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A Versatile Entry into the Synthesis of α-(Monofluoromethyl) Amino Acids : Preparation of α-(Monofluoromethyl) Serine and (*E*)-Dehydro-α-(monofluoromethyl) Ornithine.

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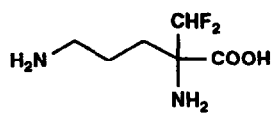
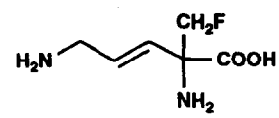
Abstract : A new entry to the synthesis of α-(monofluoromethyl) amino acids is described. The synthesis is based on a Strecker reaction on an α-(monofluoromethyl) ketone. As an example, α-(monofluoromethyl) serine was synthesized and used as starting material for a new synthesis of (*E*)-dehydro-α-(monofluoromethyl) ornithine.

α-(Fluoromethyl) amino acids have received considerable attention during the last two decades because of their enzyme-activated irreversible inhibitory activity.[2,3,4] An intensive effort aimed at the design and synthesis of specific inhibitors of polyamine biosynthesis has led to the discovery of α-(difluoromethyl) ornithine (DFMO, **1**), nowadays used for the treatment of the African sleeping sickness,[3,4b] and (*E*)-dehydro-α-(monofluoromethyl) ornithine (Δ-MFMO, **2**),[4] both irreversible inhibitors of ornithine decarboxylase (EC 4.1.1.17, ODC).



1 (DFMO)



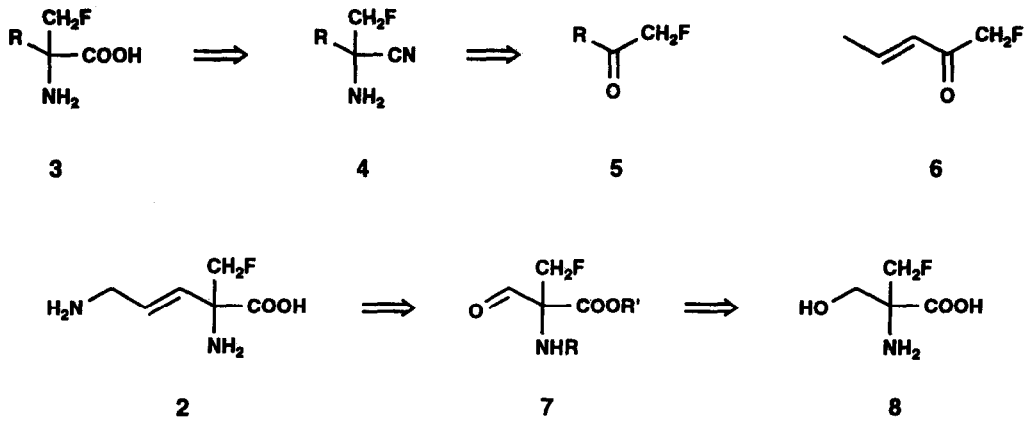
2 (Δ-MFMO)

While the difluoromethyl analogs can easily be prepared,[4] the monofluoromethyl derivatives necessitate an alternative and more expeditious synthetic method, involving a Grignard reaction with fluoroacetonitrile, followed by an *in situ* Strecker type synthesis.[4a,5] However, the use of fluoroacetonitrile, especially for large scale preparations, has considerable drawbacks: the compound is toxic as such, as well as indirectly *via* its possible conversion to monofluoroacetic acid, it is volatile and is not commercially available.[4a] Furthermore, the allylic bromination step in the synthesis of Δ-MFMO (**2**)[4a] has proven to be irreproducible on large scale, due to problems of heat transfer. This led us to investigate alternative strategies to prepare **2** and, more generally, to prepare α-(monofluoromethyl) amino acids.[6]

A possible entry into the synthesis of α-(monofluoromethyl) amino acids is depicted in scheme I. The Strecker synthesis on an α-(monofluoromethyl) ketone **5**, which can be obtained via different routes,[7] leads to amino nitrile **4**, a direct precursor of amino acid **3** via acid hydrolysis. However, this strategy could not be applied to the synthesis of Δ-MFMO (**2**), since it was observed that the unsaturated ketone **6** under Strecker reaction conditions did not yield the desired aminonitrile.[8] Eventually, we decided to prepare Δ-MFMO (**2**) from α-(monofluoromethyl) serine (**8**), prepared with the new strategy depicted in scheme I. For the introduction of

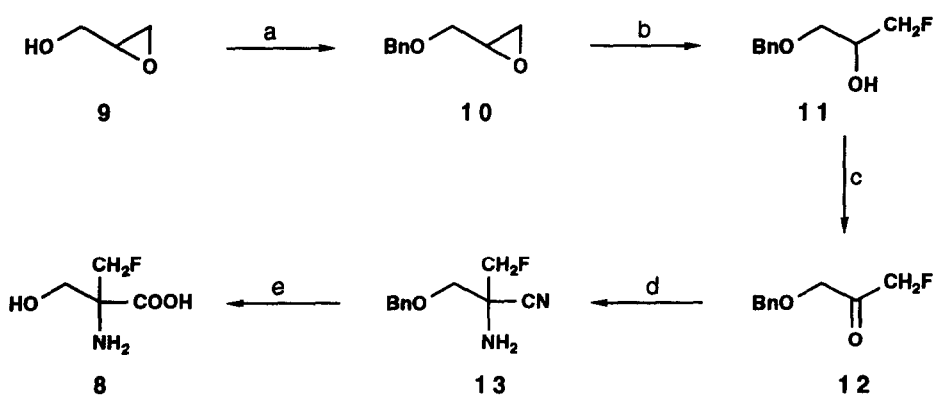
the (*E*)-allylic amine moiety, we planned to rely on the thermal rearrangement of an allylic trichloroacetimidate as described by Overman,[9] *via* vinylmagnesium bromide addition onto the aldehyde **7**.

Scheme I



The synthesis of α-(monofluoromethyl) serine (**8**) is outlined in scheme II. Benzylation of glycidol (**9**) was carried out using benzylbromide and potassium *t*-butoxide in THF. The benzylether **10** was then treated with potassium hydrogen difluoride in triethyleneglycol at 130°C,[10] affording regioselectively the fluorohydrin **11**, which was oxidized to ketone **12** using the Swern oxidation.[11] Treatment of ketone **12** with ammonium chloride and sodium cyanide in water afforded very cleanly the amino nitrile **13**, which upon acid hydrolysis at 100°C gave rise to α-(monofluoromethyl) serine (**8**) in 38% yield from glycidol.[12]

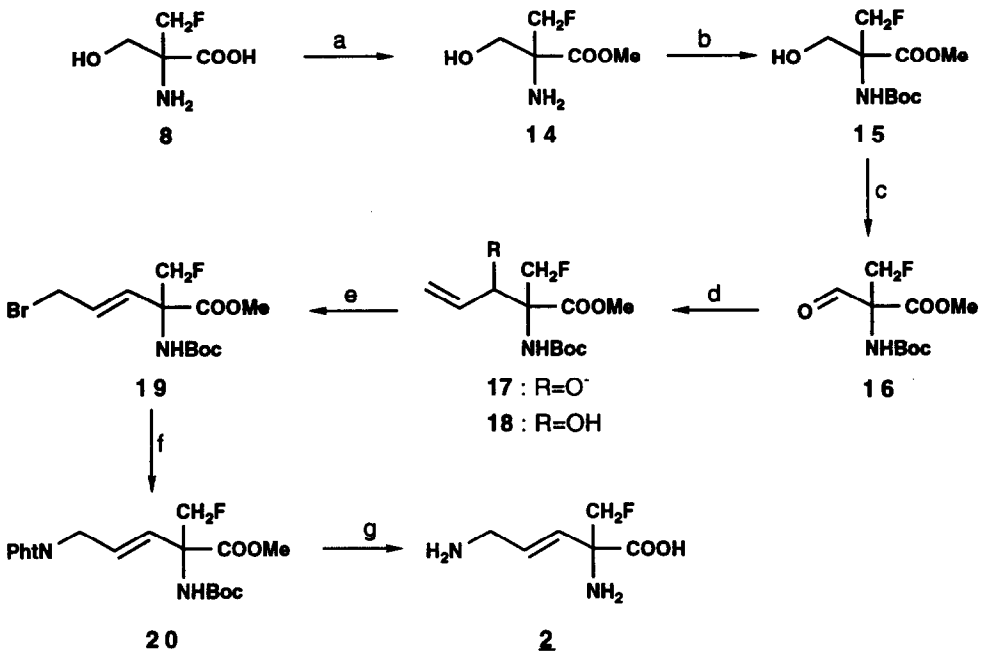
Scheme II



a) BnBr, KO*t*-Bu, THF, 0°C, 82%; b) KHF_2, triethyleneglycol, 130°C, 3 h, 80%; c) $(COCl)_2$, DMSO, CH_2Cl_2, -60°C, then NEt_3, 92%); d) NaCN, NH_4Cl, H_2O, 80% ; e) HCl, H_2O, reflux, 24 h, then propyleneoxide, *i*-PrOH, 79%

The conversion of **8** to Δ-MFMO (**2**) is outlined in scheme III. The acid function in **8** is esterified (HCl/methanol/trimethylorthoformate) to give **14**, and the amino function is protected as a *t*-butyl carbamate using di *t*-butylcarbonate and triethylamine in THF to afford **15**. The alcohol function in **15** was most efficiently oxidized with pyridinium chloro chromate and molecular sieves in dichloromethane.[13] Some problems were encountered during the vinyl magnesium bromide addition onto aldehyde **16**, due to the instability of the intermediate alkoxide **17**. At higher temperatures a Grob type fragmentation[14] occurred, leading to the formation of acrolein and dehydro-(N-Boc)-alanine. When the reaction temperature was maintained at -78°C and the reaction quenched after 3 minutes at low temperature with acetic acid, the allylic alcohol **18** could be isolated in 70% yield.

Scheme III



a) MeOH, $CH(OMe)_3$, HCl, reflux, 24 h; b) $(Boc)_2O$, NEt_3, THF, 84% from **8**; c) PCC, mol sieves, CH_2Cl_2, 80%; d) vinylMgBr, THF, 3 min, -78°C, then HOAc, -78°C, 70%; e) $(CH_3)_2CC(Br)NMe_2$, CH_2Cl_2, 70%; f) PhtNK, DMF, 80°C, 84%; g) H_2O, HCl, reflux, 24 h, then propylene oxide, *i*-PrOH, 82%

The stage was set to try our initial plan, namely to introduce the (*E*)-allylic amine moiety *via* the Overman rearrangement.[9] However, all our efforts (different bases, different solvents, different modes of addition) to introduce the trichloroacetimidate group in **18** were unsuccessful. All conditions we used gave either no reaction or gave only the Grob fragmentation products. We then decided to convert the hydroxyl function in **18** to a leaving group, hoping to introduce the aminofunction using a SN2' type substitution reaction. After many trials with different reagents, we were gratified to observe that treatment of **18** with tetramethyl-α-

bromoenamine[15] gave directly the (*E*)-allylic bromide **19**. The stereochemistry of the double bond was ascertained by n.m.r. ($J_{HC=CH}$ = 16 Hz) and by converting **19** to Δ-MFMO (**2**). Treatment of the bromide **19** with potassium phtalimide in dimethylformamide at 80°C gave the N-phtalimide derivative **20**, which was hydrolized in concentrated aqueous hydrochloric acid to yield (*E*)-dehydro-α-(monofluoromethyl) ornithine (**2**), displaying spectral data identical to those from the compound obtained from the earlier synthesis.[4a]

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12. α-(monofluoromethyl) serine (**8**): mp (*i*-PrOH) 184-185°C ; ^{1}H NMR (60 MHz, D_2O) δ 3.9 (2H, br s, $C\underline{H}_2OH$), 4.85 (1H, d, J_{HF} = 45.5 Hz, $C\underline{H}_2F$), 4.90 (1H, d, J_{HF} = 44.5 Hz, $C\underline{H}_2F$) ; Anal. calcd for $C_4H_8FNO_3$: C, 35.04; H, 5.88; N, 10.22; Found : C, 35.07; H, 5.70; N, 10.10
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