

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 C₆ 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 SnCl₄-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

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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

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D-myo-Inositol 1,4,5-tris(phosphate) (IP₃) (**1**) (Figure 1) is an intracellular second messenger that mediates the release of calcium from nonmitochondrial stores¹ 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) (IP₄) (**2**) may control regulation of Ca²⁺ reentry into the cell and modulate the IP₃-sensitive Ca²⁺ pools.^{3c} Clarification of the physiological role of IP₄ would be facilitated by the isolation and characterization of its cellular receptor (IP₄R). Recently, we reported the synthesis⁴

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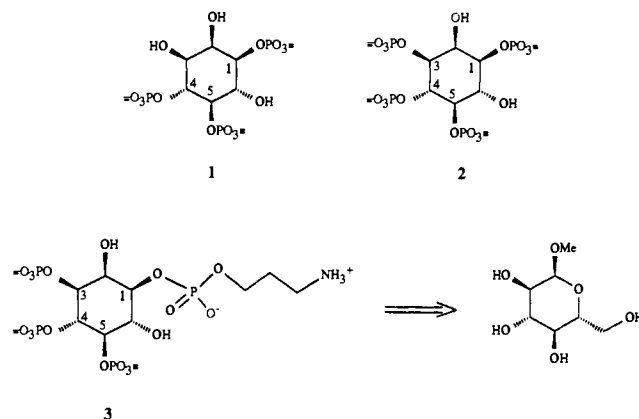
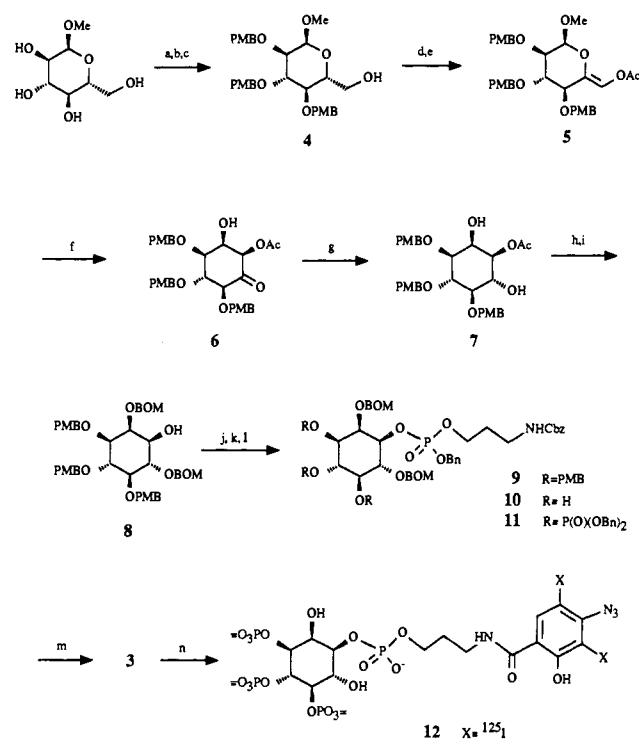


Figure 1. *D*-myo-Inositol 1,4,5-tris(phosphate) (IP₃, **1**), *D*-myo-inositol 1,3,4,5-tetrakis(phosphate) (IP₄, **2**), and derivation of P-1-modified IP₄ from the glucose carbon skeleton.

Scheme I^a



^a Reagents and conditions: (a) Trityl chloride, DAP, Et₃N, DMF, room temperature, 12 h; (b) NaH, PMB-Cl, DMF, reflux, 12 h; (c) 5% H₂SO₄-MeOH, acetone, room temperature, 30 min; (d) oxalyl chloride, DMSO, Et₃N, CH₂Cl₂, -78 °C to room temperature; (e) Ac₂O, K₂CO₃, CH₃CN, 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, CH₃CN, room temperature, 30 min; (h) BOM-Cl, Bu₄NBr, H⁺ sponge, CH₃CN, room temperature, to 35 °C, to 55 °C; (i) NaOH, MeOH, reflux, 2 h; (j) (i) (*i*-Pr₂N)-(OBn)P(OCH₂CH₂CH₂NHCbz), tetrazole, CH₂Cl₂, room temperature, 3 h; (ii) MCPBA, -48 °C for 3 min, 0 °C for 15 min; (k) DDQ, wet CH₂Cl₂, room temperature, 6 h; (l) (i) (BnO)₂P(*i*-Pr₂N), tetrazole, CH₂Cl₂, room temperature, 12 h; (ii) MCPBA, -48 °C to room temperature, 2 h; (m) (i) Pd-C, H₂, 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) [¹²⁵I]NaI, lodobeads, 100 mM Na₂HPO₄ (pH 7.5), room temperature, 10 min.

of a P-1-tethered⁵ derivative of racemic IP₄ (**3**) and the corresponding bioaffinity matrix which allowed isolation and purifi-

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

cation of rat brain IP₄R.⁶ The application of a radioiodinated photoaffinity analogue, [¹²⁵I]ASA-IP₄, for identification of specific binding subunits has also been described (ASA = 4-azido-salicylamide).⁷ However, since the receptor only recognizes the D isomer of IP₄,⁸ we now describe a novel route to enantiomerically pure, P-1-tethered IP₄ via a Ferrier rearrangement¹⁰ of a suitably protected D-glucose derivative.

Selective modification required a protecting-group strategy that would differentiate the C-1 hydroxyl from the other three hydroxyls destined for phosphorylation. The stereochemical requirements of *myo*-inositol and the disposition of the phosphates in IP₄ can be readily satisfied by a Ferrier rearrangement of a selectively protected D-glucose derivative¹¹ (Figure 1). The synthesis of the optically active C-1 phosphodiester analogue of IP₄ bearing a reactive aminopropyl tether is summarized in Scheme I. Tritylation of methyl α -D-glucopyranoside¹² followed by treatment with NaH and *p*-methoxybenzyl chloride provided the fully protected pyranoside in 63% overall yield. Selective detritylation was achieved in 90% yield with 5% H₂SO₄-MeOH and acetone as a cosolvent.¹³ Swern oxidation of alcohol 4 provided the aldehyde (>90% hydrated), and treatment with Ac₂O and K₂CO₃ gave the (*Z*)-enol acetate 5 in 85% yield from 4.¹⁴ Ferrier rearrangement of 5 in the presence of mercuric trifluoroacetate and aqueous NaCl furnished the inosose 6 with the desired axial stereochemistry at the 2-OH (less than 10% equatorial)¹⁰ in 60% yield. Stereoselective reduction of the β -hydroxy ketone with sodium triacetoxyborohydride¹⁵ provided the *myo*-inositol skeleton 7 with the C-1 position differentially protected from the C-3, C-4, and C-5 hydroxyls.

We then focused on protecting the two remaining hydroxyls in diol 7. For racemic, P-1-tethered IP₄,⁴ hydrogen-labile benzyl protecting groups were employed at the C-2 and C-6 hydroxyls. Since base lability and ease of migration of the acetyl group can cause serious problems in polyhydroxy derivatives, benzylation at the C-2 and C-6 hydroxyls required mild, neutral conditions. Benzylation using the trichloroacetimidate method was unsuccessful due to the low solubility of the diol 7 and the acid sensitivity of the *p*-methoxybenzyl (PMB) groups. Instead, the more reactive benzyloxymethyl (BOM) group was selected. Although reaction of diol 7 with benzyloxymethyl chloride and diisopropylethylamine¹⁶ failed, the BOM groups were readily introduced at C-2

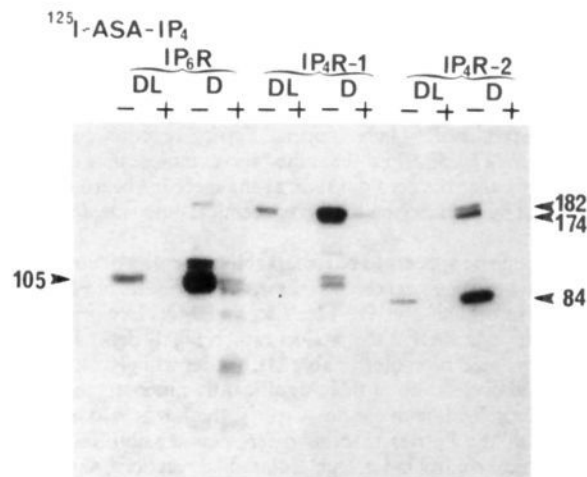


Figure 2. Photoaffinity labeling of purified IP₄ and IP₆ receptors by racemic (DL) and optically active (D) IP₄ photolabel 13. Proteins purified from rat cerebellum by IP₄ affinity chromatography⁶ were photolabeled with 13 (10 nM) as described in the absence (-) or presence (+) of 200 μ M IP₄.⁷ DL and D preparations of 13 were nominally of the same specific activity, based on synthesis using identical amounts and aliquots of the same batch of [¹²⁵I]NaI; equal molar equivalents were present in each incubation sample. IP₆R is the first eluting peak, and IP₄R-1 and IP₄R-2 are the second and third eluting peaks from the affinity column;⁶ the molecular sizes (in kDa) of the major bands are indicated.

and C-6 in 69% yield with BOM-Cl, H⁺ sponge, and *n*-Bu₄NBr in CH₃CN.¹⁷ To minimize acetyl migration, the BOM groups were introduced stepwise (23 °C for 10 h, 35 °C for 8 h, then 55 °C for 3 h). Basic methanolysis gave the C-1 alcohol 8 (95%), which served as the pivotal intermediate to a series of enantiomerically pure, P-1-modified IP₄ analogues.

Condensation of the alcohol 8 with (benzyloxy)[(3-(*N*-carboxybenzoylamino)propyl)oxy](diisopropylamino)phosphine^{5c} in the presence of tetrazole and subsequent oxidation with MCPBA furnished the fully protected aminopropyl-tethered inositol 9 in 85% yield. Removal of the PMB groups with DDQ in wet CH₂Cl₂ gave the triol 10 in 78% yield after SiO₂ chromatography. Phosphitylation of the triol followed by MCPBA oxidation (as for 8) gave the fully protected IP₄ derivative 11 (73% yield). Hydrogenolysis removed the benzyl and BOM groups to provide the optically active, P-1 aminopropyl tethered *D*-*myo*-Ins(1,3,4,5)P₄ (3) in quantitative yield after ion-exchange chromatography (Chelex, sodium form). The proton-decoupled ³¹P NMR spectrum of this compound showed four singlets, δ 0.48, 3.59, 4.21, and 5.29 ppm, corresponding to the C-1 phosphodiester and the C-3, C-4, and C-5 phosphates, respectively.

Coupling 3 to *N*-hydroxysuccinimide-activated agarose (Affi-Gel 10) buffered at pH 8.5 provided an enantiomerically pure IP₄ affinity column, which has been employed in the purification of the IP₄R (data not shown).¹⁸ Furthermore, reaction of this intermediate with *N*-hydroxysuccinimide 4-azidosalicylate in aqueous DMF, followed by radioiodination using Iodobeads, furnished the enantiomerically pure D-[¹²⁵I]ASA-IP₄ photolabel 12. Figure 2 compares the efficacy of the optically active photolabel with that of the racemic material. It is evident from the intensity of the bands that D-12 is a substantially more sensitive and efficient probe than DL-12 for active-site modification of the IP_n binding sites of these receptors.

Optically active derivatives of IP₄ modified at C-1 are now readily produced via a Ferrier rearrangement of glucose. Applications of this methodology in the synthesis of C-1 tritium labeled D-IP₄ and its photolabile derivatives for the characterization of the IP₄ binding site are in progress.

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Supplementary Material Available: Full experimental and spectral details for this synthesis (10 pages). Ordering information is given on any current masthead page.

Catalytic Asymmetric Synthesis of Optically Active 2-Alkanols via Hydrosilylation of 1-Alkenes with a Chiral Monophosphine-Palladium Catalyst

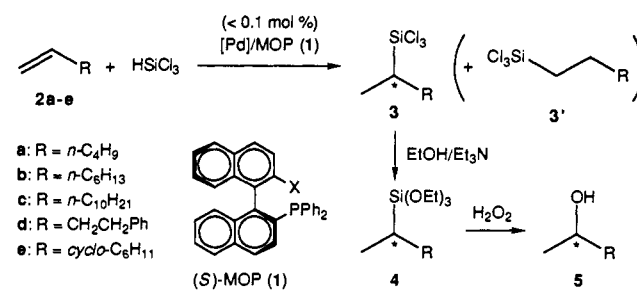
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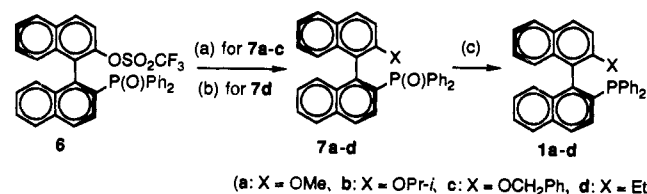
Catalytic asymmetric functionalization of simple prochiral olefins is an important goal in synthetic organic chemistry.^{1,2} We report here the first successful conversion of alkyl-substituted terminal olefins into optically active secondary alcohols (>94% ee),³ which is realized by palladium-catalyzed asymmetric hydrosilylation in the presence of a new chiral monodentate phosphine ligand (MOP, 1) followed by oxidation of the carbon-silicon bond⁴ (Scheme I).

It is well-documented⁵ that the hydrosilylation of terminal olefins is catalyzed by platinum, rhodium, or nickel complexes to proceed with anti-Markovnikov selectivity leading to 1-silylalkanes. Rather surprisingly, only a little attention has been paid to the use of palladium catalysts for the hydrosilylation of 1-alkenes^{6,7} in spite of their frequent use for the reaction of 1,3-dienes

Scheme I



Scheme II^a



^a(a) (i) 3 N NaOH, 1,4-dioxane, methanol; (ii) MeI, *i*-PrI or PhCH₂Br (3–10 equiv), K₂CO₃ (2–4 molar equiv), acetone, reflux, 3–24 h (7a, 99%; 7b, 92%; 7c, 87%). (b) EtMgBr (1.1 equiv), NiCl₂(dppf) (2 mol %), Et₂O, reflux, 24 h (7d, 81%). (c) Et₃N (7–20 equiv), Cl₃SiH (5 equiv), xylene, 120 °C, 3–5 h (1a, 97%; 1b, 84%; 1c, 96%; 1d, 79%).

and styrenes.^{5,6} In order to develop a catalyst possessed of high catalytic activity, high regioselectivity giving 2-silylalkanes, and high enantioselectivity in addition, we examined several types of phosphine-palladium catalysts for the reaction of 1-hexene (2a) with trichlorosilane. It was found that palladium complexes coordinated with a chelating bis(phosphine), dppb,⁸ chiraphos,⁹ or BINAP,¹⁰ did not catalyze the hydrosilylation at 80 °C, while the reaction took place at 40 °C with monodentate phosphine ligands.^{11,12} Among the monodentate phosphine ligands, (S)-2-(diphenylphosphino)-2'-methoxy-1,1'-binaphthyl (MOP, 1a)¹³ turned out to be by far the best ligand, giving a high yield of 2-(trichlorosilyl)hexane (3a) with high regioselectivity¹⁴ as well as high enantioselectivity.

Chiral monophosphines (MOPs, 1) are the ligands we have designed with a view to using them for the catalytic asymmetric reactions where a monophosphine ligand is required to generate a catalytically active species.¹⁵ The present palladium-catalyzed hydrosilylation is one of the cases. The phosphines 1a–d were readily prepared in high yields starting with known optically active

(8) 1,4-Bis(diphenylphosphino)butane.

(9) (S,S)-2,3-Bis(diphenylphosphino)butane: Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* 1977, 99, 6262.

(10) (R)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl: Takaya, H.; Mashima, K.; Koyano, K.; Yagi, M.; Kumabayashi, H.; Taketomi, T.; Akutagawa, S.; Noyori, R. *J. Org. Chem.* 1986, 51, 629.

(11) For example, the reaction in the presence of 0.1 mol % of a palladium-triphenylphosphine catalyst (P/Pd = 2/1) at 40 °C for 24 h gave a 12% yield of hexylsilanes consisting of 1- and 2-isomers in a ratio of 91/9, accompanied by isomerization of 1-hexene into internal olefins. See also ref. 6.

(12) It is reasonable to expect that a monodentate phosphine ligand generates a palladium catalyst that is more active for the hydrosilylation than a chelating bis(phosphine) ligand. The former can form square-planar palladium(II) intermediate PdH(SiCl₃)L(CH₂=CHR) (L = monophosphine), which offers a coordination site for the activation of olefin.

(13) Preparation of (S)-1a from (S)-2'-methoxy-1,1'-binaphthyl-2-carboxylic acid has been reported: Hattori, T.; Shijo, M.; Kumagai, S.; Miyano, S. *Chem. Express* 1991, 6, 335.

(14) The high catalytic activity and regioselectivity of the palladium-MOP complex may be related to the reactivity of key intermediate Pd(2-alkyl)L(silyl). It seems that MOP ligand can accelerate the reductive elimination of 2-silylalkane and/or retard the β-hydrogen elimination forming 2-alkenes. Triphenylphosphine or tri-*o*-tolylphosphine caused the isomerization of a terminal olefin into internal olefins during the hydrosilylation while MOP did not (see footnote 11).

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(5) For reviews: (a) Ojima, I. In *The Chemistry of Organic Silicon Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley: Chichester, 1989; p 1479. (b) Speier, J. L. *Advanced Organometallic Chemistry*; Stone, F. G. A., West, R., Eds.; Academic Press: New York, 1979; Vol. 17, p 407. (c) Lukevics, E.; Belyakova, Z. V.; Pomerantseva, M. G.; Voronkov, M. G. In *Journal of Organometallic Chemistry Library*; Seyferth, D., Davies, A. G., Fisher, E. O., Normant, J. F., Reutov, O. A., Eds.; Elsevier: Amsterdam, 1977; Vol. 5. (d) Ojima, I.; Kogure, T. *Rev. Silicon, Germanium, Tin Lead Compd.* 1981, 5, 7.

(6) It has been reported that reaction of 1-octene with HSiCl₃ catalyzed by Pd(PPh₃)₄ at 100 °C gives 1-octylsilane in 85% yield: Tsuji, J.; Hara, M.; Ohno, K. *Tetrahedron* 1974, 30, 2143.

(7) Regioselective hydrosilylation of CF₃CH=CH₂ with HSiMeCl₂ or HSiCl₃ catalyzed by PdCl₂(PPh₃)₂ has been reported: Ojima, I.; Yatabe, M.; Fuchikami, T. *J. Organomet. Chem.* 1984, 260, 335.