# Chiral Trifluoromethylated 2-Butenolides for the Construction of 6-Deoxy-6,6,6-trifluorosugars

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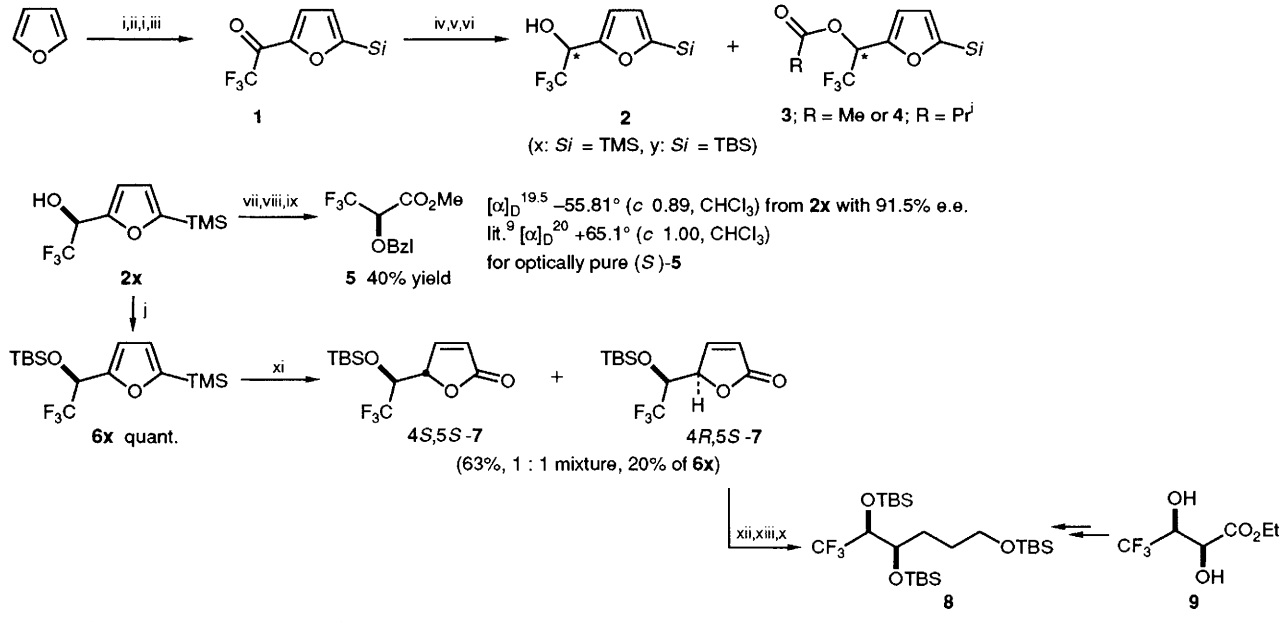
Optically active 2-butenolides with a trifluoromethyl ($CF_3$) group are synthesized *via* enzymatic optical resolution and are selectively transformed into 6,6,6-trifluororhodinose and amicetose by base-promoted 1,2-migration of a *tert*-butyldimethylsilyl moiety in a highly efficient manner.

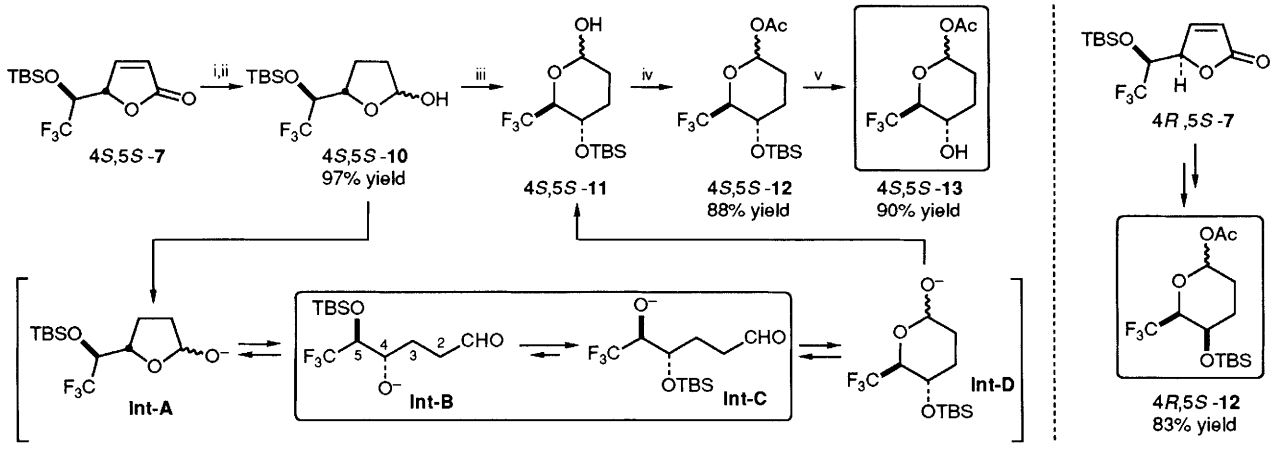
Mono- or di-fluorinated carbohydrates[1] or inositols,[2] sometimes showing excellent biological activities or enzymatic inhibitory effects,[3] are compounds of current interest, while few reports have appeared on the corresponding $CF_3$ analogues,[4] mainly owing to the difficulty in accessing such molecules without racemization *via* conventional fluorination methodology. This requires the design and construction of a new type of trifluoromethylated chiral building unit[5] to open an alternative route. Here, we would like to report the enzymatic synthesis of novel optically active butenolides with a $CF_3$ group derived from the corresponding furanols, which were further transformed into 6,6,6-trifluororhodinose and amicetose derivatives utilizing the 1,2-shift of a *tert*-butyldimethylsilyl group.

The synthetic pathway to the optically active furanols **2** is shown in Scheme 1. Repetitive anion generation by $Bu^nLi$ and its trapping by appropriate electrophiles such as trimethylsilyl- (TMS) or *tert*-butyldimethylsilyl- (TBS) chloride at the first stage and ethyl trifluoroacetate at the second stage in a one-pot manner efficiently afforded the ketones **1**.[6] These ketones were then reduced without further purification to furnish the racemic furanols **2**† in approximately 80% total yield and these products were subjected to the usual esterification condition to be converted into the substrates **3** and **4** for the enzymatic transformation. As shown in Table 1, excellent resolutions of both esters **3x** and **y** were realized by lipase PS to give chiral alcohols **2** with the (*S*)-configuration in 98 and >99% e.e. (enantiomeric excess) at 39 and 48% conversion, respectively. In the latter case, the corresponding enantiomer

† Furyl ketones **1** were stable enough to be isolated by distillation (b.p. 80–85 °C at 15 mmHg **1x** and 89–93 °C, 4 mmHg **1y**. Furanols **2** were found to possess a relatively unstable nature, which was highly dependent on the bulkiness of the attached *Si* moiety (stability decreased by the following order: TBS>TMS≫H). It is recommended to convert them into the stable hydroxyl-protected form such as esters (like compounds **3** or **4**) or silyl ethers (like compound **6**) when they are kept for more than 1 week.




**Scheme 1** i, Bu$^n$Li; ii, *Si*-Cl; iii, $CF_3CO_2Et$; iv, $NaBH_4$; v, RC(O)Cl, pyr.; vi, lipase; vii, NaH; BzlBr; viii, $O_3$; ix, $CH_2N_2$; x, TBS–Cl, imidazole; xi, MMPP–AcOH; xii, Pd/C, $H_2$; xiii, LAH; pyr = pyrrolidine; LAH = lithium aluminium hydride




**Scheme 2** i, Pd/C, $H_2$; ii, DIBAL-H; iii, KOBu$^t$; iv, $Ac_2O$, pyr.; v, TBAF (1.1 equiv); DIBAL-H = diisobutylaluminium hydride; tetrabutylammonium fluoride

with 94% e.e. was also obtained after hydrolysis of the recovered acetate, whose optical purity would be readily improved by further subjection to the enzymatic hydrolysis. Their absolute stereochemistries were assigned by the conversion of furanol **2x** from unreacted acetate by lipase PS to the known *O*-benzylated methyl 3,3,3-trifluorolactate **5**[9] as in Scheme 1, followed by comparison of their optical rotation values.

Conversion of the chiral furanol **2x** into butenolides **7** was investigated according to the previous literature[10] and MMPP‡ was found to be the reagent of choice (Scheme 1). This oxidative transformation allowed us to directly isolate 2-butenolide **7** as a 1 : 1 diastereoisomer mixture when **6x** was employed.§ Furthermore, hydrogenation and reduction of the more polar diastereoisomer 4*R*,5*S*-**7** after chromatographic separation and protection of the resultant two hydroxy groups by TBS–Cl furnished **8**. Assignment of its stereochemistry was successfully done by the comparison of its NMR data to that of the same compound derived from the structurally defined diol ester **9**.[5a]

As described earlier, the obtained butenolides would be expected to be useful chiral building blocks for the preparation of 6-deoxy-6,6,6-trifluorosugars[11] by the ring-opening cyclization process after derivatization into their lactol forms. On the other hand, since a TBS moiety at the hydroxy group in 4*S*,5*S*-**7** prohibits this isomerization, the utilization of this protective group would be the key to attaining a high selectivity between the furanose and the pyranose (4*S*,5*S*-**10** and 4*S*,5*S*-**11**). The base-promoted reaction (Scheme 2) might be expected to give the equilibration between **Int-A** and **Int-B**. However, owing to the influence of the strongly electron withdrawing $CF_3$ moiety, a TBS migration from the oxygen at C-5 to C-4 might be anticipated and would permit the second equilibration in favour of **Int-C** to **Int-B**, which leads to the pyranose sugar, 4*S*,5*S*-**11** *via* **Int-D**. For the verification of this hypothesis, the reaction was carried out under diluted conditions [0.05 mol $dm^{-3}$ in tetrahydrofuran (THF) at

‡ Magnesium monoperoxyphthalate (MMPP) purchased from Aldrich Co., Ltd.

§ Free alcohol or acetate instead of a TBS-protected form were not appropriate for the present reaction.[10] Details will be published elsewhere.

**Table 1** Enzymatic hydrolysis for the ester **3** or **4**[a]

| Ester | R | *Si*[b] | Lipase[c] | Conv. (%) | Time/h | Optical purity (% e.e.)[d] | E value[e] |
|---|---|---|---|---|---|---|---|
| **3x** | Me | TMS | MY | 52 | 23 | 64 (*R*) | 9 |
| **3x** | | TMS | PS | 39 | 9 | 98 (*S*) | 189 |
| **3y** | | TBS | MY | 52 | 47 | 46 (*R*) | 4 |
| **3y** | | TBS | PS | 48 | 22 | >99 (*S*) | 645 |
| **4x** | Pr$^i$ | TMS | MY | 33 | 40 | 77 (*R*) | 11 |
| **4x** | | TMS[f] | PS | 0 | 120 | — | — |
| **4y** | | TBS | MY | 40 | 56 | 27 (*R*) | 2 |
| **4y** | | TBS | PS | 26 | 117 | 97 (*S*) | 102 |

[a] The reaction was conducted on a 2 mmol scale. [b] TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl. [c] MY from *Candida rugosa*[7] (Meito Sangyo Co., Ltd., Japan), PS from *Pseudomonas cepacia*[7] (Amano Pharmaceutical Co., Ltd., Japan). [d] Determined by capillary GC (GE XE-60 at 160 °C) after derivatization into their MTPA esters. [e] In detail, see ref. 8. [f] No reaction was observed even after 120 h.

−78 °C, 2 h] with 1.1 equiv. of KOBu$^t$ to afford, after *in situ* acetylation of the lactol, the desired pyranose 4*S*,5*S*-**12** in 88% yield along with the corresponding acetylated furanose only in 5% yield. Removal of a TBS group has led us to isolate the 6,6,6-trifluoro analogue of D-amicetose 4*S*,5*S*-**13** {7 : 1 inseparable anomer mixture, $[\alpha]_D^{23}$ + 8.79° (*c* 0.90, $CHCl_3$)}. The diastereoisomeric 4*R*,5*S*-**7** furnished the D-rhodinose derivative 4*R*,5*S*-**12**¶ {3 : 2 separable anomer mixture, $[\alpha]_D^{23}$ + 19.63° (*c* 1.21, $CHCl_3$) and $[\alpha]_D^{24}$ −37.65° (*c* 1.17, $CHCl_3$), respectively} in a similar fashion.

Here, we reported the development of a novel methodology for the preparation of 6-deoxy-6,6,6-trifluorosugars by 1,2-migration of a TBS group utilizing the electron-withdrawing nature of a $CF_3$ group as a key step to attain a selectivity of 95 : 5 in favour of pyranose over furanose. Conversion of these useful chiral butenolides, 4*S*,5**S-7** and 4*R*,5*S*-**7**, into a variety of analogues of 6-deoxysugars is in progress.

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6 The same type of compound, trifluoromethyl furyl ketone (**1**, *Si* = H), was previously reported by using trifluoroacetic anhydride in 65% yield. See, F. A. J. Kerdesky and A. Basha, *Tetrahedron Lett.*, 1991, **32**, 2003 and references cited therein.

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11 In the course of our study, the first synthesis of 6-deoxy-6,6,6-trifluoro-sugars was reported in a less selective way (pyranose : furanose = 72 : 28 ~ 34 : 66, depending on the stereostructure of the substrate). R. C. Bansal, B. Dean, S. Hakomori and T. Toyokuni, *J. Chem. Soc., Chem. Commun.*, 1991, 796. See also Y. Hanzawa, J. Amada and T. Taguchi, 15th Japan fluorine chemistry symposium, Tokyo, abstract P-15 on the preparation of 6,6,6-trifluorodaunosamine derivative.


¶ This compound 4*R*,5*S*-**12** was found to be relatively unstable under isolation process by silica gel chromatography after deprotection of a TBS group, the reason for which is not clear yet.