Tetrahedron: Asymmetry Vol. 4, No. 5, pp. 1059-1062, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

Preparation of 6-Deoxy-6,6,6-trifluoro-D-mannose and D-Allose from Enzymatically Resolved 2-Butenolides

Takashi Yamazaki,* Kenji Mizutani, and Tomoya Kitazume*

Department of Bioengineering, Tokyo Institute of Technology, Nagatsuta, Midori-ku,Yokohama 227, Japan

(*Received* 18 *January* 1993)

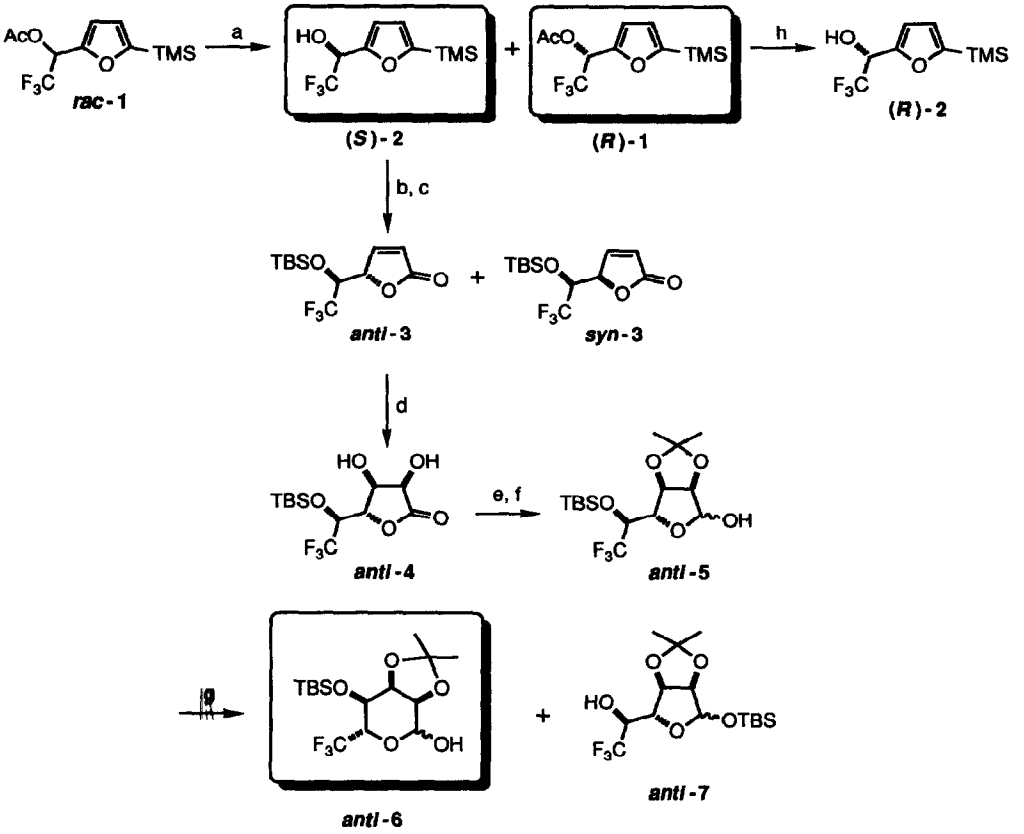
Abstract: Both 6-deoxy-6,6,6-trifluoro-D-mannose and D-allose, possessing a diastereomeric relationship, were conveniently prepared from trifluorinated 2-butenolides, which was prepared via the enzymatic resolution with high efficiency.

6-Deoxy sugars are recognized as one of the most important class of materials because a various type of naturally occurring antibiotics contain such sugars, which also play a significant role on their biological activities or stabilities.[1] On the other hand, in connection with the fact that introduction of fluorine(s) is the widely accepted strategy for the modification of biological activities,[2] many kinds of fluorine-containing sugars have been reported thus far, while most of them have been the ones possessing only one or two fluorines in their framework.[3] This is mainly because such mono- or difluorosugars are relatively easy to be obtained through the well developed fluorination methodology by employing such a reagent as DAST[4] (Et_2NSF_3) for the transformation of a carbonyl group (ketones or aldehydes) to difluoromethylene or difluoromethyl groups, respectively, or alkaline metal fluorides[5] for the preparation of monofluorinated compounds via, for example, the corresponding tosylates in a high degree of retention of stereochemistry. However, the corresponding trifluoromethyl analogs have been rare in the literature,[6] which might stem from the fact that there are no convenient method for their construction in stereo- as well as chemoselective manners. Our basic strategy to prepare compounds with this group is the employment of the appropriately functionalized chiral building blocks,[7] and here, during our continuing study, the authors would like to describe our result for the preparation of 6-deoxy-6,6,6-trifluoro-D-mannose and D-allose from the same starting material, trifluorinated 2-butenolide ***anti*-3** obtained from the corresponding furanol **2** by highly efficient enzymatic resolution.[8]

The key intermediate in the present study, 2-butenolide ***anti*-3**[8] was prepared as shown in Scheme 1. The asymmetric transformation of ***rac*-1** by lapse PS (Amano Pharmaceutical Co., Japan) showed its *E* value of 189, suggesting the very effective optical resolution. Thus, at 50% conversion, 50% (98% ee) of (***S*)-2** and 48% (94% ee) of (***R*)-1** were obtained after silica gel chromatography. The former was silylated as usual (93% yield) and was further oxidized by the modified Kuwajima-Urabe procedure[9] to furnish the desired trifluoromethylated 2-butenolide **3** as a 1:1 diastereomer mixture. For the purpose of obtaining one of the either isomer selectively, this mixture (***syn*- and *anti*-3**) was subjected under the basic conditions (treated with LDA at -78 °C, followed by quenching the reaction mixture by acetic acid) to be successfully epimerized at their γ-position and 84% of *anti*-selectivity was attained (89% yield). Another important material, ***anti*-4**, was also produced by oxidation with potassium permanganate in the presence of a catalytic amount of 18-crown-6[10] with excellent diastereoselectivity[11] (42% yield with recovery of 33% of ***anti*-3**). This would be the reflection of the effective shielding of the butenolide ring by such a sterically demanding substituent as 1-*t*-butyldimethylsiloxy-2,2,2-trifluoroethyl group.

The access to the CF_3 analog of D-allose from ***anti*-4** was realized by the ready three-step process. Thus,

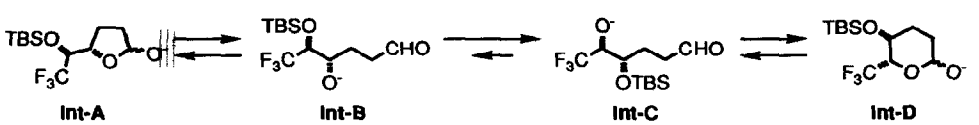
Scheme 1



a) lipase PS, b) TBSCl, imidazole, c) MMPP / AcOH, d) $KMnO_4$, cat. 18-crown-6
e) $Me_2C(OMe)_2$, H^+, f) DIBALH, g) $KOBu^t$, h) K_2CO_3, MeOH

protection of diol function of ***anti*-4** as its acetonide followed by the DIBALH reduction furnished ***anti*-5**, which was then subjected to the previously reported base-promoted isomerization conditions (Scheme 2).[12] The driving force of this process is assumed to be the difference of the alkoxide stability between **Int-B** and **Int-C**, the latter being more favorable due to the effect of the strongly electron withdrawing CF_3 group and eventually recyclized to be converted to **Int-D**. The sequence shown in Scheme 1 transformed ***anti*-5** into a mixture of the desired product ***anti*-6**,[13] starting material ***anti*-5**, and another type of TBS migration product ***anti*-7** in 35, 46, and 17% yield, respectively. The lower yield might be explained by the rigidity of the molecule due to the fused

Scheme 2



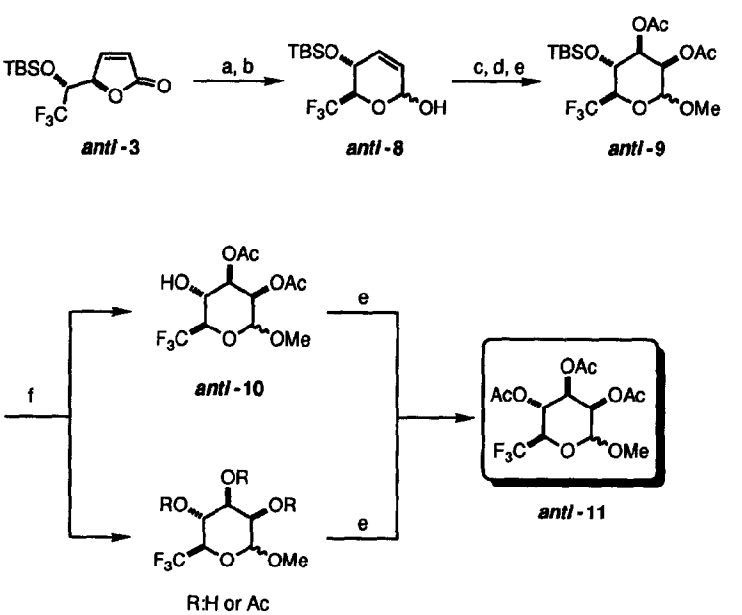
acetonide five-membered ring prohibiting the smooth ring opening (see, for example, the step from **Int-A** to **Int-B** in Scheme 2) , which is in sharp contrast to the previous cases observed for the preparation of D-amicetose and D-rhodinose with a CF_3 moiety. In spite of the lower conversion, since each product was easily separated by silica gel column chromatography, the recovered ***anti*-5** could be again subjected to the same reaction conditions.

On the other hand, the preparation of 6-deoxy-6,6,6-trifluoro-D-mannose requires dihydroxylation from the opposite olefinic face. From the mechanistic consideration, this might be solved by simply changing the order of dihydroxylation and isomerization steps: thus, if the transformation of ***anti*-3** into ***anti*-8** is successful, then a bulky TBSO moiety would cover the β-face of the latter and the proximity of potassium permanganate to the less hindered α-face could realize the construction of the desired stereostructure (Scheme 3).

This hypothesis was in fact verified as depicted in Scheme 3. DIBALH reduction of ***anti*-3** followed by the action of $KOBu^{-t}$ effected the isomerization to furnish ***anti*-8** in 63% yield along with the lactol from ***anti*-3**[14] (33% yield). After separation and derivatization into methyl glycoside, permanganate oxidation has led to a stereochemically pure diol as our expectation (55% yield and 14% of recovery) and the product was isolated as the diacetate form (***anti*-9**). Desilylation of ***anti*-9** afforded ***anti*-10** (62%) along with a mixture of unidentified materials. The fact that this mixture and ***anti*-10**, after separation, were acetylated to produce the same compound ***anti*-11**[13] allowed us to speculate that the above unknown mixture was consisted from regioisomeric acetates as described in Scheme 3 (92% total yield for the deprotection-acetylation steps).

The present work describes the novel and easy pathway to access both trifluoromethylated 6-deoxy-D-mannose (D-rhamnose) and D-allose in a highly stereoselective manner via the base-promoted TBS migration as the key step. The preparation of other deoxy-6,6,6-trifluorinated sugars are in progress in our laboratory, whose results as well as the full detail of this work will be published elsewhere.

Scheme 3



a) DIBALH, b) $KOBu^{-t}$, c) MeOH, H^+, d) $KMnO_4$, cat. 18-crown-6,

e) Ac_2O, pyr, f) TBAF

References

1) *Bioactive Carbohydrates in Chemistry, Biochemistry, and Biology*, Kennedy, J. F.; White, C. A., Eds.; Ellis Horwood: Chichester, 1983; Chapter 12.
2) a) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*, John Wiley & Sons: New York, 1991. b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123-3197. c) Filler, R.; Kobayashi, Y. *Biomedical Aspects of Fluorine Chemistry*; Kodansha & Elsevier Biomedical: Tokyo, 1982.
3) For a review, see a) Tsuchiya, T. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 91-277. b) *Fluorinated Carbohydrates Chemical and Biochemical Aspects* (ACS symposium Series No. 374), Taylor, N. F., Ed; ACS: Washington, D. C., 1988.
4) Hudlicky, M. *Org. React.* **1988**, *35*, 513-637.
5) Sharts, C. M.; Sheppard, W. A. *Org. React.* **1974**, *21*, 125-406.
6) a) Bansal, R. C.; Dean, B.; Hakomori, S.; Toyokuni, T. *J. Chem. Soc., Chem. Commun.* **1991**, 796-798. b) Hanzawa, Y.; Uda, J.; Kobayashi, Y.; Ishido, Y.; Taguchi, T.; Shiro, M. *Chem. Pharm. Bull.* **1991**, *39*, 2459-2461. c) Differding, E.; Frick, W.; Lang, R. W.; Martin, P.; Schmit, C.; Veenstra, S.; Greuter, H. *Bull. Soc. Chim. Berg.* **1990**, *99*, 647-671.
7) a) Kitazume, T.; Yamazaki, T. In *Selective Fluorination in Organic and Bioorganic Chemistry* (ACS Symposium Series No. 456), Welch, J. T., Ed.; ACS, Washington, D. C., 1991, Chapter 12. b) Yamazaki, T.; Haga, J.; Kitazume, T. *Chem. Lett.* **1991**, 2175-2178. c) Yamazaki, T.; Okamura, N.; Kitazume, T. *Tetrahedron : Asymmetry* **1990**, *1*, 521-524.
8) Yamazaki, T.; Mizutani, K.; Takeda, M.; Kitazume, T. *J. Chem. Soc., Chem. Commun.* **1992**, 55-57. Some figures in this communication were incorrectly drawn. See, *J. Chem. Soc., Chem. Commun.* **1992**, 796 on their correction. The full detail will be also published elsewhere.
9) Kuwajima, I.; Urabe, H. *Tetrahedron Lett.*, **1981**, *22*, 5191-5194.
10) Mukaiyama, T.; Tabusa, F.; Suzuki, K. *Chem. Lett.* **1983**, 173-174.
11) Only one isomer with the depicted stereochemistry was obtained.
12) For the related silyl migration reactions, see the following. a) Mulzer, J.; Schöllhorn, B. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 431-432 (with a *t*-butyldiphenylsilyl group). b) Jones, S. S.; Reese, C. B. *J. Chem. Soc. Perkin Trans. 1* **1979**, 2762-2764 (with a *t*-butyldimethylsilyl group). See also, Watanabe, Y.; Fujimoto, T.; Ozaki, S. *J. Chem. Soc., Chem. Commun.* **1992**, 681-683.
13) ***anti*-6**: mp 87.5-88.0 °C. ^{1}H NMR δ 0.08 and 0.11 (3 H each, s, Si(C*H*$_3$)$_2$), 0.88 (9 H, s, C(C*H*$_3$)$_3$), 1.33 and 1.50 (3 H each, s, C(C*H*$_3$)$_2$), 3.26 (1 H, d, *J* = 3.85 Hz, O*H*), 4.12 and 4.43 (1 H each, dd and m, *J* = 3.12, 6.80 Hz, C*H*CHCHOH), 4.16 (1 H, dq, *J* = 8.60, 7.21 Hz, CF$_3$C*H*), 4.47 (1 H, dd, *J* = 2.75, 8.51 Hz, CF$_3$CHC*H*), 5.02 (1 H, t, *J* = 3.45 Hz, C*H*OCH$_3$). ^{13}C NMR δ -4.99 and -4.70 (s each, Si(*C*H$_3$)$_2$), 18.02 (s, *C*(CH$_3$)$_3$), 24.84 and 26.78 (s each, C(*C*H$_3$)$_2$), 25.61 (s, C(CH$_3$)$_3$), 64.47, 74.17, and 76.08 (s each, *C*HCHCHCHOCH$_3$), 71.12 (q, *J* = 29.6 Hz, CF$_3$*C*H), 93.98 (s, *C*HOCH$_3$), 112.50 (s, *C*(CH$_3$)$_2$), 123.53 (q, *J* = 281.8 Hz, *C*F$_3$). ^{19}F NMR δ 4.2 (d, *J* = 6.2 Hz). IR (KBr) ν 3400, 3000, 2950, 2900, 2875. HRMS calcd for C$_{15}$H$_{28}$F$_3$O$_5$Si *m/e* (M+H) 373.1658, found 373.1660. ***anti*-11**: R$_f$ 0.49 (AcOEt:Hex = 1:2). ^{1}H NMR δ 2.01, 2.05, and 2.17 (3 H each, s, C(O)C*H*$_3$), 3.47 (3 H, s, OC*H*$_3$), 4.15 (1 H, ddq, *J* = 0.59, 9.83, 6.00 Hz, CF$_3$C*H*), 4.81 (1 H, d, *J* = 1.84 Hz, C*H*OCH$_3$), 5.24 (1 H, dd, *J* = 1.79, 3.36 Hz, C*H*CHOCH$_3$), 5.35 (1 H, dd, *J* = 3.40, 9.93 Hz, C*H*CHCHOCH$_3$), 5.54 (1 H, t, *J* = 9.84 Hz, CF$_3$CHC*H*). ^{13}C NMR δ 20.51, 20.63, and 20.83 (s each, C(O)*C*H$_3$), 55.89 (s, OCH$_3$), 64.04, 68.33, and 68.84 (s each, CF$_3$CHCHCHCH), 68.33 (q, *J* = 31.3 Hz, CF$_3$CH), 98.68 (s, *C*HOCH$_3$), 123.32 (q, *J* = 280.3 Hz, *C*F$_3$), 169.16, 169.82, and 170.04 (s each, *C*=O). ^{19}F NMR δ 5.4 (d, *J* = 6.9 Hz). IR (neat) ν 2950, 2850, 1765, 1750. HRMS calcd for C$_{13}$H$_{18}$F$_3$O$_8$ *m/e* (M+H) 359.0953, found 359.0977.
14) The lactol from ***anti*-3** itself could not be recovered because of its unstable nature under the isolation conditions, giving furan shown in the right.