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A SIMPLIFIED ROUTE TO THE PHOSPHATIDYLINOSITOL CASCADE INHIBITOR ---- (-)-1L-1-DEOXY-1-FLUORO-*MYO*-INOSITOL

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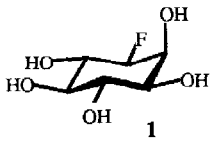
Summary: A two step synthesis of the title compound from the rubber serum by-product, quebrachitol, is reported.

As part of an effort to elucidate the biological role of the various inositol phosphates generated in the response of a cell to a drug, hormone, or neuropeptide,[1] we have recently described the synthesis of (-)-1L-1-deoxy-1-fluoro-*myo*-inositol (**1**) (which also corresponds to 3-deoxy-3-fluoro-*myo*-inositol in the D series) and (+)-1D-1-deoxy-1-fluoro-*myo*-inositol (**2**).[2] These compounds have been investigated for their effects on cellular growth in PC12 cells and found to



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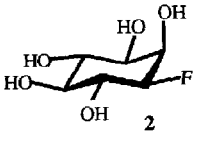

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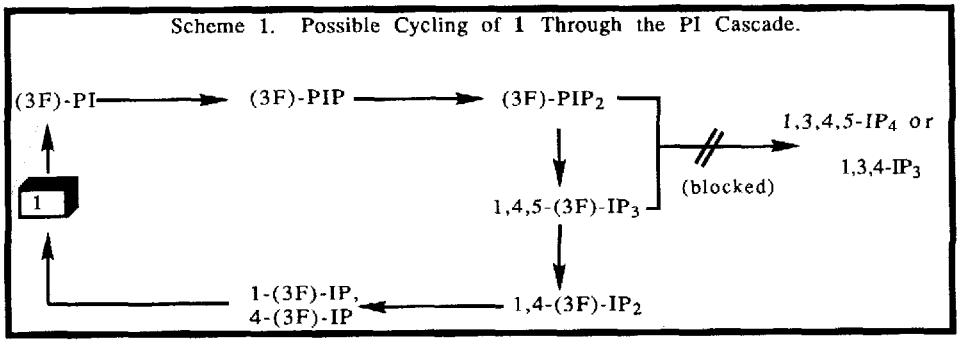
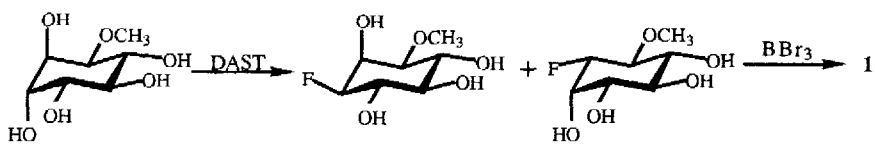
markedly inhibit cellular replication in a dose dependent manner.[3] Based upon [^{3}H]-*myo*-inositol uptake studies, we currently believe that **1** is capable of entering into the PI cycle thereby blocking the eventual production of both inositol 1,3,4,5-tetrakisphosphate and inositol 1,3,4-trisphosphate (see accompanying Scheme 1).

Scheme 1. Possible Cycling of **1** Through the PI Cascade.

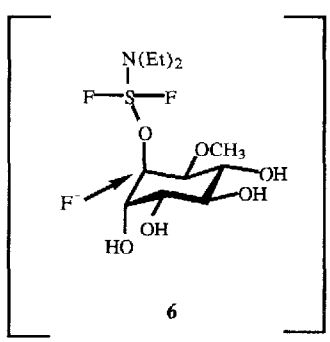


To probe such possibilities further, it became necessary to acquire **1** in optically pure form on a large scale. Consequently, our previously reported route to **1** which requires ten synthetic steps and an expensive chemical resolution employing (*S*)-(-)-camphanic acid chloride was found wanting. In searching for a simpler route to **1**, the existence of the optically active inositol isomer quebrachitol came to our attention. This molecule is available as a waste product from natural rubber serum, and possesses the requisite "masked" element of symmetry essential to providing a short route to **1** in optically pure form.

Quebrachitol (**3**), isolated from waste rubber solids by ethanol extraction, was simply treated with neat DAST (diethylaminosulfur trifluoride), at 20 °C (water bath), and the resulting mixture of the two *O*-methyl, fluoro isomers **4** and **5** was deprotected with BBr_3 in methylene chloride to provide **1** in 35-50% overall yield.[4] The product obtained by this simple two-step protocol showed identical properties (^1H NMR, IR, MS, TLC and optical rotation) with the product obtained previously by the multi-step sequence.[2] The "latent" symmetry of 3-deoxy-3-fluoro-1-*O*-methyl-*myo*-inositol (**4**) and its 3-deoxy-3-fluoro-4-*O*-methyl analogue (**5**) is revealed upon their exposure to BBr_3. Evidently, the mixture of isomers **4** and **5** is formed by the selective replacement of either one of the two axial hydroxyl groups by a fluorine atom. This result may be the consequence of the more favored attack by fluoride on the DAST intermediate formed from an axial hydroxy group (see structure 6). Intermolecular attack of a fluoride ion from the axial direction upon the DAST intermediate formed from an equatorial hydroxyl group is made difficult by 1,3-diaxial interactions.[6]



Quebrachitol(3) **4** **5**



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The two step experimental procedure follows:

DAST (391 mg, 2.42 mmol) was added to the solid quebrachitol (157 mg, 0.81 mmol) at 20°C, using a water bath, under argon with stirring. After 45 min, methanol (1 mL) was added cautiously at -40 °C. The methanol was removed under reduced pressure, and the residue was chromatographed on silica gel using 8:1 EtOAc/MeOH as the eluent to afford a mixture of D-3-deoxy-3-fluoro-1-*O*-methyl-*myo*-inositol (**4**) and D-3-deoxy-3-fluoro-4-*O*-methyl-*myo*-inositol (**5**) as a light yellow solid (yield 57%).[5]

The two *O*-methyl derivatives (80 mg, 0.41 mmol) were treated with boron tribromide (1.1 g, 4.1 mmol) in 3 mL of methylene chloride at 25 °C for 18 h. The reaction mixture was quenched by the cautious addition of 2 mL of methanol at -40 °C, and the methanol was removed by rotary evaporation. The addition and removal of methanol was repeated several times, water (5 mL) was added, and the mixture was extracted with methylene chloride. Evaporation of the water provided **1** as a white solid in 88% yield: $[\alpha]_D$ -7.01° (c 0.047, H_2O); ^{19}F NMR Φ -202, ddd, J = 48, 12, 9 Hz. The ^1H NMR data are as reported previously.

The present method affords access to **1** on the gram scale. To the best of our knowledge this work represents the first successful attempt to monofluorinate a minimally protected inositol. Further studies to probe the biological action of this inositol isostere on cellular growth and differentation are in progress and will be reported separately.[7,8]

Acknowledgement. We are indebted to the Mental Health Clinical Research Center (Proposal No. 159) for financial aid.

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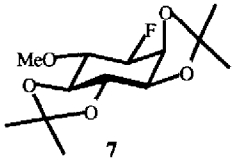
2. A. P. Kozikowski, Y. Xia, and J. M. Rusnak, *J. Chem. Soc., Chem. Commun.*, 1301 (1988). For related work see: S. S. Yang, T. R. Beattie and T.Y. Shen, *Tetrahedron Lett.*, **23**, 5517 (1982); S. S. Yang and T. R. Beattie, *J. Org. Chem.*, **46**, 1718 (1981); C. Jiang, J. D. Moyer and D. C. Baker, *J. Carbohydr. Chem.*, **6**, 319 (1987); J. Gigg, R. Gigg, S. Payne and R. Conant, *J. Chem. Soc., Perkin Trans. I*, 423 (1987); A. M. Cooke, B. V. L. Potter and R. Gigg, *Tetrahedron Lett.*, **28**, 2305 (1987); C. B. Reese and J. G. Ward, *Tetrahedron Lett.*, **28**, 2309 (1987); M. R. Hamblin, B. V. L. Potter and R. Gigg, *J. Chem. Commun.*, 626 (1987).

3. The biological studies are being carried out in collaboration with Dr. James Byrd of the Western Psychiatric Institute and Clinic.

4. The selective transformation of a single secondary hydroxyl group of a carbohydrate to a fluorine atom in the presence of other unprotected secondary hydroxyls has precedent. See, *inter alia*: (a) P. J. Card and G. S. Reddy, *J. Org. Chem.*, **48**, 4734 (1983); (b) C. W. Somawardhana and E. G. Brunngraber, *Carbohydr. Res.*, **121**, 51 (1983); (c) P.J. Card, *J. Org. Chem.* **48**, 393 (1983).

5. The diacetonide derivative **7** of 3-deoxy-3-fluoro-4-*O*-methyl-*myo*-inosi^tol (**5**) was also prepared to confirm the structure of this intermediate. The following spectral data were obtained: ^{1}H NMR (C_6D_6) δ 4.63 (br d, H_3, J = 47.2 Hz), 4.32 (ddd, H_6, J = 10.8, 7, 5 Hz), 4.19 (dd, H_5, J = 7.3, 7.3 Hz), 3.97 (ddd, H_4, J = 31.7, 7.3, 2.6 Hz), 3.71 (H_2, dd, J = 19.2, 7.6 Hz), 3.35 (dd, H_1, J = 10.8, 7.6 Hz), 3.11 (s, 3H), 1.55 (s, 3H), 1.34 (s, 3H), 1.27 (s, 3H), 1.19 (s, 3H); ^{19}F NMR ($CDCl_3$) Φ -185.7 (dddd, 51, 31.6, 19.4, 4.8 Hz); mass spectrum (70 eV), m/z 276 (M^+), 261 (M^+-CH_3). The proton assignments were made on the basis of extensive decoupling experiments. It is noteworthy that the $J_{H3,H4}$ and $J_{F,H4}$ values are abnormal, in that the former is unusually small (~2 Hz) whereas the latter is unusually large (~31 Hz). These values probably reflect a non-chair conformation of the inositol ring. The diacetonide **7** also gave the desired fluoroinositol **1** on treatment with boron tribromide.



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6. A similar argument has been offered for the selective formation of 4-deoxy-4-fluoro-hexoses from α-sugars. See reference 4b. For a review of the chemistry and applications of DAST, see, M. Hudicky, *Org. React.*, **35**, 513 (1988).

7. For a recent report of the synthesis of the 2,2-difluoro-2-deoxy analogues of racemic *myo*-inositol 1,3,4-trisphosphate, see: M. F. Boehm and G. D. Prestwich, *Tetrahedron Lett.*, **29**, 5217 (1988).

8. For a report on syntheses of D- and L-*myo*-inositol 1,4,5-trisphosphate using D-*chiro*-inositol from D-pinitol and L-*chiro*-inositol from L-quebrachitol which appeared subsequent to the completion of our studies, see: W. Tegge and C.E. Ballou, *Proc. Natl. Acad. Sci. USA*, **86**, 94 (1989). (+)-1D-1-Deoxy-1-fluoro-*myo*-inositol (**2**) should in principle be readily available from an isomer of quebrachitol, namely D-pinitol, which is extractable from pine sugar.

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