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A concise synthesis of L-4,4-difluoroglutamine†

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Abstract—L-4,4-Difluoroglutamine **1** of high optical purity was prepared from (*R*)-Garner's aldehyde **2** using Reformatsky reaction as the key step for introducing the fluorinated side-chain.

In living cells, glutamine and glutamate are the main storage forms of nitrogen for the synthesis of macromolecules.[1] If glutamate is able to deliver its α-amino group by transamination, labilisation of the glutamine nitrogen requires the intervention of the catalytic machinery of glutamine-dependent amidotransferases to perform amide bond cleavage.[2] It was therefore hypothesised that fluorinated analogues of glutamine, particularly with fluorine in the α-position to the amide group, might interfere in the later process due to the strong electron-withdrawing effect of fluorine atom(s) without significant steric consequence.[3,4] It might affect in particular the formation/decomposition of the acyl-enzyme (γ-glutamylthioester) intermediate which is the signature of class II amidotransferases.[2] With this in view, the synthesis of L-4,4-difluoroglutamine was undertaken in our laboratory.

Despite several attempts, 4,4-difluoroglutamine was only synthesised in racemic form starting from DL-4,4-difluoroglutamic acid[5] whereas three stereoselective syntheses of L-4,4-difluoroglutamic acid have been recently reported.[6–8] We describe herein the first synthesis of L-4,4-difluoroglutamine **1** from D-serine (Scheme 1). (*R*)-Garner's aldehyde **2** easily obtained from D-serine[9,10] or prepared from naturally occurring L-serine[11] is the key intermediate of the present synthesis.

The fluorinated side-chain was introduced by a Reformatsky reaction of aldehyde **2** with ethyl bromodifluoroacetate under ultrasonic conditions[12–14] to afford cleanly a diastereoisomeric mixture of alcohols **3** (d.r. = 7/1, 81% overall yield). Although they could be separated by flash chromatography, the diastereoisomers were used as a mixture in the next step. Alcohols **3** were converted[15] into the imidazolylthiocarbonates **4** in 80% yield assuming quick elution during flash column chromatography. Barton–McCombie radical deoxygenation of **4** with triethylsilane and benzoyl peroxide[12,16] gave crude **5** in quantitative yield.

As previously observed with closely related compounds,[17–19] the oxazolidine ring cleavage and subsequent oxidation of the resulting alcohol were problematic. Ring cleavage of oxazolidine **5** was achieved in about 30% yield using Dowex H^+ resin[20] or TFA in methanol.[17] This poor yield in formation of alcohol **6** may reflect its high tendency to undergo lactonisation, even at low temperature (–20°C) due to the enhanced electrophilic character of α,α-difluorocarboxylate moiety. Furthermore, subsequent oxidation of alcohol **6** using Jones' reagent[18] or PDC/DMF[20] gave acid **7** in, at best, 60% yield.

Alternatively, compound **7** was prepared in a two-step sequence by deoxygenation of compound **4** as mentioned above to afford protected amino alcohol **5** which was sequentially deprotected and oxidised using stoichiometric amounts of periodic acid in the presence of a catalytic amount of chromium trioxide[17,21] to yield directly L-4,4-difluoroglutamic acid derivative **7** in 46% overall yield from **4**. Aminolysis[5,22] of ester **7** to **8** proceeded smoothly in 82% yield. Deprotection of amino group afforded the desired L-4,4-difluoroglu-

Keywords: Garner's aldehyde; Reformatsky reaction; Barton–McCombie deoxygenation; fluorinated amino acids; glutamine.

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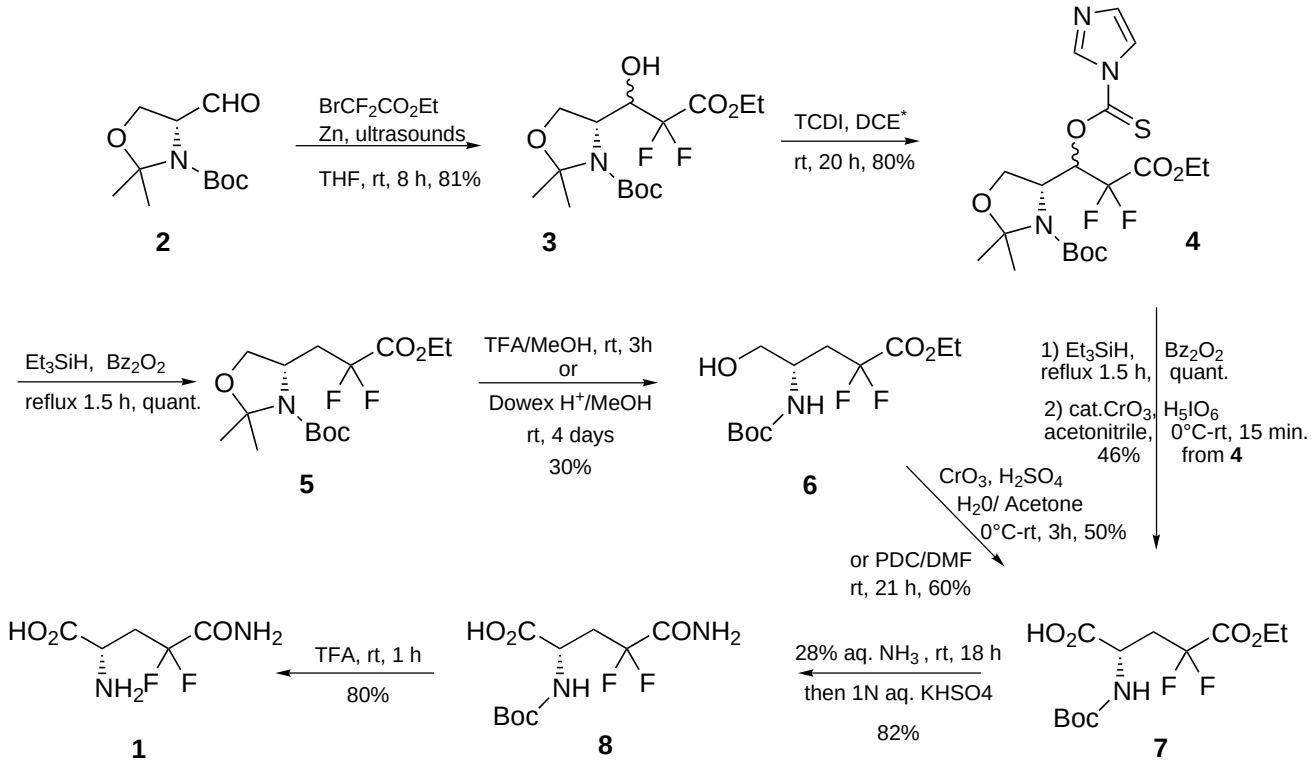

(TCDI : thiocarbonyldiimidazole; DCE : 1,2-dichloroethane)

Scheme 1.

tamine **1**[23] in 80% yield with e.e. >99% as determined using chiral HPLC.

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23. Analytical data for compound **1**: white solid; mp 171°C (dec.) (CH_3OH/Et_2O); ^1H NMR (400 MHz, D_2O): δ 2.56 (1H, m), 2.74 (1H, m), 4.23 (dd, $J=3.7$, 8.5 Hz, 1H); ^{13}C NMR (100.6 MHz, D_2O): δ 34.4 (t, $J=25$ Hz), 48.3, 116.1 (t, $J=250$ Hz), 168.7 (t, $J=28$ Hz), 171.0; ^{19}F NMR (376 MHz, $D_2O/CFCl_3$ ext.): δ −104.2 (ddd, $J=252$, 14, 21 Hz, 1F), −103.3 (ddd, $J=252$, 12, 22 Hz, 1F); MS (DCI, NH_3): m/z 183 $(M+H)^+$; IR (KBr): 3400–2500, 1738, 1651, 1599 cm^{-1}; $[\alpha]_D^{20}=+16.7°$ (c 1.05, 1N HCl). e.e. >99% (HPLC analysis at 195 nm, Chrownpak CR(+) column, aq. $HClO_4$, pH 1.5, 0.4 mL/min, 0°C, retention times: 3.48 and 4.56 min for the D-and L-enantiomers, respectively. The D-enantiomer was synthesised from L-serine following Scheme 1.