JOC Article

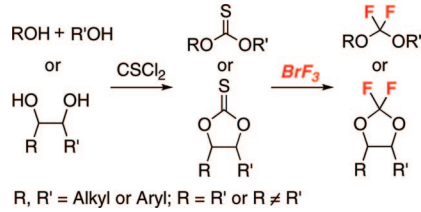
Constructing the OCF_2O Moiety Using BrF_3

Youlia Hagooly and Shlomo Rozen*

School of Chemistry, Tel-Aviv University, Tel-Aviv 69978, Israel

rozens@post.tau.ac.il

Received May 22, 2008



A general preparation for aromatic and aliphatic, cyclic as well as linear, symmetric and asymmetric difluoromethylenedioxy derivatives is described. The alcohols were reacted with thiophosgene to give thiocarbonates, which in turn were reacted with BrF_3. The fluorination step is complete in seconds with moderate to high yields under mild conditions.

Introduction

There is a continuous effort to develop new fluorine-containing compounds, as is evident from the thousands of books, publications, reviews and journals devoted to this subject. It is enough to say that this interest has spread to all fields of chemistry from energy-related issues, materials, and agriculture to biologically interesting compounds.

Among the numerous fluorine-containing compounds, the ones possessing trifluoromethyl and difluoromethylene groups are of special value for many medicinal and industrial uses.[1] The important trifluoromethoxy group and its positive influence on various organic compounds are also well documented.[2] The properties of the difluoromethylenedioxy group (OCF_2O), on the other hand, has remained relatively unexplored. Recently, however, it is becoming a focus of interest due to its special contributions in pharmaceuticals.[3,4] For instance, a series of novel 2-aminothio phenecarboxamide derivatives containing the OCF_2O moiety have been developed as potential chemotherapeutic agents for cancer treatment.[5] Also, dioxolane derivatives with this group were found to be suitable for use in secondary lithium batteries and capacitors,[6] and optical fibers such as bis(alkoxy)difluoromethane possess good thermal stability, high glass transition temperatures, and low dielectric constants.[7]

Only a few reactions leading to difluoroethers have been reported,[8] and even fewer are specifically designed for constructing the difluorodiether group (OCF_2O). Aromatic derivatives of this type have been prepared mainly by reacting various nucleophilic fluoride reagents (e.g., HF, AgF, SbF_3, $Bu_4NH_2F_3$) with either dichlorodioxomethylene derivatives or thiocarbonates.[9,10] However, only few leads to alicyclic derivatives could be found.[7,11] The lack of a general method for preparing a wide spectrum of symmetric and asymmetric difluoromethylenedioxy (OCF_2O) compounds is conspicuous.

For the past 15 years, we have investigated various halogen fluoride reagents, such as IF and BrF, as nucleophilic fluorinating agents.[12] One of the most successful reagents of this group proved to be bromine trifluoride (BrF_3), especially in constructing the CF_2[13] and the CF_3[14,15] moieties at various sites in organic molecules. The main feature of the mechanism governing most

(1) Feiring, A. E. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum: New York, London, 1994; pp 339−372.
(2) Leroux, F.; Jeschkle, P.; Schlosser, M. *Chem. Rev.* **2005**, *105*, 827–856.
(3) Zhu, G.; Gandhi, V. B.; Gong, J.; Thomas, S.; Woods, K. W.; Song, X.; Li, T.; Diebold, R. B.; Luo, Y.; Liu, X.; Guan, R.; Klinghofer, V.; Johnson, E. F.; Bouska, J.; Olson, A.; Marsh, K. C.; Stoll, V. S.; Mamo, M.; Polakowski, J.; Campbell, T. J.; Martin, R. L.; Gintant, G. A.; Penning, T. D.; Li, Q.; Rosenberg, S. H.; Giranda, V. L. *J. Med. Chem.* **2007**, *50*, 2990–3003.
(4) Su, J.; Tang, H.; McKittrick, B. A.; Burnett, D. A.; Zhang, H.; Smith-Torhan, A.; Fawzi, A.; Lachowicz, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4548–4553.
(5) Brennan, C.; Kluender, C. E.; Wickens, P.; Enyedy, I. J.; Hong, Z.; Jones, B.; Kumarasinghe, E. S.; Chuang, C.; Phillips, B.; Dixon, J. PCT Int. Appl. WO 2006023707, 2006.
(6) Nakano, T.; Shiono, K. Ger. Offen. DE 19700656, 1997.
(7) Yang, Y.; Mikes, F.; Koike, Y.; Okamoto, Y. *Macromolecules* **2004**, *37*, 7918–7923.
(8) (a) Bunnelle, W. H.; McKinnis, B. R.; Narayanan, B. A. *J. Org. Chem.* **1990**, *55*, 768–770. (b) Rozen, S.; Mishani, E. *J. Chem. Soc., Chem. Commun.* **1993**, 1761–1762.
(9) Saint-Jalmes, L. *J. Fluorine Chem.* **2006**, *127*, 85–90.
(10) Guidotti, J.; Schanen, V.; Tordeux, M.; Wakselman, C. *J. Fluorine Chem.* **2005**, *126*, 445–449.
(11) Kuroboshi, M.; Hiyama, T. *Synlett* **1994**, 251–252.
(12) (a) Hebel, D.; Rozen, S. *J. Org. Chem.* **1988**, *53*, 1123. (b) Rozen, S.; Mishani, E.; Bar-Haim, A. *J. Org. Chem.* **1994**, *59*, 2918–2918.

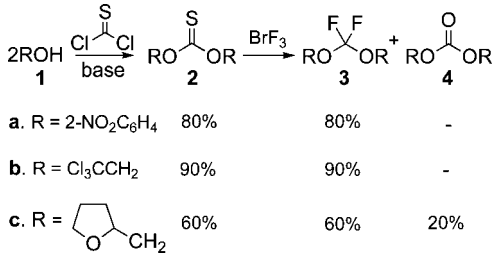
10.1021/jo801116n CCC: $40.75
Published on Web 08/12/2008

reactions with BrF_3 involves the complexation of the soft acidic bromine with a soft base (e.g., sulfur or nitrogen atoms) in the target molecule. The fluorides in this reagent then react selectively with the activated carbon, forming the desired products, while minimizing unwanted destructive radical side reactions.[16] These reactions helped us, among other things, to construct the OCF_2Cl group,[17] and we present here a route leading to a general synthesis of the OCF_2O moiety.

Results and Discussion

The reaction of 2 molar equiv of 2-nitrophenol (**1a**) with 1 molar equiv of thiophosgene in the presence of sodium hydroxide formed *O*,*O*-bis(2-nitrophenyl)thiocarbonate (**2a**).[18] Despite the tendency of aromatic rings to be brominated by the strong electrophilic bromine in BrF_3, the fluorination on the carbon bonded to the sulfur atom in **2a** was much faster.[19] The new bis(2-nitrophenoxy)difluoromethane (**3a**) was thus formed in 80% yield (Scheme 1).

SCHEME 1. Formation of Symmetric Bis(alkoxy/aryloxy)difluoromethane Derivatives (3)

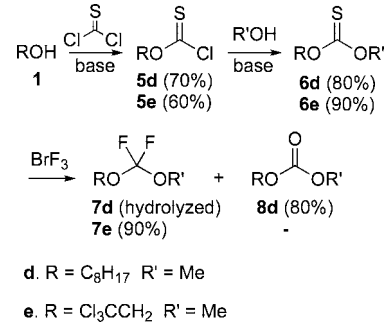


Similarly, the reaction of 1 molar equiv of thiophosgene and 2 molar equiv of 2,2,2-trichloroethanol (**1b**) in the presence of triethylamine (Et_3N) led to *O*,*O*-bis(2,2,2-trichloroethyl)thiocarbonate (**2b**)[20] in 90% yield. The 1-min reaction of this thiocarbonate with 1 molar equiv of BrF_3 afforded the symmetric bis(2,2,2-trichloroethoxy)difluoromethane (**3b**) in 90% yield.

The aliphatic (tetrahydrofuran-2-yl)methanol (**1c**) was also converted to the corresponding thiocarbonate (**2c**) and reacted with BrF_3 to form bis(2-tetrahydrofuranylmethoxy)difluoromethane (**3c**) in 60% yield. Unlike the two previous examples, however, **3c** was accompanied with 20% of bis(2-tetrahydrofuranylmethyl)carbonate (**4c**).[21] With time, if no special precautions were taken, **3c** was completely hydrolyzed to **4c** (Scheme 1). It should be noted that certain types of compounds (see below) were also found to be hydrolytically sensitive, preventing us from obtaining for them analytically pure samples.

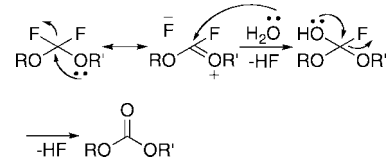
To produce asymmetric bis(alkoxy)difluoromethane derivatives, a stepwise process was required. The reaction between 1-octanol (**1d**), Et_3N and thiophosgene provided octyl chlorothioformate (**5d**),[22] which then was added to a methanol solution, forming the asymmetric precursor *O*-methyl-*O*-octylthiocarbonate (**6d**) in 80% yield. The reaction of **6d** with BrF_3 led to 1-(difluoro(methoxy)methoxy)octane (**7d**), which if not specially protected hydrolyzed, as did **3c**, to methyl octyl carbonate (**8d**)[23] in 80% yield (Scheme 2). When instead of octanol, trichloroethanol was used, forming *O*-methyl-*O*-2,2,2-trichloroethylthiocarbonate (**6e**) via 2,2,2-trichloroethyl chlorothioformate (**5e**),[20] the reaction with BrF_3 led to a new and hydrolytically stable 1,1,1-trichloro-2-(difluoro(methoxy)methoxy)ethane (**7e**) in 90% yield (Scheme 2).

SCHEME 2. Formation of Asymmetric Bis(alkoxy)difluoromethane Derivatives (7d, 7e)



The stability of the OCF_2O group in compounds possessing electron-withdrawing groups (EWGs), such as **3a**, **3b**, and **7e**, and the ready hydrolysis of **3c** and **7d** may be explained by fluorine hyperconjugation activating the difluoromethylene toward reaction with the nucleophilic water to form eventually the dialkyl carbonates **4c** and **8d**. The presence of an EWG next to the OCF_2O moiety, even on one side of the molecule as in **7e**, decreases the hyperconjugation capability and as a result increases the stability toward hydrolysis. The slow decomposition of **3c** having a somewhat remote oxygen atom at each side of the difluoromethylenedioxy group reflects an intermediate behavior (Scheme 3).

SCHEME 3. Hydrolysis of Difluoromethylenedioxo Derivatives with No EWG



The protons released during the hydrolysis process and those originating from the workup serve as catalyst for the decomposition by forming a hydrogen bond with the leaving fluorides.[24] Indeed when compounds such as **7d** were quickly purified and kept under basic condition (MeOH/NaOMe or MeOH/Et_3N), the hydrolysis was retarded.

(13) (a) Hagooly, A.; Sasson, R.; Rozen, S. *J. Org. Chem.* **2003**, *68*, 8287–8289. (b) Rozen, S.; Ben-David, I. *J. Org. Chem.* **2001**, *66*, 496–500. (c) Sasson, R.; Hagooly, A.; Rozen, S. *Org. Lett.* **2003**, *5*, 769–771.

(14) Ben-David, I.; Rechavi, D.; Mishani, E.; Rozen, S. *J. Fluorine Chem.* **1999**, *97*, 75–78.

(15) (a) Sasson, R.; Rozen, S. *Tetrahedron* **2005**, *61*, 1083–1086. (b) Rozen, S.; Mishani, E. *J. Chem. Soc. Chem. Commun.* **1994**, 2081–2082. (c) Hagooly, A.; Rozen, S. *Chem. Commun.* **2004**, 594–595.

(16) Rozen, S. *Acc. Chem. Res.* **2005**, *38*, 803–812.

(17) Hagooly, Y.; Sasson, R.; Welch, M. J.; Rozen, S. *Eur. J. Org. Chem.* **2008**, *19*, 2875–2880.

(18) Frolov, A. F.; Novikova, G. V. *Uch. Zap. Yarosl. Tekhnol. Inst.* **1957**, *2*, 115–127; *Chem. Abstr.* **1960**, *54*, 496h.

(19) Rozen, S.; Lerman, O. *J. Org. Chem.* **1993**, *58*, 239–240.

(20) Fr. Demande FR 2295038, 1976.

(21) Williams, J. L. R.; Reynolds, D. D.; Dunham, K. R.; Tinker, J. F. *J. Org. Chem.* **1959**, *24*, 64–68.

(22) Fikse, M. A.; Bylund, W. E.; Holubowitch, N. E.; Abelt, C. J. *Synthesis* **2006**, *24*, 4118–4120.

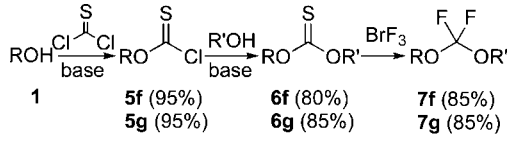
(23) Tundo, P.; Rossi, L.; Loris, A. *J. Org. Chem.* **2005**, *70*, 2219–2224.

(24) (a) Rozen, S.; Mishani, E. *J. Chem. Soc. Chem. Commun.* **1993**, 1761–1762. (b) Rozen, S.; Rechavi, D.; Hagooly, A. *J. Fluorine Chem.* **2001**, *111*, 161–165. (c) Hagooly, A.; Rozen, S. *J. Org. Chem.* **2004**, *69*, 7241–7245.

Aromatic rings in general also prevent easy hydrolysis of the difluoromethylenedioxo containing compounds. We prepared 2,4-dichlorophenylthioformate (**5f**),[25] reacted it with 3-nitrophenol, and formed *O*-2,4-dichlorophenyl-*O*-2-nitrophenylthiocarbonate (**6f**) in 80% overall yield. The consecutive reaction between **6f** and BrF_3 resulted in the novel asymmetric 1-difluoro-(2,4-dichloro-(2-nitro-phenoxy)-methoxy)-benzene (**7f**) in 85% yield, which indeed was hydrolytically stable (Scheme 4).

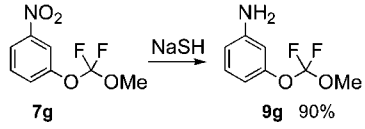
Aryl-alkyl difluoromethylenedioxy compounds could also be prepared. *O*-Methyl-*O*-3-nitrophenylthiocarbonate (**6g**) was made from 3-nitrophenyl chlorothioformate (**5g**)[25] and methanol followed by reaction with BrF_3 to form the novel asymmetric 1-(difluoro(methoxy)methoxy)-3-nitrobenzene (**7g**) in 85% yield. It should be noted that the nitro group could be reduced by NaSH to the corresponding hydrolytically stable 3-(difluoro(methoxy)methoxy)aniline (**9g**), hinting that any aromatic ring considerably retards hydrolysis. What is more, compounds of type **9g** can serve as entries to a wide range of new and desirable molecules.

SCHEME 4. Formation of Asymmetric Bis(aryloxy/alcoxy)difluoromethane Derivatives (7f, 7g)



f. R = 2,4-$Cl_2C_6H_3$; R' = 3-$NO_2C_6H_4$

g. R =3-$NO_2C_6H_4$; R' = Me

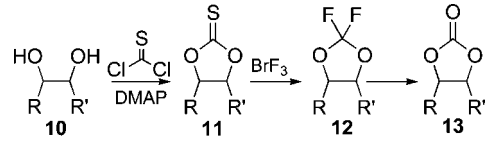


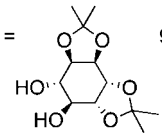
The present method allows construction of cyclic aliphatic difluorodioxolanes as well. There are only two compounds of this type reported in the literature,[11] which are sensitive to hydrolysis resulting in the respective carbonates. This happens also to the 2,2-difluoro-4-propyl-1,3-dioxolane (**12h**) prepared from **11h** and BrF_3. If not kept strictly anhydrous, **12h** quickly hydrolyzed to *O*,*O*-(1,2-pentane)carbonate (**13h**)[26] (Scheme 5). Similar behavior was noted when 2,2-difluoro-4-(methoxymethyl)-1,3-dioxolane (**12i**) was converted to 4-propyl-1,3-dioxolan-2-one (**13i**)[25] in 75% yield. With mono chloro substitution the hydrolysis proved to be much slower, as demonstrated by 2,2-difluoro-4-(chloromethyl)-1,3-dioxolane (**12j**) made from **11j**.[27] It took a few days for this compound to be transformed to 4-(chloromethyl)-1,3-dioxolan-2-one (**13j**)[25] in 80% yield (Scheme 5). A full stability was achieved when bromine atoms were attached at each side of the aliphatic difluorodioxolane, as demonstrated by 2,2-difluoro-4,5-bis(bromomethyl)-1,3-dioxolane (**12k**) obtained in 90% yield from **11k**[28] and BrF_3. This result emphasizes once again the important role of EWGs near the difluoromethylenedioxy moiety for the stability of molecules of this type.

(25) These compounds are commercially available.
(26) Rybina, G. V.; Srednev, S. S.; Bobyleva, L. I. *Russ. J. Appl. Chem.* **2003**, *76*, 842–843.
(27) Kim, C.; Park, M.; Song, B.; Park, K. *Bull. Korean Chem. Soc.* **2003**, *24*, 1371–1373.
(28) Weinstein, B.; Orton, E. U.S. Patent 4,525,540, 1985.

Using the same approach **11l** was prepared from 1,2:5,6-bis-*O*-(1-methylethylidene)-D-*chiro*-inositol (**10l**) and thiophosgene. The reaction of **11l** with BrF_3 led to the formation of the novel and stable **12l** obtained in 90% yield. The specific rotation of **12l** may indicate that the reaction with thiophosgene and BrF_3 did not affect the chiral centers of the molecule. This notion was supported by experiments with the chiral shift reagent $Pr(fod)_3$ revealing only one set of peaks indicating the presence of only one diastereoisomer.

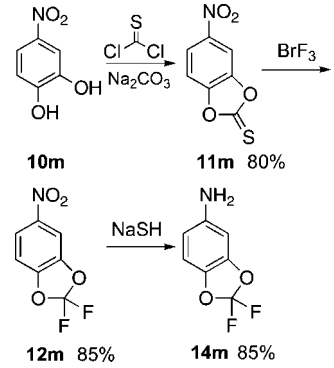
SCHEME 5. Formation of Alkyl-2,2-difluoro-1,3-dioxolane Derivatives (12)



h.R = $CH_3CH_2CH_2$ R' = H	60%	hydrolyzed	80%
i.R = $MeOCH_2$ R' = H	70%	hydrolyzed	75%
j.R = $ClCH_2$ R' = H	80%	hydrolyzed	80%
k.R = CH_2Br R' = CH_2Br	90%	90%	
l. = 	90%	90% $[\alpha]^{25}_D$ = -22	

Aromatic difluorodioxole derivatives present in some chemotherapy drugs[5] may also be prepared using BrF_3. Involving both hydroxyl groups in the 1,2-dihydroxy-4-nitrobenzene (**10m**) in the reaction with thiophosgene formed the 5-nitrobenzo(1,3)dioxole-2-thione (**11m**) in high yield. This thiocarbonate was reacted with BrF_3 to form 2,2-difluoro-5-nitrobenzo(1,3)dioxole (**12m**)[25] in 85% yield (Scheme 6). The nitro group in **12m** could be reduced to the chemically reactive amine and the stable 2,2-difluorobenzo(1,3)dioxole-5-amine (**14m**)[25] was obtained in 85% yield.

SCHEME 6. Formation of 2,2-Difluoro-5-nitrobenzo(1,3)-dioxole and 2,2-Difluorobenzo(1,3)dioxole-5-amine (12m, 14m)



In conclusion, this work describes a general method for the preparation of aromatic and aliphatic symmetric and asymmetric bis(alkoxy)difluoromethane and difluorodioxolane derivatives. We hope that the good yields and the moderate reaction conditions employing BrF_3 will further enrich the chemistry done with this reagent, which for example is extensively used

for preparation of anesthetics.[29] If handled properly the work with BrF_3 is straightforward and does not require any special or complicated equipment.

Experimental Section

General Procedure for the Preparation of *O*,*O*-Dialkyl/diarylthiocarbonates Derivatives. A solution of the appropriate alcohol (20 mmol) and Et_3N (2.8 mL, 20 mmol) in 15 mL of THF was added dropwise to a stirred solution of 0.8 mL of thiophosgene (10 mmol) in 15 mL of THF at 0 °C. Stirring was continued for 20 min. The precipitated salt was filtered, and the red liquid evaporated to provide a crude mixture containing the corresponding symmetric liquid *O*,*O*-dialkylthiocarbonates in 70−90% yield. Purification was performed using flash chromatography, although no attempt was made to prepare analytically pure samples. As for the preparation of nonsymmetric *O*,*O*-dialkylthiocarbonate derivatives, a larger excess of thiophosgene (49.8 mmol) was used at 0 °C. The corresponding alkyl chlorothioformates were usually obtained in 80−90% yield. They were passed through a flash chromatography column and added to a mixture of 20 mL of the appropriate alcohol and 3.5 mL of Et_3N. After 1 h of stirring at room temperature, the solvent was evaporated and the desired product purified by flash chromatography. In the case of aromatic alcohols, NaOH was used as a base. For the preparation of *O*,*O*-alkyl 1,3-dioxolane-2-thiones, the appropriate alkyl diols (10 mmol) were dissolved in a solution of 2.9 g of 4-di(methylamino)pyridine (DMAP) (24 mmol) in 20 mL of $CHCl_3$ and added dropwise to a stirred solution of 0.76 mL of thiophosgene (10 mmol) in 15 mL of $CHCl_3$.[30] The reaction mixture was stirred during 4 h at room temperature. The layers were separated, and the organic layer washed with saturated ammonium chloride followed by saturated NaCl solution and dried over $MgSO_4$. The desired product was separated by flash chromatography.

General Procedure for the Preparation of the Difluoro Derivatives with BrF_3. The appropriate thiocarbonate or the (1,3)-dioxole-2-thione derivatives were dissolved in 20−25 mL of $CHCl_3$ in glass flask and cooled to 0 °C. The best results were achieved when the reagent (1 molar equiv) BrF_3 was dissolved in a few milliliters of $CFCl_3$, cooled to 0 °C, and added dropwise at the same temperature using a glass dropping funnel. The reaction mixture was then washed with aqueous Na_2SO_3 till colorless. The aqueous layer extracted three times with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent followed by flash chromatography yielded the desired fluorinated compounds. Below, only a couple of detailed examples are shown. The rest of the materials are described in Supporting Information.

***O*,*O*-Bis(2-nitrophenyl)thiocarbonate (2a).**[18] Prepared from 2-nitrophenol (**1a**) (2 g) as described in the general procedure in 80% yield: 1.2 g, red oil; ^{1}H NMR 8.21 (2 H, dd, $J_1 = 8$ Hz, $J_2 = 1.5$ Hz), 7.78 (2 H, td, $J_1 = 8$ Hz, $J_2 = 1.5$ Hz), 7.56−7.46 ppm (4 H, m); ^{13}C NMR 191.8, 146.5, 141.2, 135.8, 128.3, 126.6, 125.9 ppm.

Thiocarbonate of 1,2:5,6-Bis-*O*-(1-methylethylidene)-D-*chiro*-inositol (11l). was prepared from 1,2:5,6-bis-*O*-(1-methylethylidene)-D-*chiro*-inositol (**10l**) (1.0 g, 4 mmol) as described in the general procedure in 90% yield: 1.0 g, white crystals; mp 210.8−211.7 °C; ^{1}H NMR 4.63 - 4.58 (4 H, m), 4.31 (2 H, s), 1.53 (6 H, s), 1.38 ppm (6 H, s); ^{13}C NMR 191.4, 111.3, 83.5, 78.5, 74.2, 27.2, 24.7 ppm.

Bis(2-nitrophenoxy)difluoromethane (3a). was prepared from **2a** (980 mg) as described in the general procedure in 80% yield: 1.2 g, yellow crystals, mp 54 °C; ^{1}H NMR 7.79 (2 H, dd, $J_1 = 8$ Hz, $J_2 = 1.5$ Hz), 7.55 (2 H, td, $J_1 = 8$ Hz, $J_2 = 1.5$ Hz), 7.43−7.27 ppm (4 H, m); ^{13}C NMR 120.6 (t, $J = 259$ Hz), 142.9, 142.0, 134.2, 127.6, 125.8, 124.1 ppm; ^{19}F NMR −55.5 ppm (s); HRMS (ESI-Qq TOF) *m*/*z* calcd for $C_{13}H_8N_2F_2NaO_6$ 349.0242 $(MNa)^+$, found 349.0197 $(MNa)^+$. Anal. Calcd for $C_{13}H_8F_2N_2O_6$: C, 47.86; H, 2.47; N, 8.58. Found: C, 47.83; H, 2.34; N, 8.30.

Difluoromethylation of 1,2:5,6-Bis-*O*-(1-methylethylidene)-D-*chiro*-inositol (12l). was prepared from **11l** (1.0 g) as described in the general procedure in 90% yield (920 mg); white crystals, mp 141−142 °C; ^{1}H NMR 4.53 (2 H, s), 4.46−4.44 (2 H, m), 4.08−4.07 (2 H, m), 1.52 (6 H, s), 1.36 ppm (6 H, s); ^{13}C NMR 131.0 (t, $J = 248$ Hz), 111.3, 80.8, 76.7, 74.7, 27.2, 24.6 ppm; ^{19}F NMR −57.7 ppm (2 F, s); HRMS (ESI-Qq TOF) *m*/*z* calcd for $C_{13}H_{19}F_2O_6$ 309.1144 $(MH)^+$, found 309.1161 $(MH)^+$. Anal. Calcd for $C_{13}H_{18}F_2O_6$: C, 50.65; H, 5.89; F, 12.33. Found: C, 50.83; H, 5.92; F, 11.96. $[\alpha]^{25}_D = -22$ (*c* 0.9, EtOH).

Acknowledgment. This work was supported by the USA-Israel Binational Science Foundation (BSF), Jerusalem, Israel.

Supporting Information Available: Addition experiment details, NMR's spectra of all difluoromethylenedioxo derivatives and their novel precursor described in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801116N

(29) (a) Rozov, L. A.; Huang, C.; Halpern, D. F.; Vernice, G. G. U.S. Patent 5,283,372, 1994. (b) Rozov, L. A.; Huang, C. G.; Halpern, D. F.; Vernice, G. G.; Ramig, K. *Tetrahedron: Asymmetry* **1997**, *8*, 3023–3025.

(30) Corey, E. J.; Hopkins, B. *Tetrahedron Lett.* **1982**, *23*, 1979–1982.