Novel Stereoselective Syntheses of Chiral 2,6-Dideoxy-6,6,6-trifluoro Sugars *via* Enzymatic Resolution of Trifluoromethylated Propynylic Alcohol

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All stereoisomers of homochiral 2,6-dideoxy-6,6,6-trifluoro sugars are conventionally synthesized from the same optically pure CF_3-containing propynylic alcohol *via* the novel one-pot reaction of 2-bromo-3,3,3-trifluoropropene, followed by optical resolution by enzymatic esterification.

In recent years, the unique biological properties of fluorinated compounds have promoted the development of methods for their syntheses.[1] The study of fluorinated sugars is especially attractive because their nonfluorinated counterparts are found in many naturally occurring bioactive compounds.[2] Many publications have appeared concerning mono- or di-fluorinated sugars and their interesting biological characteristics have also been reported.[3] In contrast, there are few reports on sugars with a CF_3 group directly attached to the ring system.[4,5] It is expected that the stronger electron-withdrawing nature of this group, compared with mono- or di-fluoromethyl moieties, might have a greater influence on the neighbouring functionalities. We have already reported syntheses of several chiral 6-deoxy-6,6,6-trifluorosugars.[5] However, our previous methods required longer reaction steps and the types of structure accessible were limited. We now describe our preliminary results on the preparation of 2,6-dideoxy-6,6,6-trifluoro sugars *via* a different route, to produce compounds that were hitherto inaccessible.

Our basic strategy is shown in Fig. 1. The target CF_3-sugars can be conveniently obtained from triols **I** *via* 'direct (one-step)' regioselective protection and oxidation. This unique strategy is based on the characteristics of the strongly electron-withdrawing CF_3 group: since it affects the nature of the neighbouring functionalities only in an inductive manner, the closest hydroxy function should be the least nucleophilic and most resistant to oxidation. For the preparation of triols **1**, we selected propynylic alcohol **II** as the starting material owing to its accessibility from allylic alcohols with both *E*- and *Z*-configurations, and the possibility of introduction of the requisite two hydroxy groups by use of their carbon–carbon double bonds. Therefore, at least two diastereoisomeric triols **I** should be obtained from the same chiral propynylic alcohol **II** after enzymatic optical resolution.

In general, for the preparation of trifluoromethylated propynylic alcohols like **3**, the expensive 3,3,3-trifluoropropyne has been employed as the starting material.[6] Here, a novel efficient method was developed using 2-bromo-3,3,3-trifluoropropene **1** obtained from the much less expensive 3,3,3-trifluoropropene.[6b] Treatment of **1** with 2 equiv. of lithium diisopropylamide (LDA) gave lithium acetylide which was smoothly trapped with the aldehyde **2** to furnish the desired racemic propynylic alcohol **3** in 92% yield (Scheme 1).

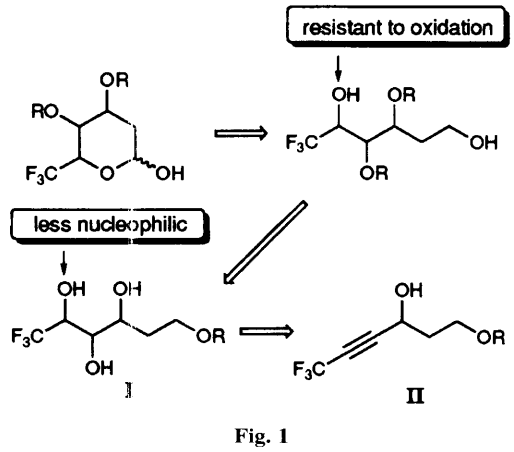
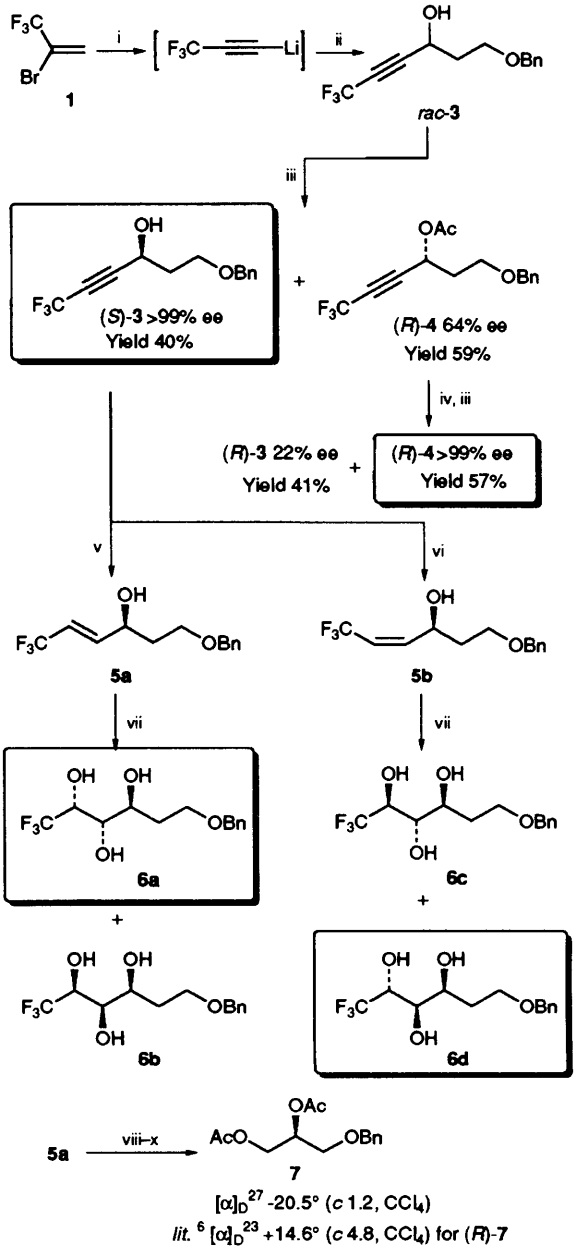


Fig. 1

Enzymatic optical resolution of this alcohol was achieved by using lipase QL (*Alkaligenes sp.*, Melto Sangyo Co., Ltd., Japan) in *n*-hexane (0.5 mol dm^{-3}) with vinyl acetate (2 equiv.) at 40 °C for 12 h, which afforded the (*S*)-alcohol **3** and (*R*)-acetate **4** at 60% conversion (E = 20). After hydrolysis of **4** with K_2CO_3–MeOH, further enzymatic esterification using the same lipase gave optically pure (*R*)-**4**. The absolute configuration was



Scheme 1 *Reagents and conditions*: i, 2 equiv. LDA; ii, $BnOCH_2CH_2$-CHO **2**; iii, lipase QL, vinyl acetate–*n*-hexane; iv, K_2CO_3–MeOH; v, Red-Al; vi, Lindlar cat., H_2; vii, cat. OsO_4, NMO; viii, O_3; ix, LAH; x, AcCl, pyridine

determined by comparison of the optical rotation with the literature[7] after conversion into the known diacetate **7**.

The optically active propynylic alcohol (*S*)-**3** was reduced to the *E*-allylic alcohol **5a** by treatment with Red-Al at −78 °C in toluene (92%). The hydrogenolysis of **3** with Lindlar catalyst gave *Z*-allylic alcohol **5b** in 96% yield.

Several attempts at the diastereoselective dihydroxylation of the unsaturated bonds in **5a,b** failed, presumably because of their low electrophilicity, except for the catalytic OsO_4 reaction (Scheme 1). It has been reported that the relative stereochemistry of the major isomer by this process is consistently *anti* between the original hydroxy group and the newly introduced one at the adjacent carbon, irrespective of the stereochemistry of the starting allylic alcohols.[8] This dihydroxylation of **5a** furnished an 86:14 separable diastereoisomeric mixture of triols **6a** and **6b**. The relative configuration of **6a** was assumed to be 3,4-*anti* from the coupling constants of the corresponding 1,3-dioxanes. In contrast, *Z*-isomer **5b** gave **6d** as the major isomer (**6c**:**6d**, 26:74) with the unexpected 3,4-*syn* configuration. The reason for this opposite facial selectivity† is not clear at present.

As discussed above, for the one-step differentiation of the three hydroxy groups, thermodynamic conditions would be appropriate, thus we selected acetonide formation. Compound **6a** was successfully converted into the desired 1,2-acetonide **8** in 91% yield (the corresponding 1,3-acetonide was obtained in only 3% yield) (Scheme 2). After debenzylation of **8**, the primary alcohol of the resulting diol was oxidized by pyridinium dichromate (PDC) to afford a mixture of the desired **9** and the overoxidized lactone, which was transformed into **9** by treatment with diisobutylaluminium hydride (DIBAL-H) (77% from **8**). Thus, preparation of the CF_3 analogue of L-oliose was attained in only 4 steps from triol **6a**.

In the case of triol **6b**, a similar procedure cannot be employed because the hydroxy and carbonyl functions required for the cyclization are located *trans* to each other. So we have employed our previously reported silyl migration from a less nucleophilic hydroxy group to the other under thermodynamically controlled conditions.[4] *tert*-Butyldimethylsilyl (TBS) protection of **6b** afforded a mixture of bissilyl ethers, which, without purification, was successfully converted to the desired **10b** as the sole product (70% from **6b**, 22% of monosilyl ethers were recovered) by treatment with Bu^{t}OK in THF at −78 °C. Debenzylation, oxidation with PDC and reduction with DIBAL-H gave the CF_3-analogue of D-boivinose **11b** in 61% yield from **10b** (Scheme 2).

From an inseparable diastereoisomeric mixture of **6c** and **6d**, bissilylation and silyl migration afforded **10c** (24%) and **10d** (63%), and each bissilyl ether after separation was converted into **11c** (84%) and **11d** (83%) by the same procedure (Scheme 2).

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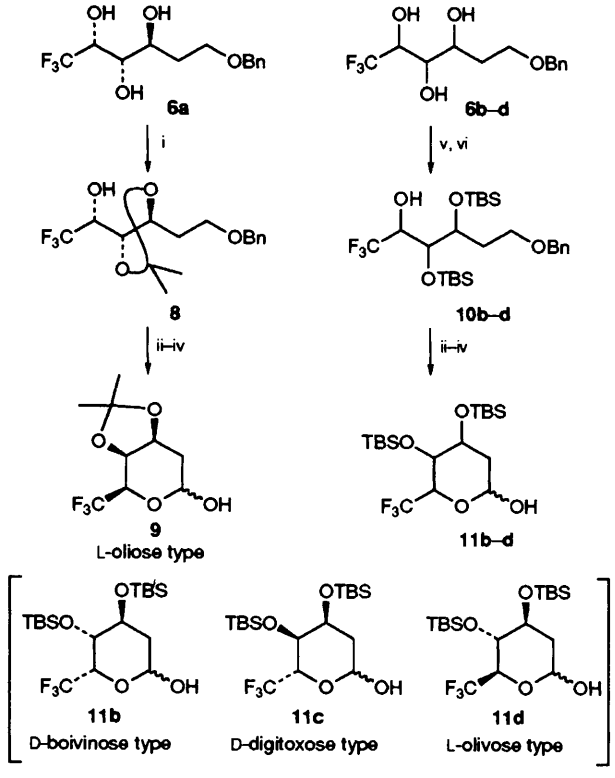

Scheme 2 *Reagents and conditions*: i, $Me_2C(OMe)_2$, H^+; ii, Raney Ni (W2), H_2; iii, PDC; iv, DIBAL-H; v, TBSCl, imidazole; vi, Bu^{t}OK

Footnote

† This type of facial selectivity was reported by Stork *et al.*[9]

References

1 J. T. Welch and S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley, New York, 1991; G. Resnati, *Tetrahedron*, 1993, **42**, 9385; J. T. Welch, *Selective Fluorination in Organic and Bioorganic Chemistry*, ACS Symposium Series 456, ACS, Washington DC, 1991.

2 T. Tsuchiya, *Adv. Carbohydr. Chem. Biochem.*, 1990, **48**, 91; *Fluorinated Carbohydrates*, ACS Symposium series 374, ed. N. F. Taylor, ACS, Washington DC, 1988.

3 For example, see: Y. Takagi, H.-I. Park, T. Tsuchiya, S. Umezawa, T. Takeuchi, K. Komuro and C. Nosaka, *J. Antibiot.*, 1989, **42**, 1315.

4 E. Differding, W. Frick, R. W. Lang, P. Martin, C. Schmit, S. Veenstra and H. Greuter, *Bull. Soc. Chim. Belg.*, 1990, **99**, 647; R. C. Bansal, B. Dean, S. Hakomori and T. Toyokuni, *J. Chem. Soc., Chem. Commun.*, 1991, 796; Y. Hanzawa, J. Uda, Y. Kobayashi, Y. Ishido, T. Taguchi and M. Shiro, *Chem. Pharm. Bull.*, 1991, **39**, 2459.

5 T. Yamazaki, K. Mizutani and T. Kitazume, *J. Org. Chem.*, 1993, **58**, 4246.

6 (*a*) D. J. Burton, Z.-Y. Yang and P. A. Morken, *Tetrahedron*, 1994, **50**, 2993; (*b*) F. G. Drakesmith, O. J. Stewart and P. Tarrant, *J. Org. Chem.*, 1968, **33**, 280.

7 M. H. Brookes and B. T. Golding, *J. Chem. Soc., Perkin Trans. 1*, 1988, 9.

8 J. K. Cha, W. J. Christ and Y. Kishi, *Tetrahedron*, 1984, **40**, 2247; E. Vedejs and W. H. Dent III, *J. Am. Chem. Soc.*, 1989, **111**, 6861; K. N. Houk, H.-Y. Duh, Y.-D. Wu and S. R. Moses, *J. Am. Chem. Soc.*, 1986, **108**, 2754; D. A. Evans and S. W. Kaldor, *J. Org. Chem.*, 1990, **55**, 1698; and references cited therein.

9 G. Stork and M. Kahn, *Tetrahedron Lett.*, 1983, **24**, 3951.