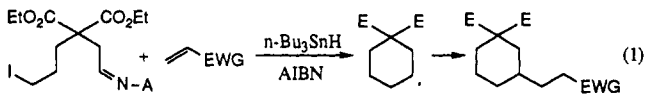
7b were cyclized without significant differences in their reactivity. Furthermore, it is noteworthy that no reduction products were observed except for **1b**.

We have briefly examined the feasibility of the cyclization–intermolecular addition sequence[11] because this illustrates a unique feature of the present method, demonstrating the formation of two carbon–carbon bonds in succession at the same carbon (eq 1).[12] The addition of a 0.1 M benzene solution of *n*-Bu_3SnH (2



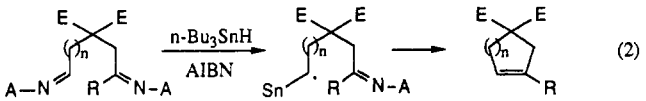
(1)

10

11: EWG = CN (86%)
12: = COOMe (87%)

equiv) and AIBN (0.1 equiv) by a syringe pump over 2 h to a 0.1 M refluxing benzene solution of the iodide **10** and acrylonitrile (10 equiv) with additional stirring for 1 h afforded **11** in 86% yield. A similar result was realized with methyl acrylate.

Our attention was next given to the use of the aziridinyl imines as radical precursors, and our approach relied on intermolecular addition of *n*-Bu_3Sn radical to an aziridinyl imine group to generate the α-*n*-Bu_3Sn-substituted carbon-centered radical, as shown in eq 2. Thus, treatment of **13a** with *n*-Bu_3SnH (0.3 equiv) and

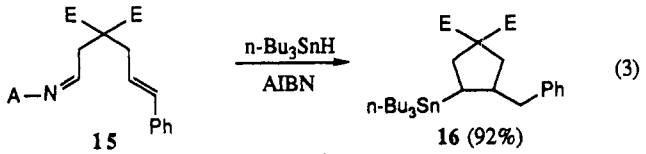


(2)

13a n=1, R=Me
13b n=1, R=H
13c n=2, R=H

8a (82%)
14b (62%)
14c (65%)

AIBN (0.1 equiv) in toluene (0.05 M in the substrate) at 110 °C for 6 h afforded **8a** in 82% yield,[13] demonstrating the efficacy of an aziridinyl imine group as a radical precursor as well as a radical acceptor. This cyclization will be especially valuable in the construction of cyclic systems bearing a carbon–carbon double bond. An additional example using the cinnamyl group as a radical acceptor, in which further functionalization of the *n*-Bu_3Sn group would be possible,[14] is shown in eq 3.[15]



(3)

15

16 (92%)

In conclusion, the radical cyclization of aziridinyl imines provides a reliable method for the formation of five- and six-membered-ring radicals. The ability of aziridinyl imines to function as radical precursors as well as radical acceptors enhances the synthetic utility of the present method. Further studies on radical reactions using aziridinyl imines are now in progress.

Acknowledgment. We thank Lucky Ltd. and The Organic Chemistry Research Center for financial support of this work. We are also grateful to Drs. Chwang Siek Pak and Sung-Eun Yoo of Korea Research Institute of Chemical Technology for their help.

(9) The structures of **6a** and **6b** were further ascertained by ^1H NMR analysis of the destannylated products after treatment of **6a** and **6b** with DCl, respectively.

(10) Satisfactory spectral data and high-resolution mass spectra were obtained for the reaction products.

(11) (a) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1983**, *105*, 6765. (b) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303. (c) Stork, G.; Sher, P. M.; Chen, H.-L. *J. Am. Chem. Soc.* **1986**, *108*, 6384.

(12) Nagai, M.; Lazor, J.; Wilcox, C. S. *J. Org. Chem.* **1990**, *55*, 3440.

(13) Additional AIBN (0.1 equiv) was added after 2 h.

(14) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: 1987 and references cited therein.

(15) Treatment of **15** with *n*-Bu_3SnH (1.1 equiv) and AIBN (0.1 equiv) in benzene (0.01 M) at 80 °C for 4 h afforded **16** in 92% yield. The ratio of cis and trans isomer (**16**) could not be determined by ^1H NMR.

Registry No. 1a, 137435-35-9; **1b**, 137435-36-0; **1c**, 137435-37-1; **2a**, 4167-77-5; **2c**, 1139-13-5; **3**, 137435-38-2; **4**, 137435-39-3; **5a**, 137435-40-6; **5b**, 137435-41-7; **6a**, 137435-42-8; **6b**, 137435-43-9; **7a**, 137435-44-0; **7b**, 137435-45-1; **8a**, 2698-64-8; **8b**, 74160-66-0; **9a**, 137435-46-2; **9b**, 93638-77-8; **10**, 137435-47-3; **11**, 137435-48-4; **12**, 137435-49-5; **13a**, 137435-50-8; **13b**, 137435-51-9; **13c**, 137435-52-0; **14b**, 21622-00-4; **14c**, 38511-09-0; **15**, 137435-53-1; **16**, 137435-54-2; acrylonitrile, 107-13-1; methyl acrylate, 96-33-3; diethyl (2-bromoethyl)(2-oxoethyl)propanedioate, 137435-55-3; diethyl (2-oxoethyl)[2-(phenylseleno)ethyl]-propanedioate, 137435-56-4; diethyl (3-bromopropyl)(2-oxoethyl)-propanedioate, 137435-57-5; diethyl (4-bromo-2-butenyl)(2-oxoethyl)-propanedioate, 137435-58-6; diethyl (2-oxoethyl)-2-propynylpropanedioate, 137435-59-7; diethyl (2-oxopropyl)-2-propynylpropanedioate, 137435-60-0; diethyl (2-bromo-2-propenyl)(2-oxoethyl)propanedioate, 137435-61-1; diethyl (2-bromo-2-propenyl)(2-oxopropyl)propanedioate, 137435-62-2; diethyl (3-iodopropyl)(2-oxoethyl)propanedioate, 137435-63-3; diethyl (2-oxoethyl)(2-oxopropyl)propanedioate, 137435-64-4; diethyl bis(2-oxoethyl)propanedioate, 137435-65-5; diethyl (2-oxoethyl)-(3-oxopropyl)propanedioate, 137435-66-6; diethyl (2-oxoethyl)(3-phenyl-2-propenyl)propanedioate, 137435-67-7; 1-amino-2-phenylaziridine, 19615-20-4; 1-(2′-phenylaziridinyl)-4,4-bis(ethoxycarbonyl)-piperidine, 137435-68-8.

Biomimetic Synthesis of Enantiomerically Pure D-*myo*-Inositol Derivatives

Steven L. Bender* and Richard J. Budhu

Department of Chemistry
University of California at Irvine
Irvine, California 92717

Received August 28, 1991

Since D-*myo*-inositol 1,4,5-trisphosphate (D-1,4,5-IP_3) was identified as the second messenger in a vast number of important signal transduction processes,[1] numerous syntheses of 1,4,5-IP_3 and other inositol phosphates have been reported.[2,3] These studies have established effective methodology for the polyphosphorylation of partially protected *myo*-inositol derivatives, but no *generalizable* synthesis of enantiomerically pure inositol derivatives has been reported whereby the protection pattern and functionality may be controlled in a versatile manner. Our approach to this problem was inspired by biosynthetic considerations. The enzyme *myo*-inositol-3-phosphate synthase (EC 5.5.1.4) converts glucose-6-phosphate to D-*myo*-inositol 3-phosphate by an interesting sequence of chemical transformations (Scheme I), including a stereospecific intramolecular aldol reaction (i.e., **1** → **2** → **3**).[4] Herein we report our initial studies on a biomimetic conversion of glucopyranoside derivatives to enantiomerically pure *myo*-inositol derivatives.[5]

Our approach relies on the Ferrier reaction to generate a "mercury enolate" **8** that, as a functional equivalent of **2**, undergoes the desired carbocyclization process to provide the inosose **7** (Scheme II). Although the Ferrier reaction is well-established for the stereoselective conversion of unsubstituted enol ethers **4**

(1) Berridge, M. J.; Irvine, R. F. *Nature (London)* **1984**, *312*, 315–321.

(2) *Inositol Phosphates and Derivatives: Synthesis, Biochemistry, and Therapeutic Potential*; Reitz, A. B., Ed.; ACS Symposium Series 463; American Chemical Society: Washington, DC, 1991.

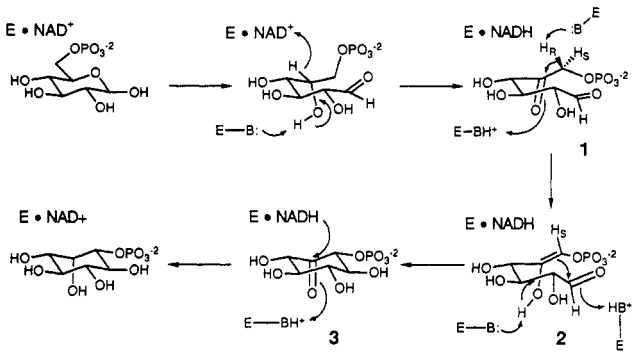
(3) For recent reviews, see: (a) Potter, B. V. L. *Nat. Prod. Rep.* **1990**, 1–24. (b) Billington, D. C. *Chem. Soc. Rev.* **1989**, *18*, 83–122.

(4) (a) Wong, Y.-H. H.; Sherman, W. R. *J. Biol. Chem.* **1985**, *261*, 11083. (b) Donahue, T. F.; Henry, S. A. *J. Biol. Chem.* **1981**, *256*, 7077. (c) Maeda, T.; Eisenberg, F., Jr. *J. Biol. Chem.* **1980**, *255*, 8458. (d) Eisenberg, F., Jr.; Maeda, T. In *Inositol and Phosphoinositides*; Bleasdale, J. E., Eichberg, J., Hauser, G., Eds.; Humana: New Jersey, 1985; p 3. (e) Frey, P. A. In *Pyridine Nucleotide Coenzymes: Chemical, Biochemical, and Medical Aspects*; Dolphin, D., Avramovic, O., Poulson, R., Eds.; Wiley: New York, 1987; Vol. 2, pp 461–511.

(5) For previous nonstereoselective, alkali-promoted cyclizations of hexos-5-ulose derivatives, see: (a) Kiely, D. E.; Fletcher, H. G., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 3289–3290. (b) Kiely, D. E.; Fletcher, H. G., Jr. *J. Org. Chem.* **1969**, *34*, 1386–1390. (c) Kiely, D. E.; Sherman, W. R. *J. Am. Chem. Soc.* **1975**, *97*, 6810–6814.

0002-7863/91/1513-9883$02.50/0

Scheme I



Scheme II

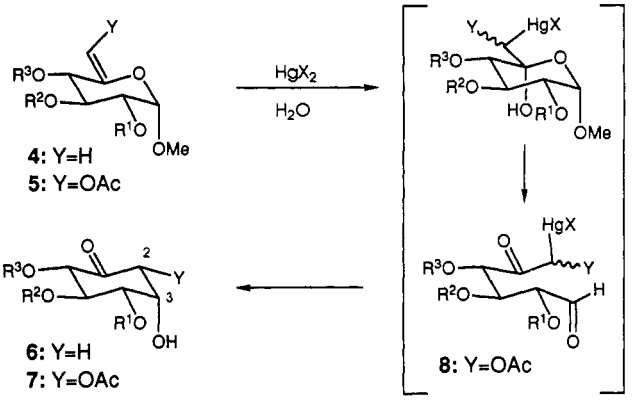


Table I

series	protecting groups	*Z*:*E* ratio of **5**[b]	yield (%) of (*Z*)-**5**[a]	yield (%) of **7**[c]	**7**:**12**:**13**:**14**[d]
a	$R^1 = R^2 = R^3 = Me$	95:5	74	57[d]	81:19:nd:nd
b	$R^1 = R^2 = R^3 = Bn$	95:5	85	59	85:15:nd:nd
c	$R^1 = R^2 = R^3 = Et_3Si$	97:3	82	50	64:8:25:3
d	$R^1 = t\text{-}BuMe_2Si$, R^2 = pMB, R^3 = Bn		88	51	63:17:19[e]:nd

[a] The overall yield of purified (*Z*)-**5** from **9**. [b] *Z*:*E* ratio was determined by ^1H NMR analysis of the unpurified reaction mixture. [c] Isolated yield after chromatography (except **7a**). [d] Diastereomer ratios (and yield for **7a**) were determined by ^1H NMR spectral analysis of the unpurified reaction mixtures; nd = not detected. [e] The stereochemical assignment of **14c** is based on analogy with **13c**.

to the corresponding 6-deoxyinososes **6**,[6,7] the absence of literature precedent for terminally substituted enol ethers (e.g., **5**) precluded any prediction as to the stereochemical outcome of the intramolecular aldol reaction, particularly with respect to the stereocenter at C_2.

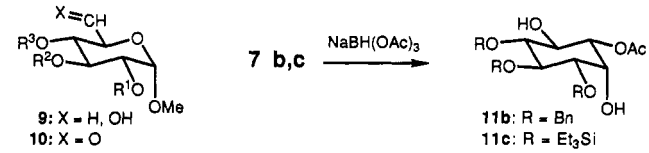
The enol acetates **5a–d** required for the Ferrier reaction proved to be readily accessible. The alcohols **9a–d**, prepared by conventional methods from methyl α-D-glucopyranoside in two to four steps,[8] were smoothly oxidized ($(ClCO)_2$, Me_2SO, Et_3N, CH_2Cl_2)[9]

Table II

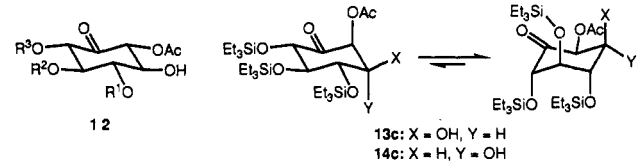
Lewis acid[a]	**7**:**12**:**13**:**14**	combined yield (%)[b]
Et_2AlCl	33:<1:62:5	83
$SnCl_4$	87:~1:10:2	83
$SnCl_4$ (from (*E*)-**5c**)	67:~1:12:11	*c*
$TiCl_4$	24:4:66:6	79
B-Br-9-BBN	87:<2:10:3	52
$ZnCl_2$ (Et_2O, 0 °C)	62:<2:37:1	*c*
$BF_3{\cdot}Et_2O$	no reaction	*c*

[a] Unless otherwise indicated, cyclizations were carried out by addition of **8c** to a solution of the Lewis acid (2 equiv) in CH_2Cl_2 at −78 °C. [b] Ratios and yields (overall from (*Z*)-**5c**) were determined by integration of ^1H NMR resonances for C_2–H's relative to an internal standard (Ph_3CH). [c] Yield not determined.

to the sensitive aldehydes **10a–d**. Without purification, the aldehydes were converted (6 equiv of K_2CO_3, 10 equiv of Ac_2O, MeCN, 80 °C)[10] to the enol acetates **5a–d** with high selectivity for the *Z* isomer[11] (Table I). Oxymercuration of **5** ($Hg(O_2CF_3)_2$, 4:1 acetone/H_2O, 0 °C, 10 min) resulted in the formation of organomercurial intermediates that did not cyclize to the product inososes until excess chloride ion was added (4–8 equiv of NaCl, then 25 °C, 20 h). In each case, the major product **7** was easily isolated by chromatography as the pure (>97%) diastereomer in moderate yield.[11] To complete the biomimetic sequence, **7b** and **7c** were efficiently converted to the enantiomerically pure *myo*-inositol derivatives **11b** and **11c** by a completely stereoselective hydroxyl-directed hydride reduction ($NaBH(OAc)_3$, AcOH, MeCN, 25 °C).[11-13]



In accord with previous observations,[6,7] we observe moderate stereoselectivity for products with the hydroxyl function axial (i.e., **10** vs **13**). On the other hand, a strong preference for an equatorial disposition of the acetoxy group at C_2 is apparent. The triethylsilyl-protected enol acetate **5c** appears to give analomous results, in that **13c**, which is epimeric to **7c** at both the α and β carbons, is a major component of the product mixture. According to ^1H NMR spectral analysis,[11] however, **13c** exists predominately in the alternative chair form in which the three (triethylsilyl)oxy groups as well as the hydroxyl group are axial.[14] Thus, the formation of **13c** is consistent with the tentative empirical rule that products with equatorial acetoxy and axial hydroxy functions are preferred.



Oxymercuration of the enol acetate (*Z*)-**5c**, followed by addition of sodium chloride and *immediate* workup, provides the α-mer-

(6) (a) Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1*, **1979**, 1455–1458. (b) Blattner, R.; Ferrier, R. J.; Haines, S. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2413–2416. (c) Blattner, R.; Ferrier, R. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1008–1010. (d) Blattner, R.; Ferrier, R. J.; Prasit, P. *J. Chem. Soc., Chem. Commun.* **1980**, 944–945.

(7) (a) Semeria, D.; Philippe, M.; Delaumeny, J.-M.; Sepulchre, A.-M.; Gero, S. D. *Synthesis* **1983**, 710–713. (b) Creitien, F.; Chapleur, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1268–1269. (c) Machado, A. S.; Olesker, A.; Luckacs, G. *Carbohydr. Res.* **1985**, *135*, 231–239. (d) Machado, A. S.; Olesker, A.; Castillon, S.; Lukacs, G. *J. Chem. Soc., Chem. Commun.* **1985**, 330–332. (e) Vass, G.; Krausz, P.; Quiclet-Sire, B.; Delaumeny, J.-M.; Cleophas, J.; Gero, S. D. *C. R. Acad. Sci., Ser. 2* **1985**, *301*, 1345–1306. (f) Pelyvas, I. F.; Sztaricskai, F.; Szilagyi, A.; Somogyi, A. *Carbohydr. Res.* **1988**, *175*, 227–2239. (g) Dyong, I.; Hagedorn, H.-W.; Thiem, J. *Liebigs Ann. Chem.* **1986**, 551–563.

(8) Experimental procedures and spectral data for all new compounds may be found in the supplementary material.

(9) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.

(10) Cook, S. L.; Secrist, J. A., III. *J. Am. Chem. Soc.* **1979**, *101*, 1554–1564.

(11) Stereochemistry was assigned by analysis of vicinal coupling constants and/or by difference NOE experiments.

(12) (a) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273–276. (b) Turnbull, M. D.; Hatter, G.; Ledgerwood, D. E. *Tetrahedron Lett.* **1984**, *25*, 5449.

(13) To take advantage of this hydroxyl-directed reduction, we designed the stereochemical course of our aldol and reduction steps to differ from that of the enzyme-catalyzed process.

(14) These conformational preferences were also indicated by an extensive (but not statistically complete) Monte Carlo conformational search (Macromodel v3.1) of **7c** and **14c**. Details will be reported in the full paper.

curio ketone **8c** as predominantly one diastereomer.[15] Oxymercuration of (*E*)-**5c** gave, as expected, predominantly the diastereomeric α-mercurio ketone epi-**8c**; in both cases, the diastereoselectivity of the oxymercuration reaction approaches 90%. The absolute configuration at C_6 of these intermediates remains to be established. Under normal Ferrier reaction conditions, (*Z*)-**5c** and (*E*)-**5c** afford the same ratio of inosose diastereomers, indicating that the configuration at the mercury-bearing carbon of **8c** has no influence on the stereochemical outcome of the aldol reaction.

Although **8c** appears to be remarkably stable as a dilute solution in aprotic solvents, exposure to Lewis acids results in rapid conversion to the inososes **7c**, **12c**, **13c**, and **14c**. Exploratory experiments indicate that the product ratio is highly dependent upon the Lewis acid promoter (Table II). Interestingly, the $SnCl_4$-promoted cyclization of **8c** is significantly more stereoselective than the cyclization of epi-**8c**. Clearly, the Lewis acid promoted version of the Ferrier reaction offers new possibilities for stereochemical control in intramolecular aldol reactions, and further characterization of this process is underway. In addition, application of this methodology to the total synthesis of biologically interesting inositol polyphosphates is in progress and will be reported in subsequent publications.[16]

Acknowledgment. This research was supported by University of California Cancer Research Coordinating Committee funds (Grant CRCC 12894).

Supplementary Material Available: Experimental details and characterization data for new compounds **5a–d**, **7a–d**, **8c**, **9c,d**, **10a–d**, **11b,c**, **12a–d**, **13c**, and **14c** (12 pages). Ordering information is given on any current masthead page.

(15) In some experiments, an initial oxymercuration adduct **15** (corresponding to the first intermediate in Scheme II) was obtained as the initial product, which, upon standing, lost MeOH at a variable rate to give **8c**.

(16) One application of this methodology may be found in the accompanying paper: Estevez, V. A.; Prestwich, G. D. *J. Am. Chem. Soc.*, following paper in this issue.

Synthesis of Enantiomerically Pure, P-1-Tethered Inositol Tetrakis(phosphate) Affinity Labels via a Ferrier Rearrangement

Virginia A. Estevez and Glenn D. Prestwich*

Department of Chemistry, State University of New York Stony Brook, New York 11794-3400

Received September 3, 1991

D-*myo*-Inositol 1,4,5-tris(phosphate) (IP_3) (**1**) (Figure 1) is an intracellular second messenger that mediates the release of calcium from nonmitochondrial stores[1] via binding to a transmembrane receptor protein.[2] Several other inositol polyphosphates have also been implicated in the regulation of calcium levels.[3] Of these, D-*myo*-inositol 1,3,4,5-tetrakis(phosphate) (IP_4) (**2**) may control regulation of Ca^{2+} reentry into the cell and modulate the IP_3-sensitive Ca^{2+} pools.[3c] Clarification of the physiological role of IP_4 would be facilitated by the isolation and characterization of its cellular receptor (IP_4R). Recently, we reported the synthesis[4]

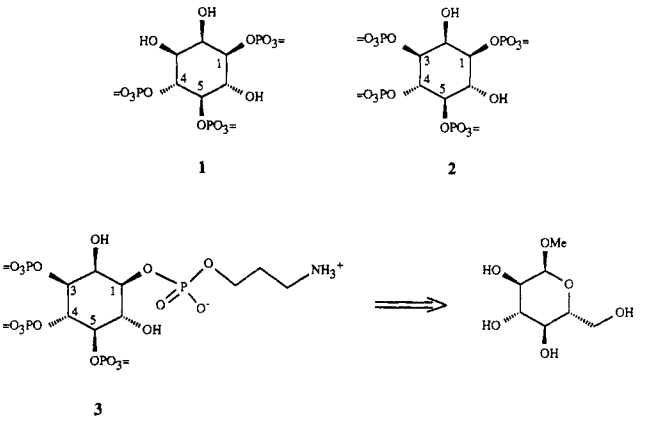
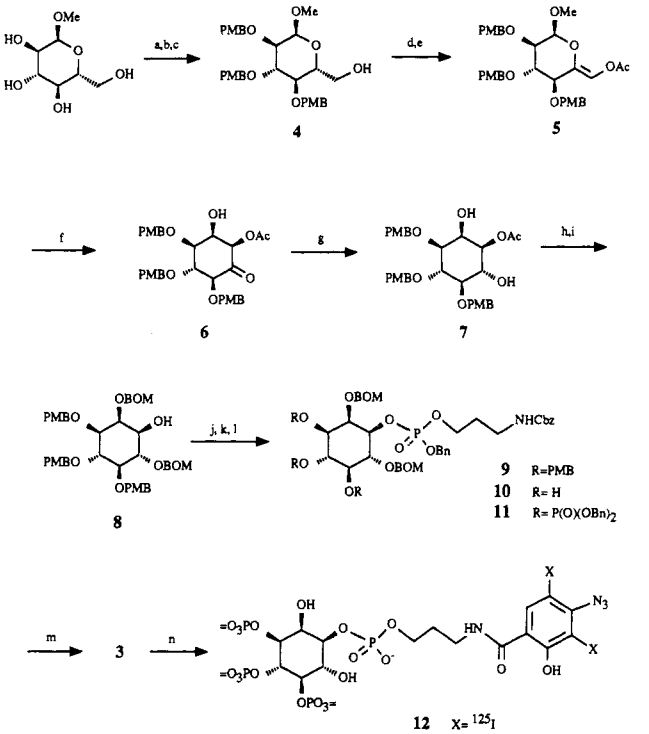


Figure 1. D-*myo*-Inositol 1,4,5-tris(phosphate) (IP_3, **1**), D-*myo*-inositol 1,3,4,5-tetrakis(phosphate) (IP_4, **2**), and derivation of P-1-modified IP_4 from the glucose carbon skeleton.

Scheme I[a]



[a] Reagents and conditions: (a) Trityl chloride, DAP, Et_3N, DMF, room temperature, 12 h; (b) NaH, PMB-Cl, DMF, reflux, 12 h; (c) 5% H_2SO_4–MeOH, acetone, room temperature, 30 min; (d) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78 °C to room temperature; (e) Ac_2O, K_2CO_3, CH_3CN, 80 °C, 8 h; (f) (i) $Hg(OAc)_2$, 3:2 acetone: water, room temperature, 30 min; (ii) saturated NaCl, room temperature, 24 h; (g) $NaBH(OAc)_3$, HOAc, CH_3CN, room temperature, 30 min; (h) BOM-Cl, Bu_4NBr, H^+ sponge, CH_3CN, room temperature, to 35 °C, to 55 °C; (i) NaOH, MeOH, reflux, 2 h; (j) (i) (*i*-Pr_2N)(OBn)P($OCH_2CH_2CH_2NHCbz$), tetrazole, CH_2Cl_2, room temperature, 3 h; (ii) MCPBA, −48 °C for 3 min, 0 °C for 15 min; (k) DDQ, wet CH_2Cl_2, room temperature, 6 h; (l) (i) $(BnO)_2P$(*i*-Pr_2N), tetrazole, CH_2Cl_2, room temperature, 12 h; (ii) MCPBA, −48 °C to room temperature, 2 h; (m) (i) Pd–C, H_2, 95% EtOH, 50 psi, room temperature, 5.5 h; (ii) Na-Chelex chromatography; (n) (i) NHS–ASA, DMF, 0.25 M TEAB (pH 8.0), room temperature, 12 h; (ii) DEAE cellulose chromatography; (iii) [^{125}]NaI, Iodobeads, 100 mM Na_2HPO_4 (pH 7.5), room temperature, 10 min.

of a P-1-tethered[5] derivative of racemic IP_4 (**3**) and the corresponding bioaffinity matrix which allowed isolation and purifi-

(1) (a) Berridge, M. J. *Annu. Rev. Biochem.* **1987**, *56*, 159–193. (b) Berridge, M. J.; Irvine, R. F. *Nature* **1989**, *341*, 197–203.

(2) Supattapone, S.; Worley, P. F.; Baraban, J. M.; Snyder, S. H. *J. Biol. Chem.* **1988**, *263*, 1530–1534.

(3) (a) Nicoletti, F.; Bruno, V.; Fiore, L.; Cavallaro, S.; Canonico, P. *J. Neurochem.* **1989**, *53*, 1026–1030. (b) Vallejo, M.; Jackson, T.; Lightman, S.; Handley, M. *Nature* **1989**, *330*, 656–658. (c) Irvine, R. F.; Moore, R. M. *Biochem. J.* **1986**, *240*, 917–920.

(4) Estevez, V. A.; Prestwich, G. D. *Tetrahedron Lett.* **1991**, *32*, 1623–1626.

0002-7863/91/1513-9885$02.50/0