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A Potentially Divergent and Rapid Route to Analogues of Deoxycyclitols, Pentopyranoses, 6-Deoxyhexoses, and Hexoses

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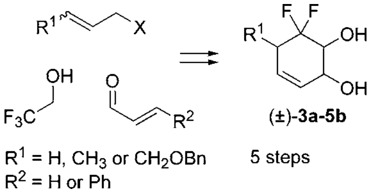
ABSTRACT



Direct precursors to analogues of pentopyranoses, 6-deoxyhexoses, and hexoses, in which a CF_2 center replaces the pyranose oxygen, have been synthesized rapidly from trifluoroethanol. A simple scaleable allylation reaction delivers ethers which undergo dehydrofluorination/metalation, followed by addition to either acrolein or cinnamaldehyde, to afford allylic alcohols. Fluorine-assisted [3,3]-rearrangement followed by reduction with sodium borohydride delivers diols, which undergo RCM smoothly to afford cyclohexene diols.

Carbasugars or carbocyclic analogues of saccharides have received considerable attention from synthetic chemists because of the challenges posed by the need to control contiguous cyclic arrays of stereogenic centers, and from biomedicinal chemists because of the enormous importance of sugar-processing enzymes and the great utility of molecules that inhibit or probe their action.[1] The replacement of the ring oxygen of a pyranose with a CH_2 group has profound changes upon reactivity and conformation—linkages made to C-1 are now ethers, not acetals, and the anomeric effect[2] has been removed completely. We wondered if the presence of a CF_2 center in place of the pyran oxygen would lead to interesting analogues **2** of saccharides **1** (R = H, Me, CH_2OH), which are pentopyranoses, 6-deoxyhexoses, and hexoses, respectively (Figure 1).

The substitution is challenging because the most common approach to the synthesis of difluorocompounds uses fluorinating agents such as DAST or DeoxoFluor to transform a ketonic carbonyl group.[3] The transformation of sugars into a range of deoxy difluoroanalogues by the isolation of one hydroxyl group, oxidation to a ketone carbonyl, and fluorination with DAST is well-known though the presence of adjacent hydroxyl groups can raise complex stereoelectronic

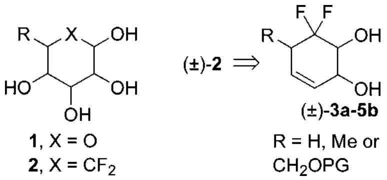


Figure 1. Proposed analogues **2** of saccharides **1** and pivotal generic precursors **3a-5b**.

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[1] For recent reviews, see: (a) Sears, P.; Wong, C. H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2301. (b) Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077. (c) Vogel, P. *Chimia* **2001**, *55*, 359. (d) Yuasa, H.; Hashimoto, H. *Trends Glycosci. Glycotechnol.* **2001**, *13*, 31.

[2] Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: Berlin, 1983; p 78.

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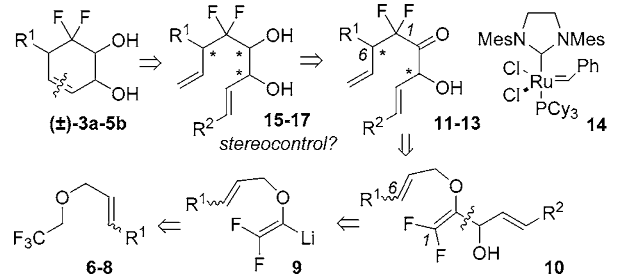
issues.[4] Similarly, there are a number of examples where readily available *myo*-inositol has been transformed by this approach into 2-deoxy-2,2-difluoro[5] and 5-deoxy-5,5-difluoro species,[6] some of which show some interesting enzymology.[7] However, there are no obvious starting materials for such a route to (±)-**3a**−**5b** where R = Me or CH$_2$OPG and definitely no one strategy which can deliver all three classes of analogue from a common class of starting material. We planned a flexible route, which would deliver three classes of precursors (±)-**3a**−**5b** to carba-sugars by a common strategy from trifluoroethanol. The retrosynthetic analysis is presented in Scheme 1.

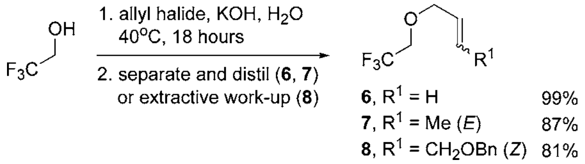
Scheme 1. Retrosynthetic Analysis



Cyclohexene diols (±)-**3a**−**5b** would be versatile substrates for various stereoselective alkene transformations and we knew that RCM reactions using the commercial second generation Grubbs' catalyst[8] **14** were likely to tolerate the two hydroxyl groups in **15**−**17**.[9] Reduction of hydroxyketone **11**−**13** would introduce a third stereogenic center, while the first two could be set in the [3,3]-Claisen rearrangement, if efficient transcription of alkene configuration could be achieved. The rearrangement would of course be facilitated by the rehybridization from sp^2 to sp^3 of the CF$_2$ center. The key step would then involve a dehydrofluorination/metalation of a trifluoroethyl ether **6**−**8** and the addition of the alkenylmetal reagent **9** to an enal electrophile to deliver allylic alcohol (±)-**10**. The route would avoid purification wherever possible and would be carried out on a multigram scale, *prioritising rapid delivery of the target compounds from inexpensive and commercial starting materials*. Minimal use of protecting group chemistry would also be a feature of the route and we would be happy to synthesize mixtures of diastereoisomeric products at this stage, provided separation could be achieved, because small libraries of sugar analogues would then become available. We therefore sought the execution of syntheses illustrative of each class of proposed analogue.

We previously[10] used phase-transfer-catalyzed allylation or Falck's Mitsunobu procedure[11] to prepare the ethers, but allyl ethers **6**−**8** were synthesized in water by a simple and scaleable procedure (Scheme 2).

Scheme 2. Synthesis of Allyl Ethers **6**−**8**



We were able to prepare 1 mol batches of the volatile ethers **6** (99%) and **7** (87%), which were won from the reaction mixture in a separating funnel and redistilled directly from calcium hydride to ensure dryness. Less volatile ether **8** was prepared in the same way (81%), but on a smaller scale, from a known chloride, and isolated following an extractive workup.[12]

Ether **6** underwent dehydrofluorination/metalation at low temperature (*n*-butyllithium at −100 °C) to deliver the crude acrolein adducts (on the basis of ^{19}F NMR evidence), which proved volatile and extremely difficult to handle. Also, there was significant contamination of the products with hept-1-en-3-ol, formed by the direct addition of *n*-butyllithium to acrolein. This side reaction highlights the problems involved

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(3) (a) Singh, R. P.; Shreeve, J. M. *Synthesis* **2002**, 2561. (b) Dax, K.; Albert, M.; Ortner, J.; Paul, B. J. *Carbohydr. Res.* **2000**, *327*, 47. (c) Dax, K.; Albert, M.; Ortner, J.; Paul, B. J. *Curr. Org. Chem.* **1999**, *3*, 287.

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(5) For synthesis of 2-deoxy-2,2-difluoro species, see: (a) Boehm, M. F.; Prestwich, G. D. *Tetrahedron Lett.* **1988**, *29*, 5217. (b) Sawyer, D. A.; Potter, B. V. L. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 705. (c) Sawyer, D. A.; Potter, B. V. L. *J. Chem. Soc., Perkin Trans. 1* **1992**, 923. (d) Zhai, H. X.; Ping-Sheng, L.; Morris, J. C.; Mensa-Wilmot, K.; Shen, T. Y. *Tetrahedron Lett.* **1995**, *36*, 7403.

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(7) (a) Morris, J. C.; Ping-Sheng, L.; Zhai, H. X.; Shen, T. Y.; Mensa-Wilmot, K. *J. Biol. Chem.* **1996**, *271*, 15468. (b) Morris, J. C.; Ping-Sheng, L.; Zhai, H. X.; Shen, T. Y.; Mensa-Wilmot, K. *Biochem. Biophys. Res. Commun.* **1998**, *244*, 873. For related species, see (c) Lampe, D.; Liu, C.; Mahon, M. F.; Potter, B. V. L. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1717. (d) Kozikowski, A. P.; Fauq, A. H.; Wilcox, R. A.; Nahorski, S. R. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1295. (e) Rich, R. H.; Lawrence, B. M.; Bartlett, P. A. *J. Org. Chem.* **1994**, *59*, 693. (f) Jiang, S.; Singh, G.; Boam, D. J.; Coggins, J. R. *Tetrahedron: Asymmetry*. **1999**, *10*, 4087. (g) Eguchi, T.; Sasaki, S.; Huang, Z.; Kakinuma, K. *J. Org. Chem.* **2002**, *67*, 3979. For a recent review fluorinated cyclitol analogues as probes, see: (h) Schedler, D. J. A.; Baker, D. C. *Carbohydr. Res.* **2004**, *339*, 1585.

(8) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247.

(9) For strong direct precedents, see: (a) Ackermann, L.; El Tom, D.; Furstner, A. *Tetrahedron* **2000**, *56*, 2195. (b) Hyldtoft, L.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 8444. (c) Conrad, R. M.; Grogan, M. J.; Bertozzi, C. R. *Org. Lett.* **2002**, *4*, 1359. (d) Heo, J. N.; Holson, E. B.; Roush, W. R. *Org. Lett.* **2003**, *5*, 1697.

(10) (a) Garayt, M. R.; Percy, J. M. *Tetrahedron Lett.* **2001**, *42*, 6377. For other examples of the dehydrofluorination/metalation approach, see: (b) Nakai, T.; Tanaka, K.; Ishihawa, N. *Chem. Lett.* **1976**, 1263. (c) Ichikawa, J.; Sonoda, T.; Kobayashi, H. *Tetrahedron Lett.* **1989**, *30*, 6379. (d) Patel, S. T.; Percy, J. M.; Wilkes, R. D. *Tetrahedron* **1995**, *51*, 9201. (e) Howarth, J. A.; Owton, W. M.; Percy, J. M.; Rock, M. H. *Tetrahedron* **1995**, *51*, 10289. (f) Harrington, P. E.; Tius, M. A. *J. Org. Chem.* **1999**, *64*, 4025. (g) See Cox, L. R.; DeBoos, G. A.; Fullbrook, J. J.; Percy, J. M.; Spencer, N. S.; Tolley, M. *Org. Lett.* **2003**, *5*, 337 for applications of dehydrofluorination/metalation methodology in asymmetric synthesis.

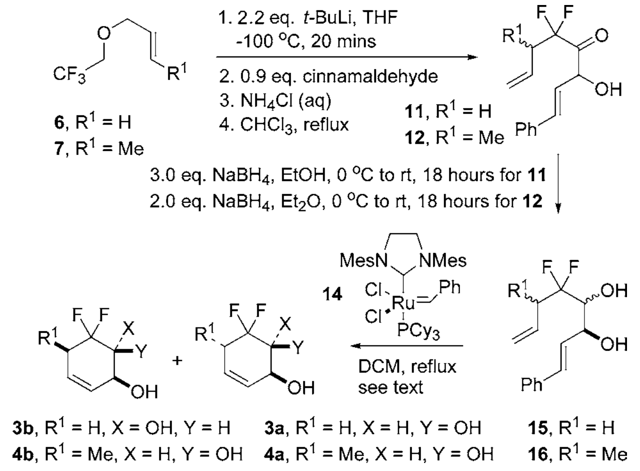
(11) Falck, J. R.; Yu, J.; Cho, H.-S. *Tetrahedron Lett.* **1994**, *35*, 5997.

(12) (a) Audouard, C.; Garayt, M. R.; Kérourédan, E.; Percy, J. M.; Yang, H. submitted to *J. Fluorine Chem.* (b) The study was based on the seminal preliminary publication by Metcalf and co-workers: Metcalf, B. W.; Jarvi, E. T.; Burkhart, J. P. *Tetrahedron Lett.* **1985**, *26*, 2861.

in attempting to react unstabilized difluoroalkenylmetal reagents with carbonyl electrophiles; often the addition reactions occur slowly at low temperature and compete ineffectively with decomposition. Attempts to minimize the latter pathway necessitate premature addition of the electrophile before dehydrofluorination/metalation has reached completion. When we used cinnamaldehyde as the electrophile and limiting reagent, and *tert*-butyllithium as the base, the addition side reaction was suppressed completely. Presumably the more reactive alkyllithium ensures more rapid conversion of the ether, but the difference between the two aldehydes is less easy to explain.

The crude products rearranged smoothly in chloroform at reflux in 25 min to afford **11**, and then reduction with sodium borohydride in ethanol occurred with some stereoselectivity (5:1 mixture of diastereoisomers). The diastereoisomers were separated and purified (major diastereoisomer, 57%, minor 11% from **6**) by careful SiO_2 flash column chromatography on a 10 mmol scale (Scheme 3).

Scheme 3. Preparation of Racemic Cyclohexene Diols **3a**−**4b**



RCM proceeded rapidly in each case (15 min, 1% **14**) to afford *cis*-**3a** (86%) and *trans*-**3b** (82%). Crystal structures were obtained for both, identifying the *anti*-1,2-diastereoisomer of diol **15** as the major product from the reduction (Figure 2).

The sense of borohydride reduction appears to be in broad agreement with the literature describing α-hydroxyketone reduction in which *anti*-products are favored.[13]

A similar sequence delivered diols **16** as a mixture of diastereoisomers on up to a 70 mmol scale. Inspection of the $\{^1H\}^{19}F$ NMR spectrum of the crude reaction mixture at 400 MHz revealed that two diastereoisomers dominated the reaction mixture (ratio 17:10:1:1), which also contained two minor species, along with trace amounts of cinnamyl alcohol.

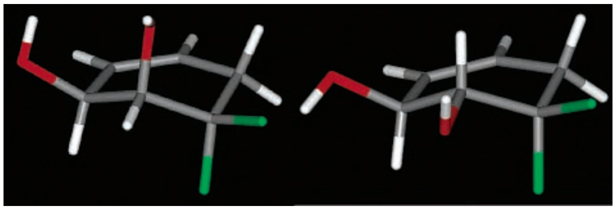


Figure 2. X-ray crystal structures of racemic cyclohexenediols *cis*-**3a** and *trans*-**3b**, showing clearly the relationship between the stereogenic centers set in the reduction step.

Kugelrohr distillation allowed the removal of the cinnamyl alcohol (which is an inhibitor of the RCM reaction) and the isolation of the two major diols (1.7:1, 51%). RCM required 24 h for complete consumption of starting material with 1% of **14** (apparently 10^2 times slower than the reaction of **15**), but was complete in 6 h with 2.5% loading. Crystal structures were obtained for the major and minor products confirming that the reaction had delivered *cis*,*trans*-**4a** (33%) and *all-cis*-**4b** (15%) (with 16% of a mixed fraction containing the two diastereoisomers) after SiO_2 flash column chromatography.

The stereochemical outcome of the sequence requires some comment. There appears to be either a very limited level of 1,4-control (<2:1) of the rearrangement from the initial sp^3-hybridized stereogenic center[14] or a rapid epimerization reaction at the hydroxyketone level. We cannot distinguish between these mechanisms on the basis of the data in hand. In either case, the level of 1,2-control over hydroxyketone reduction appears to be higher than in the case of **11**.

Dehydrofluorination/metalation of **8** and addition to acrolein was carried out on up to a 60 mmol scale at −78 °C to afford a less volatile product.[15] Rearrangement in hot chloroform (85 °C, 3 h) and then reduction ($NaBH_4$, EtOH) afforded a mixture of crude diols (35% on a 50 mmol scale), which could be purified by careful SiO_2 flash column chromatography. RCM occurred smoothly in refluxing dichloromethane to afford two separable cyclohexene diols, assigned as **5a** and **5b** (3.6:1) (65%) and (18%), respectively.

The **5a**/**5b** mixture was also converted to separable bisacetates **18** (57%) and **19** (16%) and separable acetonides **20** (56%) and **21** (16%) (Scheme 4). Structures were then assigned by coupling constant analysis and NOESY experiments, supported by insight obtained from **4b**. The assignment of the major diastereoisomer as *all-cis* was confirmed by the conversion of **5a** to monoacetate **22** under stannylene conditions and the solution of the crystal structure (Scheme 5). Dihydroxylation of all *cis*-**4b** was achieved upon exposure

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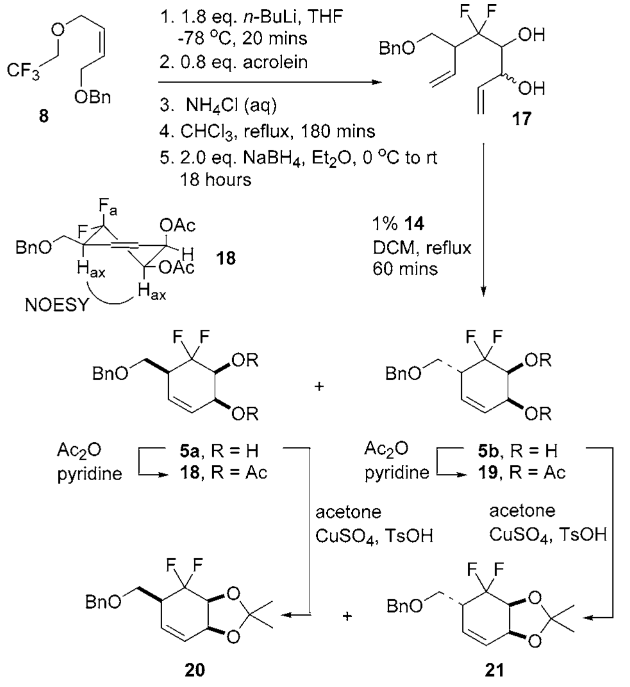
[13] (a) Davis, A. P. In *Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1996; Vol. E21, Vol. 7, D2.3.3.1.1.2, p 3994. (b) Yamada, M.; Horie, T.; Kawai, M.; Yamamura, H.; Araki, S. *Tetrahedron* **1997**, *53*, 15685.

[14] (a) Frauenrath, H. In *Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1996; Vol. E21, D.1.6, p 3504. (b) For an asymmetric Claisen reaction of a related system, see: Ito, H.; Sato, A.; Kobayashi, T.; Taguchi, T. *Chem. Commun.* **1998**, 2441.

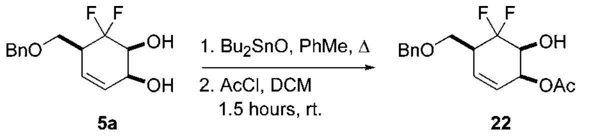
[15] This difference in alkenylmetal stability is discussed more fully in ref 12.

Scheme 4. Preparation of Hexose Analogue Precursors from **8**

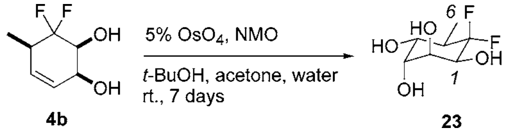


to UpJohn conditions,[16] delivering tetrol **23** stereoselectively in good yield (79% on a sub-mmol scale), which can be identified from the NMR spectra (Scheme 6).

Scheme 5. Preparation of Monoacetate **22** Used for the Assignment of Relative Configuration



Scheme 6. Preparation of Tetrol **23** from **4b**



Tetrol **23**, from all *cis*-**4b**, contains a dt in the ^{19}F NMR spectrum (arising from flanking axial protons), while H-4 in the ^{1}H NMR spectrum contains a relatively large ^3J coupling (11 Hz) consistent with a *trans*-diaxial coupling to H-5. This product arises from dihydroxylation *trans* to both the C−O bond at C-2 and the methyl group at C-5 in the expected sense.[17]

These results suggest strongly that a very wide range of carba-sugar structures can be generated rapidly from trifluoroethanol. This chemistry is unique as a method for the rapid syntheses of difluorinated molecules of this level of complexity and relevance to saccharides, and the full scope and limitations will be defined in our laboratory.

Acknowledgment. We thank the EPSRC for Grant No. GR/R96835 (fellowships to C.A., H.Y., studentship to E.K.) and FMC Lithium for a generous gift of *tert*-butyllithium.

Supporting Information Available: Preparation of and data for **16** and **4a/4b**, **17,** and **23**, X-ray data for **3a** and **3b**, **4a** and **4b**, and **22**, and ^{1}H and ^{13}C NMR spectra of **3a**−**5b** and **18**−**23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.

[17] Cha, J. K.; Kim, N. S. *Chem. Rev.* **1995**, *95*, 1761.