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Basic and Reductive Sulfone-Directed Ring-Opening Reactions of Difluorinated Oxa[2.2.1]bicycloheptanes

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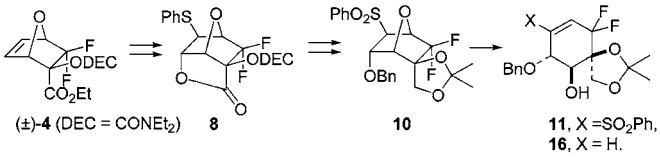
ABSTRACT



Phenylsulfenyl chloride reacts with racemic endo Diels–Alder adduct 4 (DEC = $CONEt_2$) to afford lactone 8, which can be reduced and protected in a series of high-yielding steps. Key sulfone 10 can be ring opened under strong base conditions to afford vinyl sulfone 11. Attempted desulfonation resulted in the formation of a monofluoroalkene, but a direct desulfonation/eliminative ring opening with strain relief delivered highly functionalized monocyclic species 16.

Nature makes a wide range of cyclitols, some of which have useful properties.[1] Those that feature a hydroxymethyl group and alkene functionality include ferrudiol **1**, zeylenol **2**, and piperonol B **3** (Figure 1).[2] Fluorination of carbohydrates[3] and cyclitols[4] is a well-established tactic for modifying functional group behavior, disrupting or identifying essential hydrogen bonding interactions, and preventing phosphorylation at key sites. Synthetic methodology relies upon DAST or related fluorinations to transform hydroxyl or ketonic carbonyl groups with the incorporation of one or two fluorine atoms. Extensive functional group manipulations can be required to present a single group to the reagent, and even then, the course of fluorination reactions can be unpredictable. De novo methods using building blocks[5] for the construction of difluorinated analogues of monosaccharides or cyclitols are not well established; indeed, we are not aware of any

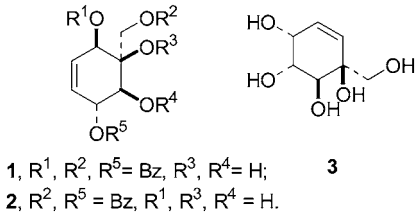


Figure 1. Hydroxymethyl conduritol natural products.

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(1) Balci, M. *Pure Appl. Chem.* **1997**, *69*, 97−104.
(2) For recent syntheses, see: (a) Hiroya, K.; Ogasawara, K. *Chem. Commun.* **1999**, 2197−2198. (b) Arjona, O.; Iradier, F.; Manas, R. M.; Plumet, J. *Tetrahedron Lett.* **1998**, *39*, 8335−8336.
(3) Tsuchiya, T. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 91−267.
(4) (a) Lampe, D.; Liu, C.; Mahon, M. F.; Potter, B. V. L. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1717−1727. (b) Kozikowski, A. P.; Fauq, A. H.; Wilcox, R. A.; Nahorski, S. R. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1295−1300. (c) Prestwich, G. D.; Marecek, J. F. ACS Symposium Series 463; American Chemical Society: Washington, DC, 1991; pp 122−131. (d) Rich, R. H.; Lawrence, B. M.; Bartlett, P. A. *J. Org. Chem.* **1994**, *59*, 693−694. (e) Jiang, S.; Singh, G.; Boam, D. J.; Coggins, J. R. *Tetrahedron: Asymmetry* **1999**, *10*, 4087−4090. (f) Eguchi, T.; Sasaki, S.; Huang, Z.; Kakinuma, K. *J. Org. Chem.* **2002**, *67*, 3979−3984.

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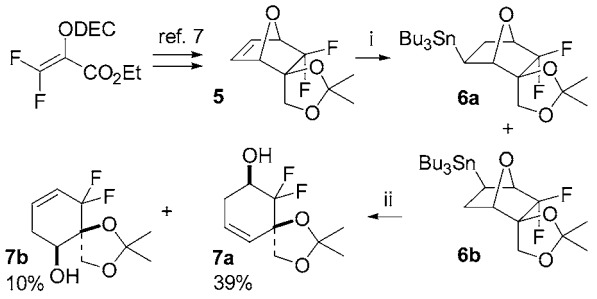
previous syntheses of (ring) fluorinated analogues of (hydroxymethyl)conduritols or compounds related to **1**−**3** by this approach.

On the basis of a key contribution by Wakselman et al.,[6] we made progress with the synthesis, and furan Diels−Alder reaction, of a fluorinated dienophile.[7] Cycloadducts could be obtained in good yield; however, direct Lautens hydrostannylation[8] of **4** failed, and hydrostannylation of **5** was not regioselective, with **6a** and **6b** being formed in a 1:1 ratio (Scheme 1).

Scheme 1. Lautens Chemistry Affords Ring-Opened Products but in Low Yield and with Low Regioselectivity[a]



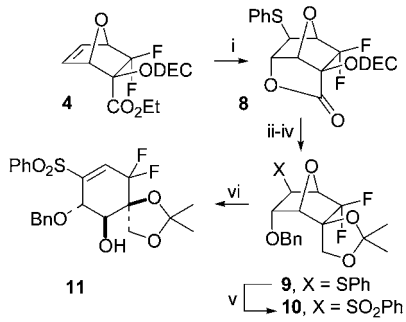
[a] Reaction conditions: (i) Bu_3SnH, Pd_2dba_3·$CHCl_3$; (ii) MeLi, Et_2O.

Furthermore, one of the stannane regioisomers (**6b**) afforded only a low yield of ring-opened product **7b**, suggesting further destructive reaction of the ring-opened product.[9]

However, we have now found that major racemic endo cycloadduct **4** can be converted to highly functionalized difluorinated cyclohexenols, related structurally to **1** and **2**, rapidly, regioselectively, and efficiently. Ester **4** failed to react with the NCS/thiophenol reagent combination,[10] but a smooth reaction occurred with freshly prepared phenylsulfenyl chloride[11] and crystalline lactone **8** could be isolated in excellent (89%) yield on a 20 g scale. Slightly lower yields of lactone could be obtained using the convenient in situ method of Suzuki[12] (PhSSPh, SO_2Cl_2, DCM). We then reduced the lactone and carbamate in one pot (excess LAH), protected the 1,2-diol selectively as the acetonide, and benzylated the secondary hydroxyl group to afford **9** (Scheme 2).

These three steps were performed in an overall yield of 62% without purification apart from trituration of the crude products with hexane. Oxidation to sulfone **10** with *m*CPBA

Scheme 2. Lactonization Allows Regioselective Elaboration of the Endo Cycloadduct[a]

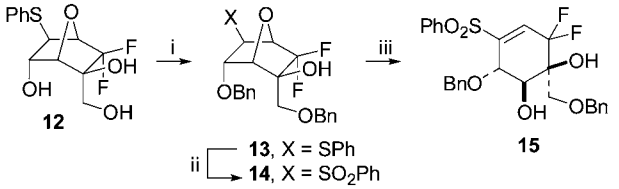


[a] Reaction conditions: (i) PhSCl, $CHCl_3$, 89%; (ii) LAH, THF, reflux, 80%; (iii) acetone, $CuSO_4$, TsOH, 85%; (iv) NaH, THF, then $PhCH_2Br$, Bu_4NI (10 mol%), 91%; (v) *m*CPBA, CH_2Cl_2, 89%; (vi) *n*-BuLi (1.5 equiv), THF, from −78 to −30 °C, 89%.

proceeded smoothly. Treatment of the sulfone with *n*-BuLi in THF at −78 °C for 1 h, followed by warming to −30 °C and quenching, resulted in ring opening to **11**.[13]

A strategy involving a lower degree of protection was also attempted (Scheme 3). Exposure of triol **12** (resulting from

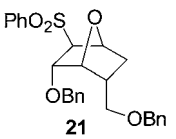
Scheme 3. Exploring a Minimal Protection Strategy for the Ring-Opening Reaction[a]



[a] Reaction conditions: (i) NaH, THF, then benzyl bromide, Bu_4NI (10 mol%), 20%; (ii) *m*CPBA (3 equiv), CH_2Cl_2, 83%; (iii) *n*-BuLi (4 equiv), THF, from −78 to −30 °C, 13%.

the reduction of **8**) to sodium hydride and benzyl bromide gave dibenzylated compound **13** in low yield; even with large excesses of sodium hydride and benzyl bromide, the major product was the diol in which only the primary hydroxyl group had been benzylated. Oxidation to the sulfone **14** proceeded smoothly; however, ring opening of the sulfone required a larger excess (4 equiv) of *n*-BuLi than expected, and the yield of the corresponding vinyl sulfone **15** was much lower than that for **11**. Because of this discouraging result, we did not progress the diol through a similar sequence.

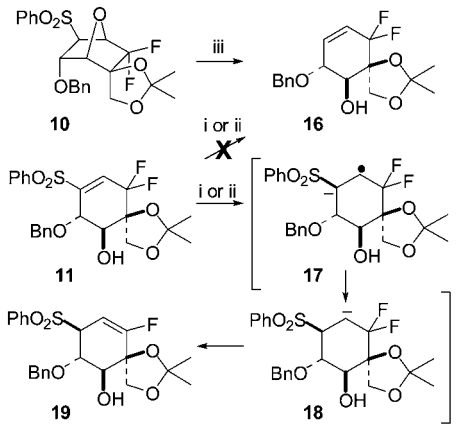
(5) Percy, J. M. *Top. Curr. Chem.* **1997**, *193*, 131−195.
(6) Leroy, J.; Molines, H.; Wakselman, C. *J. Org. Chem.* **1987**, *52*, 290−292.
(7) Crowley, P. J.; Moralee, A. C.; Percy, J. M.; Spencer, N. S. *Synlett* **2000**, 1737−1740.
(8) Lautens, M.; Klute W. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 442−445.
(9) We were able to generate **7a** directly in 30% yield[7] by treating **5** with *t*-BuMgBr generated in situ.
(10) Hopkins, P. B.; Fuchs, P. L. *J. Org. Chem.* **1978**, *43*, 1208−1217.
(11) Leclaire, M.; Jean, P.; Lopez, R.; Ricard, L.; Plessix, H.; Lallemand, J. Y. *Tetrahedron* **1995**, *51*, 6983−6998.
(12) Suzuki, H.; Satake, H.; Uno, H.; Shimizu, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4471−4473.
(13) We confirmed the result by X-ray diffraction (see Supporting Information). In contrast, the ring opening of **21** required a highly optimized solvent system (TMEDA/DCM/PhMe).



Clearly the CF_2 centre could have an effect on the reaction by increasing

Vinyl sulfone **11** displays an extremely attractive array of functionality from which analogues of zeylenol could be prepared following reductive desulfonylation to **16**. However, exposure of **11** to conventional amalgam conditions resulted in the formation of a relatively complex reaction mixture, though running the reaction below ambient temperature afforded a monofluorinated major product **19** (Scheme 4) in only 19% yield.

Scheme 4. Reductive Defluorination and Desulfonation Reactions of the Intermediate Sulfones[a]



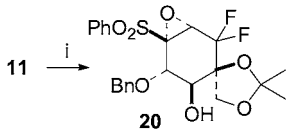
[a] Reaction conditions: (i) 6% Na/Hg, EtOH, −40 °C; (ii) Mg (3 equiv), $HgCl_2$ (0.5 equiv), EtOH, rt; (iii) Mg (3 equiv), $HgCl_2$ (0.25 equiv), EtOH, 0 °C, 61%.

Reduction to the same major product also occurred under the magnesium/mercuric ion conditions of Lee and co-workers.[14] The major reaction pathway under these conditions was likely to involve a sequence in which radical anion **17** is protonated and then reduced further to trigger defluorination from **18** to afford defluorination product **19**.[15]

However, when we exposed **10** to the Lee conditions, we discovered **16** as the sole fluorinated product in good yield (61%) after limited optimization. This reaction, directly analogous to a Julia olefination,[16] presumably involves radical/anion pair formation, further reduction of the radical, rapid carbanion inversion, and strain-relieving ring opening. This sequence represents the method of choice[17] for the preparation of **16**, a precursor to a range of (hydroxymethyl conduritol) analogues, from **4**.

These studies show that cycloadduct **4** can be converted regioselectively and efficiently into highly functionalized difluorinated cyclohexenes under a range of conditions and without the defluorination and aromatization that impaired the progress of Wakselman and co-workers toward analogues of shikimic acids. A direct and regioselective sequence from a difluorinated dienophile to highly functionalized difluorinated cyclohexenols has therefore been demonstrated for the first time. Current studies are assessing the generality of the chemistry with adducts from different furans and seeking ring-opening methods that avoid the use of the phenylsulfonyl group. Also of interest are oxidative reactions of the alkenyl group through which hydroxyketone and aminoketone motifs could be developed.

Scheme 5. Stereoselective Oxidation of **11**[a]



[a] Reaction conditions: (i) H_2O_2, NaOH, MeOH, 70%.

As an example, treatment of **11** with alkaline hydrogen peroxide afforded epoxide **20** as the major isolable stereoisomer in good yield (Scheme 5). The crystal structure is shown in Figure 2.

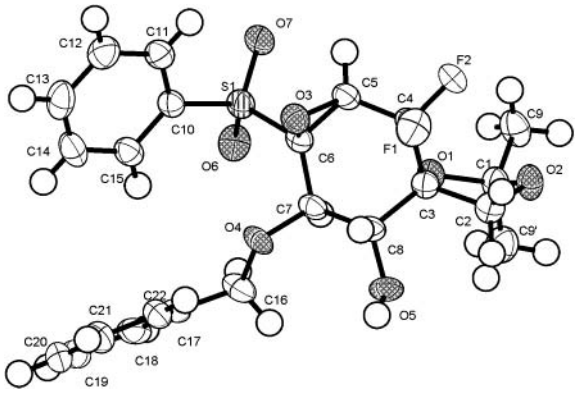
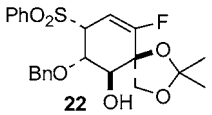


Figure 2. ORTEP plot for epoxide **20**.

the nucleofugacity of the departing oxyanion. See: (a) Acena, J. L.; Arjona, O.; de la Pradilla, R. F.; Plumet, J.; Viso, A. *J. Org. Chem.* **1992**, *57*, 1945−1946. (b) Acena, J. L.; Arjona, O.; Delapradilla, R. F.; Plumet, J.; Viso, A. *J. Org. Chem.* **1994**, *59*, 6419−6424.

(14) Lee, G. H.; Choi, E. B.; Pak, C. S. *Tetrahedron Lett.* **1993**, *34*, 4541−4542.

(15) The trans stereochemistry is predicted on the basis of PM3 calculations (MacSpartan Pro) of the relative energies of **19** and the cis stereoisomer **22**, which appears to be 4.75 kcal/mol less stable.



For similar, reductive defluorinations, see: Otaka, A.; Mitsuyama, E.; Watanbe, H.; Tamamura, H.; Fujii, N. *Chem. Commun.* **2000**, 1081−1082.

(16) For a related example involving antiperiplanar elimination of a methoxide anion, see ref 2b.

(17) Desulfonations of functionalized vinyl sulfones are known but not under amalgam conditions; for relevant examples that use BuMgCl/Pd(OTFA)$_2$, see: (a) Bialecki, M.; Vogel, P. *Helv. Chim. Acta* **1995**, *78*, 325−343. (b) Fabre, J. L.; Julia, M. *Tetrahedron Lett.* **1983**, *24*, 4311−4314. Marino reported a desulfonation of a dienyl sulfone under SmI_2 conditions; see, Marino, J. P.; McClure, M. S.; Holub, D. P.; Comasseto, J. V.; Tucci, F. C. *J. Am. Chem. Soc.* **2002**, *124*, 1664−1668. We did not explore this method because the direct conversion of **10** to **16** is shorter and more efficient.

Acknowledgment. We thank Dr. A. Arany (University of Birmingham, 2000−2001) for growing crystals of **11**. We thank Zeneca Agrochemicals (now Syngenta) and the Department of Trade and Industry for an Industrial CASE Award (A.C.M.) and the Engineering and Physical Sciences Research Council of Great Britain for generous support (GR/M94922) of fellowships (A.A. and A.C.M.) and a studentship (V.S.). We thank Dr. D. B. Berkowitz (University of Nebraska) for useful discussions about reductive desulfonation.

Supporting Information Available: Experimental procedures for preparation of **8**, **11**, and **12**, NMR (^{1}H, ^{13}C, and ^{19}F) spectra for **8**, **11**, **12**, and **16**, and crystal structure data for **11**, **15**, and **20**.

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