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AN EFFICIENT RESOLUTION OF 3-TRIFLUOROMETHYL-γ-BUTYROLACTONE AND ITS CONVERSION TO 5,5,5-TRIFLUOROLEUCINOL

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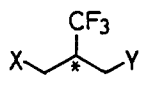
Summary: 3-Trifluoromethyl-γ-butyrolactone(2) was effectively resolved via its diastereomeric amide(3). 5,5,5-Trifluoroleucinol hydrochloride(8) were prepared in enatiomerically pure form and the absolute configurations were determined by CD spectra of dibenzoyl derivatives(9) and X-ray analysis of the N-benzoyl derivative(11).

Fluorinated organic compounds are of increasing interest, particularly for the synthesis of biologically active compounds.[1] Exploration of versatile fluorinated chiral building-block which is enatiomerically 100% pure is considered to be a crucial process to achieve the above purpose. Although a number of approaches for the preparation of fluorinated chiral molecules have been reported, there appeared few reports dealing with efficient methods for asymmetrically bifunctionalized molecule(e.g. 1) in which trifluoromethyl group is substituted on chiral tertiary carbon atom.[2] Weinges reported the resolution of 4,4,4-trifluoro-3-methylbutan-1-ol(6) and its conversion to (2S,4R)- and (2S,4S)-5,5,5-trifluoroleucine(7).[3] This seems to have only limited use as a chiral building-block because of its functionality and the efficiency of the resolution.

In this paper we report an efficient resolution of 3-trifluoromethyl-γ-butyrolactone(2) via the amide(3) and its conversion and the determination of absolute configuration of 5,5,5-trifluoroleucinol derivative(8).



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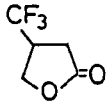

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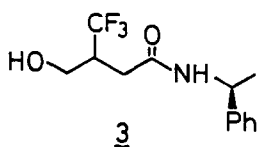
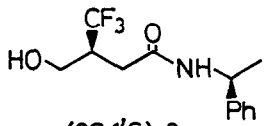
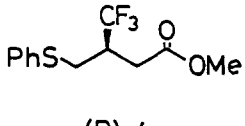


3

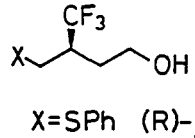
Separation of the diastereomeric mixture of the hydroxy amide(3) was found to be easily achieved by the combined use of fractional recrystallization and column chromatography. Thus, recrystallization($CHCl_3$) of the crude hydroxy amide(3) prepared from (±)-2(10g)[4] and (S)-(-)-α-methylbenzylamine (1.1 equiv., toluene, refl., 6h) gave (3R, 1'S)-3(5.35g, mp 144-145°C) followed by the column chromatography(SiO_2, Wako-gel C-200) of the filtrate gave (3S, 1'S)-3(6.67g, mp 82.5-83°C, Rf=0.53) and further (3R, 1'S)-3(2.18g, Rf=0.31).[6,7] Treatment of each diastereomer of 3 with c-HCl gave the lactone(2) in high yield [(3S, 1'S)-3 → (S)-(-)-2, $[\alpha]_D^{19}$-17.7° (c=1.9, Et_2O); (3R, 1'S)-3 → (R)-(+)-2, $[\alpha]_D^{24}$+16.8°(c=2.24 Et_2O)].



(3S,1'S)-3



(R)-4



X=SPh (R)-5
X=H (R)-6

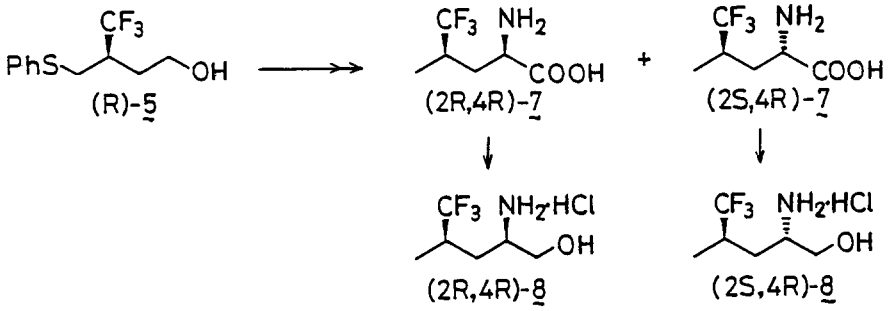
Each diastereomerically pure hydroxyamide(3) could be converted to 4,4,4-trifluoro-3-methylbutanol(6) and 5,5,5-trifluoroleucinol hydrochloride(8) without racemization through the following procedures (for simplicity only (3S, 1'S)-2 series is illustrated). Substitution of the hydroxyl group of 3 with phenylthio group(MsCl-Et_3N, CH_2Cl_2, 0°C then PhSH-NaH, THF, r.t.), hydrolysis of amide(c-HCl, AcOH, refl., 13h) followed by esterification(MeOH, AcCl) afforded the ester [(R)-(-)-4 from (3S, 1'S)-3, 55% $[\alpha]_D^{23}$-79.6°(c=1.4 MeOH); (S)-(+)-4 from (3R, 1'S)-3, 70% $[\alpha]_D^{23}$+79.6°(c=3.07 MeOH)]. Reduction of the ester 4(DIBAL-H, Et_2O, 0°C), benzoylation(PhCOCl-Py, CH_2Cl_2), desulfurization [Raney-Ni(W-2), acetone, r.t.] followed by saponification(2N-KOH, r.t.) gave the alcohol 6[(R)-(+)-6, $[\alpha]_D^{26}$+13.4°(c=0.33 $CHCl_3$) from (R)-(+)-4; (S)-(-)-6 from (S)-(-)-4, $[\alpha]_D^{26}$ -13.8°(c=0.94 $CHCl_3$)]. Racemization could not be detected during the above procedures by examining the ^{1}H-nmr (400 MHz) and ^{19}F-nmr(188 MHz) spectra of the MTPA ester[8] of the alcohols (5 and 6). The absolute configration of 6 was tentatively assigned as indicated by comparison of the optical rotation with that reported by Weinges.[3]

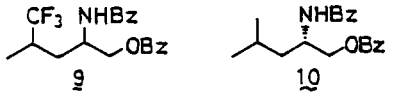
Conversion of the phenylthiobutanol(5) to the leucinol hydrochloride(8) was achieved as follows: Oxidation of 5(DMSO-ClCOCOCl-Et_3N, CH_2Cl_2),[9] Strecker reaction(KCN-NH_4Cl-NH_4OH, EtOH; 60-70%), chromatographic separation of the resulted diastereomers of the amino nitrile, acid hydrolysis(c-HCl,

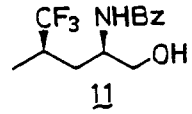
50-60°C) followed by desulfurization[Raney-Ni(W-2), H_2O, 90°C] afforded 5,5,5-trifluoroleucine(7, 64-79%)[10] which, in turn, reduced ($NaBH_4$-BF_3·Et_2O, THF)[11] to the leucinol isolated as the hydrochloride(8, 71-87%).[12] Both leucine(7) and leucinol(8) were diastereomerically pure based on their nmr spectra.

The absolute configuration at C-2 position of each enantiomers of 8 was determined by comparison of the CD-spectra of the dibenzoyl derivative(9) with that of (S)-leucinol derivative(10). (2S)-9 like (2S)-10 showed positive Cotton effect (270-210nm, MeOH), while (2R)-10 showed negative Cotton effect.

In order to unambiguously confirm the molecular structure of 8, one of the diastereomers of (2R)-8 was benzoylated and recrystallized($CHCl_3$) to afford fine crystals of 11 for X-ray analysis(see Figure). Thus, 11 was confirmed to be (2R, 4R)-isomer. On the basis of this, the CD-spectra and ^{1}H-nmr spectra the absolute configuration of 8 was fully confirmed as indicated.







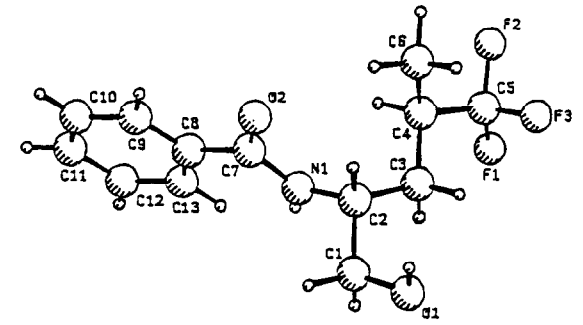


Fig. Molecular Structure of 11

As described in this report an efficient resolution of the lactone(2) provides versatile trifluoromethylated chiral building-blocks[13,14] and further applications are currently being explored.

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4) The lactone(2) was prepared by hydrogenation(5% Pd-C, MeOH, 88%) or $NaBH_4$ reduction($EtOH-H_2O-Et_2O$, -10-0°C, 85%) of 4-trifluoromethyl-2(5H)-franone.[5]

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6) Absolute configuration indicated is correlated to the leucinol derivatives (8) determined by the CD-spectra and X-ray analysis.

7) Tlc was performed by Merck Kieselgel $60PF_{254}$(0.25 mm thickness) using the solvent system of hexane-AcOEt(1:2). It is noted that the increment of the acidity of the hydroxyl group of 3 to facilitate the separation of diastereomers by column chromatography may be of importance as we compared the resolution factor of 3 with that of the hydroxyamide having CH_3 group instead of CF_3 group as well as those of other substitutents[X=H, OAc, SPh, or SO_2Ph, Y=$CH_2CONHCH(CH_3)Ph$] in 1.

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10) (2S, 4S)-7: $[\alpha]_D^{20}$-16.3° (c 1.29, H_2O) [lit. -17.0° (c 1, H_2O)][3]; (2R, 4S)-7: $[\alpha]_D^{20}$-17.45° (c 1.29, H_2O); (2S, 4R)-7: $[\alpha]_D^{23}$+17.73° (c 1.01, H_2O) [lit, +17.6° (c 1, H_2O)][3]; (2R, 4R)-7: $[\alpha]_D^{23}$+17.1° (c 1.06, H_2O).

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12) (2R, 4S)-8: ^{1}H-NMR(D_2O)δ 1.215(3H, d, J=6.9Hz), 1.725(1H, ddd, J=5.4, 9.4 and 14.2Hz), 2.109(1H, ddd, J=4.9, 9.3 and 14.2Hz), 2.542(1H, m), 3.544 (1H, m), 3.702(1H, dd, J=6.2 and 12.6Hz), 3.899(1H, dd, J=3.4 and 12.6Hz); (2S, 4S)-8: ^{1}H-NMR(D_2O)δ 1.199(3H, d, J=6.9Hz), 1.732(1H, ddd, J=6.2, 8.5 and 14.8Hz), 2.015(1H, ddd, J=5.6, 8 and 14.8Hz), 2.533(1H, m), 3.52(1H, m), 3.688(1H, dd, J=6.6 and 12.4Hz), 3.889(1H, dd, J=3.7 and 12.4Hz).

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