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Highly stereoselective route to aldol products incorporating fluorine-containing 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.
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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 instances[2] can be found in the literature of the construction of this specific structure mainly because of the less ready availability[3] 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 techniques[4] or the direct introduction methods of fluorine-containing groups[5] 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 system[8] 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 difluoromethylated 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 H^4–H^5 and H^3–H^4 of

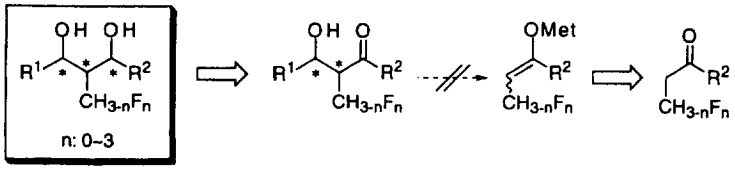

Figure 1.

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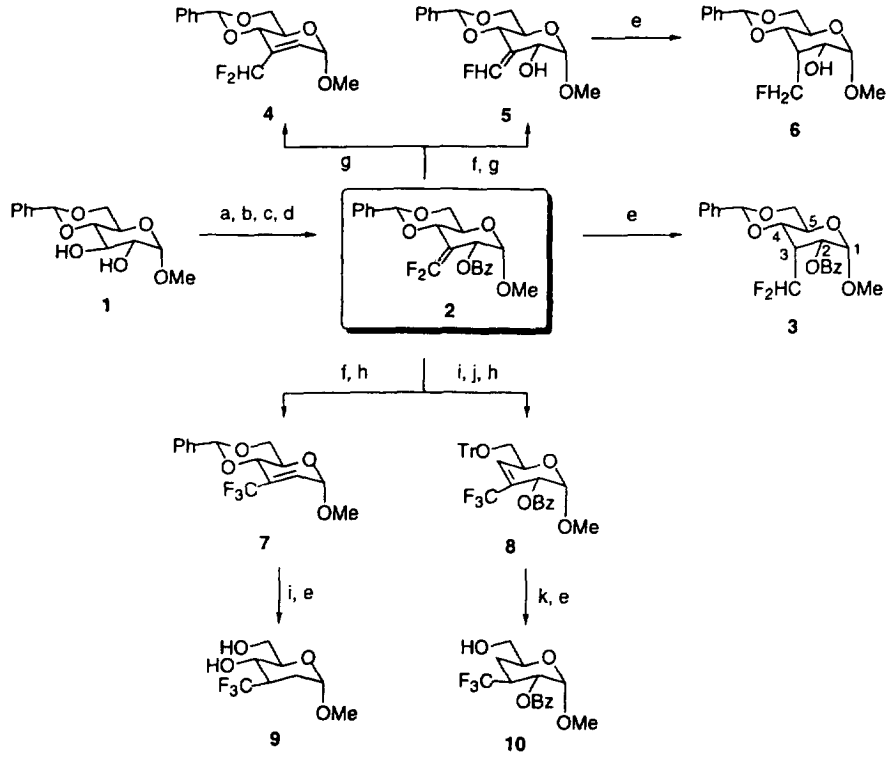
10.0 Hz and 2.9 (or 4.9) Hz, respectively, demonstrated the axial–axial relationship for the former and, thus, the equatorial position of hydrogen at the difluoromethyl attached carbon atom.



a: *n*-Bu_2SnO/MeOH, b: BzCl, c: Swern ox. (or PDC), d: CF_2Br_2, HMPT, e: Pd/C, H_2/AcOEt
f: DIBALH, g: Red-Al, h: DAST, i: AcOH/H_2O, heat, j: TrCl, Et_3N/CH_2Cl_2, k: TFA/MeOH-H_2O

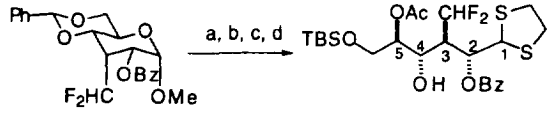
Scheme 1.

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-Al[10] 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 condition[11] (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 H^2 which was observed at 3.91 ppm with coupling constants of 10.7, 5.5, 3.8 Hz (between H^2–OH, H^2–H^3, and H^2–H^1, respectively), concluding the axial location of the monofluoromethyl group.

Now, with homochiral mono- as well as difluoromethylated glucose derivatives in hand, our attention turned to the preparation of the corresponding trifluoromethylated counterparts. Tellier and Sauvêtre previously reported[12] the efficient transformation of γ,γ-difluoroallylic alcohols into the corresponding trifluorinated internal olefins by DAST (diethylaminosulfur trifluoride; Et_2NSF_3)-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 ^{1}H 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.



3 **11**

a: BBr_3/CH_2Cl_2, b: $(HSCH_2)_2$, $BF_3{\cdot}OEt_2/CH_2Cl_2$
c: TBSCl, imidazole/CH_2Cl_2, d: AcCl, py./CH_2Cl_2

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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References

1. V. P. Kukhar' and V. A. Soloshonok, *Fluorine-containing Amino Acids Synthesis and Properties*; John Wiley & Sons: New York, 1995; G. Resnati, *Tetrahedron*, **1993**, *42*, 9385; J. T. Welch and S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, John Wiley & Sons: New York, 1990.
2. T. Konno, T. Yamazaki and T. Kitazume, *Tetrahedron*, **1996**, *52*, 199; T. Hanamoto and T. Fuchikami, *J. Org. Chem.*, **1990**, *55*, 4969; T. Yokozawa, N. Ishikawa and T. Nakai, *Chem. Lett.*, **1987**, 1971; T. Yokozawa, M. Yamaguchi, T. Nakai and N. Ishikawa, *Nippon Kagakukai Shi*, **1985**, 2202; T. Yokozawa, N. Ishikawa and T. Nakai, *Tetrahedron Lett.*, **1984**, *25*, 3987.
3. H. Yamanaka, T. Takekawa, K. Morita and T. Ishihara, *Tetrahedron Lett.*, **1996**, *37*, 1829; G.-Q. Shi, X.-H. Huang and F. Hong, *J. Chem. Soc., Perkin Trans 1*, **1996**, 763; K. Iseki, T. Nagai and

Y. Kobayashi, *Tetrahedron Lett.*, **1993**, *34*, 2169; J.-P. Bouillon, C. Maliverney, R. Merényi and H. G. Viehe, *J. Chem. Soc. Perkin Trans. 1*, **1991**, 2147; Q.-Y. Chen and S.-W. Wu, *J. Chem. Soc., Chem. Commun.*, **1989**, 705; I. Rico, D. Cantacuzène and C. Wakselman, *Tetrahedron Lett.*, **1981**, *22*, 3405.

4. M. Hudlicky, *Org. React.*, **1988**, *35*, 513; C.-L. J. Wang, *Org. React.*, **1985**, *34*, 31.
5. T. Hagiwara and T. Fuchikami, *Synlett*, **1995**, 717; R. Krishnamurti, D. R. Bellew and G. S. K. Prakash, *J. Org. Chem.*, **1991**, *56*, 984; T. Umemoto and S. Ishihara, *Tetrahedron Lett.*, **1990**, *31*, 3579; P. G. Gassman and N. J. O'Reilly, *J. Org. Chem.*, **1987**, *52*, 2481; T. Kitazume and N. Ishikawa, *J. Am. Chem. Soc.*, **1985**, *109*, 5186.
6. N. Shinohara, J. Haga, T. Yamazaki, T. Kitazume and S. Nakamura, *J. Org. Chem.*, **1995**, *60*, 4363; K. Mizutani, T. Yamazaki and T. Kitazume, *J. Chem. Soc., Chem. Commun.*, **1995**, 51; T. Yamazaki, H. Iwatsubo and T. Kitazume, *Tetrahedron: Asym.*, **1994**, *5*, 1823.
7. Very recently, the similar type of structure was reported. See the following: T. F. Herpin, J. S. Houlton, W. B. Motherwell, B. P. Roberts and J.-M. Weibel, *Chem. Commun.*, **1996**, 613; S. Lavaire, R. Plantier-Royon and C. Portella, *J. Carbohydr. Chem.*, **1996**, *15*, 361; P. Munier, M.-B. Giudicelli, D. Picq and D. Anker, *J. Carbohydr. Chem.*, **1996**, *15*, 739; U. Wucherpfennig, T. A. Logothetis, U. Eilitz and K. Burger, *Tetrahedron*, **1996**, *52*, 131; T. Konno, H. Umetani and T. Kitazume, *J. Org. Chem.*, **1997**, *62*, 137.
8. W. A. Vinson, K. S. Prickett, B. Spahic and P. R. O. de Montellano, *J. Org. Chem.*, **1983**, *48*, 4661.
9. D. M. Hall, *Carbohydr. Res.*, **1980**, *86*, 158.
10. S. Hayashi, T. Nakai, N. Ishikawa, D. J. Burton, D. G. Naae and H. S. Kesling, *Chem. Lett.*, **1979**, 983.
11. E. J. Buuene, A. J. Huggard and J. C. Tatlow, *J. Chem. Soc. C*, **1952**, 735.
12. F. Tellier and R. Sauvêtre, *J. Fluorine Chem.*, **1993**, *62*, 183.

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