Synthesis and Biological Activity of the D-3-Deoxy-3-fluoro and D-3-Chloro-3-deoxy Analogues of Phosphatidylinositol

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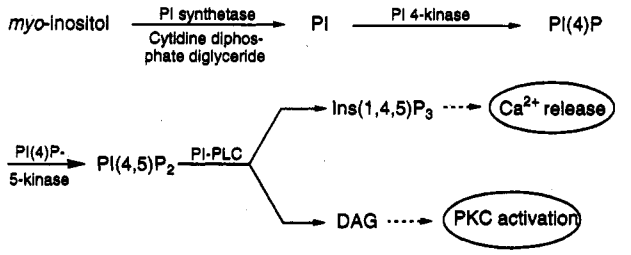
The naturally occurring inositol derivative, L-quebrachitol (1), serves as starting material for the synthesis of D-3-deoxy-3-fluoro- and D-3-chloro-3-deoxy-*myo*-inositol (4, 28). Their transformation into the title compounds 22 and 40 (abbreviated as FPI and CPI, respectively) is accomplished by benzylation of all hydroxyl groups but OH-1 to which the phosphatidic acid side chain is subsequently attached using the phosphoramidite protocol, and hydrogenolytic deprotection. Compounds 4 and 28, as reported earlier, exhibit moderate and high selectivity, respectively, in the growth inhibition of *v-sis* transformed vs wild type murine NIH 3T3 cells if *myo*-inositol is absent but are inactive in the presence of physiological inositol levels. On the other hand, FPI possesses a nearly 2 orders of magnitude higher activity but no selectivity both in the absence or presence of *myo*-inositol. CPI is inactive as is the simplified analogue 24 of FPI in which the phosphatidic acid moiety has been replaced by an octadecyl group.

Introduction

Since the seminal discovery of Michell[1] in 1975 that phosphoinositides may be intimately involved in agonist-stimulated cell surface receptor activation and specific cellular responses, fundamental molecular mechanisms underlying these processes have been under intensive scrutiny. While finer details are still under investigation, the broad outlines of this phosphoinositide-based signal transduction have been well documented.[2] The key step of this major signaling pathway involves the phosphoinositide specific phospholipase C (PI-PLC)-mediated hydrolysis of a minor phospholipid component of the cell membrane, phosphatidylinoisitol 4,5-bisphosphate (PI(4,5)P_2), to generate two key second messengers, D-*myo*-inositol 1,4,5-trisphosphate (Ins(1,4,5)P_3) and diacylglycerol (DAG) (Scheme 1). DAG remains in the cell membrane and serves to activate protein kinase C (PKC) which, in turn, phosphorylates other proteins.[3] Ins(1,4,5)P_3, being water soluble, diffuses into the cytosol and through activation of its well-characterized receptor on the endoplasmic reticulum mobilizes Ca^{2+} from non-mitochondrial stores. Together, PKC activation and Ins(1,4,5)P_3-mediated Ca^{2+} release trigger intracellular events culminating in, *inter alia*, aspects of cellular proliferation and differentiation.[4] Consistent with its second messenger role is the requirement that Ins(1,4,5)P_3 must be inactivated following Ca^{2+} release. One of the two known pathways by which this is achieved is the Ins(1,4,5)P_3-3-kinase mediated phosphorylation at the D-3 position of the *myo*-inositol ring to form D-*myo*-inositol 1,3,4,5-tetrakisphosphate (Ins(1,3,4,5)P_4), which effectively acts as an off-switch for the Ca^{2+} signal.[5]

Scheme 1



A parallel signaling pathway, independent of the PI turnover described above, has been recently reported[6] and involves PI-3-kinase mediated phosphorylation of the D-3 position of PI, PI(4)P, and PI(4,5)P_2 to generate a novel series of corresponding D-3-phosphorylated phosphoinositides which have been proposed to act as second messengers by activating DNA synthesis and cytoskeletal reorganization.[7] This process which, like oncogenes, mediates proliferative effects through its association with the well-known receptor tyrosine kinases may have far-reaching consequences in cellular growth and development and is under active investigation.

Searching for a pivotal point common to PI turnover as well as PI-3-kinase-mediated cellular responses, we pursued the notion that modifications targeted at the D-3 position of *myo*-inositol and the *myo*-inositol ring of PI might provide (a) a point of intervention in proliferative metabolism; (b) tools for studying phosphoinositide signal transduction; and (c) a way to develop mechanism-based novel antineoplastic therapeutic agents.[8] Thus, we prepared variously D-3 modified derivatives of *myo*-inositol. Our preliminary results regarding the growth inhibitory effects of these *myo*-inositol analogues in wild-type and *v-sis* transformed NIH 3T3 cells have been reported.[9] Two

† Mayo Foundation for Medical Education and Research.
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(1) Michell, R. *Biochem. Biophys. Acta* **1975**, *415*, 81.
(2) (a) Berridge, M. J. *Nature* **1993**, *361*, 315. (b) Streb, H.; Irvine, R. F.; Berridge, M. J. *Nature* **1983**, *306*, 67.
(3) Nishizuka, Y. *Nature* **1988**, *334*, 661.
(4) Brunton, V. G.; Workman, P. *Cancer Chemother. Pharmacol.* **1993**, *32*, 1.
(5) (a) Nahorski, S. R.; Batty, I. *Trends Pharm. Sci.* **1986**, *7*, 83. (b) Luckhoff, A.; Clapham, D. E. *Nature* **1992**, *355*, 356.
(6) Carpenter, C. L.; Cantley, L. C. *Biochemistry* **1990**, *29*, 11147.
(7) (a) Kaplan, D. R.; Whitman, M.; Schaffhausen, B.; Pallas, D. C.; White, M.; Cantley, L.; Roberts, T. M. *Cell* **1987**, *50*, 1021. (b) Downes, C. P.; Cartner, A. N. *Cell. Signaling* **1991**, *3*, 501. (c) Coughlin, S. R.; Escobedo, J. A.; Williams, L. T. *Science* **1989**, *243*, 1191.

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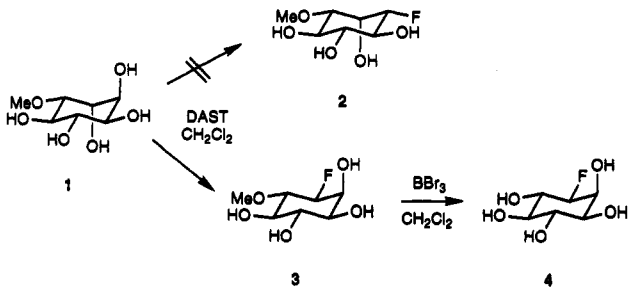
Scheme 2

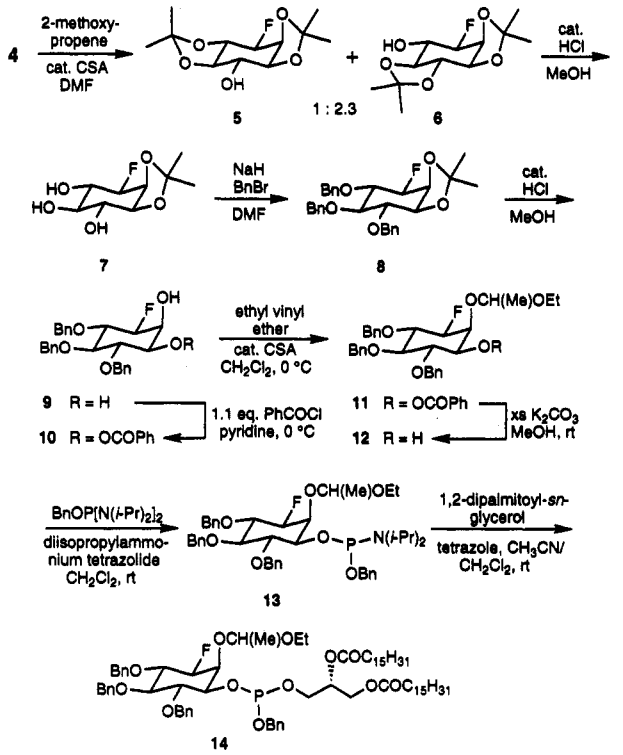


analogues, D-3-chloro- and D-3-azido-3-deoxy-*myo*-inositol, exhibited an interesting selective growth inhibition of the transformed cells cultured in the absence of *myo*-inositol. Neither compound can, however, compete effectively for incorporation into modified PI against normal serum levels (40 μM) of *myo*-inositol and is therefore inactive under these conditions. To avoid such competition, we have more recently synthesized and tested the D-3-deoxy-3-fluoro[10] and D-3-chloro-3-deoxy[11] analogues of PtdIns (FPI and CPI, respectively), and we report herein the details of this investigation.

Synthesis of FPI

The required starting material, D-3-deoxy-3-fluoro-*myo*-inositol (4), was synthesized in two steps from quebrachitol (1) by a modification (see Experimental Section) of our published procedure[12] which calls for reaction of 1 with (diethylamido)sulfur trifluoride (DAST), followed by removal of the *O*-methyl group with boron tribromide. In correction of our initial communication,[12] we note that the product of the DAST fluorination is exclusively D-3-deoxy-3-fluoro-4-*O*-methyl-*myo*-inositol (3); it is not accompanied by its 1-*O*-methyl isomer (2) (Scheme 2) as originally formulated. Compound 4 thus obtained was transformed[13] into a 1:2.3 mixture of the diacetonides 5 and 6 by reaction with the theoretical amount (i.e., 4 equiv, half of which binds the methanol formed) of 2-methoxypropene in DMF in the presence of a catalytic amount of camphorsulfonic acid (Scheme 3). An excess of 2-methoxypropene should be avoided since it causes increased formation of colored impurities. The resulting mixture of diacetonides both of which possess a stable *cis*-dioxolane ring in 1,2-position as well as labile *trans*-dioxolane rings in either of the adjacent positions 4,5 or 5,6 needs not to be separated for the subsequent carefully controlled hydrolysis to the 1,2-monoacetonide 7. With positions 1 and 2 thus temporarily blocked, permanent benzyl protective groups were installed at the hydroxyl groups in positions 4, 5, and 6 by reaction with an excess of both

Scheme 3



sodium hydride and benzyl bromide in DMF. THF is not suitable as a solvent because of poor solubility of the intermediate sodium alkoxides.

After acidic cleavage of the remaining acetonide, the next task consisted of differentiating the hydroxyl goups in position 1 (equatorial) and 2 (axial). Whereas the latter could *a priori* be assumed to be less reactive than the former, and further use of protective groups therefore unnecessary, we took the more cautious approach of blocking the axial hydroxyl group prior to formation of the phosphate ester. Besides avoiding potential trouble in separating the desired protected FPI from 2-phosphorylated byproduct both of which are large molecules differring only in a minor aspect, blocking of the 2-OH group also precludes the formation of cyclic phosphates. Initially we followed as a model our synthesis of D-3-deoxy-3-fluoro-*myo*-inositol 1,4,5-trisphosphate[13] in which the 1-hydroxyl group was benzoylated under controlled conditions, the 2-hydroxyl group transformed to its 1-ethoxyethyl ether, and the benzoate saponified. This sequence worked well in the present case, too, and the phosphorus atom was subsequently introduced with *O*-benzyl *N,N,N',N'*-tetraisopropylphosphorodiamidite and diisopropylammonium tetrazolide.[14] Further coupling of the resulting phosphoramidite 13 with 1,2-dipalmitoyl-*sn*-glycerol and tetrazole yielded uneventfully the phosphite 14. Attempted oxidation, however, of this intermediate to the corresponding phosphate with *tert*-butyl hydroperoxide[15] resulted in a mixture, the ^{1}H NMR spectrum of which indicated partial loss of the ethoxyethyl group.

Rather than searching for compatible oxidation conditions, we preferred to change the protective group in such a way as to prevent problems of this kind in future work. The protective groups on hydroxyls 4, 5, and 6 being

(8) PI of plant origin, which is in part derived from *chiro*- rather than *myo*-inositol (i.e., it contains an inverted hydroxyl group at C-3) has been reported to be highly selective for several tumor cell lines, including multiple drug resistant lines: (a) Jett, M.; Alving, C. R. *Biochem. Biophys. Res. Commun.* **1983**, *114*, 863. (b) Jett, M.; Fine, R. L.; Kowan, K.; Chabner, B. A. *Proc. Am. Assoc. Cancer Res.* **1987**, *28*, 284.

(9) Powis, G.; Aksoy, I. A.; Melder, D. C.; Aksoy, S.; Eichinger, H.; Fauq, A. H.; Kozikowski, A. P. *Cancer Chemother. Pharmacol.* **1991**, *29*, 95.

(10) Kozikowski, A. P.; Tückmantel, W.; Powis, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1379.

(11) Fauq, A. H.; Kozikowski, A. P.; Gallegos, A.; Powis, G. *Med. Chem. Res.* **1993**, *3*, 17.

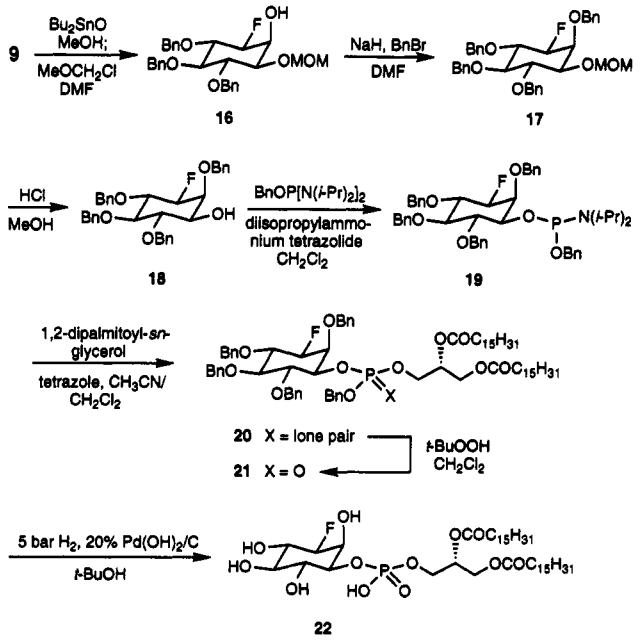
(12) Kozikowski, A. P.; Fauq, A. H.; Rusnak, J. M. *Tetrahedron Lett.* **1989**, *30*, 3365.

(13) Kozikowski, A. P.; Fauq, A. H.; Aksoy, I. A.; Seewald, M. J.; Powis, G. *J. Am. Chem. Soc.* **1990**, *112*, 7403.

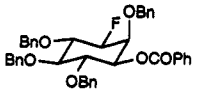
(14) (a) Barone, A. D.; Tang, J.-Y.; Caruthers, M. H. *Nucleic Acid Res.* **1984**, *12*, 4051. (b) Beaucage, S. L. *Tetrahedron Lett.* **1984**, *25*, 375.

(15) Engels, J.; Jäger, A. *Angew. Chem. Suppl.* **1982**, 2010.

Scheme 4



benzyl, the most obvious choice was to install another benzyl group. Unfortunately, ester (as well as alternative silyl) protective groups are prone to migration under basic conditions, thus precluding the use of the standard benzylation protocol (NaH, BnBr) in this case. The benzoate **10** decomposed on treatment with benzyl bromide and silver oxide in DMF.[16] Small amounts of the desired tetrabenzyl derivative **15** were obtained in 53% yield using



O-benzyl trichloroacetimidate and a catalytic amount of trifluoromethanesulfonic acid[17] in ether.[18] The substrate proved quite unreactive and required a considerable excess of reagent to reach even the indicated conversion; unreacted starting material was as tediously separated from one byproduct, trichloroacetamide, as was the tetrabenzyl ether from the other, *N*-benzyltrichloroacetamide. The formation of these side products can usually be slowed down by choosing a less-polar reaction medium[17] in which, however, the substrate was insufficiently soluble. While saponification of the benzoate ester uneventfully yielded the free alcohol, the encountered difficulties warranted a reconsideration of the temporary protective group for OH-1.

An acid-sensitive, base-resistant protective group would permit benzylation at OH-2 under standard basic conditions. We chose methoxymethyl (MOM) and introduced it via the cyclic stannylene derivative of the diol **9** (Scheme 4); intermediates of this type exhibit an improved equatorial/axial selectivity over the free diol.[19] Whereas addition of an excess of *bromo*methyl methyl ether to a DMF solution of the stannylene derivative at room temperature resulted in exothermic and almost quantitative formation of the bis(methoxymethyl) derivative, 1.1 equiv of *chloro*methyl methyl ether at 0 °C furnished a 75% yield (13% of recovered starting material) of isomerically pure 1-(methoxymethyl) derivative **16**. *O*-Benzylation and acidic cleavage of the MOM ether proceeded uneventfully to form the pivotal intermediate, tetrabenzyl ether **18**. The same methodology for introduction of the phosphatidic acid side chain was used successfully as for the ethoxyethyl-protected intermediate **14**, and as expected, the oxidation of phosphite **20** to phosphate **21** with *tert*-butyl hydroperoxide proceeded in high yield and without side reactions.

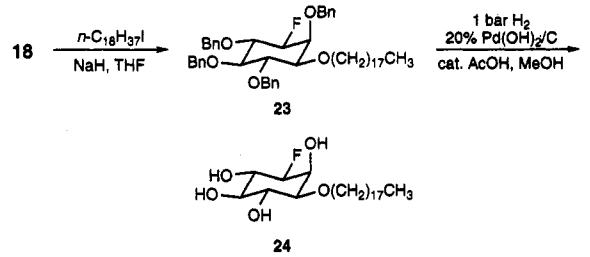
The final deprotection by simultaneous hydrogenolytic removal of all five benzyl groups proved unexpectedly difficult. Hydrogenolyses conducted at atmospheric pressure over 10% Pd/C, 20% $Pd(OH)_2/C$, or PtO_2 in solvent mixtures containing chloroform, ethyl acetate, methanol, ethanol, *tert*-butanol, or acetic acid did not go to completion. The reactions could not be followed by TLC due to formation of a multitude of partially debenzylated intermediates of widely different polarity and the unknown chromatographic behavior of the final product. Crude products from such mixtures obtained by filtration and evaporation would only to a small extent redissolve in the same solvents for NMR analysis, and such solutions as were obtained by filtration from amorphous materials generally exhibited a gel-like consistency, low stability, and uncharacteristic, broad NMR resonances including aromatic signals of persisting benzyl groups. Sonication did not improve this outcome. At elevated hydrogen pressure (70 psi), PtO_2 and *tert*-butyl alcohol furnished a product which was free of aromatic protons but exhibited supernumerary intense aliphatic signals around δ 1.7 and 3.5 (in $CDCl_3$) as well as signals for methine carbons at δ 39.4 and 38.9, and for methylene carbons at δ 26.9 and 26.2 (135° DEPT in C_6D_6). This indicates that some benzyl groups have undergone hydrogenation to cyclohexylmethyl groups, rather than hydrogenolysis, a result which is well in keeping with the known behavior of platinum catalysts.[20] Returning to 20% $Pd(OH)_2/C$ as the catalyst, we found that hydrogenation at 70 psi did completely debenzylate the starting material. Attempted purification of the crude products by filtration over a short silica gel column resulted again in the formation of intractable amorphous solids. Even though the eluents used (chloroform/methanol and 2-propanol/water mixtures) gave a well-defined spot on TLC, it was concluded that the product was not stable toward silica gel. Only when *tert*-butyl alcohol was used as the solvent, and chromatography of the crude product omitted, was FPI (**22**) eventually obtained in good yield and purity. The product is an amorphous solid well soluble in methanol/chloroform and warm ethanol and exhibits NMR spectra (^1H, ^{13}C, ^{19}F, ^{31}P) in agreement with the proposed structure.

Synthesis of a Simplified Analogue of FPI

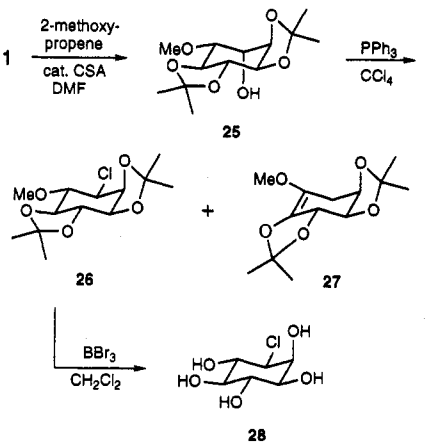
The tetrabenzyl ether **18** was additionally used as an intermediate to prepare D-3-deoxy-3-fluoro-1-*O*-octadecyl-*myo*-inositol (**24**) (Scheme 5), a highly simplified analogue of FPI in which, of course, the negative charge which the phosphate function bears at physiological pH is missing.

(16) (a) Kuhn, R.; Löw, I.; Trischmann, H. *Chem. Ber.* **1957**, *90*, 203. (b) Croon, I.; Lindberg, H. *Acta Chem. Scand.* **1959**, *13*, 593.
(17) Wessel, H.-P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247.
(18) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.
(19) Review: David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643.
(20) Rylander, P. N. *Catalytic Hydrogenation in Organic Synthesis*; Academic Press: New York, 1979; pp 175–176 and 271.

Scheme 5



Scheme 6



Thus, a Williamson ether synthesis between **18** and 1-iodooctadecane delivered the 1-octadecyl ether **23** which readily underwent hydrogenolysis to deliver **24**.

Synthesis of CPI

Whereas the general plan outlined above for the preparation of FPI could be followed, the higher ability of Cl in comparison with F to act as a leaving group required modification of the reaction conditions in the benzylation steps. The inositol analogue needed as the starting material, D-3-chloro-3-deoxy-*myo*-inositol (**28**), was obtained as communicated[21] (Scheme 6) from quebrachitol (**1**) by diacetonide formation and nucleophilic substitution using the triphenylphosphine/carbon tetrachloride reagent system.[22] Despite numerous attempts,[23] the moderate yield in this step could not be improved as a consequence of competing elimination. The byproduct **27**, surprisingly, has the double bond in 4,5-position rather than adjacent to C-3 as evidenced by the presence of only 3 (rather than 4) low-field NMR signals for methine protons as well as an AB quartet at δ 2.64 and 2.34 for a methylene group (3-H). Both parts of this signal exhibit a vicinal coupling constant of 7–7.5 Hz with 2-H (If the double bond were located in 1,2-position, one of the 3-H signals should exhibit a larger trans-diaxial coupling constant with 4-H.). The mechanism of this double bond migration is at present unknown. The *O*-methyl group and acetonide protective groups were then simultaneously removed with boron tribromide, and diacetonide protection of **28** was restored

(21) Kozikowski, A. P.; Fauq, A. H.; Powis, G.; Melder, D. C. *Med. Chem. Res.* **1991**, *1*, 277.

(22) Review: Appel, R. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801 (*Angew. Chem.* **1975**, *87*, 863).

(23) Other protocols tried include: (i) $(PhO)_3P$, NCS (Bose, A. K.; Lal, B. *Tetrahedron Lett.* **1973**, 3937); (ii) Ph_3P, NCS (Wiley, G. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc.* **1964**, *86*, 965); (iii) Ph_3P, $Cl_3CCOCCl_3$ (Magid, R. M.; Talley, B. G.; Souther, S. K. *J. Org. Chem.* **1981**, *46*, 824); (iv) $ZnCl_2$, Ph_3P, EtOOCN=NCOOEt (Ho, P.-T.; Davies, N. *J. Org. Chem.* **1984**, *49*, 3027).

Scheme 7

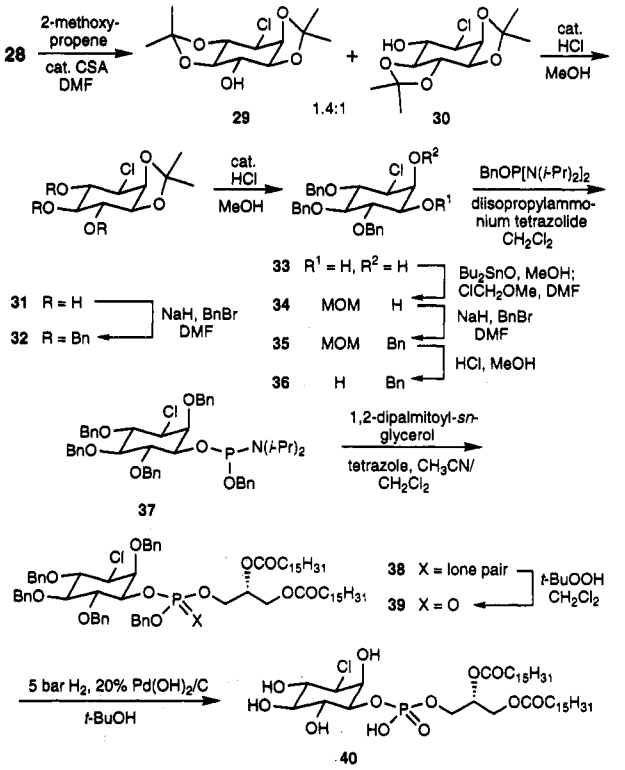


Table 1. Growth Inhibition of NIH 3T3 Cells by D-3 Modified *myo*-Inositol and PI Analogues[a]

compound	cell type: wild	cell type: *v-sis*
3-F-Ins (**4**)	7000 ± 130	1100 ± 600
3-F-Ins (**4**) + Ins[b]	NT[c]	NT
3-FPI (**22**)	110 ± 20	107 ± 15
3-FPI (**22**) + Ins[b]	99 ± 13	81 ± 11
24	NT	NT
3-Cl-Ins (**28**)	NT	390 ± 70
3-Cl-Ins (**28**) + Ins[b]	NT	NT
3-CPI (**40**)	NT	NT

[a] IC_{50} (μM). [b] In the presence of 40 μM *myo*-inositol. [c] Nontoxic.

in the usual manner (Scheme 7). The resulting 1:1.45 mixture of diacetonides **29** and **30** was without separation subjected to partial hydrolysis which furnished the 1,2-monoacetonide **31**. Tribenzylation of this intermediate had to be conducted under careful temperature control and even then proceeded in only 42% yield due to competing epoxide formation and HCl elimination. The remaining steps proceeded in very close analogy with those described above for FPI. Gratifyingly, the final hydrogenolysis step did not only leave the chlorine atom untouched but even proceeded in better yield than in the case of FPI, to produce CPI (**40**) as a colorless amorphous solid with NMR and mass spectroscopic data in agreement with the proposed structure.

Biological Results

Growth inhibition assays were performed as described earlier.[9] The activities of FPI (**22**)[10] and CPI (**40**)[11] have been the subject of preliminary communications and are summarized in Table 1 together with those of their parent inositol analogues **4** and **28**. FPI inhibited the growth of wild type mouse NIH 3T3 cells in an inositol-free medium with an IC_{50} nearly 2 orders of magnitude lower compared with the parent modified inositol **4**. This value remained

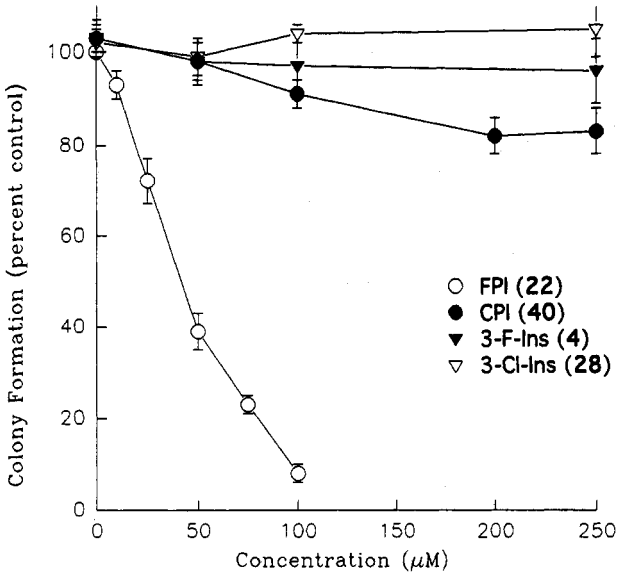


Figure 1. Inhibition by compounds **4**, **22**, **28**, and **40** of colony formation by HT-29 human colon tumor cells in soft agarose.

virtually unchanged when the medium contained physiological concentrations (40 μM) of *myo*-inositol, thus validating the rationale which had led us to prepare this compound. Virtually the same activity, however, was also found toward *v-sis* transformed NIH 3T3 cells whereas **4** exhibited a 6- to 7-fold increased activity toward those cells. Not surprisingly, the simplified analogue **24** did not inhibit cell growth. CPI was virtually inactive (<20% growth inhibition at maximum tested concentration) in both cell types. FPI also inhibited colony formation[24] by HT-29 human colon tumor cells in soft agarose (IC_{50} 37 ± 3 μM; Figure 1). The drastic difference in activity between FPI and CPI parallels the activities of the corresponding inositols[21] toward the wild type cells but stands in sharp contrast to the rather gradual and opposite trend which the same inositol analogues exhibit toward the *v-sis* transformed cells and demonstrates that further work is needed to elucidate the structural requirements for cell growth inhibition and, as a long term goal, the mechanism of action of these compounds.

Experimental Section

General Methods. Anhydrous solvents: Tetrahydrofuran (THF) was dried over sodium/benzophenone. Dimethylformamide (DMF) was distilled in an aspirator vacuum over CaH_2. Methylene chloride was distilled over phosphorus pentoxide, and for use in phosphoramidite coupling redistilled over CaH_2. Acetonitrile was distilled over phosphorus pentoxide and redistilled over calcium hydride. Methanol was refluxed for several hours over magnesium turnings and then distilled. Toluene and triethylamine were distilled over calcium hydride. Ethyl acetate and hexane were distilled; other solvents not referred to as "dry" were used as received. Commercial grade tetrazole (Aldrich) was initially purified by vacuum sublimation (*Caution, explosion hazard!*), but later used as received. Diisopropylammonium tetrazolide[25] and *O*-benzyl *N,N,N',N'*-tetraisopropylphosphorodiamidite[26] were prepared by literature methods. Quebrachitol was extracted with 10% water in ethanol at reflux temperature from dried rubber latex serum which was a gift from the Rubber Research Institute of Malaysia, 260, Jalan Ampang, 50450 Kuala Lumpur, Malaysia. Other reagents were commercially available and were used as received. Column chromatography was performed on EM Science No. 7734-7 silica gel 60, particle size 0.063–0.200 mm, and thin-layer chromatography on EM Science No. 5715 silica gel 60 F_{254} glass plates, layer thickness 0.25 mm. TLC spots were visualized with permanganate solution. Melting points were measured in open capillaries and are uncorrected. NMR spectra (proton frequency: 300 MHz) were referenced to internal TMS or HDO (^1H, $\delta = 0$ and 4.75), $CDCl_3$, C_6D_6, or DMSO-d_6 (^{13}C, δ = 77.09, 128.0, and 39.5), external $CFCl_3$ (^{19}F), and external 85% H_3PO_4 (^{31}P), respectively.

D-3-Deoxy-3-fluoro-4-*O*-methyl-*myo*-inositol (3). *Caution! (Diethylamido)sulfur trifluoride (DAST) is highly toxic and reacts explosively with water. The reaction requires careful temperature control but even so occasionally runs away, resulting in charring and sudden evolution of a large gas volume but no or little heat.* In a 25-mL flask equipped with a stirring bar, a pasty mixture of 0.97 g (5 mmol) of quebrachitol and 0.6 mL of CH_2Cl_2 was cooled to −40 °C (bath temperature), and 1.9 mL (15 mmol) of DAST was added dropwise with stirring. The reaction mixture was stirred at −40 to −30 °C for 30 min, at −20 °C for 2.5 h, at 0 °C for 2.8 h, and finally at rt for 30 min. After dilution with 10 mL of CH_2Cl_2 and stirring for another 5 min, the mixture was poured into a stirred suspension of 10 g of silica gel in 100 mL of methanol (Several parallel runs can be quenched into a proportionally larger amount). The mixture was evaporated and the residue chromatographed on silica gel with CH_2Cl_2/methanol 6:1 and then 4:1 to yield, after evaporation and crystallization from methanol/methylene chloride, 516 mg (53%) of the product **3** as colorless crystals (on larger scale runs, significantly lower yields were obtained): mp 166–168 °C; ^1H NMR (D_2O) δ 4.51 (ddd, 1 H, J = 47.5, 10, 3 Hz), 4.22 (dt, 1 H, J = 9 Hz (d), 3 Hz (t)), 3.66–3.54 (m, 2 H), 3.53 (s, 3 H), 3.46 (dm, 1 H, J = 10 Hz (d)), 3.29 (t, 1 H, J = 9.5 Hz); ^{13}C NMR (D_2O) δ 94.60 (d, 1 H, J = 180.5 Hz), 83.26 (d, 1 H, J = 16.5 Hz), 75.08, 74.81 (d, 1 H, J = 14.5 Hz), 72.79 (d, 1 H, J = 16.5 Hz), 72.30 (d, 1 H, J = 11 Hz), 62.33; ^{19}F NMR (D_2O) δ −199.45 (dt, J = 46 Hz (d), 8.5 Hz(t)); IR (KBr) 3364, 2939, 1363, 1111, 1055 cm^{-1}; MS (EI) m/z 197 (M + H^+), 178, 167, 160, 87 (100%); HRMS (M + H^+, $C_7H_{14}FO_5$) calcd 197.0825, found 197.0825; $[\alpha]_D$ −4.9° (c = 10.8 g L^{-1}, H_2O).

D-3-Deoxy-3-fluoro-*myo*-inositol (4). To a suspension of 2.65 g (13.5 mmol) of intermediate **3** in 90 mL of CH_2Cl_2 was added dropwise with ice cooling 10.2 mL (108 mmol) of BBr_3 whereon the starting material went into solution. The reaction mixture was stirred under a $CaCl_2$ tube at rt for 19 h. After cooling to −40 °C (bath temperature), 25 mL of methanol was added dropwise (*very exothermic reaction*). The solution was evaporated to dryness, and the residue was taken up in 80 mL of methanol and again evaporated to dryness. This procedure was repeated three times (to remove trimethyl borate and hydrobromic acid). The final evaporation residue was taken up in 50 mL of deionized water and washed with two 25-mL portions of CH_2Cl_2. The aqueous phase was evaporated, and the residue was taken up in a boiling mixture of 100 mL of methanol and 13 mL of deionized water. Crystallization set in on cooling after addition of 120 mL of ethyl acetate; a small second fraction was obtained by working up the mother liquor. The total yield was 2.43 g (99%) of colorless needles: mp 220–220.5 °C; ^1H NMR (D_2O) δ 4.42 (ddd, 1 H, J = 47, 10, 3 Hz), 4.25 (dt, 1 H, J = 8 Hz (d), 3 Hz (t)), 3.86 (dt, 1 H, J = 12.5 Hz (d), 10.5 Hz (t)), 3.60, 3.50 (ABq, 2 H, J = 10 Hz, A part split into d with J = 10.5 Hz, B part split into narrow m), 3.34 (t, 1 H, J = 9 Hz); ^{13}C NMR (D_2O) δ 92.73 (d, J = 178.5 Hz), 74.98 (d, J = 13 Hz), 72.97, 71.62 (d, J = 19 Hz), 70.84 (d, J = 29 Hz), 70.81; ^{19}F NMR (D_2O) δ −202.23 (ddd, J = 48, 12, 9 Hz); MS (EI) m/z 183 (M + H^+), 164, 102, 73 (100%); $[\alpha]_D$ −7.5° (c = 5.75 g L^{-1}, H_2O). Anal. Calcd for $C_6H_{11}FO_5$ (182.15): C, 39.56; H, 6.09. Found: C, 39.88; H, 5.78.

D-3-Deoxy-3-fluoro-1,2-*O*-isopropylidene-*myo*-inositol (7). A solution of 3.54 g (19.4 mmol) of D-3-deoxy-3-fluoro-*myo*-inositol (**4**), 7.6 mL (78 mmol) of 2-methoxypropene, and 100 mg of camphorsulfonic acid in 30 mL of dry DMF was stirred in a closed flask at 80 °C for 4 h (Although little pressure buildup is observed, it is recommended to use a safety shield.). After cooling,

(24) Alley, M. C.; Powis, G.; Appel, P. L.; Kooistra, P. L.; Lieber, M. M. *Cancer Res.* **1984**, *44*, 549.
(25) Caruthers, M. H.; Barone, A. D.; Beaucage, S. L.; Dodds, D. R.; Fisher, E. F.; McBride, L. J.; Matteucci, M.; Stabinsky, Z.; Tang, J.-Y. *Methods Enzymol.* **1987**, *154*, 287.
(26) Bannwarth, W.; Trzeciak, A. *Helv. Chim. Acta* **1987**, *70*, 175.

2 mL of triethylamine was added, and the volatiles were pumped off. The residue was taken up in CH_2Cl_2, adsorbed on 20 g of silica gel, and chromatographed on silica gel with ethyl acetate/hexane 1:1 (R_f approximately 0.6 and 0.4, respectively), to yield, after evaporation, 4.24 g (84%) of a mixture of the diacetonides 5 and 6 as a yellowish solid of which the individual components have been separated and characterized earlier.[13] This material was dissolved in a mixture of 140 mL of dry CH_2Cl_2 and 70 mL of dry methanol, and 40 μL of acetyl chloride was added. The mixture was stirred under exclusion of moisture at 23 °C with close TLC monitoring (silica gel, CH_2Cl_2/methanol 5:1; approximate R_f values for 4, 7, and the diacetonide mixture are 0, 0.4, and 0.75, respectively). After 1 h, most of the diacetonides had reacted while only a small amount of 4 had been formed. The reaction was quenched by adding 0.5 mL of triethylamine, 30 g of silica gel was added, and the mixture was evaporated and chromatographed on silica gel with CH_2Cl_2/methanol mixtures. With a 9:1 ratio of eluents, 0.38 g (9%) of the diacetonide mixture was recovered after which the ratio was changed to 5:1 to elute 2.89 g (80%) of the monoacetonide 7 as a colorless semisolid of sufficient purity for the following step. Changing the eluent further to 2-propanol/water 19:1 permitted the recovery of 0.24 g (8%) of 4 which, like the recovered diacetonide, could be recycled. The analytical sample was recrystallized from methanol/ethyl acetate: colorless needles, mp 147 °C; ^{1}H NMR (DMSO-d_6) δ 5.30 (d, 1 H, J = 5 Hz, O*H*), 5.08 (d, 1 H, J = 5 Hz, O*H*), 5.00 (d, 1 H, J = 5 Hz, O*H*), 4.52 (ddd, 1 H, J = 47, 8, 4 Hz, C*H*F), 4.36 (m, 1 H), 3.92 (t, J = 6.5 Hz), 3.58 (ddt, 1 H, J = 12.5 Hz (d), 8.5 Hz (t), 5 Hz (d)), approximately 3.35 (1 H, overlapping with H_2O signal), 3.00 (dt, 1 H, J = 9 Hz (t), 5 Hz (d)), 1.40 (s, 3 H), 1.27 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 108.89, 91.15 (d, J = 183 Hz), 78.87, 73.82, 73.52 (d, J = 10 Hz), 73.35, 70.89 (d, J = 18 Hz), 27.66, 25.82; IR (Nujol) 3397, 2922, 2853, 1374, 1227, 1156, 1105, 1034, 866 cm^{-1}; MS (EI) m/z 223 (M + H$^+$), 207 (100%), 165, 129, 109, 73, 59; HRMS (M$^+$ − CH_3, $C_8H_{12}FO_5$) calcd 207.0669, found 207.0669; $[\alpha]_D$ −42.7°, $[\alpha]_{578}$ −43.7° (c = 6.9 g L^{-1}, methanol).

D-4,5,6-Tri-*O*-benzyl-3-deoxy-3-fluoro-1,2-*O*-isopropylidene-*myo*-inositol (8). Under an argon atmosphere, 1.03 g (25.7 mmol) of NaH (60% dispersion in oil) was washed with dry THF and suspended in 10 mL of dry DMF. With ice cooling, 3.1 mL (26 mmol) of benzyl bromide was added dropwise, followed by a solution of 0.57 g (2.57 mmol) of the monoacetonide 7 in 2.5 mL of dry DMF. The mixture was stirred at ice bath temperature for 3 h, at 8–10 °C for 3.5 h, and at rt for another 3 h. After recooling in an ice bath, 1 mL of water was added *cautiously*, and the mixture was directly filtered over silica gel. Larger runs require previous removal of the solvent. Residual benzyl bromide was eluted with ethyl acetate/hexane 1:9 and then the product with ethyl acetate/hexane 1:6. Evaporation and drying *in vacuo* left 1.21 g (96%) of the tribenzyl ether 8 as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.38–7.22 (m, 15 H), 4.88–4.67 (m, 7 H), 4.52 (ddd, 1 H, J = 13, 6, 3 Hz), 4.30 (t, 1 H, J = 6 Hz), 4.05 (dt, 1 H, J = 11 Hz (d), 8.5 Hz (t)), 3.83 (dd, 1 H, J = 8, 7 Hz), 3.53 (t, 1 H, J = 8 Hz), 1.52 (s, 3 H), 1.39 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.17, 138.11, 137.91, 128.36, 128.28, 127.95, 127.86, 127.79, 127.63, 110.47, 90.20 (d, J = 185.5 Hz), 81.23, 81.12, 79.43 (d, J = 19.5 Hz), 78.42 (d, J = 5 Hz), 74.51 (d, J = 25 Hz), 73.90, 73.70, 73.50, 27.02, 25.41; IR (neat film) 3033, 2986, 2932, 1497, 1455, 1372, 1215, 1073, 866, 737, 696 cm^{-1}; MS (EI) m/z 477 (M$^+$ − CH_3), 401, 295, 91 (100%); HRMS (M$^+$ − CH_3, $C_{29}H_{30}FO_5$) calcd 477.2077, found 477.2077; $[\alpha]_D$ −11.7°, $[\alpha]_{578}$ −12.0° (c = 9.6 g L^{-1}, $CHCl_3$). Anal. Calcd for $C_{30}H_{33}FO_5$ (492.59): C, 73.15; H, 6.75. Found: C, 72.59; H, 6.58.

D-4,5,6-Tri-*O*-benzyl-3-deoxy-3-fluoro-*myo*-inositol (9). A solution of 2.16 g (4.4 mmol) of the tribenzyl ether 8 in 100 mL of methanol was stirred with 5 drops of concd HCl at rt for 21 h. After addition of 1 mL of triethylamine, the solvent was evaporated. The residue was taken up in CH_2Cl_2 and adsorbed on 10 g of silica gel. Filtration over silica gel with ethyl acetate/hexane 2:3, evaporation, and drying *in vacuo* yielded 1.98 g (100%) of the diol 9 as a waxy colorless solid: mp 102–104 °C; ^{1}H NMR ($CDCl_3$) δ 7.40–7.23 (m, 15 H), 4.96, 4.71 (ABq, 2 H, J = 11 Hz), 4.93, 4.77 (ABq, 2 H, J = 11 Hz), 4.86, 4.81 (ABq, 2 H, J = 11 Hz), 4.48 (ddd, 1 H, J = 47, 9.5, 3 Hz, C*H*F), 4.32 (br d, 1 H, J = 8 Hz), 4.13 (dt, 1 H, J = 12 Hz (d), 9.5 Hz (t)), 3.83 (t, J = 9.5 Hz), approximately 3.5 (1 H, overlapping), 3.48 (t, 1 H, J = 9.5 Hz), 2.54 (br s, 1 H, O*H*), 2.45 (br d, 1 H, J = 3 Hz, O*H*); ^{13}C NMR ($CDCl_3$) δ 138.24, 138.18, 128.66, 128.42, 128.08, 128.00, 127.85, 127.79, 127.73, 93.00 (d, J = 183.5 Hz), 81.94 (d, J = 12.5 Hz), 80.85, 80.22 (d, J = 17 Hz), 75.77, 75.61, 75.44, 70.51 (d, J = 11.5 Hz), 70.11 (d, J = 18.5 Hz); IR (neat film) 3386, 3031, 2926, 1497, 1455, 1358, 1150, 1129, 1059, 1021, 729, 696 cm^{-1}; MS (EI) m/z 361 (M$^+$ − C_7H_7), 197, 107, 91 (100%); HRMS (M$^+$ − C_7H_7, $C_{20}H_{22}FO_5$) calcd 361.1451, found 361.1451; $[\alpha]_D$ −29.4°, $[\alpha]_{578}$ −30.8° (c = 10.2 g L^{-1}, $CHCl_3$).

D-4,5,6-Tri-*O*-benzyl-3-deoxy-3-fluoro-1-*O*-(methoxymethyl)-*myo*-inositol (16). A solution of 1.05 g (2.32 mmol) of the diol 9 in 80 mL of dry methanol was refluxed under argon with 575 mg (2.31 mmol) of di-*n*-butyltin oxide for 2 h after which time a clear solution was obtained. The cooled solution was evaporated to dryness and evaporated twice more with 10 mL of toluene each time. The residue was taken up in 10 mL of dry DMF and cooled under argon with an ice bath. A solution of 193 μL (2.54 mmol) of chloromethyl methyl ether (*Caution, carcinogen!*) in 5 mL of dry toluene was added over a period of 50 min. Stirring in the ice bath was continued for 1 h, 200 mL of water was added, and the product was extracted into 3 × 50 mL of CH_2Cl_2. After drying over $MgSO_4$, 10 g of silica gel was added, and the solvent was evaporated. The residue was chromatographed on silica gel with ethyl acetate/hexane mixtures, changing the composition from 1:3 (to elute a forerun) to 1:2 for the product and finally to 1:1 for unreacted starting material. The respective solutions, after evaporation and drying *in vacuo*, yielded 139 mg (13%) of starting material and 867 mg (75%) of 16. The analytical sample was obtained from methylene chloride/hexane as cotton-like needles: mp 118–119 °C; ^{1}H NMR ($CDCl_3$) δ 7.39–7.26 (m, 15 H), 4.91–4.72 (m, 8 H), 4.49 (ddd, 1 H, J = 47, 9.5, 3 Hz, C*H*F), 4.38 (1 H, overlapping), 4.13 (dt, 1 H, J = 10.5 Hz (d), 7.5 Hz (t)), 3.97 (t, 1 H, J = 9.5 Hz), 3.58 (br d, 1 H, J = 10 Hz), 3.46 (t, 1 H, J = 9.5 Hz), 3.40 (s, 3 H), 2.47 (br s, 1 H, O*H*); ^{13}C NMR ($CDCl_3$) δ 138.31, 138.16, 128.31, 128.01, 122.76, 127.59, 96.74, 92.78 (d, J = 184 Hz), 81.81 (d, J = 12.5 Hz), 80.50, 79.66 (d, J = 18 Hz), 76.32, 76.18, 75.93, 75.38, 69.89 (d, J = 17.5 Hz), 55.74; IR (neat film) 3476, 3029, 2909, 1453, 1356, 1152, 1090, 1040, 899, 735, 695 cm^{-1}; MS (EI) m/z 451 (M$^+$ − CH_2OCH_3), 405 (M$^+$ − C_7H_7), 373, 91 (100%); $[\alpha]_D$ +37.7°, $[\alpha]_{578}$ + 39.9° (c = 11.4 g L^{-1}, $CHCl_3$). Anal. Calcd for $C_{29}H_{33}FO_6$ (496.58): C, 70.14; H, 6.70. Found: C, 70.34; H, 6.61.

D-2,4,5,6-Tetra-*O*-benzyl-3-deoxy-3-fluoro-1-*O*-(methoxymethyl)-*myo*-inositol (17). Under an argon atmosphere, 94 mg (2.35 mmol) of NaH was washed with dry THF. A solution of 584 mg (1.18 mmol) of the intermediate 16 in 5 mL of dry DMF was added dropwise at rt (water bath), followed by 0.42 mL (3.5 mmol) of benzyl bromide. After stirring in the water bath for 5 h, 5 drops of water were added, and the mixture was directly chromatographed on silica gel with ethyl acetate/hexane mixtures (1:7 for the forerun, 1:4 for the product). Evaporation and drying *in vacuo* left 680 mg (98%) of the product 17 as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.43–7.25 (m, 20 H), 4.90–4.75 (m, 6 H), 4.77, 4.65 (ABq, 2 H, J = 7 Hz), 4.49 (ddd, 1 H, J = 48, 9.5, 2.5 Hz), 4.20–4.09 (m, 2 H), 4.02 (t, 1 H, J = 9.5 Hz), 3.55 (br d, 1 H, J = 9 Hz), 3.45 (t, 1 H, J = 9 Hz), 3.34 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.50, 138.43, 138.28, 128.31, 128.18, 128.08, 127.78, 127.67, 127.54, 96.55, 93.66 (d, J = 187 Hz), 82.30 (d, J = 13 Hz), 81.01, 80.22 (d, J = 17 Hz), [76.74, 76.29, 76.13, 75.96, 75.78, 75.36 (grouping uncertain)], 74.54, 55.62; IR (neat film) 3031, 2928, 1497, 1455, 1358, 1090, 1036, 916, 735, 696 cm^{-1}; MS (EI) m/z 541 (M$^+$ − CH_2OCH_3), 495 (M$^+$ − C_7H_7), 463, 181, 91 (100%); HRMS (M$^+$ − C_7H_7, $C_{29}H_{32}FO_6$) calcd 495.2183, found 495.2183; $[\alpha]_D$ +16.1°, $[\alpha]_{578}$ +16.3° (c = 8.1 g L^{-1}, $CHCl_3$).

D-2,4,5,6-Tetra-*O*-benzyl-3-deoxy-3-fluoro-*myo*-inositol (18). A solution of 874 mg (1.49 mmol) of the tetrabenzyl ether 17 in 30 mL of methanol, 3 mL of water, and 0.3 mL of concentrated HCl was heated under reflux for 5 h. After cooling, the mixture was evaporated, and the residue was chromatographed on silica gel with ethyl acetate 1:6 (forerun) and then 1:3 (product) to leave, after evaporation and drying *in vacuo*, 757 mg (94%) of the product 18 as a colorless solid: mp 49–50.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.40–7.27 (m, 20 H), 4.93–4.69 (m, 8 H), 4.52 (ddd, 1 H, J = 47.5, 9.5, 2.5 Hz, C*H*F), 4.18–4.07 (m, 2 H), 3.80 (t, 1 H, J = 9.5 Hz), 3.53 (m, 1 H), 3.46 (t, 1 H, J = 9 Hz), 2.21 (d, 1 H,

J = 6.5 Hz, O*H*); ^{13}C NMR ($CDCl_3$) δ 138.30, 138.20, 138.11, 128.47, 128.34, 128.05, 127.99, 127.82, 127.72, 127.63, 93.74 (d, J = 187.5 Hz), 82.11 (d, J = 14 Hz), 81.66, 80.38 (d, J = 17 Hz), 77.83 (d, J = 16.5 Hz), 75.80, 75.52, 75.36, 74.96, 71.00 (d, J = 11.5 Hz); IR (neat film) 3451, 3033, 1455, 1360, 1069, 737, 698 cm^{-1}; MS (EI) m/z 451 ($M^+ - C_7H_7$), 181, 91 (100%); $[\alpha]_D$ -19.9°, $[\alpha]_{578}$ -20.9° (c = 9.3 g L^{-1}, $CHCl_3$). Anal. Calcd for $C_{34}H_{35}FO_5$ (542.65): C, 75.26; H, 6.50. Found: C, 75.10; H, 6.41.

D-2,4,5,6-Tetra-*O*-benzyl-3-deoxy-3-fluoro-*myo*-inositol 1-(*O*-benzyl-*N,N*-diisopropylphosphoramidite) (19). Under an argon atmosphere at rt (water bath), 36 mg (0.21 mmol) of diisopropylammonium tetrazolide was suspended in 1.5 mL of dry CH_2Cl_2, and 0.18 mL (0.51 mmol) of *O*-benzyl *N,N,N',N'*-tetraisopropylphosphorodiamidite was added dropwise within 10 min, followed by a solution of 228 mg (0.42 mmol) of the alcohol **18** in 2.5 mL of dry CH_2Cl_2. The mixture was stirred in the water bath for 20 h, and then 5 mL of saturated $NaHCO_3$ solution was added. The phases were separated, and the aqueous phase was extracted with 2 × 10 mL of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and evaporated, and the residue was rapidly filtered over 30 g of silica gel which had previously been deactivated by shaking with 0.5 mL of triethylamine, using ethyl acetate/hexane 1:4 as the eluent. Evaporation and drying *in vacuo* afforded 318 mg (97%) of the phosphoramidite **19** as a colorless syrup: ^1H NMR ($CDCl_3$; MD major, md minor diastereoisomer) δ 7.40–7.19 (m, 25 H), 4.97–4.55 (m, 10 H), 4.43 (ddd, 1 H of md, J = 48, 9, 2.5 Hz), 4.35 (ddd, 1 H of MD, J = 48, 9, 2.5 Hz), 4.25–4.05 (m, 2 H), 4.01 (t, 1 H, J = 10 Hz), 3.80 (br t, 1 H of MD, J = 10.5 Hz), 3.75–3.61 (m, 1 H of md + 2 H), 3.45 (t, 1 H of md, J = 9 Hz), 3.41 (t, 1 H of MD, J = 9 Hz), 1.20–1.13 (m, 12 H); $^{19}F\{^1H\}$ NMR ($CDCl_3$) δ -199.16 (md), -199.57 (MD); $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 151.27 (MD), 147.37 (md); IR (neat film) 3033, 2967, 2928, 1497, 1455, 1364, 1028, 801, 733, 696 cm^{-1}; MS (EI) m/z 628 ($M^+ - OC_7H_7 - C_3H_8$), 234, 219, 83 (100%); HRMS ($M^+ - OC_7H_7 - C_3H_8$, $C_{37}H_{40}FNO_5P$) calcd 628.2628, found 628.2628.

D-2,4,5,6-Tetra-*O*-benzyl-3-deoxy-3-fluoro-*myo*-inositol 1-[Benzyl (*R*)-2,3-bis(hexadecanoyloxy)propyl phosphite] (20). To 251 mg (441 μmol) of 1,2-dipalmitoyl-*sn*-glycerol and 58 mg (0.83 mmol) of tetrazole in 1.5 mL of dry CH_2Cl_2 was added at rt under argon a solution of 318 mg (408 μmol) of the phosphoramidite **19** in 1.5 mL of dry CH_3CN. The resulting mixture was stirred for 5 h at rt and then for 64 h at 35–40 °C. After cooling, 10 mL of saturated $NaHCO_3$ solution was added, phases were separated, and the aqueous phase was extracted with 3 × 20 mL of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and evaporated, and the residue was filtered over silica gel with ethyl acetate/hexane 1:8. Evaporation and drying *in vacuo* yielded 404 mg (79% relative to **19**) of the phosphite **20** as a colorless glass: ^1H NMR ($CDCl_3$; MD major, md minor diastereoisomer) δ 7.41–7.20 (m, 25 H), 5.09 (m, 1 H, 2-H of glycerol), 4.90–4.70 (m, 10 H), 4.51 (ddd, 1 H of MD, J = 48, 9.5, 2.5 Hz, C*H*F), 4.39 (ddd, 1 H of md, J = 48, 9.5, 2.5 Hz, C*H*F), 4.25–3.94 (m, 7 H), 3.88–3.71 (m, 2 H), 3.46 (t, 1 H of MD, J = 9 Hz), 3.44 (t, 1 H of md, J = 9 Hz), 2.28–2.17 (m, 4 H), approximately 1.55 (4 H, overlapping with H_2O, β-CH_2 of palmitoyl), 1.25 (m, 48 H), 0.88 (t, 6 H, J = 7 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$) δ -199.92 (MD), -199.95 (md); $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ 140.91 (md), 140.56 (MD); IR (neat film) 3033, 2924, 2853, 1744, 1456, 1164, 1024, 735, 696 cm^{-1}; MS (EI) m/z 550, 451, 367, 91 (100%).

D-2,4,5,6-Tetra-*O*-benzyl-3-deoxy-3-fluoro-*myo*-inositol 1-[Benzyl (*R*)-2,3-bis(hexadecanoyloxy)propyl phosphate] (21). To an ice-cooled solution of 353 mg (283 μmol) of the phosphite **20** in 3 mL of dry CH_2Cl_2 under argon was added in 4 equal portions in 20-min intervals a total of 800 μL (400 μmol) of a 0.5 M solution of anhydrous *tert*-butyl hydroperoxide in CH_2Cl_2. Stirring was continued in the ice bath for 90 min and then at rt for 20 min. The mixture was evaporated and filtered over silica gel with ethyl acetate/hexane 1:4 to obtain 351 mg (98%) of the phosphate **21** as a colorless syrup: ^1H NMR ($CDCl_3$; MD major, md minor diastereoisomer) δ 7.38–7.20 (m, 25 H), 5.14–4.68 (m, 11 H), 4.51 (ddd, 1 H of md, overlapping, C*H*F), 4.49 (ddd, 1 H of MD, J = 48, 9, 2.5 Hz, C*H*F), approximately 4.42–4.32 (m, 1 H), 4.28–3.87 (m, 7 H), 3.47 (t, 1 H of md, J = 9 Hz), 3.44 (t, 1 H of MD, J = 9 Hz), 2.28–2.17 (m, 4 H), 1.65–1.45 (m, 4 H), 1.25 (m, 48 H), 0.88 (t, 6 H, J = 6.5 Hz); $^{19}F\{^1H\}$ NMR ($CDCl_3$) δ -200.59 (MD), -200.65 (md); $^{31}P\{^1H\}$ NMR ($CDCl_3$) δ -1.08 (MD), -1.21 (md); IR (neat film) 2924, 2853, 1744, 1026, 696 cm^{-1}; MS (EI) m/z 550, 451, 367, 239, 91 (100%); (FAB) m/z 640, 551, 313, 181.

D-3-Deoxy-3-fluoro-*myo*-inositol 1-[(*R*)-2,3-Bis(hexadecanoyloxy)propyl hydrogen phosphate] (FPI, 22). A solution of 54.2 mg (42.9 μmol) of the protected phosphate **21** in 6 mL of *tert*-butyl alcohol was hydrogenated in a Parr shaker under 5 bar of H_2 at rt for 23.5 h over 23.5 mg of 20% $Pd(OH)_2/C$ (Aldrich, containing 50% of water). The catalyst was removed by centrifugation and washed with *tert*-butyl alcohol, the solution was evaporated, and the residue was dried *in vacuo* to leave 27.9 mg (80%; variability of the yield over 6 runs: 71–89%) of FPI (**22**) as a colorless amorphous solid: mp 132–133 °C (after sintering); ^1H NMR ($CDCl_3/CD_3OD$ 2:1) δ 5.27 (m, 1 H), 4.45–4.35 (m, 2.5 H), 4.27–4.15 (m, 3.5 H), 4.02 (br, 1 H), 3.97 (dt, 1 H, J = 9.5 Hz (t), 12 Hz (d)), 3.86 (br t, 1 H, J = 8.5 Hz), 3.24 (t, 1 H, J = 9.5 Hz), 2.36 (t, 2 H, J = 7.5 Hz), 2.33 (t, 2 H, J = 7.5 Hz), 1.62 (m, 4 H), 1.27 (m, 48 H), 0.89 (t, 6 H, J = 7 Hz); ^{13}C NMR ($CDCl_3/CD_3OD$ 2:1) δ 173.67, 173.30, 91.30 (d, J = 182.5 Hz), 73.46 (d, J = 12.5 Hz), 70.82 (d, J = 4 Hz), 70.42 (d, J = 18 Hz), 69.52 (d, J = 6 Hz), 69.08 (d, J = 17.5 Hz), 64.85, 64.79, 61.86, 33.84, 33.73, 31.60, 29.34, 29.18, 29.00, 28.79, 24.53, 22.32, 13.57; ^{19}F NMR ($CDCl_3/CD_3OD$ 2:1) δ -204.51 (ddd, J = 47, 11, 10 Hz); ^{31}P NMR ($CDCl_3/CD_3OD$ 2:1) δ -0.94 (br); IR (KBr) 3416, 2920, 2851, 1740, 1630, 1468, 1383, 1038 cm^{-1}; $[\alpha]_D$ -1.3°, $[\alpha]_{578}$ -1.3°, $[\alpha]_{365}$ -4.2° (c = 5.6 g L^{-1}, $CHCl_3$/MeOH 2:1).

D-2,4,5,6-Tetra-*O*-benzyl-3-deoxy-3-fluoro-1-*O*-octadecyl-*myo*-inositol (23). To 27 mg (0.67 mmol) of 60% NaH which had previously been washed with THF was added at rt under argon a solution of 145 mg (267 μmol) of compound **9** in 0.8 mL of THF. After 5 min, a solution of 255 mg (0.67 mmol) of 1-iodooctadecane in 0.4 mL of THF was added. The reaction mixture was stirred at rt for 18.5 h. Two drops of water were added, the mixture was evaporated, and the residue was chromatographed on silica gel with ethyl acetate/hexane mixtures. An eluent ratio of 1:15 removed a forerun, a ratio of 1:9 eluted 84 mg (40%) of the product **23**, and 60 mg (41%) of starting inositol was recovered on further elution with ethyl acetate/hexane 1:3. The product is a colorless glass which gradually solidifies to a wax: mp 53–54 °C; ^1H NMR ($CDCl_3$) δ 7.43–7.20 (m, 20 H), 4.93–4.75 (m, 8 H), 4.43 (ddd, 1 H, C*H*F, J = 48, 9.5, 2.5 Hz), 4.20–4.09 (m, 2 H), 3.99 (t, 1 H, J = 9.5 Hz), 3.55–3.43 (m, 2 H), 3.43 (t, 1 H, J = 9 Hz), 3.22 (d, 1 H, J = 10 Hz), 1.65–1.55 (m, 2 H), 1.42–1.18 (m, 30 H), 0.88 (t, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 138.89, 138.74, 138.58, 138.53, 128.35, 128.24, 128.15, 128.02, 127.87, 127.79, 127.70, 127.57, 93.65 (d, J = 187 Hz), 82.34 (d, J = 13.5 Hz), 81.33, [80.50, 80.28, 80.16 (grouping uncertain)], 75.99, 75.84, 75.42, 75.19, 74.53, 71.07, 31.97, 30.24, 29.76, 29.60, 29.41, 26.31, 22.74, 14.17; IR (film) 3030, 2926, 1454, 1358, 1088, 733, 696 cm^{-1}; MS (EI) m/z 704 ($M + H^+ - C_7H_7$), 491 (100%), 452, 368, 236, 205; $[\alpha]_{578}$ -5.1° (c = 11.8 g L^{-1}, $CHCl_3$). Anal. Calcd for $C_{52}H_{71}FO_5$ (795.13): C, 78.55; H, 9.00. Found: C, 78.44; H, 8.75.

D-3-Deoxy-3-fluoro-1-*O*-octadecyl-*myo*-inositol (24). To a solution of 5.8 mg (7.3 μmol) of compound **23** in 0.5 mL of ethyl acetate and 0.5 mL of methanol were added 2.2 μL of acetic acid and 5.8 mg of 20% $Pd(OH)_2/C$. The mixture was stirred under 1 bar of H_2 for 19.5 h and evaporated, and the residue was filtered over silica gel with CH_2Cl_2/methanol (14:1, then 9:1) to obtain 3.0 mg (95%) of the product **24** as a colorless amorphous solid: mp 122–123 °C; ^1H NMR ($CDCl_3/CD_3OD$ 3:1) δ 4.40–4.30 (m, 1.5 H, high-field part of C*H*F signal hidden under adjacent CD_3OH), 3.96 (dt, 1 H, J = 12 Hz (d), 9.5 Hz (t)), 3.75 (t, 1 H, J = 9.5 Hz), 3.66 (dt, 1 H, J = 9 Hz (d), 7 Hz (t)), 3.51 (dt, 1 H, J = 9 Hz (d), 7 Hz (t)), 3.23 (t, 1 H, J = 9.5 Hz), 3.12 (dm, 1 H, J = 9.5 Hz (d)), 1.68–1.56 (m, 2 H), 1.40–1.20 (m, 30 H), 0.88 (t, 3 H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3/CD_3OD$ 3:1) δ 92.22 (d, J = 183 Hz), 78.72 (d, J = 10.5 Hz), 73.54 (d, J = 15 Hz), 71.46, 70.58 (d, J = approximately 19 Hz), 70.45, 67.19 (d, J = 17 Hz), 31.66, 29.51, 29.43, 29.26, 29.09, 25.69, 22.40, 13.70; ^{19}F NMR ($CDCl_3/CD_3OD$ 3:1, $CFCl_3$ int.) δ -203.30 (dt, J = 47.5 Hz (d), 12 Hz (t)); IR (film) 3410, 2917, 2851, 1474, 1109, 1076, 1028, 718 cm^{-1}; MS (EI) m/z 435 ($M + H^+$), 323 (100%), 251, 183, 164, 147, 146, 128, 110;

FAB-HRMS (M + H$^+$, $C_{24}H_{45}FO_5$) calcd 435.3486, found 435.3463; $[\alpha]_{578}$ −18.9° (c = 2.7 g L^{-1}, $CHCl_3$/MeOH 1:1).

D-3-Chloro-3-deoxy-1,2:5,6-di-*O*-isopropylidene-4-*O*-methyl-*myo*-inositol (26) and D-4,5-Didehydro-3-deoxy-1,2:5,6-di-*O*-isopropylidene-4-*O*-methyl-*myo*-inositol (27). The precursor, L-3,4:5,6-di-*O*-isopropylidene-2-*O*-methyl-*chiro*-inositol (**25**) was prepared from L-quebrachitol by the method of Paulsen.[27] A solution of 5.84 g (21.3 mmol) of this material in 300 mL of anhydrous CCl_4 was purged with argon for 30 min, 8.4 g (32 mmol) of Ph_3P was added in one portion, and the mixture was heated under reflux for 18 h. After cooling and filtration from a precipitate, water was added, and the phases were separated. The aqueous phase was extracted with two portions of CH_2Cl_2, and the combined organic phases were dried over $MgSO_4$. Evaporation yielded an oil which was chromatographed on silica gel with ethyl acetate/hexane 1:7 and then 1:4 to obtain, in the order of elution, 0.98 g (18%) of **27** and 2.13 g (34%) of **26**. Compound **26**: white solid; mp 123–124 °C; ^{1}H NMR ($CDCl_3$) δ 4.51 (dd, 1 H, J = 6, 5.5 Hz), 4.37 (dd, 1 H, J = 8, 6 Hz), 4.10–4.00 (m, 2 H), 3.82 (dd, 1 H, J = 8.5, 5.5 Hz), 3.39 (dd, 1 H, J = 10.5, 8.5 Hz), 1.69 (s, 3 H), 1.45 (s, 3 H), 1.44 (s, 3 H), 1.40 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 112.45, 111.00, 82.97, 78.45, 77.42, 76.58, 76.17, 59.12, 58.93, 27.11, 26.97, 26.91, 25.57; IR (film) 2985, 1375, 1226, 1101 cm^{-1}; MS (EI) m/z 294/292 (M$^+$), 279/277 (33/100%), 239/237, 161/159, 133/131; $[\alpha]_D$ +22.5° (c = 5.7 g L^{-1}, $CHCl_3$). Compound **27**: oil; ^{1}H NMR ($CDCl_3$) δ 4.50–4.42 (m, 2 H), 4.14 (dd, 1 H, J = 15.5, 8 Hz), 3.73 (s, 3 H), 2.64 (dd, 1 H, J = 15.5, 7.5 Hz), 2.34 (ddd, 1 H, J = 15.5, 7, 2 Hz), 1.52 (s, 3 H), 1.50 (s, 3 H), 1.45 (s, 3 H), 1.35 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 127.81, 122.59, 113.11, 109.99, 80.20, 78.29, 73.04, 58.01, 31.38, 27.27, 26.52, 25.12, 24.74; MS (EI) m/z 256 (M$^+$), 241, 123 (100%), 95; $[\alpha]_D$ +7.5° (c = 7.0 g L^{-1}, $CHCl_3$).

D-3-Chloro-3-deoxy-*myo*-inositol (28). To a stirred solution of 4.60 g (15.6 mmol) of compound **26** in 50 mL of CH_2Cl_2 was slowly added at 0 °C 7.5 mL (78 mmol) of neat BBr_3. After 15 min, the cold bath was removed, and the brown suspension was stirred overnight. The mixture was again cooled to 0 °C, and 15 mL of dry methanol was *cautiously* added dropwise. Volatiles were removed in vacuo, and the residue was evaporated three times with 15 mL each of methanol. A volume of 15 mL of water was added, and the aqueous phase was washed with 3 × 3 mL of CH_2Cl_2 to remove most of the colored impurities. Water was evaporated under reduced pressure, and the residual solid was washed with ethanol to yield 2.59 g (86%) of fine colorless crystals. The analytical sample was obtained by recrystallization from water/ethanol: no mp up to 200 °C where decomposition sets in; ^{1}H NMR (D_2O) δ 4.16 (t, 1 H, J = 2.5 Hz), 3.97 (dd, 1 H, J = 10.5, 2.5 Hz), 3.70 (dd, 1 H, J = 10.5, 9.5 Hz), 3.66 (t, 1 H, J = 9.5 Hz), 3.57 (dd, 1 H, J = 10, 3 Hz), 3.31 (t, 1 H, J = 9.5 Hz); ^{13}C NMR (D_2O) δ 77.55, 75.21, 75.01, 74.60, 74.12, 64.90; IR (KBr) 3489, 3445, 3364, 3239, 1138, 1090, 997, 692 cm^{-1}; $[\alpha]_D$ +19.2° (c = 2.5 g L^{-1}, H_2O). Anal. Calcd for $C_6H_{11}ClO_5$ (198.60): C, 36.29; H, 5.58. Found: C, 36.41; H, 5.37.

D-3-Chloro-3-deoxy-1,2:4,5-di-*O*-isopropylidene-*myo*-inositol (29) and D-3-Chloro-3-deoxy-1,2:5,6-di-*O*-isopropylidene-*myo*-inositol (30). A suspension of 2.66 g (13.7 mmol) of compound **28**, 5.2 mL (55 mmol) of 2-methoxypropene, and 110 mg (0.47 mmol) of camphorsulfonic acid in 50 mL of dry DMF was stirred and heated at 65 °C for 5 h. The mixture was cooled, 2 mL of triethylamine was added, and volatiles were distilled off under reduced pressure. The residue was directly chromatographed on silica gel using a gradient of ethyl acetate/hexane 2:3 to 3:2 to yield 1.81 g (48%) of diacetonide **29** and 1.25 g (34%) of diacetonide **30** as colorless solids. Analytical samples were obtained by crystallization from ethyl acetate/hexane. Compound **29**: mp 190–192 °C; ^{1}H NMR ($CDCl_3$) δ 4.47 (t, 1 H, J = 4.5 Hz), 4.15 (dd, 1 H, J = 11, 4.5 Hz), 4.06 (dd, 1 H, J = 6.5, 4.5 Hz), 3.97 (dd, 1 H, J = 11, 9 Hz), 3.94 (m, 1 H), 3.37 (dd, 1 H, J = 11, 9 Hz), 2.73 (d, 1 H, O*H*, J = 3 Hz), 1.57 (s, 3 H), 1.50 (s, 3 H), 1.48 (s, 3 H), 1.41 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 112.31, 109.93, 81.44, 78.98, 76.83, 76.16, 73.88, 54.52, 27.67, 26.41, 26.36, 25.49; IR (film) 3367, 2987, 1373 cm^{-1}; MS (EI) m/z 280/278 (M$^+$), 265/263 (33/100%), 147/145, 131/129, 119/117, 111/109; $[\alpha]_D$ +8.5° (c = 14.8 g L^{-1}, $CHCl_3$). Anal. Calcd for $C_{12}H_{19}ClO_5$ (278.73): C, 51.71; H, 6.87. Found: C, 51.84; H, 6.79. Compound **30**: mp 153–154 °C; ^{1}H NMR ($CDCl_3$) δ 4.51 (t, 1 H, J = 4.5 Hz), 4.27 (dd, 1 H, J = 9, 4.5 Hz), 4.13 (dd, 1 H, J = 9, 3 Hz), 3.95 (dd, 1 H, J = 9, 4.5 Hz), 3.79 (dd, 1 H, J = 10, 9 Hz), 3.33 (t, 1 H, J = 10 Hz), 2.73 (d, 1 H, O*H*, J = 3 Hz), 1.58 (s, 3 H), 1.46 (s, 3 H), 1.45 (s, 3 H), 1.41 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 112.61, 110.55, 78.87, 77.19, 76.41, 73.21, 61.35, 28.34, 26.86, 26.75, 25.99; IR (film) 3466, 2985, 1373, 1230 cm^{-1}; MS (EI) m/z 280/278 (M$^+$), 265/263 (33/100%), 147/145, 131/129, 119/117, 111/109, 83; $[\alpha]_D$ +6.5° (c = 2.3 g L^{-1}, $CHCl_3$). Anal. Calcd for $C_{12}H_{19}ClO_5$ (278.73): C, 51.71; H, 6.87. Found: C, 51.93; H, 6.91.

D-3-Chloro-3-deoxy-1,2-*O*-isopropylidene-*myo*-inositol (31). By the same procedure as described for the fluoro analogue **7**, 2.00 g (7.18 mmol) of the diacetonide mixture **29**/**30** (isomer separation not necessary) yielded 1.47 g (86%) of the monoacetonide **31** as a white solid: mp 112–114 °C; ^{1}H NMR (D_2O) δ 4.62 (t, 1 H, J = 4.5 Hz), 4.22 (dd, 1 H, J = 10, 4.5 Hz), 4.13 (dd, 1 H, J = 8, 4.5 Hz), 3.74 (t, 1 H, J = 9.5 Hz), 3.64 (dd, 1 H, J = 10, 8 Hz), 3.20 (t, 1 H, J = 9.5 Hz), 1.57 (s, 3 H), 1.43 (s, 3 H); ^{13}C NMR (D_2O) δ 113.04, 81.27, 78.95, 76.72, 75.70, 74.88, 60.81, 29.70, 27.72; IR (film) 3387, 2982, 1369, 1219, 1087 cm^{-1}; MS (EI) m/z 241/239 (M + H$^+$, 33/100%), 225/223, 147/145, 111/109; $[\alpha]_D$ −3.0° (c = 6.0 g L^{-1}, H_2O). Anal. Calcd for $C_{12}H_{19}ClO_5$ (238.67): C, 45.29; H, 6.33. Found: C, 45.38; H, 6.28.

D-4,5,6-Tri-*O*-benzyl-3-chloro-3-deoxy-1,2-*O*-isopropylidene-*myo*-inositol (32). To 1.45 g (30 mmol) of NaH (50% in oil, washed with THF before use) and 3.6 mL (30 mmol) of benzyl bromide in 16 mL of dry DMF was added dropwise at 0 °C under Ar 0.80 g (3.35 mmol) of the triol **31** in 8 mL of DMF. The mixture was stirred at 0 °C for 5 h and then allowed to warm to 18 °C over a period of 2 h. A complex mixture of olefinic products was formed at longer reaction times or higher temperatures. After cautious addition of 10 mL of saturated aqueous NH_4Cl solution, the mixture was diluted with 100 mL of water and extracted with 3 × 100 mL of ether. The combined organic phases were washed with water and brine, dried over $MgSO_4$, and evaporated. Chromatography of the residue on silica gel using a gradient of 12–15% ethyl acetate/hexane furnished 0.70 g (42%) of the tribenzyl ether **32** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.4–7.2 (m, 15 H), 4.9–4.7 (m, 6 H), 4.48 (dd, 1 H, J = 5.5, 3.5 Hz), 4.20 (dd, 1 H, J = 6.5, 5.5 Hz), 4.16 (dd, 1 H, J = 10, 3.5 Hz), 3.90 (dd, 1 H, J = 10, 8 Hz), 3.80 (dd, 1 H, J = 8, 6.5 Hz), 3.48 (dd, 1 H, J = 8, 6.5 Hz), 1.54 (s, 3 H), 1.46 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.24, 138.13, 138.02, 128.37, 128.31, 128.23, 128.15, 127.98, 127.84, 127.70, 110.02, 82.91, 81.57, 80.77, 78.95, 75.69, 75.07, 73.76, 58.48, 27.47, 25.69; IR (film) 3020, 3010, 2936, 1375, 1072, 736 cm^{-1}; $[\alpha]_D$ −6.7° (c = 25.8 g L^{-1}, $CHCl_3$).

D-4,5,6-Tri-*O*-benzyl-3-chloro-3-deoxy-*myo*-inositol (33). Hydrolysis of 0.67 g (1.32 mmol) of intermediate **32** was carried out in the same fashion as for the fluoro analogue to obtain 0.52 g (84%) of the diol **33** as a white solid: ^{1}H NMR (C_6D_6) δ 7.5–7.4 (m, 2 H), 7.4–7.3 (m, 3 H), 7.3–7.1 (m, 10 H), 4.9–4.8 (m, 5 H), 4.73 (d, 1 H, J = 11.5 Hz), 3.96 (dd, 1 H, J = 10.5, 9.5 Hz), 3.77 (t, 1 H, J = 9.5 Hz), 3.66 (m, 1 H), 3.46 (dd, 1 H, J = 10.5, 2.5 Hz), 3.28 (t, 1 H, J = 9.5 Hz), 3.14 (m, 1 H), 2.04 (d, 1 H, O*H*, J = 2.5 Hz), 1.98 (d, 1 H, O*H*, J = 6 Hz); ^{13}C NMR (C_6D_6) δ 139.08, 138.91, 138.77, 84.19, 81.63, 81.38, 75.88, 75.41, 75.24, 72.79, 72.57, 62.67 (several signals overlapping with those of the solvent); IR (film) 3445, 2899, 1361, 1058 cm^{-1}; MS (EI) m/z 379/377 (M$^+$ − Bn, 33/100%), 107; $[\alpha]_D$ −13.8° (c = 4.1 g L^{-1}, $CHCl_3$). Anal. Calcd for $C_{27}H_{29}ClO_5$ (468.98): C, 69.15; H, 6.23. Found: C, 69.04; H, 6.18.

D-4,5,6-Tri-*O*-benzyl-3-chloro-3-deoxy-1-*O*-(methoxymethyl)-*myo*-inositol (34). The same procedure as described for the fluoro analogue **16** was applied to 0.99 g (2.12 mmol) of the diol **33** to give 1.00 g (92%) of the MOM ether **34** as a white solid: mp 129–130 °C; ^{1}H NMR ($CDCl_3$) δ 7.4–7.2 (m, 15 H), 4.9–4.8 (m, 7 H), 4.73 (d, 1 H, J = 6.5 Hz), 4.23 (m, 1 H), 4.0–3.9 (m, 3 H), 3.59 (dd, 1 H, J = 9.5, 2.5 Hz), 3.47 (m, 1 H), 3.40 (s, 3 H), 2.59 (d, 1 H, O*H*, J = 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 138.36, 138.35, 138.05, 128.36, 128.17, 127.84, 127.78, 127.64, 97.02, 84.26, 81.24, 80.60, 78.23, 76.30, 75.96, 72.15, 62.42, 55.83; $[\alpha]_D$ +40.3° (c = 3.7 g L^{-1}, $CHCl_3$). Anal. Calcd for $C_{29}H_{33}ClO_6$ (513.03): C, 67.89; H, 6.48. Found: C, 67.94; H, 6.32.

(27) Paulsen, H.; Röben, W. *Liebigs Ann. Chem.* **1983**, 1073.

D-2,4,5,6-Tetra-*O*-benzyl-3-chloro-3-deoxy-1-*O*-(methoxymethyl)-*myo*-inositol (35). The same procedure as described for the fluoro analogue **17** was applied to 0.99 g (1.93 mmol) of the intermediate **34** to give 1.07 g (91%) of the tetrabenzyl ether **35** as a white solid: mp 71–72 °C; ^{1}H NMR ($CDCl_3$) δ 7.5–7.2 (m, 20 H), 4.97 (d, 1 H, J = 11 Hz), 4.9–4.8 (m, 8 H), 4.68 (d, 1 H, J = 6.5 Hz), 4.10–3.85 (m, 3 H), 3.89 (dd, 1 H, J = 10.5, 2.5 Hz), 3.59 (dd, 1 H, J = 7.5, 2.5 Hz), 3.46 (t, 1 H, J = 9 Hz), 3.38 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 138.71, 138.69, 138.21, 128.49, 128.36, 127.95, 127.90, 127.74, 97.09, 84.82, 82.05, 81.24, 80.10, 78.88, 77.76, 77.12, 76.65, 76.26, 76.08, 76.02, 74.98, 62.19, 56.02; IR (film) 2893, 1356, 1028 cm^{-1}; MS (EI) m/z 559/557 ($M^+ - CH_2OCH_3$), 513/511 (M^+ – Bn, 33/100%), 389, 253, 181; $[\alpha]_D$ +21.6° (c = 6.3 g L^{-1}, $CHCl_3$). Anal. Calcd for $C_{36}H_{39}ClO_6$ (603.16): C, 71.69; H, 6.52. Found: C, 71.53; H, 6.51.

D-2,4,5,6-Tetra-*O*-benzyl-3-chloro-3-deoxy-*myo*-inositol (36). The same procedure as described for the fluoro analogue **18** was applied to 255 mg (0.42 mmol) of the intermediate **35** to give 230 mg (97%) of the alcohol **36** as a colorless oil: ^{1}H NMR (C_6D_6) δ 7.5–7.4 (m, 4 H), 7.3–7.1 (m, 16 H), 5.0–4.7 (m, 7 H), 4.61 (d, 1 H, J = 11.5 Hz), 4.08 (t, 1 H, J = 9.5 Hz), 3.93 (t, 1 H, J = 9.5 Hz), 3.69 (t, 1 H, J = 2.5 Hz), 3.60 (dd, 1 H, J = 9, 2.5 Hz), 3.35 (t, 1 H, J = 9 Hz), 3.21 (dd, 1 H, J = 9.5, 2.5 Hz), 2.11 (br s, 1 H); ^{13}C NMR (C_6D_6) δ 138.97, 138.83, 84.64, 82.33, 81.29, 80.79, 76.60, 75.91, 75.47, 75.16, 73.21, 62.25 (several signals overlapping with those of the solvent); MS (EI) m/z 469/467 (M^+ – Bn), 285, 247, 233/231, 181, 117 (100%); $[\alpha]_D$ –21° (c = 37 g L^{-1}, $CHCl_3$).

D-2,4,5,6-Tetra-*O*-benzyl-3-chloro-3-deoxy-*myo*-inositol 1-[*O*-Benzyl *N*,*N*-diisopropylphosphoramidite] (37). Following the procedure for the fluoro analogue **19**, 73 mg (131 μmol) of intermediate **36** was reacted with 37 mg (217 μmol) of diisopropylammonium tetrazolide and 156 μL (444 μmol) of *O*-benzyl *N*,*N*,*N*′,*N*′-tetraisopropylphosphorodiamidite in 4 mL of CH_2Cl_2 to give 94 mg (90%) of the phosphoramidite **37** as a colorless oil: ^{1}H NMR ($CDCl_3$; MD major, md minor diastereoisomer) δ 7.5–7.2 (m, 25 H), 5.1–4.9 (m, 2 H), 4.9–4.7 (m, 7 H), 4.62 (m, 1 H), 4.10 (m, 1 H), 4.1–3.8 (m, 2.5 H), 3.7–3.6 (m, 3.5 H), 3.46 (t, 1 H of md, J = 9 Hz), 3.42 (t, 1 H of MD, J = 9 Hz), 1.2–1.1 (m, 12 H); ^{31}P{^{1}H} NMR ($CDCl_3$) δ 151.80, 147.01; IR (film) 2964, 1456, 1363, 1261, 1090, 1028 cm^{-1}.

D-2,4,5,6-Tetra-*O*-benzyl-3-chloro-3-deoxy-*myo*-inositol 1-[Benzyl (*R*)-2,3-bis(hexadecanoyloxy)propyl phosphate] (39). In the same manner as described for the fluoro analogue **20**, 300 mg (378 μmol) of phosphoramidite **37**, 429 mg (754 μmol) of 1,2-dipalmitoyl-*sn*-glycerol, and 105 mg (1.5 mmol) of tetrazole furnished 375 mg (79%) of the phosphite **38** as a colorless oil which was immediately oxidized as described above to the phosphate **39**. Thus, 64 mg (51 μmol) of **38** with 250 μL of *tert*-butyl hydroperoxide (0.5 M in CH_2Cl_2) yielded, after chromatography on silica gel with ethyl acetate/hexane 1:4, 59 mg (91%) of the phosphate **39** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.4–7.2 (m, 25 H), 5.2–4.9 (m, 3 H), 4.9–4.7 (m, 8 H), 4.3–4.1 (m, 3 H), 4.1–3.8 (m, 6 H), 3.44 (t, 1 H, J = 9 Hz), 2.3–2.2 (m, 4 H), 1.6–1.5 (m, 4 H), 1.4–1.2 (m, 48 H), 0.88 (t, 6 H, J = 6.5 Hz); ^{31}P{^{1}H} NMR ($CDCl_3$) δ –0.80, –0.93.

D-3-Chloro-3-deoxy-*myo*-inositol 1-[(*R*)-2,3-Bis(hexadecanoyloxy)propyl hydrogen phosphate] (CPI, 40). Hydrogenolysis of 62 mg (48.5 μmol) of the protected phosphate **39** under the same conditions as for FPI (**22**) gave 37 mg (92%) of CPI (**40**) as a white powder: ^{1}H NMR (DMSO-d_6) δ 5.16 (br s, 1 H), 4.30 (br d, 1 H, J = 10 Hz), 4.15–4.0 (m, 4 H), 3.95–3.80 (m, 2 H), 3.56 (t, 1 H, J = 9 Hz), 3.46 (t, 1 H, J = 9 Hz), 3.02 (t, 1 H, J = 8.5 Hz), 2.27 (m, 4 H), 1.55–1.4 (m, 4 H), 1.35–1.1 (m, 48 H), 0.85 (t, 6 H, J = 7 Hz); ^{13}C NMR (DMSO-d_6) δ 172.41, 172.19, 77.77 (d, J = 6 Hz), 75.64, 72.10, 71.04, 70.48 (d, J = 6 Hz), 69.60 (d, J = 8.5 Hz), 64.07, 63.90, 61.90, 33.50, 33.34, 31.27, 29.06, 28.94, 28.71, 28.41, 24.41, 24.36, 22.07, 13.84; ^{31}P NMR (DMSO-d_6) δ 3.37; IR (KBr) 3431, 2918, 2850, 1741, 1653, 1467, 1384, 1022 cm^{-1}; MS (plasma desorption) m/z 875 ($M^+ + 2\ Na^+ + H^+$), 851 ($M^+ + Na^+$); (CI) m/z 551; $[\alpha]_D$ –1.6° (c = 2.5 g L^{-1}, $CHCl_3$/MeOH 2:1).

Growth Inhibition Assay. The procedure of ref 9 was followed. Briefly, wild type and *v-sis* transformed murine NIH 3T3 cells were plated at a density of 5000 cells in 1.6-cm diameter culture wells for 24 h in Dulbecco's Modified Eagle Medium (DMEM) with 10% heat-inactivated fetal calf serum. The cells were then grown in regular or *myo*-inositol free DMEM with 10% dialyzed heat-inactivated fetal calf serum in the presence of the inositol analogues. Adherent cells were harvested after 3 d and counted with an automated cell counter. Incubations were conducted in quadruplicate. The concentrations of inositol analogues which cause 50% inhibition of cell growth (IC_{50}) are shown in Table 1.

Colony Formation. The procedure of ref 24 was followed. Briefly, 35-mm culture dishes were charged with a base layer consisting of 0.5 mL of DMEM containing 10% fetal calf serum and 0.7% agarose or 0.5% agar. On day 0, HT-29 human colon carcinosarcoma cells in bulk culture were dissociated with trypsin and EDTA, washed once in growth medium, and subcultured by layering 1 × 10^4 viable cells in 0.5 mL of growth medium with 0.3% agarose over each base layer. Cultures were examined with the aid of an inverted stage microscope, and only cultures containing uniformly distributed single cell suspensions (<10 30-μm diameter cell clusters and no 60-μm clusters) were accepted for subsequent evaluation. Cultures were maintained in cell culture incubators at 37 °C and 100% relative humidity under an atmosphere of 5% CO_2 and 95% air. On day 1 (i.e., 24 h later), an upper layer of 1 mL of growth medium containing the inositol analogue was added to the dishes. Colony formation was examined at daily intervals by conventional light microscopy. The tumor cells formed a sufficient number of detectable colonies (>60-μm diameter) for analysis following 7–10 d of incubation. Viable colonies were stained with 2-(*p*-iodophenyl)-3-(*p*-nitrophenyl)-5-phenyltetrazolium chloride (INT, Aldrich Chemical Co.) and colonies counted using a Bausch & Lomb FAS-II image analysis system. Cultures treated with inositol analogues were set up in triplicate. Control cultures containing vehicle alone, together with a positive control (doxorubicin, 0.01–1 mg L^{-1}), were run concomitantly. The results are shown in Figure 1.

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Supplementary Material Available: ^{1}H NMR spectra of compounds **3**, **7**, **9**, **17**, **19–22**, **24**, **26**, **27**, **32**, **36**, **37**, **39**, and **40**, and ^{13}C NMR spectra of compounds **3**, **7**, **9**, **17**, **22**, **24**, **26**, **27**, **32**, **36**, and **40** (27 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.