%; d) MeMgBr (3 M in Et_2O, 4 equiv), toluene–THF (1:1), 0 °C, 76%; e) DAST (2 equiv), CH_2Cl_2, –78 °C, 42%.

In order to avoid the formation of **6**, we chose to convert the primary alcohol **2** (Scheme 2) to the corresponding cyclic carbamate **7**. Using *p*-toluenesulfonic anhydride in anhydrous dichloroethane, the oxazolidinone **7** was obtained in 83% yield. Double addition of methylmagnesium bromide to the benzyl ester moiety gave the water soluble alcohol **8** which was isolated by continuous liquid-liquid extraction employing dichloromethane.[7] Fluorination using DAST in anhydrous dichloromethane afforded the desired fluorinated derivative **9** along with 6% of the *endo*-olefin **10** which was easily removed by chromatography. Hydrolysis of **9** under basic conditions[8] followed by selective N-protection furnished **11** in 91% yield for the two steps. Oxidation of the protected β-amino alcohol to the corresponding carboxylic acid **12** was achieved using periodic acid with a catalytic amount of chromium trioxide in wet acetonitrile.[9] Ultimately, deprotection of the amine using 20% trifluoroacetic acid in dichloromethane produced the desired (*S*)-γ-fluoroleucine **13**, isolated in quantitative yield as a stable TFA salt. The enantiomeric excess of **13** was determined to be >98% based on a comparative ^1H NMR analysis of its Mosher amide **14**[10] to its racemic analog prepared by a different route (Figure 1).

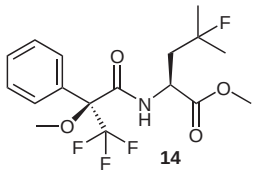


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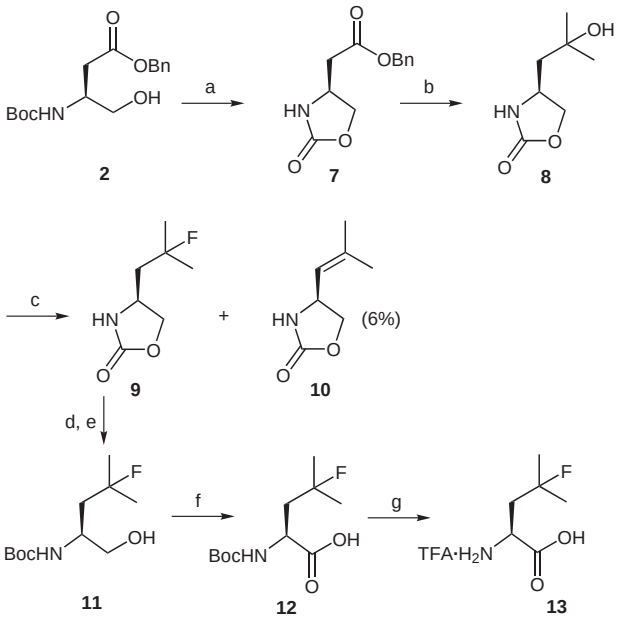
Figure 1

SYNLETT 2005, No. 8, pp 1279–1280
Advanced online publication: 03.05.2005
DOI: 10.1055/s-2005-868494; Art ID: S00705ST



Scheme 2 *Reagents and conditions*: a) $(p\text{-Tos})_2O$ (1.1 equiv), pyridine, dichloroethane, 0 °C, at r.t. for 1 h, then at 90 °C for 2 h, 83%; b) MeMgBr (3 M in Et_2O, 4 equiv), toluene–THF (1:1), –20 °C to 0 °C, 72%; c) DAST (1 equiv), CH_2Cl_2, –78 °C to r.t., 70%; d) KOH (3 equiv), EtOH (90%)–H_2O, 100 °C, 4 h; e) $(Boc)_2O$ (1.5 equiv), Et_3N, CH_2Cl_2, 91% (last two steps); f) H_5IO_6 (2.5 equiv), CrO_3 (cat.), 0.75% v/v H_2O/MeCN, 0 °C, 50 min, 65%; g) 20% TFA in CH_2Cl_2, 99%.

In conclusion, we have developed a convenient and efficient procedure for the preparation of optically pure (*S*)-γ-fluoroleucine in multigram quantities using commercially available *N*-(*tert*-butoxycarbonyl)-L-aspartic acid 4-benzyl ester as a starting material. No erosion of chirality occurred during the synthesis.

Acknowledgment

We thank Dr. Cameron W. Black and Dr. Chun-Sing Li for valuable chemistry discussions.

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(7) **Experimental Procedure for the Synthesis of Compound 8.**
MeMgBr (681 mL of 3 M solution in Et_2O, 2.04 mol) was added to a mixture of toluene (1 L) and THF (1 L) at –20 °C. A solution of the benzyl ester **7** (120 g, 510 mmol) in THF (500 mL) was added dropwise maintaining the temperature below –10 °C and the mixture was aged at 0 °C for 2 h. The mixture was slowly added to a mixture of H_2O (3 L) and HOAc (600 mL) and the mixture was stirred at r.t. for 2 h. The aqueous layer was separated and the organic layer was extracted with H_2O (2 × 600 mL). The product was extracted from the combined aqueous layers using CH_2Cl_2 and a continuous extractor (2 d). The CH_2Cl_2 extract was evaporated to dryness and co-evaporated with *n*-heptane. The residue was purified by chromatography on silica gel using EtOH and CH_2Cl_2 (1:25) to afford compound **8** (62 g, 72%). $[\alpha]_D^{20}$ –7.0 (*c* 1.0, MeOH). ^1H NMR (500 MHz, CD_3COCD_3): δ = 1.25 (3 H, s), 1.27 (3 H, s), 1.73 (1 H, dd, *J* = 13.9, 6.1 Hz), 1.81 (1 H, dd, *J* = 13.9, 6.6 Hz), 3.67 (1 H, s), 4.01 (1 H, dd, *J* = 8.4, 7.3 Hz), 4.12–4.18 (1 H, m), 4.49 (1 H, dd, *J* = 8.3, 8.3 Hz), 6.26 (1 H, s). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.05, 71.14, 71.00, 50.19, 47.66, 32.14, 28.86. Anal. Calcd for $C_7H_{13}NO_3$: C, 52.82; H, 8.23; N, 8.80. Found: C, 52.69; H, 8.19; N, 8.76. HRMS-FAB (glycerol, KCl): *m/z* $[M + K]^+$ calcd for $C_7H_{13}NO_3K$: 198.1878; found: 198.0532.

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