H_2O/CH_3CN (1:1, v/v; 1.0 mL) as added to ethanol adduct **13b** (20.2 mg, 0.067 mmol) in a 5-mL reaction flask. The resulting homogeneous solution was stirred at room temperature for 48 h. The mixture was then diluted with water (2 mL) and extracted with $CHCl_3$ (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and chromatographed (silica gel, 4:1 hexane/2-propanol) to afford 10.6 mg (28%) of **15** as a white solid (1:1 mixture of diastereomers by ^1H NMR analysis).

(c) **Preparation in CH_3CN/H_2O from Quinone Methide 6c.** A solution of 2',3'-isopropylideneadenosine (36.9 mg, 0.121 mmol, 1.20 equiv) and H_2O/CH_3CN (1:1, v/v; 1.0 mL) was added to quinone methide **6c** (prepared from 25.8 mg, 0.101 mmol, of phenol **9**) in a reaction flask. The resulting homogeneous solution was stirred at room temperature for 48 h. The mixture was then diluted with water (2 mL) and extracted with $CHCl_3$ (3 × 5 mL). The combined organic extracts were dried (Na_2SO_4), concentrated, and chromatographed (silica gel, 4:1 hexane/2-propanol) to afford 13.2 mg (24%) of **15** as a white solid (1:1 mixture of diastereomers by ^1H NMR analysis).

15 (mixture of diastereomers): ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 3 H), 1.38 (s, 3 H), 1.60 (s, 3 H), 1.64 (s, 3 H), 2.09 (br s, 6 H), 2.26 (br m, 2 H), 2.46 (s, 6 H), 2.60–2.85 (br m, 2 H), 2.85–3.10 (br m, 2 H), 3.93 (d, J = 12.1 Hz, 1 H), 3.98 (d, J = 12.5 Hz, 1 H), 4.51 (s, 2 H), 5.10 (m, 3 H), 5.19 (t, J = 5.29 Hz, 1 H), 5.72 (br d, J = 7.21 Hz, 2 H), 5.76–5.82 (m, 2 H), 6.18 (t, J = 11.5 Hz, 2 H), 6.50 (d, J = 8.2 Hz, 1 H), 6.63 (br s, 1 H), 7.34–7.48 (m, 4 H), 7.58 (d, J = 8.1 Hz, 2 H), 7.72 (s, 1 H), 7.77 (s, 1 H), 8.31 (d, J = 8.0 Hz, 2 H), 8.45 (s, 1 H), 8.46 (s, 1 H), 11.48 (br s, 2 H); IR (CCl_4) 3422, 3255, 2938, 1763, 1624, 1583, 1477, 1383, 1374, 1332, 1210, 1114, 1082, 1054, 852 cm^{-1}; MS (FAB, positive ion, nitrobenzyl alcohol matrix) m/z 561 (M^+, 50), 518 (6), 398 (7), 346 (14), 308 (33), 212 (100); HRMS calcd for $C_{29}H_{31}N_5O_7$ 561.2223, found 561.2238. Anal. Cald for $C_{29}H_{31}N_5O_7$: C, 62.02; H, 5.56; N, 12.47. Found: C, 61.34; H, 5.45; N, 12.50.

The two diastereomers were subjected to HPLC (8-μm Rainin Dynamax silica gel column, 4.6 × 250 mm, 5:1 hexane/2-propanol; flow rate, 0.8 mL·min^{-1}; retention time, 15.62 and 16.76 min) to afford the high R_f diastereomer analytically pure. High-R_f diastereomer: ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (s, 3 H), 1.6 (s, 3 H), 2.10 (br s, 3 H), 2.26–2.32 (m, 1 H), 2.46 (s, 3 H), 2.60–2.80 (br m, 1 H), 2.80–3.20 (br m, 1 H), 3.76 (t, J = 11.8 Hz, 1 H), 3.94 (d, J = 12.7 Hz, 1 H), 4.51 (s, 1 H), 5.10 (d, J = 5.8 Hz, 1 H), 5.19 (t, J = 5.3 Hz, 1 H), 5.72 (br d, J = 7.1 Hz, 1 H), 5.81 (d, J = 4.8 Hz, 1 H), 6.14 (d, J = 11.2 Hz, 1 H), 6.50 (d, J = 8.2 Hz, 1 H), 7.37–7.48 (m, 2 H), 7.58 (d, J = 8.2 Hz, 1 H), 7.77 (s, 1 H), 8.31 (d, J = 8.0 Hz, 1 H), 8.46 (s, 1 H), 11.48 (br s, 1 H).

Acknowledgment. This work was supported by funds provided by the University of California Cancer Research Coordinating Committee and the Natioanl Institutes of Health (GM 39354). We thank Mr. Ron New and Dr. Richard Kondrat for determination of mass spectra.

Registry No. 6c, 126457-70-3; **7**, 52103-68-1; **8**, 126391-81-9; **9**, 107866-26-2; **10**, 126457-71-4; **11**, 126457-72-5; **13a**, 126457-73-6; **13b**, 126457-74-7; **14**, 362-75-4; **15** (isomer 1), 126457-75-8; **15** (isomer 2), 126457-76-9; 9,10-bis(acetyloxy)-1,4-dihydroanthracene, 126457-77-0.

Efficient Synthetic Routes to Fluorinated Isosteres of Inositol and Their Effects on Cellular Growth

Alan P. Kozikowski,*,† Abdul H. Fauq,† Garth Powis,‡ and Deborah C. Melder‡

Contribution from the Departments of Chemistry and Behavioral Neuroscience, University of Pittsburgh, Chevron Science Center, Pittsburgh, Pennsylvania 15260, and the Department of Pharmacology, Mayo Clinic, 200 First Street, S.W., Rochester, Minnesota 55905.
Received October 10, 1989

Abstract: Efficient synthetic routes to several fluorinated isosteres of inositol have been developed that are based upon the unexpected selectivity observed in the (diethylamido)sulfur trifluoride reaction of polyhydroxylated cyclohexane derivatives. The conversion of D-pinitol to 1D-1,5-dideoxy-1,5-difluoro-*neo*-inositol and to 1D-1-deoxy-1-fluoro-*myo*-inositol is reported along with a mechanistic rationale for their formation. Furthermore, the cell growth inhibitory properties of three fluorinated inositol analogues on NIH 3T3 (normal fibroblasts) and v-*sis*-transformed NIH 3T3 cells are described. These inositol isosteres hold promise as tools for furthering our understanding of the phosphatidylinositol cascade and may also offer a new strategy in the treatment of neoplastic diseases.

One of the major advances in cell biology in recent years has been the discovery of a series of intracellular signaling pathways that couple the messages derived from the binding of biologically active molecules with receptors in the cell surface to effector mechanisms within the cell. These signaling pathways have been found in all cell types and modulate the actions of hormones, neurotransmitters, growth factors, and oncogenes.[1] One of the most extensively studied signaling pathways is the phospholipase C dependent hydrolysis of membrane phosphoinositide to form inositol polyphosphates and diacylglycerol.[2] As part of the larger effort to understand the mechanism of inositol-based intracellular signaling in relation to cell growth control, we have been interested in the synthesis of fluorinated isosteres of *myo*-inositol which may act as antimetabolites for the inositol pathway.[3] Such isosteres could act either by blocking the formation of certain inositol phosphates or by forming fraudulent analogues.

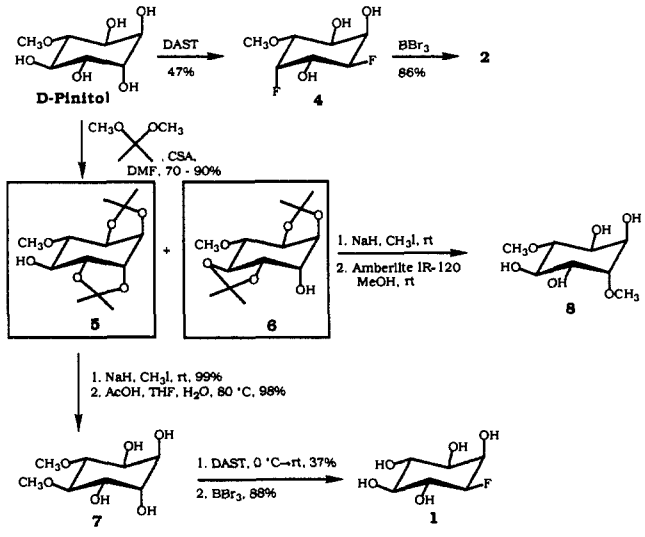
In this article we detail an expedient route to 1D-1-deoxy-1-fluoro-*myo*-inositol (**1**) as well as 1D-1,5-dideoxy-1,5-difluoro-*neo*-inositol (**2**). The synthesis of the latter compound rests upon the surprising regioselectivity observed in the fluorination reaction of an inositol derivative with DAST ((diethylamido)sulfur trifluoride). While we have already reported a 10-step route to the

† University of Pittsburgh.
‡ Mayo Clinic.

(1) Abdel-Latif, A. A. *Pharmacol. Res.* **1986**, *38*, 228. Berridge, M. J. *Biochim. Biophys. Acta* **1987**, *907*, 33. Rasmussen, H. *N. Engl. J. Med.* **1986**, *314*, 1094 and 1164. *Inositol Lipids in Cell Signaling*; Michell, R. H., Drummond, A. H., Downes, C. P., Eds.; Academic Press: London, 1989.
(2) Putney, J. W.; Takemura, H.; Hughes, A. R.; Horstman, D. A.; Thastrup, O. *FASEB J.* **1989**, *3*, 1899. Whitman, M.; Cantley, L. *Biochim. Biophys. Acta* **1988**, *948*, 327.
(3) Kozikowski, A. P.; Xia, Y.; Rusnak, J. M. *J. Chem. Soc., Chem. Commun.* **1988**, 1301. Kozikowski, A. P.; Fauq, A. H.; Rusnak, J. M. *Tetrahedron Lett.* **1989**, *30*, 3365 and references cited therein. For a recent review on the synthesis of *myo*-inositol phosphates, see: Billington, D. C. *Chem. Soc. Rev.* **1989**, *18*, 83.

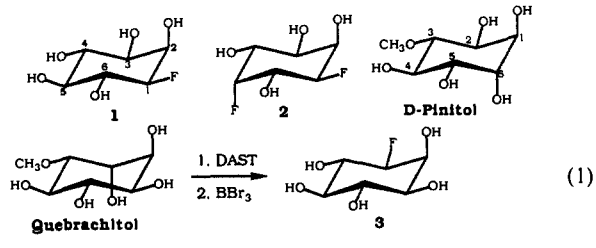
0002-7863/90/1512-4528$02.50/0

Scheme I. Synthetic Routes to Fluorinated Isosteres of *myo*-Inositol



1-fluoro isostere of *myo*-inositol,[3] this route was inadequate for the purpose of producing the compound in the quantities needed for the biological studies. The chemistry used to synthesize the title compounds, a rationalization of the startling selectivity observed in the DAST reaction of a polyhydroxylated cyclohexane derivative, and a preliminary description of the cell growth inhibitory properties exhibited by these fluorinated isosteres of inositol are presented herein.

While *myo*-inositol served as the starting material for the preparation of **1** in our earlier work,[3] we now chose D-pinitol as a possible precursor, for its use would avoid the necessity of carrying out a chemical resolution step. D-Pinitol, which is available from several conifers,[4] is an isomer of L-quebrachitol, a product isolated as a byproduct of the rubber tree industry. Since in recent work we found that quebrachitol could be converted to (−)-1D-3-deoxy-3-fluoro-*myo*-inositol (**3**) in two steps by DAST treatment followed by demethylation with BBr_3 (eq 1),[3] it appeared reasonable that D-pinitol should also undergo a selective fluorination reaction to provide the 1-fluoro isostere after demethylation.

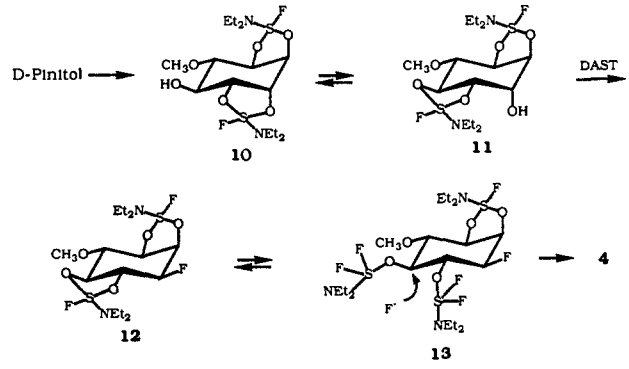


(1)

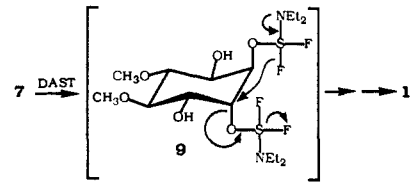
Surprisingly, when a powdered sample of crude D-pinitol was reacted with DAST, a single new product was isolated in 47% yield which proved to be the difluoro compound **4** by a combination of ^1H, ^{13}C, and ^{19}F NMR and mass spectroscopy (Scheme I). The structure of **4** was further confirmed by a single-crystal X-ray analysis.[5] Demethylation with BBr_3 then furnished 1D-1,5-dideoxy-1,5-difluoro-*neo*-inositol (**2**).

Thus, to procure the monofluoro isostere **1**, it became necessary to selectively protect the C-4 hydroxy group of D-pinitol. This was best accomplished by first converting pinitol to the readily separable diacetonides **5** and **6** (ratio 1.4:1, respectively, Scheme I).[6] Intermediate **5** was then methylated and the acetonides cleaved to afford **7**. On DAST treatment followed by BBr_3 demethylation the 1-fluoro compound **1** was obtained. The spectral and analytical data acquired for **1** were fully consistent with that obtained for the 1-fluoro isostere generated in 10 steps by the *myo*-inositol route.[3] This five-step sequence can be completed within a few days time and is clearly superior to the earlier route. Interestingly, the dimethyl compound **8** available from the diacetonide **6** failed to react with DAST under the reaction conditions employed for **7**.

Scheme II. A Possible Mechanism for the Selective Conversion of D-Pinitol to Difluoride **4**



The regioselectivity observed in the reaction of the C_2 symmetric molecule **7** can be understood through the more ready displacement of an activated axial hydroxyl group as opposed to displacement of an equatorial hydroxyl (see **9** in eq 2).[7]



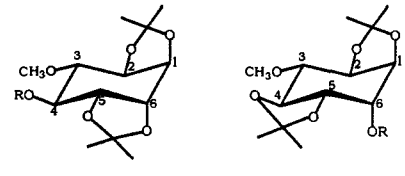
(2)

While the selective conversion of D-pinitol to **2** is less obvious, we tentatively suggest that D-pinitol may react with the excess DAST to generate an equilibrating mixture of bis-dioxathiolanes **10** and **11** (Scheme II).[8] The latter dioxathiolane, which bears an axial hydroxyl, now reacts with additional DAST to provide

(4) D-Pinitol is available by extraction from sugar pine, soft and white pines, and redwood: Berthelot, M. *C. R. Hebd. Seances Acad. Sci.* **1855**, *41*, 392. Linstedt, G. *Acta Chem. Scand.* **1951**, *5*, 129. Sherrard, E. C.; Kurth, E. F. *Ind. Eng. Chem.* **1928**, *20*, 722.

(5) The X-ray structure analysis was carried out under the direction of Dr. Jaime E. Abola in the Department of Chemistry's X-ray Diffraction Laboratory. In the proton NMR of **4** large vicinal H–F couplings were observed for H-4 and H-6 ($J_{F5,H6}$ = 31 Hz, $J_{F5,H4}$ = 29 Hz), whereas smaller coupling constants were observed for equatorial H-2 and axial H-6 ($J_{F1,H2}$ = 8.3 Hz, $J_{F1,H6}$ = 3.2 Hz).

(6) The regiochemical assignments of the diacetonides **5** and **6** were made on the basis of the spectral properties of their corresponding acetates **5a** and



5a, R = Ac
5b, R = Me

6a, R = Ac
6b, R = Me

6a. The C-4 proton in **5a** exhibited large vicinal coupling constants in the 300-MHz ^1H NMR ($J_{4,5}$ = 8.2 Hz, $J_{3,4}$ = 11.3 Hz) indicating its axial orientation. The corresponding coupling constants for the C-6 proton of **6a** were small ($J_{1,6}$ and $J_{5,6}$ = ~3 Hz), which are indicative of its equatorial disposition. These structural assignments were further confirmed by examining the ^{13}C NMR's of the dimethyl derivatives **5b** and **6b**. Whereas a 13-line spectrum was observed for **6b**, an eight-line spectrum clearly established the 2-fold axial symmetry of **5b**. Also see: Angyal, S. J.; MacDonald, C. G. *J. Chem. Soc.* **1952**, 686. Anderson, A. B.; MacDonald, D. L.; Fischer, H. O. L. *J. Am. Chem. Soc.* **1952**, *74*, 1479. We have recently found that if acetonide formation is carried out at 80–82 °C employing 2-methoxypropene in DMF, a 90% yield of the desired isomer **5** can be obtained. No trace of the other isomer **6** is detectable by TLC or ^1H NMR analysis of the crude reaction mixture. Additionally we note that the treatment of **6** with DAST in CH_2Cl_2 at 0 °C → room temperature for 1 h gave rise to a complicated mixture of nonfluorinated products.

(7) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; pp 224–226.

(8) For studies on the use of DAST in the carbohydrate field, see: Card, P. J.; Reddy, G. S. *J. Org. Chem.* **1983**, *48*, 4734. Card, P. J. *J. Org. Chem.* **1983**, *48*, 393. Somawardhana, C. W.; Brunngraber, E. G. *Carbohydr. Res.* **1983**, *121*, 51.

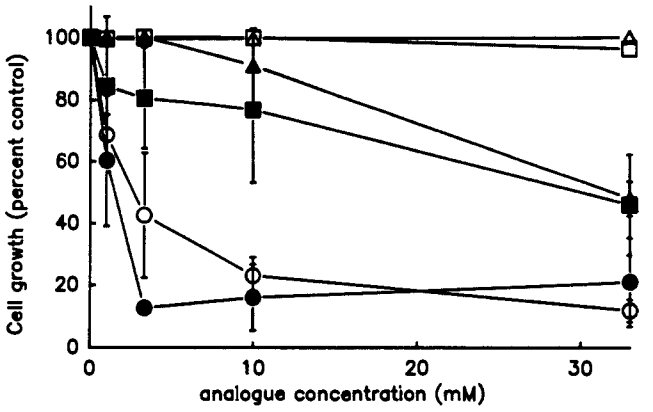


Figure 1. Concentration–response curves for inhibition of cell growth by *myo*-inositol analogues. NIH 3T3 cells (open symbols) and v-sis transformed NIH 3T3 cells (closed symbols) were plated at 3×10^5 cells/well in 1.9 $cm^2 \times 24$ well culture plates in 0.5 mL Dulbecco's modified Eagle's medium and 10% heat inactivated calf serum for 24 hr at 37 °C under 5% CO_2 in air. The medium was then replaced with *myo*-inositol-free Roswell Park Memorial Institute (RMPI) 1640 medium and 10% dialyzed fetal calf serum with added inositol analogues. The cells were allowed to grow for 4 days at 37 °C under 5% CO_2 in air, then liberated with 0.05% trypsin and 0.5 mM EDTA and counted with use of an automated cell counter. (○, ●) 1D-3-Deoxy-3-fluoro-*myo*-inositol, (△, ▲) 1D-1-deoxy-1-fluoro-*myo*-inositol, and (□, ■) 1D-1,5-dideoxy-1,5-difluoro-*neo*-inositol. Values are means of two to three experiments in which each concentration was measured with use of triplicate cultures. Bars are standard deviations.

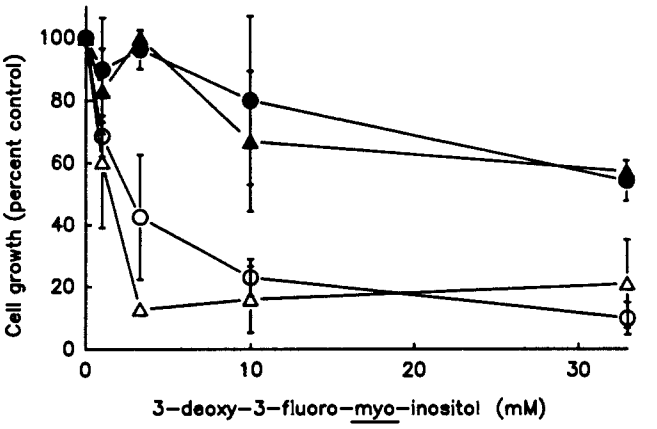


Figure 2. Inhibition of cell growth by 1D-3-deoxy-3-fluoro-*myo*-inositol in the absence and in the presence of *myo*-inositol. Cell growth was measured as described in Figure 1 with *myo*-inositol free RPMI 1640 medium and 10% dialyzed fetal calf serum (open symbols), or in RPMI 1640 medium containing 0.2 mM *myo*-inositol and 10% fetal calf serum (closed symbols). (○, ●) NIH 3T3 cells, and (△, ▲) v-sis transformed NIH 3T3 cells. Values are means of three experiments with each value measured with triplicate cultures. Bars are standard deviations. The values for *myo*-inositol-free medium are the same as in Figure 1.

the equatorial fluoride **12**. If we assume that the less stable dioxathiolane derived from the *trans*-diol can equilibrate with its open form **13**, then the DAST activated equatorial oxygen more remote from the electronically deactivating fluorine atom can undergo displacement to give **4**. Alternatively, direct fluoride ion displacement on the dioxathiolane intermediate **12** may take place as well. Nucleophilic displacement at the C-3 center is presumably impeded by the greater stability of the dioxathiolane derived from the *cis*-diol.

The growth inhibitory effects of the 1-fluoro and 3-fluoro compounds **1** and **3**, respectively, and the difluoro compound **2** on NIH 3T3 (contact inhibited Swiss mouse embryo) cells[9] and v-*sis*-transformed NIH 3T3 cells[10] (provided by Dr. S. Aaronson, NCI) were examined over a 4-day period in a *myo*-inositol-free medium. Figure 1 summarizes the concentration-dependent inhibition of cellular growth. The estimated EC_{50} values for inhibition of NIH 3T3 and v-*sis*-transformed NIH 3T3 cell growth were for 3-deoxy-3-fluoro-*myo*-inositol 13 and 2 mM, respectively, and for 1-deoxy-1-fluoro-*myo*-inositol and 1D-1,5-dideoxy-1,5-difluoro-*neo*-inositol greater than 33 mM (the highest concentration tested) in all cases. In these experiments the 3-fluoro compound was the most potent analogue tested. Of considerable importance is the observation that 3-deoxy-3-fluoro-*myo*-inositol will inhibit cell growth in the presence of *myo*-inositol in the growth medium, although about an order of magnitude less effectively than in the absence of *myo*-inositol (Figure 2). It should be noted that RPMI 1640 medium contains relatively high levels of *myo*-inositol (0.2 mM) compared to some other growth media and serum (0.03 mM).[11] A potent competitive block of [^{3}H]-*myo*-inositol uptake by 3-deoxy-3-fluoro-*myo*-inositol was also observed, a finding which demonstrates that the fluoro compound probably serves as a substrate for the *myo*-inositol transporter. While these data and results from the measurement of intracellular calcium changes (not shown here) suggest that the 3-fluoro compound is being incorporated into the cell membrane phosphoinositides, the synthesis of ^{3}H-labeled 3-deoxy-3-fluoro-*myo*-inositol will be required to verify this notion.

In summation, the unique chemical selectivity observed in the reaction of D-pinitol and quebrachitol with DAST provides an expedient route to novel, biologically active fluorinated isosteres of inositol. Further experiments will address the nature and extent to which these "unnatural" products are incorporated into the phosphatidylinositol cycle in an effort to further dissect the relevance of the various inositol phosphates to cell signaling events. Since the growth inhibitory effects of these compounds are observed at concentrations within the physiological range, it is entirely conceivable that such agents may eventually find clinical use in the treatment of neoplastic diseases.[12,13]

Experimental Section

Preparation of 1D-1,5-Dideoxy-1,5-difluoro-*neo*-inositol (2). To a stirred powdered sample of D-pinitol (150 mg, 0.77 mmol) under N_2 at −50 °C was added via syringe (diethylamido)sulfur trifluoride (neat, 0.423 mL, 3.2 mmol). The mixture was warmed to −20 °C over 0.5 h. After stirring at this temperature for 0.5 h, the mixture was warmed to 0 °C over 0.5 h. The cold bath was removed, and stirring was continued at room temperature for 2 h. After the mixture was cooled to −50 °C, methanol (2 mL) was added cautiously. The methanol was removed by rotary evaporation, and the light brown residue was directly chromatographed on silica gel 60 (230–400 mesh ASTM) with MeOH/EtOAc (1:10) as eluent to afford 71 mg (47%) of the product **4** as a white powder: $[\alpha]^{23}_D$ +26° (*c* 0.018 g/mL, MeOH); IR (Nujol) 3340, 2940, 1684, 1624, 1446, 1065, 1022 cm^{-1}; mp 196–198 °C dec; ^{1}H NMR (D_2O, 300 MHz) δ 5.15 (ddt, J = 52.2, 5.8, 3.2 Hz, H-5), 4.67 (ddd, J = 47.7, 10.5, 3.3 Hz, H-1), 4.31 (dt, J = 8.3, 2.9 Hz, H-2), 4.14 (dtd, J = 31.13, 10.7, 2.5 Hz, H-6), 3.85 (dt, J = 10.3, 2 Hz, H-3), 3.58 (ddd, J = 29.2, 10.3, 2 Hz, H-4), 3.48 (s, CH_3); ^{13}C NMR (D_2O) δ 92.46 (dd, J = 179.5, 4.3 Hz, C-1), 90.87 (dd, J = 174.6, 11.8 Hz, C-5), 79.5 (d, J = 17.0 Hz, C-2 or C-4), 70.9 (d, J = 16 Hz, C-2 or C-4), 69.5 (dd, J = 9.7, 4.8 Hz, C-3), 68.7 (t, J = 18 Hz, C-6), 59.07 (s, OCH_3); mass spectrum, m/z 199 (M^+), 180 ($M^+ - H_2O$), 160, 148, 131, 87, 43; exact mass calcd for $C_7H_{13}F_2O_4$ 199.0782, found 199.0782.

A mixture of neat BBr_3 (0.71 mmol, 68 μL) and 1D-1,5-dideoxy-1,5-difluoro-4-*O*-methyl-*neo*-inositol (20 mg, 0.10 mmol) in 1 mL of CH_2Cl_2 was stirred for 18 h under argon. The methylene chloride was evaporated under reduced pressure, and methanol (2 mL) was added cautiously at −50 °C. After the mixture was stirred for 5 min at room temperature, the methanol was removed by rotary evaporation. This operation was repeated three times, and the final residue was chromatographed on silica

(9) Jainchill, J. L.; Aaronson, S. A.; Todaro, G. *J. J. Virol.* **1909**, *4*, 549.
(10) Doolittle, R. F.; Hunkapiller, M. W.; Wood, L. E.; Devare, S. G.; Robbins, K. C.; Aaronson, S. A.; Antoniades, H. N. *Science* **1983**, *221*, 275.
(11) Nixon, D. A. *J. Physiol. (London)* **1953**, *119*, 189.
(12) For a recent study of the ability of other halogenated inositols to serve as substrates for phosphatidylinositol synthetase, see: Moyer, J. D.; Reizes, O.; Ahir, S.; Jiang, C.; Malinowski, N.; Baker, D. C. *Mol. Pharmacol.* **1988**, *33*, 683. Moyer, J. D.; Reizes, O.; Malinowski, N.; Jiang, C.; Baker, D. C. *ACS Symp. Ser.* **1988**, *No. 374*, 43. For other work in this area, also see: Boehm, M. F.; Prestwich, G. D. *Tetrahedron Lett.* **1988**, *29*, 5217.
(13) Quebrachitol has recently become available from the Aldrich Chemical Co., Inc.

gel 60 (230–400 mesh) with 30% MeOH/$CHCl_3$ as eluent to furnish the product as a white solid (16 mg, 86%): $[\alpha]^{23}_D$ +3.6° (*c* 0.016 g/mL, deionized water); IR (Nujol) 3500, 1175, 1060, 920 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 4.94 (ddt, *J* = 52.2, 6, 2.3 Hz, H-3), 4.64 (dd, *J* = 9.7, 3.2, 0.5 H-1, the other half assumed to be under D_2O peak), 4.36 (dt, *J* = 8.3, 2.9 Hz, H-6), 4.2 (dtd, *J* = 30, 10.8, 3.2 Hz, H-2), 4.0 (dd, *J* = 10.4, 2.2 Hz, 0.5 H-4), 3.94–3.82 (m, H-5 and 0.5 H-4); ^{13}C NMR (D_2O) δ 94.3 (dd, *J* = 177, 9.8 Hz, C-1 or C-3), 91.8 (dd, *J* = 175, 4.7 Hz, C-1 or C-3), 70.3 (d, *J* = 16.9 Hz, C-4 or C-6), 69.4 (d, *J* = 9.5 Hz, C-5), 69.2 (d, *J* = 16.8 Hz, C-4 or C-6), 68.0 (t, *J* = 19.4 Hz, C-2); mass spectrum, *m/z* 166 (M^+ – 18), 146, 129, 73; exact mass calcd for $C_6H_8F_2O_3$ 166.0441, found 166.0441.

Preparation of 1,2:5,6-Diisopropylidene-3-*O*-methyl-*chiro*-inositol (5) and 1,2:4,5-Diisopropylidene-3-*O*-methyl-*chiro*-inositol (6). A mixture of D-pinitol (3.68 g, 20 mmol) and 2,2-dimethoxypropane (9.8 mL, 80 mmol) in 20 mL of DMF containing $MgSO_4$ (3.0 g) and 100 mg of camphorsulfonic acid was stirred under argon at 60 °C for 16 h. Triethylamine (2 mL) was added, the bulk of DMF was removed under reduced pressure, and the residue was partitioned between saturated sodium bicarbonate solution and ethyl acetate. The organic extracts (3 × EtOAc) were washed with water and brine and dried ($MgSO_4$). After evaporation of the volatiles, the residue was chromatographed on silica gel (230–400 mesh) with 2:5 EtOAc/hexanes as eluent to afford 2.1 g of the diacetonide **5** as a crystalline solid and 1.6 g of its isomer **6** as an oil in a 1.4:1 ratio (total yield 76.2%).

The diacetonide **5** gave the following physical data: $[\alpha]^{23}_D$ –42° (*c* 0.021 g/mL, $CHCl_3$); mp 95–97 °C; IR (Nujol) 3500, 2985, 2931, 1373, 1220, 1092, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.23–4.19 (m, 4 H), 3.6 (dd, 1 H, *J* = 11.1, 6.8 Hz), 3.59 (s, 3 H), 3.19 (dd, 1 H, *J* = 11.1, 6.3 Hz), 2.96 (bs, 1 H), 1.52 (s, 3 H), 1.51 (s, 3 H), 1.35 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 110.2, 109.8, 81.3, 79.0, 78.5, 77.1, 76.7, 71.5, 59.2, 27.8, 27.7, 25.3, 25.1; mass spectrum, *m/z* 259 (M^+ – CH_3), 201, 141, 109, 99, 87, 73, 59; exact mass calcd for $C_{12}H_{19}O_6$ 259.1182, found 259.1182.

The diacetonide **6** gave the following physical data: $[\alpha]^{23}_D$ +72.5° (*c* 0.020 g/mL, $CHCl_3$); IR (thin film) 3490, 2988, 2936, 1373, 1223, 1093, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.48 (bs, 1 H), 4.36 (bd, 1 H, *J* = 8 Hz), 4.21 (t, 1 H, *J* = 6 Hz), 3.92 (t, 1 H, *J* = 11 Hz), 3.79 (dd, 1 H, *J* = 11, 3 Hz), 3.58 (s, 3 H), 3.48 (dd, 1 H, *J* = 10.8, 5 Hz), 2.39 (bs, 1 H), 1.52 (s, 3 H), 1.49 (s, 3 H), 1.45 (s, 3 H), 1.36 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.7, 109.2, 84.3, 80.6, 79.1, 77.1, 74.3, 65.9, 58.6, 27.8, 27.2, 26.6, 25.5; mass spectrum, *m/z* 259 (M^+ – 15), 201, 141, 109, 87, 59; exact mass calcd for $C_{12}H_{19}O_6$ 259.1182, found 259.1181.

Preparation of 1,2:5,6-Diisopropylidene-3,4-di-*O*-methyl-*chiro*-inositol. A 50% oil dispersion (371 mg, 7.7 mmol) was washed with hexane and suspended in 10 mL of THF under argon. Stirring was started, and a solution of the diacetonide **5** in 20 mL of THF was added via cannula. Stirring was continued at 23 °C for 45 min. Neat methyl iodide (0.96 mL, 15.5 mmol) was then added, and the resulting mixture was stirred at 23 °C overnight. The reaction was quenched by adding a saturated solution of ammonium chloride. Water was added and the product was extracted with ether (three times). The ethereal extracts were successively washed with aqueous $NaHSO_3$ solution, water, and brine and dried ($MgSO_4$). After evaporation virtually pure product (1.178 g, 99%) was obtained: $[\alpha]^{23}_D$ –42.75° (*c* 0.016 g/mL, $CHCl_3$); mp 88–89 °C; IR (thin film) 2980, 1373, 1220, 1098, 1080 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.20–4.15 (m, 4 H), 3.59 (s, 6 H), 3.28–3.26 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 109.57, 81.15, 78.81, 76.53, 59.37, 27.60, 25.07; mass spectrum, *m/z* 288 (M^+), 273, 215, 155, 73, 59; exact mass calcd for $C_{14}H_{24}O_6$ 288.1580, found 288.1573.

The 1,2:4,5-diisopropylidene 3,6-dimethyl ether was prepared from **6** under the above conditions in similar yield: mp 94–96 °C; IR (film) 2988, 2907, 1458, 1373, 1240, 1185, 1057, 891 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.30 (dd, 1 H, *J* = 5.6, 1.7 Hz), 4.15 (dd, 1 H, *J* = 5.8, 5.8 Hz), 4.0 (m, 1 H), 3.96 (t, 1 H, *J* = 10 Hz), 3.78 (dd, 1 H, *J* = 10, 2.6 Hz), 3.56 (s, 6 H), 3.43 (dd, 1 H, *J* = 10, 6 Hz), 1.5 (s, 3 H), 1.46 (s, 6 H), 1.35 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 111.29, 109.19, 84.66, 80.56, 77.91, 77.19, 59.99, 58.43, 27.78, 27.07, 26.47, 25.59; mass spectrum, *m/z* 288 (M^+), 273 (M^+ – CH_3), 256, 213, 155, 87; exact mass calcd for $C_{14}H_{24}O_6$ 288.1573, found 288.1570.

Preparation of 3,4-Di-*O*-methyl-*chiro*-inositol (7). 1,2:5,6-Diisopropylidene-3,4-di-*O*-methyl-*chiro*-inositol (0.98 g, 3.4 mmol) was dissolved in 40 mL of a mixture of acetic acid/THF/H_2O (2:1:1), and the solution was heated at 80 °C for 12 h. After cooling, the volatiles were removed by rotary evaporation. The residual acetic acid was stripped off by azeotropic distillation with toluene to give the *chiro*-inositol dimethyl ether **7** (0.69 g, 98%) as a white solid: $[\alpha]^{23}_D$ +62.9° (*c* 0.013 g/mL, MeOH); mp 187–188 °C; IR (Nujol) 3402, 3352, 1490, 1050 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 4.0 (m, 2 H), 3.81 (t, 1 H, *J* = 2.5 Hz), 3.79 (t, 1 H, *J* = 2.5 Hz), 3.6 (s, 3 H), 3.42 (dd, 1 H, *J* = 9, 2.7 Hz), 3.36 (dd, 1 H, *J* = 9, 2.7 Hz); ^{13}C NMR (75 MHz, D_2O) δ 83.18, 72.18, 70.79, 60.47; mass spectrum, *m/z* 208 (M^+), 158, 130, 116, 103, 87, 73, 57; exact mass calcd for $C_8H_{16}O_6$ 208.0947, found 208.0947.

3,6-Di-*O*-methyl-*chiro*-inositol (**8**) was obtained in similar yield by hydrolysis of 1,2:4:5-diisopylidene-3,6-di-*O*-methyl-*chiro*-inositol: $[\alpha]^{23}_D$ +52.8° (*c* 0.078 g/mL, MeOH); mp 127–128 °C; IR (Nujol) 3450, 2938, 1458, 1093 cm^{-1}; ^1H NMR (300 MHz, D_2O) δ 4.19 (t, 1 H, *J* = 3.6 Hz), 3.74 (dd, 1 H, *J* = 10, 3.4, 3.71 Hz), (dd, 1 H, *J* = 9.9, 3.3 Hz), 3.6 (dd, 1 H, *J* = 6.3, 3.6 Hz), 3.57 (s, 3 H), 3.43 (s, 3 H), 3.30 (t, 1 H, *J* = 9.9 Hz); ^{13}C NMR (75 MHz, D_2O) δ 83.04, 81.72, 72.85, 70.68, 70.38, 68.54, 60.19, 59.00; mass spectrum, *m/z* 208 (M^+ + 1), 190 (M^+ – 18), 158, 87; exact mass calcd for $C_8H_{16}O_6$ 208.0947, found 208.0947.

Preparation of 1D-1-Deoxy-1-fluoro-4,5-di-*O*-methyl-*myo*-inositol. To a stirred powder of 1D-3,4-di-*O*-methyl-*chiro*-inositol (**7**) (0.125 g, 0.60 mmol, placed in a flame-dried flask under argon, was added (diethylamido)sulfur trifluoride (372 μL, 2.82 mmol) at 0 °C. The cold bath was removed after 10 min and the light brown mixture was vigorously stirred for 1 h at 23 °C. The mixture was cooled to –20 °C and methanol (2 mL) was added cautiously. The resulting brown solution was stirred at 23 °C for 30 min. The volatiles were stripped off at reduced pressure, and the residue was chromatographed on silica gel (230–400 mesh) with a gradient of elution with 40% EtOAc/hexane–100% EtOAc to furnish the product as a glass; yield = 43 mg (37%, based on the total starting material): $[\alpha]^{23}_D$ +18.2° (*c* 0.0075 g/mL, MeOH); mp 141–143 °C; ^1H NMR (300 MHz, D_2O) δ 4.44 (ddd, 1 H, *J* = 47.6, 9.8, 2.9 Hz), 4.26 (dt, 1 H, *J* = 8.2, 2.7 Hz), 3.98 (dt, 1 H, *J* = 22.1, 9.8 Hz), 3.7–3.6 (multiplicity not clear due to signals of two methyl groups), 3.61 (s, 3 H), 3.60 (s, 3 H), 3.17 (t, 1 H, *J* = 9.5 Hz); ^{13}C NMR (75 MHz, D_2O) δ 92.0 (d, *J* = 170.8 Hz), 82.70 (d, *J* = 11.8 Hz), 81.96 (s), 70.44 (d, *J* = 18.9 Hz), 70.01 (d, *J* = 17 Hz), 69.51 (d, *J* = 10.4 H), 60.09 (s), 60.00 (s); mass spectrum, *m/z* 210 (M^+), 192 (M^+ – H_2O), 174 (M^+ – $2H_2O$), 160, 116, 87, 73; exact mass calcd for $C_8H_{15}O_5F$ 210.0562, found 210.0562.

Preparation of 1D-1-Fluoro-1-deoxy-*myo*-inositol (1). A flame-dried flask was charged with 1-deoxy-1-fluoro-4,5-di-*O*-methyl-*myo*-inositol (50 mg, 0.24 mmol) and 5 mL of methylene chloride under argon. Neat boron tribromide (200 μL, 2.13 mmol) was added via syringe at 0 °C. After 5 min, the cold bath was removed, and the mixture was magnetically stirred for 2 h at 23 °C. Methylene chloride was evaporated under reduced pressure, and methanol (4 mL) was added cautiously via syringe at –30 °C. The resulting brown solution was stirred for 1 h followed by evaporation of the volatiles at reduced pressure. The methanol addition and evaporation step was repeated five times. Distilled water (10 mL) was added and the impurities were extracted with methylene chloride. The aqueous phase was concentrated to afford 40 mg of crude product which was purified on silica gel (230–400 mesh) with 1:1 MeOH/$CHCl_3$ as eluent to yield 38 mg (88%) of **1**: $[\alpha]^{23}_D$ +6.5° (*c* 0.0035 g/mL, H_2O); ^1H NMR, ^{19}F NMR, IR, and mass spectral data were found to be identical with (–)-3-fluoro-3-deoxy-*myo*-inositol as reported previously from these laboratories (ref 3 of text).

Acknowledgment. We are indebted to the Mental Health Research Center (Proposal No. 159) and NIH Grant No. CA42286 for initial financial support of this study. We thank Professor S. J. Angyal of the University of South Wales for an initial sample of quebrachitol, the Director of the Rubber Institute of Malaysia, Kuala Lumpur for larger samples of crude quebrachitol, and Professor C. Ballou of the University of California, Berkeley for samples of both quebrachitol and pinitol.

Supplementary Material Available: Structural report for 1,5-dideoxy-1,5-difluoro-4-*O*-methyl-*neo*-inositol, including a description of data collection, atomic coordinates and isotropic thermal parameters, bond lengths, bond angles, and anisotropic thermal parameters (11 pages). Ordering information is given on any current masthead page.