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Highly stereoselective route to aldol products incorporating fluorinecontaining methyl groups starting from a single D-glucose-derived intermediate

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Abstract: Chiral aldol structures with fluorine modifications on a methyl group have been realized by utilization of the relatively rigid cyclic intermediates from the very common chiral pool compound, D-glucose, leading to attainment of the high diastereoselectivities as well as construction of differently fluorinated target materials from a single intermediate. © 1997 Elsevier Science Ltd

Substitution of an appropriate hydrogen atom or a hydroxy moiety for fluorine has recently been one of the major strategies for realizing the effective modification or enhancement of the inherent biological activities of organic compounds.¹ The well-known aldol structure would be one of the most interesting frameworks for investigating the effect of fluorine introduction at a methyl group on the basis that such a structure is widely found in the important naturally occurring biologically active substances. However, to the best of our knowledge, very few instances² can be found in the literature of the construction of this specific structure mainly because of the less ready availability³ as well as the inherent instability towards basic conditions of the requisite 3-fluorinated propionyl derivatives (Figure 1). These reasons are easily understood in terms of the electron-withdrawing nature of fluoroalkyl groups and, at the same time, the ability of fluoride as a leaving element. On the other hand, application of the traditional fluorination techniques⁴ or the direct introduction methods of fluorine-containing groups⁵ would not be recognized as the alternative solution for our purpose in view of the still unsolved problems on the regio-, stereo-, and/or chemoselectivities.

We have focused our attention to prepare various types of optically active fluorinated building blocks,⁶ and would like to report in this communication the highly diastereoselective entry of fluorine-containing methyl groups ($CH_{3-n}F_n$, n:1, 2, or 3) via the homochiral common intermediate from the readily available chiral pool, D-glucose. As far as we know, this is the first synthesis of chiral aldol structures with one to three fluorines on the methyl group.⁷

Key intermediate 2 was prepared by way of Wittig type CF_2Br_2-HMPT system⁸ from easily accessible methyl 4,6-O-benzylidene- α -D-glucopyranoside 1.⁹ Hydrogenation of 2 in the presence of 10% Pd/C realized the smooth transformation into the diffuoromethylated material 3 as a single stereoisomer with the benzylidene acetal part intact (Scheme 1). The stereochemistry at the newly created 3 position was deduced from its ¹H NMR: the coupling constants of H⁴-H⁵ and H³-H⁴ of



Figure 1.

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10.0 Hz and 2.9 (or 4.9) Hz, respectively, demonstrated the axial-axial relationship for the former and, thus, the equatorial position of hydrogen at the diffuoromethyl attached carbon atom.



a: n-Bu₂SnO/MeOH, b: BzCl, c: Swern ox. (or PDC), d: CF₂Br₂, HMPT, e: Pd/C, H₂/AcOEt f: DIBALH, g: Red-Al, h: DAST, i: AcOH/H₂O, heat, j: TrCl, Et₃N/CH₂Cl₂, k: TFA/MeOH-H₂O

Scheme 1.

The corresponding monofluoromethylated material was also prepared in a similar way. In this case, the partial reduction of a difluoromethylene group is required before palladium-mediated hydrogenation. At first, Red-Al¹⁰ was employed for this purpose, while the S_N2' type reaction unexpectedly occurred to exclusively furnish the *endo*-olefin 4 (Scheme 1). On the other hand, DIBALH was proved to be effective only for the reductive cleavage of the benzoyl group at 2 position and the resultant intermediary alcohol was further reduced with Red-Al to the desired monofluoromethylenated form 5 as a 61:39 mixture (stereochemistry not determined). Hydrogenation of thus prepared alcohol 5 smoothly proceeded in a highly stereoselective manner to yield 6 again as a sole product. Hydrolytic removal of the benzoyl moiety before the formation of a monofluoromethylene group was also tried under such usual conditions as K_2CO_3 in MeOH (decomposition), LiOOH (no reaction), or aqueous NaOH under diluted condition¹¹ (89% yield but with problems of reproducibility), but DIBALH was eventually found out to be the reagent of choice for this purpose. Stereochemistry of the newly created 3 position was determined by ¹H NMR analysis of H² which was observed at 3.91 ppm with coupling constants of 10.7, 5.5, 3.8 Hz (between H²–OH, H²–H³, and H²–H¹, respectively), concluding the axial location of the monofluoromethyl group.

Now, with homochiral mono- as well as diffuoromethylated glucose derivatives in hand, our attention turned to the preparation of the corresponding trifluoromethylated counterparts. Tellier and Sauvêtre previously reported¹² the efficient transformation of γ , γ -difluoroallylic alcohols into the corresponding trifluorinated internal olefins by DAST (diethylaminosulfur trifluoride; Et₂NSF₃)-mediated S_N2' type

addition of fluoride ion. Application of this method to the compound 2 would be quite interesting because of the availability of hydroxy equivalent functions located at 2 as well as 4 positions with different protective groups, both possibly leading to the formation of stereoisomers from the same intermediate. The desired fluorination occurred quite smoothly to furnish the *endo*-olefins 7 and 8 in 96 and 83% yields, respectively. Hydrogenation of these substrates 7 and 8 was carried out after cleaving the protective groups at 4 and/or 6 positions for eliminating the possible contamination of the deprotection products along with the desired transformation. Compound 7, after acidic removal of the benzylidene acetal, was converted to 9 in 70% yield as a 3:1 diastereomer mixture at the 3 position along with a small amount of unidentified compounds. On the other hand, the similar procedure for 8 led to the formation of 10 in 91% yield as a single stereoisomer. Stereochemistry of these products 9 and 10 was determined on the basis of the close examination of ¹H NMR coupling constants of the major products, $H^2_{ax}-H^3$ of 13.4 Hz for the former and $H^2_{ax}-H^3$ of 11.2 Hz as well as $H^4_{ax}-H^3$ of 12.8 Hz for the latter, unambiguously proved the existence of the axial hydrogen at 3 position in both instances.

Thus obtained fluorine-containing homochiral sugar derivatives would be readily transformed into the corresponding acyclic forms, and one representative example starting from 3 was shown in Scheme 2. Stepwise deprotection and protection finally afforded the monoalcohol 11 possessing 2,3-anti-3,4-anti configuration, whose potential structural symmetry increases its utility as the corresponding enantiomeric form for these stereogenic centers.



Scheme 2.

As described above, a novel preparation of homochiral mono-, di-, as well as trifluoromethylated aldol structures starting from the readily available chiral pool compound, D-glucose, has been demonstrated. Further synthetic utilizations of optically active materials shown in Scheme 1 as well as the investigation of the similar reaction at the different sites (2 or 4 positions) are under way in our laboratory.

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