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The Dioxanone Approach to (2*S*,3*R*)-2-*C*-Methylerythritol 4-Phosphate and 2,4-Cyclodiphosphate, and Various MEP Analogues

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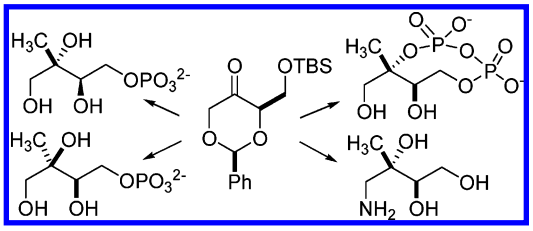

Efficient syntheses of the non-mevalonate pathway intermediates 2-*C*-methylerythritol 4-phosphate (MEP) and 2-*C*-methylerythritol 2,4-cyclodiphosphate (ME-2,4-cycloPP), as well as the parent tetrol 2-*C*-methylerythritol, in enantiopure form from (2*S*,4*R*)-*cis*-2-phenyl-4-*tert*-butyldimethylsilyloxy-1,3-dioxan-5-one are reported. The 2*S* configuration of the *C*-methyl group was installed by highly axial-face selective addition of CH_3MgBr (20:1) to the chiral dioxanone carbonyl group. Primary selective monophosphorylation and 2,4-bis-phosphorylation, followed by desilation and hydrogenolysis to the free mono- and diphosphates, and, in the latter case, cyclization to form the eight-membered phosphoryl anhydride, afforded MEP and ME-2,4-cycloPP in good yields. The C2 epimeric analogues, 2-*C*-methylthreitol and its 4-phosphate, were accessed by $LiAlH_4$ reduction of the cis,cis epoxide of (2*S*,4*R*)-4-*tert*-butyldimethylsilyloxymethyl-5-methylene-2-phenyl-1,3-dioxane, primary-selective phosphorylation, and cleavage of the silyl, benzylidene, and benzyl protecting groups. Regioselective cleavage of the acetal ring of 1,3-benzylidene 2-*C*-methylerythritol silyl ether by ozonolysis afforded a 1,2,3-triol 3-monobenzoate intermediate that was converted to the novel amino sugar, 1-amino-1-deoxy-2-*C*-methylerythritol.

Introduction

The remarkable structural diversity of isoprenoid natural products[1] originates from the ubiquitous C_5 precursors, isopentenyl and dimethylallyl diphosphates (IPP and DMAPP), and the processing of their downstream, oligomeric forms.[2] The biosynthesis of these isoprene equivalents had been attributed to the exclusive operation of the acetate-derived mevalonate pathway[3] until definitive contradictions in the labeling patterns of hopanoid triterpenes produced by bacteria and the ginkgolide diterpenes elaborated by *Ginkgo biloba* embryos were independently recognized and rationalized.[4,5] Subsequent research in many laboratories led rapidly to the identification of the intermediates, enzymes, and genes associated with the mevalonate-independent or methylerythritol phosphate (MEP) pathway (Scheme 1) to IPP and DMAPP (**7** and **8**), and considerable knowledge about their occurrence in different organisms is now

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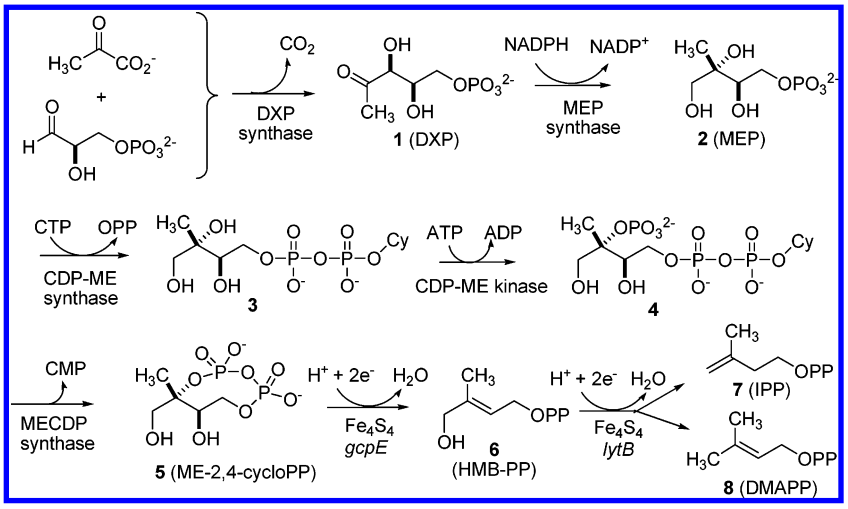
SCHEME 1



known.[2b,6] The branched chain C_5 structure (**2**) is generated by the semi-benzilic acid rearrangement catalyzed by MEP synthase (DXP reductoisomerase), the first committed step in the pathway. While many of the individual reactions have relevant chemical and biochemical precedents, the formation of the eight-membered cyclic anhydride of ME-2,4-cycloPP (**5**) and its reductive elimination to (*E*)-4-hydroxy-DMAPP (**6**) and the deoxygenation of the latter to IPP and DMAPP are especially novel features of the MEP pathway.[7]

While mammalian cells utilize the mevalonate pathway exclusively to elaborate essential isoprenoid lipids, many bacteria are wholly dependent upon the MEP route to generate vital polyprenyl components. In higher plants, the diverse forms of terpene natural products arise by concurrent operation of the mevalonate and MEP routes segregated into cytosolic and plastidial compartments.[8] The realization that the majority of bacterial human pathogens utilize the MEP pathway to biosynthesize isoprenoid constituents has focused attention on these unique enzymes as potential targets for novel therapeutic agents.[9] A significant example is the malaria parasite *Plasmodium falciparum*[10] and its effective clinical treatment with fosmidomycin, an inhibitor of MEP synthase.[11] Similarly the MEP pathway enzymes are recognized as attractive targets for the development of selective herbicides likely to be innocuous to humans.[9a,12] The final intermediate in the MEP pathway (*E*)-4-hydroxy-3-methylbut-2-en-1-yl diphosphate (**6**) is the most potent activator of human $V_\gamma 9/V\delta 2$ T cells known with an EC_{50} of 0.1 nM.[13]

Access to MEP pathway intermediates as well as their structural analogues and labeled forms is clearly essential to ongoing biochemical investigations and to the development of new antibiotics and herbicides targeting the constituent enzymes. While enzymatic methods facilitated by genetic techniques have been utilized to generate the intermediates and numerous labeled variants,[14] chemical approaches are likely to provide more general access to structural analogues. Chemical syntheses of MEP and ME-2,4-cycloPP (**3** and **5**) have relied upon asymmetric epoxidation and dihydroxylation methods, albeit with moderate enantioselectivities,[15] and upon carbohydrate deriva-

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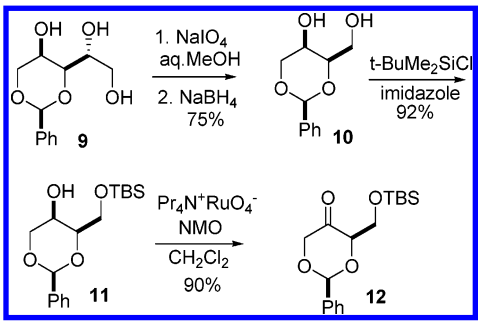
tives to obtain the correct absolute configuration.[16,17] Although homo-DXP,[18] several fluoro derivatives,[19] and one phosphonate variant[20] of deoxyxylulose phosphate (**1**) have been reported, to our knowledge the only MEP analogues reported are homo-MEP,[18b] the corresponding phosphonate isostere,[21] and trifluoromethyl stereoisomers.[22]

This Article presents a general synthetic approach to enantiopure MEP (**2**), ME-2,4-cycloPP (**5**), and various analogues including homo, nor, epimeric, and deoxy-amino variants from the chiral dioxanone **12**.[17] 2-Phenyl and other 2-substituted dioxan-5-ones are potentially useful protected forms of 1,3-dihydroxyacetone. They can be accessed by cyclo-condensation of tris(hydroxymethyl)methylamine with aldehydes or the corresponding dimethyl acetals, followed by periodate cleavage of the resulting 5-(aminomethyl)dioxan-5-ols.[23] Dioxanones have also been prepared by oxidation of the dioxanols with RuO_4^{-1}/OCl^- and the Dess−Martin periodinane.[24] The pronounced tendency of these highly reactive cyclic ketones to undergo addition of Grignard reagents and hydride on the axial face of the C═O group[24b,25] has been attributed to a stereoelectronic interaction of the incipient C−C bond with the σ^* orbital of the adjacent axial C−H bonds,[26] to minimization of torsional strain,[27] and to exterior frontier orbital extension effects.[28] *threo*-Selective aldol condensations of dioxanone enolates have been accomplished, despite competing self-condensation and reduction via hydride transfer from amide bases.[29] Asymmetric alkylations of dioxanones have been achieved through the corresponding (*R*)- and (*S*)-prolinol ether hydrazones.[30]

SCHEME 2



Results and Discussion

Enantiopure (2*S*,4*R*)-dioxanone **12**, a key intermediate in the present work, was readily prepared from commercially available D-arabitol in five steps and 50% overall yield (Scheme 2). Formation of the known 1,3-benzylidene derivative (**9**) of D-arabitol was accomplished by direct condensation with benzaldehyde and anhyd HCl according to a literature procedure.[31] Oxidative cleavage of the vicinal diol with $NaIO_4$ in aq methanol (0 °C, 30 min),[32,33] filtration of the precipitated salts, and immediate reduction of the resulting unstable aldehyde in the filtrate with $NaBH_4$ (0 °C, 1 h) afforded the known 1,3-*O*-benzylidene-D-threitol in 76% yield as a crystalline solid having ^{1}H NMR data and mp in accord with the literature.[34] Substantially lower yields were observed in similar reductions carried out in the same way, but without the filtration step.

The primary hydroxyl group of **10** was selectively protected as the *t*-butyldimethylsilyl (TBS) ether by reaction with 1.25 equiv of the silyl chloride reagent (imidazole, CH_2Cl_2, 25 °C, 8 h, 92%). Attempts to oxidize dioxanol **11** to the dioxanone by the Swern procedure[24b] and with pyridinium chlorochromate and pyridinium dichromate oxidants either failed completely or afforded unacceptably low yields. Fortunately, oxidation with 10 mol % of tetrapropylammonium perruthenate in the presence of *N*-methylmorpholine *N*-oxide (CH_2Cl_2, 25 °C, molecular sieves)[35] gave the unstable silyl-protected dioxanone **12** in 88% yield after chromatography on silica gel. Similar oxidation of *cis*-1,3-benzylideneglycerol to 2-phenyldioxanone with hypochlorite in the presence of catalytic perruthenate or RuO_4 has been reported.[24a] The dioxanone could be stored for limited times in pentane solution at −20 °C. Perhaps the instability of the dioxanone is associated with β-elimination of silanol and dimerization of the α-methylene dioxanone in a manner similar to the facile Diels−Alder dimerization of α-methylenecyclohexanone,[36] or with facile self-condensation.[29]

Reaction of the silyl-protected dioxanone **12** with CH_3MgBr in ether at −78 °C gave rise to a 20:1 mixture of tertiary alcohol adducts according to ^{1}H NMR integrations of the acetal protons (Scheme 3). The predominant and more polar isomer obtained in pure form (80%) by chromatography on silica gel was assigned to have the axial methyl configuration based on similar

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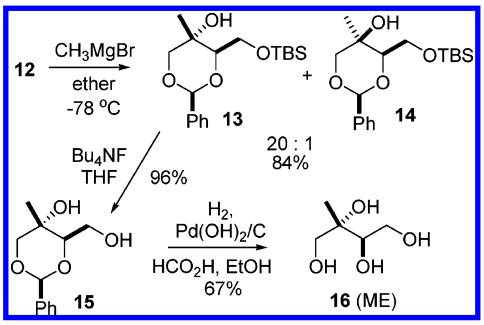
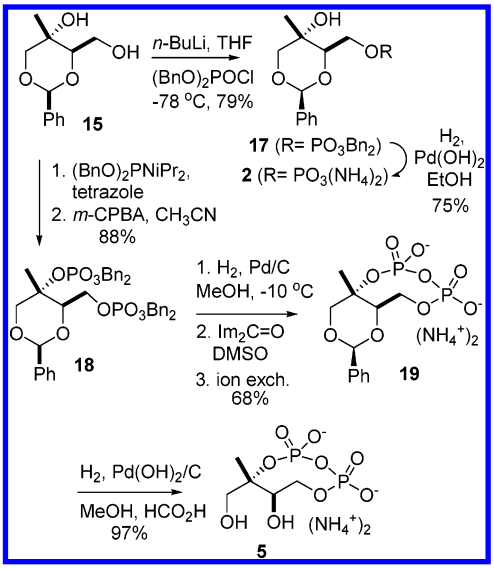
SCHEME 3



SCHEME 4



stereoselectivities in addition of alkyl Grignard reagents and metal hydrides to 2-substituted dioxanones,[24b,25,28] including ones bearing silyloxymethyl groups in the α position.[24b] The consistent bias toward nucleophilic attack on the axial C═O face of dioxanones in addition of alkyl Grignard reagents provides a general approach to *C*-alkylerythritols. Cleavage of the silyl group in **13** using *n*-Bu_4NF in THF at 0 °C afforded 1,3-benzylidene 2-*C*-methylerythritol (**15**) in 96% yield as a white solid. Subsequent hydrogenation with 20% $Pd(OH)_2/C$ and a catalytic amount of HCOOH in ethanol under an H_2 atmosphere pressure provided the parent C_5 tetrol, 2-*C*-methylerythritol (**16**, ME), in 67% yield, which had physical and spectroscopic properties in agreement with those reported by Kis et al.[16b]

Regioselective monophosphorylation[37] of **15** (Scheme 4) was accomplished in 79% yield by lithiation of the primary hydroxyl with 1.5 equiv of *n*-BuLi (hexane−THF, −75 °C) and reaction with dibenzyl chlorophosphate (prepared from dibenzylphosphite and *N*-chlorosuccinamide in benzene). Simultaneous hydrogenolysis of the primary dibenzyl phosphate and the benzylidene ring of **17** with 20% $Pd(OH)_2/C$ in ethanol under hydrogen at atmospheric pressure followed by basification with ammonia in methanol at 0 °C provided the ammonium salt of 2-*C*-methylerythritol 4-phosphate (**2**) as a white solid in 75% yield. The spectral data were identical to those reported in the literature.[16a]

The cyclic diphosphate (**5**) of 2-*C*-methylerythritol was obtained by bisphosphosphorylation using the phosphoramidite

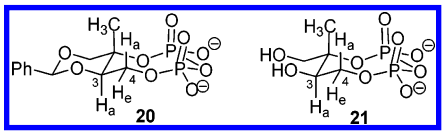


FIGURE 1. Depictions of 1,3-benzylidene-2-*C*-methylerythritol and 2-*C*-methylerythritol 2,4-cyclodiphosphates in crown conformations (**20** and **21**).

method[38] and subsequent ring closure to the bicyclic phosphoryl anhydride (Scheme 4). Reaction of 1,3-diol **15** with 3 equiv of dibenzyl *N*,*N*-diisopropyl-phosphoramidite (tetrazole, CH_3CN, 25 °C, 4 h) followed by in situ oxidation with *m*-chloroperoxybenzoic acid (0 °C) provided the corresponding tetrabenzyl diphosphate (**18**, 91%). Selective hydrogenolysis of the four benzyl phosphates in the presence of the benzylidene protecting group was achieved by exposure to hydrogen and 10% Pd/C in methanol (1 atm, −10 °C, 1 h), followed by immediate neutralization (NH_3, MeOH) to form the benzylidene-protected ammonium salt of the 2,4-diphosphate intermediate.

Cyclization of the bis-phosphoric acid form from hydrogenolysis of **18** was effected with 1,1′-carbonyldiimidazole in anhydrous DMSO (rt, 4 h).[39] The resulting imidazole salt of the cyclic diphosphate was immediately passed through an ion exchange column (NH_4^+ form) to convert to the ammonium salt. Purification by chromatography on silica gel yielded the diammonium salt of cyclic diphosphate **19** in 68% yield over three steps. The formation of the cyclic phosphoryl anhydride was evident from the ^{31}P NMR spectrum that showed direct coupling of the nonequivalent phosphorus nuclei. Finally, hydrogenolysis of the benzylidene group (H_2, 20% $Pd(OH)_2/C$, MeOH, 1 atm, 48 h) in the presence of formic acid generated the diammonium salt of 2-*C*-methyl-D-erythritol 2,4-cyclodiphosphate (**5**, ME-2,4-cycloPP) in 97% yield as a white salt, $[\alpha]^{25}_D$ +1.8° (c = 1.00).

It seems likely that the rigidifying effect of the benzylidene ring facilitates formation of the eight-membered ring by restricting rotation about the C2−C3 bond in the ring and fixing the exocyclic CH−CH_2 and C(CH_3)−O bonds in diequatorial orientations. Furthermore, the mildly acidic conditions of the final deprotection step and neutral conditions maintained during purification avoid rearrangement to the 1,2-cyclic monophosphate isomer promoted by basic conditions.[15e,40] It is noteworthy that the benzylidene ring of **19** underwent slow acid-catalyzed hydrolysis (0.1 and 0.2 M HCO_2H in D_2O, 25 °C, 7.4 days) to ME-2,4-cycloPP with the phosphoryl anhydride intact, according to ^1H NMR spectra.[17] The known acyclic *C*-methylerythritol 2,4-diphosphate[15e] was similarly generated for comparison by hydrolysis of the benzylidene ring of the 2,4-diphosphate intermediate from hydrogenolysis of **18**. Thus, the final deprotection step could presumably be accomplished by this hydrolysis procedure.

The vicinal coupling interactions between the axial H3 proton (δ 4.59 ppm, $J_{3,4}$ = 3.7, 10.1 Hz) and the pseudoaxial and pseudo-equatorial protons H4a and H4e observed in the ^1H NMR spectrum of cyclic diphosphate **19** provide evidence for the anti-periplanar orientation of H_3 and H_{4a}, and the existence

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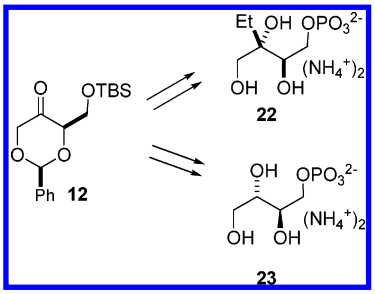
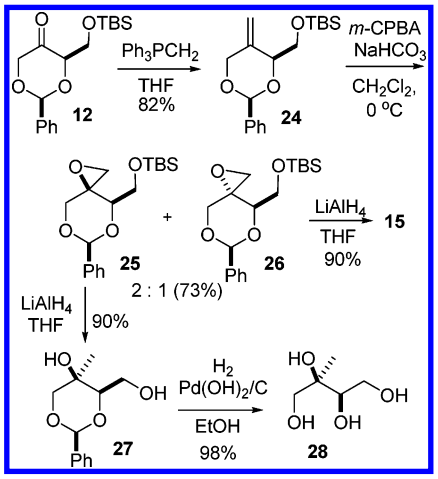
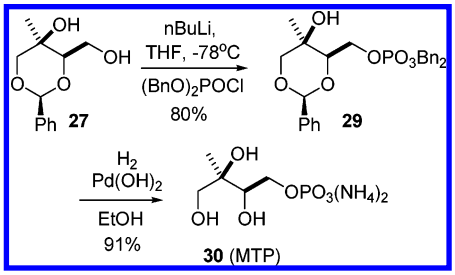
SCHEME 5



SCHEME 6



SCHEME 7



of the eight-membered ring in a crown conformation (Figure 1, **20**). Variable-temperature ^{1}H NMR spectra (MeOH: −10, −30, −50, and −70 °C) showed no evidence of line-broadening, indicating the likelihood that **19** exists as a single conformer. A similar crown conformation (**21**) of ME-2,4-cycloPP (**5**) with pseudoaxial methyl and pseudo-equatorial hydroxyl groups at C2 and C3 was proposed on the basis of coupling interactions in the ^{1}H NMR spectrum (4.22, $J_{3,4}$ = 3.6, 7.7 Hz) and MM2 calculations.[41] The resulting approximate anti-periplanar alignment of C2-OPO_3 and C3 OH in **5** would be favorable for an anti reductive elimination to form the E double of **6**.[7]

The conformationally defined dioxanone **12** and its reactive carbonyl function opened the way to direct synthesis of 5-homo, 5-nor, and 3-epi analogues of MEP as shown in Schemes 5−7. 5-Homo-MEP (**22**) was obtained in 64% overall yield by the same four-step reaction sequence used for MEP:[42] (a) axial-face addition of EtMgBr (ether, −78 °C), (b) desilation (Bu_4-NF, THF), (c) primary-selective phosphorylation (*n*-BuLi, THF−hexane, −78 °C; $ClPO_3Bn_2$ −78 to 25 °C), and (d) catalytic hydrogenolysis (H_2, 10% Pd/C, MeOH, 1 atm, −10 °C, 30 min; H_2, 20% $Pd(OH)_2$, MeOH, 1 atm, 24 h). Homo-MEP was previously generated enzymatically by the action of a DXP reductoisomerase mutant on homo-DXP, but the compound was not characterized.[18b] Homo-MEP is analogous to homo-mevalonate, the biosynthetic precursor to the Cecropia juvenile hormones.[43] Nor-MEP (D-erythritol-4-phosphate, **23**)[44] was prepared in four steps (11% overall) by analogous reactions: hydride reduction ($NaBH_4$, MeOH, 0 °C), desilation (Bu_4-NF, THF), regioselective phosphorylation ($ClPO_3Bn_2$, pyr, ca. 19% after partial conversion), and hydrogenolysis (H_2, $Pd(OH)_2$/C, EtOH).

The next target was the C2 epimer of MEP, that is, the previously unknown 2-*C*-methyl-D-threitol 4-phosphate (MTP, **30**) from the exocyclic cis,cis epoxide (**25**) as depicted in Schemes 6 and 7. Wittig methylenation of dioxanone **12** with 1 equiv of methylenetriphenylphosphorane (*n*-BuLi, Ph_3PCH_3-Br, THF, −75 °C; rt, −75 °C)[45] provided 5-methylene-1,3-dioxane **24** in 82% yield. Epoxidation with *m*-chloroperoxybenzoic acid (4 equiv, CH_2Cl_2, 4 h, 0 °C; 12 h, 25 °C) in the presence of solid $NaHCO_3$[46] yielded a 2:1 mixture of cis,cis and cis,trans diastereomers (**25** and **26**) in 73% yield. The two isomers were readily separated by silica-gel chromatography, and both were characterized by ^{1}H and ^{13}C NMR spectra. Because epoxidation of the parent 5-methylene-2-phenyl-1,3-dioxane under similar conditions (*m*-CPBA, $CHCl_3$) proceeded with only slight bias (54:46) for oxygen transfer to the axial face,[47] the somewhat enhanced ratio in the case of **24** probably reflects a small torsional interaction between the methylene and CH_2OSi substituents in the transition state leading to the minor cis,trans epoxide **26**.

Reduction of the predominant and more polar cis,cis epoxide **25** with $LiAlH_4$ in THF (1 h, 0 °C, 90%) was accompanied by desilation to give benzylidene *C*-methylthreitol (**27**), presumably as a result of precedented intramolecular hydride transfer from an oxyaluminum hydride intermediate to silicon.[48] The diol product was clearly different from the major adduct **15** formed in the Grignard reaction with dioxanone **12** after desilation (Scheme 3). A direct correlation was accomplished by $LiAlH_4$ reduction of the minor epoxide to benzylidene 2-*C*-methylerythritol **15**. The ^{1}H NMR spectra of epimers **27** and **15** in benzene-d_6 show significant differences. The resonances for the equatorial CH_3 (s, 0.65 ppm) and the adjacent CH_2 (ABdd, 3.06 and 3.48, J_{AB} = 11.3 Hz) and CH (app dd, 3.21) in the former appear at higher field ($\Delta\delta$ −0.22 to −0.61 ppm) as compared to the CH_3 (s, 1.26), CH_2 (ABdd, 3.41 and 3.70, J_{AB} = 10.5 Hz), and CH (m, 3.67) in the latter.

Hydrogenolysis of the benzylidene ring in **27** (H_2, 20% $Pd(OH)_2$, HCO_2H, EtOH, 1 atm, 12 h, 25 °C, 98%) gave the known

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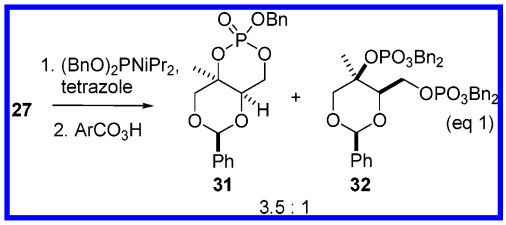
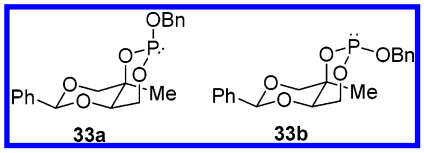
(48) (a) Paquette, L. A.; Underiner, T. L.; Gallucci, J. C. *J. Org. Chem.* **1992**, *57*, 86−96. (b) de Vries, E. F. J.; Brussee, J.; van der Gen, A. *J. Org. Chem.* **1994**, *59*, 7133−7137.

2-*C*-methylthreitol **28** (Scheme 6).[49] Selective mono-phosphorylation of the diol was effected by lithiation of **27** with 1.2 equiv of *n*-BuLi and reaction with dibenzyl chlorophosphate yielding the corresponding mono dibenzyl phosphate **29** in 79% yield (Scheme 7). Hydrogenation (20 mol % $Pd(OH)_2/C$, H_2, 1 atm, 12 h, 25 °C) followed by treatment with gaseous NH_3 gave 2-*C*-methylthreitol 4-phosphate ammonium salt (**30**) in 91% yield as a white powder. 2-*C*-Methylthreitol (**28**) has been previously synthesized both as a single enantiomer[49,50a] and in racemic form.[50b]

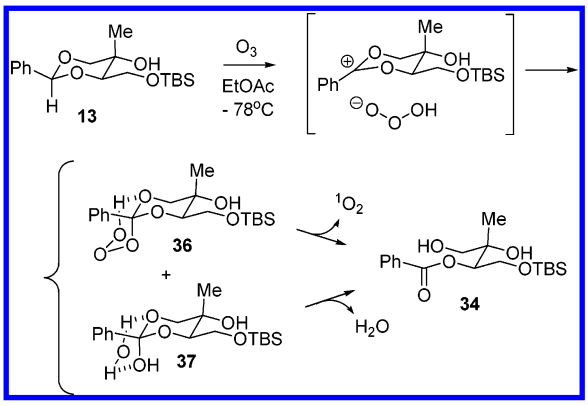


Preliminary experiments were carried out to determine whether the 2,4-cyclic diphosphate of 2-*C*-methylthreitol could be prepared by the methods given above for synthesis of ME-2,4-cycloPP (**5**). However, reaction of the benzylidene-protected derivative **27** with dibenzyl *N*,*N*-diisopropylphosphoramidite (3 equiv, CH_3CN, 0 °C, 5 h) followed by peracid oxidation afforded the cyclic phosphate **31** as the major product (ca. 35%), accompanied by small amounts (ca. 3.5:1 ratio) of the expected diphosphate **32** (eq 1). Interestingly, cyclic phosphate **31** was formed as a single isomer of unknown configuration at phosphorus. Ring formation seems likely to have occurred by tetrazole-catalyzed cyclization of the primary phosphite intermediate by displacement of one prochiral benzyloxy substituent.[15e] Because peroxide oxidations of phosphites to phosphates are known to take place with retention,[51] the cyclization evidently produces only one of the two cyclic phosphite stereoisomers **33a** or **33b**. Although isomer **33a** with an equatorial benzyloxy group appears to be sterically less hindered than **33b** (1,3 diaxial benzyloxy and methyl groups), the latter would benefit from anomeric stabilization.[52] Hence, there seems to be no basis for further conjecture about the stereochemistry of cyclic phosphate **31**. Also puzzling is the absence of cyclic phosphate in the reaction of the erythritol isomer **15** with the same phosphoramidite reagent (Scheme 4).



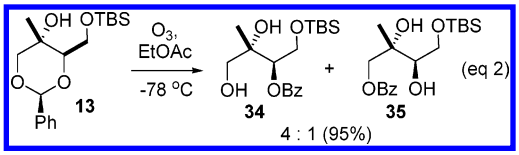
Regioselective cleavage of the benzylidene acetal of *C*-methylerythritol derivatives would open the way to prepare analogues bearing different substituents at C1 or C3. Access to a suitable derivative for effecting substitutions at the primary C1 position was achieved by ozonolysis (eq 2). Deslongchamps and co-workers originally reported that ozonolysis of bicyclic

SCHEME 8



4,6-benzylidene derivatives of methyl α-D-glucopyranoside 2,3-dimethyl ether and 2,3-diacetate in CCl_4 or acetic acid provided predominantly the primary 4,6-diol monobenzoates (60:40 and 85:15), whereas the corresponding 2,3-ditosylate gave solely the secondary 4,6-diol monobenzoate.[53]

Ozonolysis of the benzylidene ring of **13** in ethyl acetate at −78 °C for 30 min gave rise to a 4:1 mixture favoring the secondary benzoate isomer **34** (eq 2). Other solvents (CCl_4, CH_2Cl_2, MeOH) gave lower yields and/or lower selectivities than ethyl acetate. The isomers were readily separated by chromatography on silica gel (TLC R_f = 0.22 and 0.35, 1:4 EtOAc−hexane), and the predominant and more polar benzoate (**34**, 75%) was identified by the appearance of an AB doublet of doublets for the CH_2OH group (δ_H 3.39 and 3.55, J_{AB} = 12 Hz) in the ^1H NMR spectrum. In contrast, the NMR spectrum of the less polar mono benzoate (**35**, 20%) exhibited a similar AB doublet of doublets at much lower field (δ_H 4.27 and 4.33, J_{AB} = 11.7 Hz) for the C1 CH_2 bearing the benzoyloxy substituent.



The regioselective ring opening of the benzylidene acetal to the presumably more sterically crowded and less stable secondary mono-benzoate indicates kinetic control. NMR spectra of solutions generated by ozonolysis of cyclic acetals, including one 2-phenyl-1,3-dioxane, in various solvents provided evidence for hydrotrioxide and hemiortho ester intermediates that decomposed independently to the corresponding half esters.[54] Several similar mechanisms for the ring-opening step in the acetal oxidations were considered including favorable intramolecular proton transfers from the hydrotrioxide OOOH to the acetal oxygens and from the hemiortho esters through a water-bridged cyclic array. Accordingly, it seems reasonable to propose that the hydrotrioxide and hemiortho ester intermediates (**36** and **37**) from benzylidene acetal **13** would undergo ring opening via similar intramolecular proton transfers predominantly directed to the less sterically hindered acetal oxygen as illustrated in Scheme 8, thus giving rise mainly to the presumably less stable secondary benzoate **34**.

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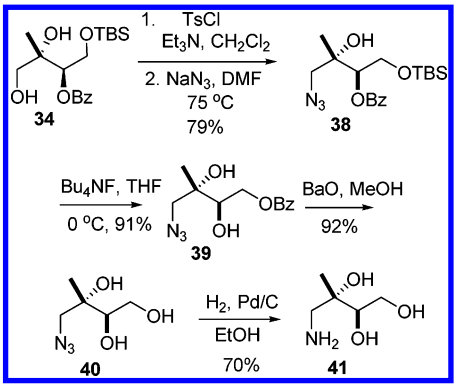
SCHEME 9



Amino sugars and aminocyclitols are important components of many antibiotics and other biologically active natural products,[55] and considerable literature exists on the synthesis, reactions, and properties of these carbohydrate derivatives.[56] We decided to undertake the synthesis of the 1-amino analogue of 2-*C*-methylerythritol by means of silyl benzoate **34** (Scheme 9).

Silyl benzoate **34** was converted to the primary tosylate. Subsequent displacement with azide anion (NaN_3, DMF, 75 °C) gave azido alcohol **38** in 79% yield over two steps. Cleavage of the silyl protecting group with *n*-Bu_4NF in THF furnished azido triol mono-benzoate **39** resulting from benzoyl migration to the adjacent primary position. Methanolysis of **39** with BaO in methanol[57] at 25 °C gave the azido triol **40** (92%), which was reduced by catalytic hydrogenation (H_2, Pd/C, EtOH) to 1-amino-1-deoxy-2-*C*-methylerythritol (**41**, 70%).[58]

Conclusion

Axial-face additions of alkyl Grignard and hydride nucleophiles to the chiral dioxanone **12** allow for efficient, stereoselective syntheses of 2-*C*-methylerythritol, and the derived 4-phosphate and 2,4-cyclodiphosphate, and their analogues, in enantiopure form. The versatility of the dioxanone approach is demonstrated by conversion of **12** to the epimeric 2-*C*-methylthreitol and its 4-phosphate, and to 1-deoxy-1-amino-2-*C*-methylerythritol via S_N2 displacement of a C1 tosylate intermediate. These schemes can be readily adapted to the synthesis of labeled variants of the MEP pathway intermediates as well as other functional or structural analogues.

Experimental Section

1,3-Benzylidene-D-erythrulose, 4-(*t*-Butyldimethylsilyl) Ether (12). The oxidation procedure reported by Griffith and Ley[35] was followed with some modifications. A suspension of 4 Å molecular sieves powder (250 mg) in dry CH_2Cl_2 (25 mL) containing alcohol **11** (500 mg, 1.5 mmol) was stirred and cooled at 0 °C. Tetrapropylammonium perruthenate (27 mg, 0.07 mmol) and 4-methylmorpholine *N*-oxide (216 mg, 1.8 mmol) were added as solids. The suspension was allowed to stir for 30 min at 25 °C at which time TLC indicated the oxidation was complete. The reaction mixture was diluted with ether (50 mL), and the supernatant liquid was passed through a silica gel plug (25 g). Elution with ether (50 mL) and evaporation of the solvent under reduced pressure gave 490 mg of crude oil, purity ca. 96% by NMR analysis. Purification by chromatography afforded 435 mg (88%) of keto silyl ether **12** as an unstable liquid that was best used soon after purification. Characterization data: TLC R_f 0.45 (20:80 EtOAc:hexane); $[\alpha]^{25}_D$ −4.75° (c = 0.99, MeOH); ^{1}H NMR (500 MHz, benzene-d_6) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.94 (s, 9H), 3.87 (dd, 1H, J = 17.6, 0.9 Hz), 3.94 (υ_B ABX, 1H, J_{AB} = 11.1 Hz, J_{BX} = 2.6 Hz), 4.00 (υ_A ABX, 1H, J_{AB} = 11.1 Hz, J_{AX} = 4.3 Hz), 4.05 (m, 1H), 4.20 (dd, 1H, J = 17.5, 1.3 Hz), 5.42 (s, 1H), 7.11 (app t, 1H, J_{app} = 7.7 Hz), 71.9 (app t, 2H, J = 7.7 Hz), 7.57 (app d, 2H, J_{app} = 7.7 Hz); ^{13}C NMR (125 MHz, benzene-d_6) δ −5.3, −5.2, 18.5, 26.0, 63.0, 72.7, 84.3, 99.1, 126.7, 129.2, 138.1, 203.9; IR ν (neat film) 3360, 3262, 3197, 3080, 3036, 2954, 2930, 2885, 2857, 1726, 1591, 1440, 1255, 1112, 837 cm^{-1}; MS m/z 323.01. Anal. Calcd for $C_{17}H_{26}O_4Si$ (MW 322.48): C, 63.32; H, 8.13; O, 9.84; Si, 8.71; Found: C, 60.96; H, 8.15.

1,3-Benzylidene-2-*C*-methyl-D-erythritol, 4-(*t*-Butyldimethylsilyl) Ether (13). A solution of keto silyl ether **12** (480 mg, 1.4 mmol) in dry Et_2O (25 mL) was stirred and cooled at −78 °C as MeMgBr (0.59 mL, 1.7 mmol, 3 M in Et_2O) was added dropwise over 2 min. After 45 min, MeOH (1 mL) was added, and the mixture was stirred for an additional 5 min, after which satd aqueous NH_4Cl (20 mL) was added. The product was extracted with ether (3 × 40 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure gave the crude product as a pale yellow oil that was a ∼20:1 mixture of equatorial and axial alcohol isomers based on the integration values of the acetal protons in the ^{1}H NMR spectrum of the crude product. Purification by flash chromatography (30:70 Et_2O:hexane) afforded silyl ether **13** (400 mg, 80%) as a colorless oil: TLC R_f 0.50 (20:80 EtOAc:hexane); $[\alpha]^{25}_D$ +37.8° (c = 1.0, MeOH); ^{1}H NMR (500 MHz, benzene-d_6) δ −0.04 (s, 3H), −0.03 (s, 3H), 0.87 (s, 9H), 1.46 (s, 3H), 3.02 (s, 1H), 3.65 (d, 1H, J = 10.9 Hz), 3.80 (m, 3H), 3.93 (d, 1H, J = 10.5 Hz), 5.37 (s, 1H), 7.13 (app t, 1H, J_{app} = 7.0 Hz), 7.20 (app t, 2H, J_{app} = 7.5 Hz), 7.61 (m, 2H); ^{13}C NMR (125 MHz, benzene-d_6) δ −5.9, −5.7, 18.0, 20.1, 25.7, 63.3, 66.4, 77.1, 81.4, 101.7, 126.6, 128.2, 128.7, 138.7; IR (neat film) ν 3514, 2954, 2929, 285, 1463, 1385, 1255 cm^{-1}; HRMS (FAB) m/z calcd for $C_{18}H_{30}O_4Si$ (M + 1)$^+$, 339.1993; found, 339.1991. Data for the minor isomer (**14**): yield, ca. 20 mg (ca. 4%); TLC R_f 0.54 (20:80 EtOAc:hexane); $[\alpha]^{25}_D$ +8.0° (c = 1.67, MeOH); ^{1}H NMR (500 MHz, benzene-d_6) δ 0.07 (s, 3H), 0.07 (s, 3H), 0.91 (s, 3H), 0.97 (s, 9H), 3.24 and 3.64 (ABdd, 2H, J = 11.4 Hz), 3.54 (dd, 1H, J = 4.7, 5.7 Hz), 3.83 (app dd, 1H, J_{app} = 5.4, 11.3 Hz), 4.06 (app dd, 1H, J_{app} = 4.6, 11.0 Hz), 5.26 (s, 1H), 7.13 (m, 1H), 7.21 (app t, 2H, J_{app} = 7.4 Hz), 7.61 (m, 2H); ^{13}C NMR (125 MHz, benzene-d_6) δ −5.4, −5.3, 18.3, 19.2, 25.9, 62.6, 66.3, 76.7, 84.5, 101.3, 126.4, 128.2, 128.8, 138.6.

1,3-Benzylidene-2-*C*-methyl-D-erythritol (15). This desilation procedure was based on that reported by Fujii et al.[59] To a solution of silyl ether **13** (900 mg, 2.1 mmol) in dry THF (5.0 mL) at 0 °C was added Bu_4NF (2.9 mL, 2.9 mmol, 1 M in THF). After 15 min, water (12 mL) was added, and the product was extracted with ether (3 × 60 mL). The ethereal extracts were combined and dried over $MgSO_4$. Evaporation of the solvents under reduced pressure and purification of the crude oil by flash chromatography (70:30 EtOAc:

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hexane) afforded 470 mg (80%) of diol **15** as a white solid: mp 99−100 °C; TLC R_f 0.42 (100% EtOAc); ^{1}H NMR (500 MHz, pyridine-d_5) δ 1.67 (s, 3H), 4.02 (d, 1H, J = 10.5 Hz), 4.14 (d, 1H, J = 10.5 Hz), 4.23 (dd, 1H, J = 11.8, 7.9 Hz), 4.40 (dd, 1H, J = 7.8, 2.5 Hz), 4.56 (dd, 1H, J = 11.8, 1.9 Hz), 5.83 (s, 1H), 6.74 (br s, 2H, OH, exch. D_2O), 7.38 (m, 3H), 7.73 (app dd, 2H, J_{app} = 7.9, 1.7 Hz); ^{13}C NMR (125 MHz, pyridine-d_5) δ 20.4, 61.2, 65.3, 78.6, 87.1, 102.3, 127.2, 128.4, 129.0, 139.5; ^{1}H NMR (500 MHz, benzene-d_6) δ 1.26 (s, 3H, CH_3), 1.59 (bs, 1H, OH, D_2O exchange), 1.92 (bs, 1H, OH, exch. D_2O), 3.41 and 3.70 (ABdd, 2H, J_{AB} = 10.5 Hz), 3.53−3.61 (m, 2H), 3.67 (m, 1H), 5.29 (s, 1H), 7.10−7.19 (m, 3H), 7.54 (d, 2H, J = 7.5 Hz); ^{13}C NMR (125 MHz, benzene-d_6) δ 19.8, 61.7, 65.9, 77.2, 82.7, 101.8, 126.6, 127.4, 128.9, 138.5; IR (neat film) ν 3356, 2940, 2870, 1456, 1400, 1382, 1264, 1215 cm^{-1}; HRMS (FAB) m/z calcd for $C_{12}H_{16}O_4$ $(M + 1)^+$, 225.1127; found, 227.1126.

2-*C*-Methyl-D-erythritol (16). Deprotection of benzylidene acetal **15** (30 mg, 0.13 mmol) was accomplished by hydrogenation (200 psi of H_2 for 12 h) using 20% $Pd(OH)_2$/C (15 mg) suspended in EtOH (0.4 mL) containing HCO_2H (2 drops). The heterogeneous reaction mixture was diluted with MeOH (6 mL) and filtered. Removal of the solvent under reduced pressure gave 12 mg (67%) of **16** as a colorless oil: $[\alpha]^{25}_D$ +13.3° (c = 0.30, H_2O, l 0.5 dm); lit.[15] $[\alpha]^{21}_D$ +6.0° (c = 0.05, H_2O), $[\alpha]^{22}_D$ +9.0° (c = 1.0, H_2O), $[\alpha]^{22}_D$ +7.2° (c = 0.4, MeOH), $[\alpha]^{22}_D$ +11.2° (c = 0.57, MeOH); ^{1}H NMR (500 MHz, D_2O) δ 1.07 (s, 3H), 3.42 (ν_B of ABq, 1H, J = 11.8 Hz), 3.53 (ν_A of ABq, 1H, J = 11.8 Hz), 3.54 (d, 1H, J = 11.6 Hz), 3.61 (dd, 1H, J = 8.7, 2.5 Hz), 3.78 (dd, 1H, J = 11.5, 2.5 Hz); ^{13}C NMR (125 MHz, D_2O) δ 20.8, 64.5, 68.8, 76.7, 77.5; MS CI (methane, 12.1 V ionizing voltage): 137.1 (M + 1, 3.5%), 102.1 (56%), 101.1 (100%, M − (H_2O + OH)), 85.1 (45%), 83.1 (37%), 71.1 (74%), 69.1 (43%), 67.1 (28%). The spectral data agreed with those reported by Kis et al.[16b]

1,3-Benzylidene-2-*C*-methyl-D-erythritol, 4-Dibenzylphosphate (17). This phosphorylation was based on the procedure described by Inage et al.[37] A solution of diol **15** (135 mg, 0.6 mmol) in dry THF (5.0 mL) was stirred and cooled at −75 °C as a solution of 1.6 M *n*-BuLi in hexane (0.56 mL, 0.9 mmol) was added dropwise. After 10 min, dibenzyl phosphorochloridate [prepared from dibenzyl phosphite (236 mg, 0.9 mmol) and *N*-chlorosuccinamide (120 mg, 0.5 mmol) in benzene (1.5 mL)][60] was added via syringe. The resultant suspension was stirred for 10 min at −75 °C and 15 min at rt. Water (2 mL) and ether (15 mL) were added, and the organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (50:50 EtOAc:hexane). The monophosphate (**17**, 230 mg, 79%) was obtained as a white solid: mp 86−87 °C; TLC R_f 0.55 (70:30 EtOAc:hexane); $[\alpha]^{25}_D$ +27.2° (c = 1.0, MeOH); ^{1}H NMR (400 MHz, acetone-d_6) δ 1.33 (s, 3H), 3.71 and 3.79 (ABdd, 2H, J_{AB} = 10.7 Hz), 4.0 (dd, J = 8.6, 1.5 Hz), 4.13 (ddd, 1H, J = 11.0, 8.2, 1.3 Hz), 4.37 (s, 1H, OH, exch. D_2O), 4.45 (ddd, 1H, J = 10.9, 6.7, 1.8), 5.03 (app t, 4H, J = 8.0 Hz), 5.59 (s, 1H), 7.34 (m, 13H), 7.50 (m, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 19.8, 65.1, 67.0, 69.5, 69.6, 78.0, 83.9, 102.1, 127.1, 128.5, 128.7, 129.0, 129.4, 136.9, 137.0, 139.0; ^{31}P NMR (161.9 MHz, acetone-d_6) δ 0.39 (s); IR (CCl_4) ν 3378, 2971, 1456, 1382, 1260, 1107, 1018. HRMS (FAB) calcd for M + H of $C_{26}H_{29}O_7P$, 485.1729; found, 485.1729.

2-*C*-Methyl-D-erythritol, 4-Phosphate, Diammonium Salt (2). To a solution of dibenzyl phosphate **17** (210 mg, 0.4 mmol) in ethanol (5.0 mL) was added 20% $Pd(OH)_2$/C (50 mg) under N_2. The resulting heterogeneous mixture was stirred under an H_2 atmosphere at rt. After 12 h, the mixture was diluted with MeOH (12 mL) and filtered, and the filtrate was cooled to 0 °C. A slow stream of NH_3 gas was bubbled through the solution for ∼2 min. Removal of the solvent under reduced pressure gave 110 mg (75%) of the ammonium phosphate (**2**) as a white solid: $[\alpha]^{25}_D$ +11.3° (c = 1.6, H_2O); published data for the acid form, lit.[61] for enzymatic product, $[\alpha]^{21}_D$ +6.4 ° (c = 0.1, H_2O); lit.[15a] for 78% ee, $[\alpha]^{25}_D$ +6.8° (c = 0.05, H_2O), lit.[15b] for 72% ee, $[\alpha]^{20}_D$ +13.4° (c = 0.8, H_2O); lit.[15c] for 50% ee, $[\alpha]^{20}_D$ + 6.1° (c = 0.02); ^{1}H NMR (500 MHz, D_2O) δ 1.12 (s, 3H), 3.32 and 3.37 (ABdd, 2H, J_{AB} = 11.8 Hz), 3.74 (dd, 1H, J = 7.5, 2.1 Hz), 3.8 (m, 1H), 3.98 (m, 1H); ^{13}C NMR (125 MHz, D_2O) δ 20.9, 67.6, 76.3, 76.7 (d, J = 6.8 Hz), 74.0; ^{31}P NMR (161.9 MHz, acetone-d_6) δ 4.95 (s); negative ion FAB MS (3:1 DTT−DTE), m/z 215.1 (39%, $C_5H_{12}O_7P$ − H). The NMR data agree with the published data for the sodium salt.[16a]

1,3-Benzylidene-2-*C*-methyl-D-erythritol 2,4-Bis(dibenzylphosphate) (18). This phosphorylation procedure was based on that described by Yu and Fraser-Reid.[38] A solution of dibenzyl *N*,*N*-diisopropylphosphoramidite[62] (460 mg, 1.3 mmol) and tetrazole (140 mg, 2.0 mmol) in CH_3CN (4 mL) was allowed to stir for 30 min at rt. A solution of diol **15** (100 mg, 0.44 mmol) in CH_3CN (2 mL) was added dropwise over 1 min. After 4 h, the reaction mixture was cooled to 0 °C and *m*-chloroperoxybenzoic acid (solid, 340 mg, 2.0 mmol) was added. The cooling bath was removed, and the reaction mixture was allowed to stir at rt. After 30 min, the mixture was diluted with Et_2O (40 mL). The ethereal layer was washed with 10% $Na_2S_2O_5$ (2 × 15 mL), satd $NaHCO_3$ (15 mL), and brine (15 mL); dried ($MgSO_4$); and evaporated to give 0.51 g of the crude phosphate as a white solid. Purification by flash chromatography (35:65, EtOAc:hexane) gave 300 mg (91%) of diphosphate **18** as a colorless oil: TLC R_f 0.55 (50:50 EtOAc:hexane); $[\alpha]^{25}_D$ +16.9° (c = 1.0 in MeOH); ^{1}H NMR (500 MHz, acetone-d_6) δ 1.63 (s, 3H), 4.00 (d, 1H, J = 10.7 Hz), 4.10 (dt, 1H, J = 11.1, 8.4 Hz), 4.16 (app dd, 1H, J = 8.3, 1.6 Hz), 4.27 (d, 1H, J = 10.5 Hz), 4.40 (ddd, 1H, J = 11.1, 6.9, 1.7 Hz), 5.00−5.12 (m, 8H), 5.60 (s, 1H), 7.30−7.50 (m, 25H); ^{13}C NMR (125 MHz, acetone-d_6) δ 18.0, 66.3 (m), 69.62 (m), 69.9 (app d, J = 4.6 Hz), 75.6 (m), 75.9 (app d, J = 6.4 Hz), 81.9 (m), 102.4 (app d, J = 7.4 Hz), 127.2, 128.7, 128.7, 128.8, 128.9, 129.1,129.1, 129.2, 129.2, 129.3, 129.3, 129.3, 129.8, 137.1 (d, J = 2.8 Hz), 137.2 (d, J = 1.8 Hz), 137.2 (d, J = 1.8 Hz), 137.2 (br s), 138.4; ^{31}P NMR (202 MHz, acetone-d_6) δ −3.31, 0.83; MS (FAB, 70 eV) m/z (rel intensity %): 745 (100), 655 (17), 467 (20), 361 (23), 279 (17), 181 (62), 133 (22); IR (CCl4) ν 3037, 2959, 1456, 1284, 1016 cm^{-1}. Anal. Calcd for $C_{40}H_{42}O_{10}P_2$ (744.68): C, 64.51; H, 5.69. Found: C, 64.47; H, 5.67.

1,3-Benzylidene-2-*C*-methyl-D-erythritol 2,4-Diphosphate, Ammonium Salt. A suspension of 2,4-bis(dibenzyl) phosphate **18** (100 mg, 0.13 mmol) and 10% Pd/C (22 mg) in MeOH (8.5 mL) was stirred at −10 °C under H_2 (1 atm, 0.52 mmol) for 20 min. The H_2 uptake was monitored with a gas burette. The catalyst was filtered off (celite), and the filtrate was neutralized with satd NH_3/MeOH solution (2 mL) at 0 °C. The resultant precipitate was collected and dissolved in 0.2% NH_4HCO_3 (5 mL). Lyophilization afforded the ammonium diphosphate intermediate (59 mg, 97%) as a flocculent, amorphous solid: ^{1}H NMR (500 MHz, D_2O) δ 1.62 (s, 3H), 3.84 (m, 1H), 4.09 and 4.30 (ABdd, 2H, J_{AB} = 10.8 Hz), 4.17 (d, 1H, J = 8.4 Hz), 4.24 (ddd, 1H, J = 1.5, 5.8, 11.4 Hz), 5.75 (s, 1H), 7.46−7.48 (m, 3H), 7.55−7.57 (m, 2H); ^{13}C NMR (125 MHz, D_2O) δ 19.8, 65.6 (d, J = 4.6 Hz), 73.1 (d, J = 6.4 Hz), 78.3, 85.6 (dd, J = 8.1, 10.5 Hz), 104.6, 129.1, 131.4, 132.6, 139.0; ^{31}P NMR (202 MHz, D_2O) δ −1.43, 3.33; MS (FAB) m/z 385 (M + 1 − 4NH_3).

1,3-Benzylidene-2-*C*-methyl-D-erythritol 2,4-Cyclodiphosphate, Ammonium Salt (19). The 2,4-bis(dibenzyl) phosphate **18**

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(300 mg, 0.4 mmol) in MeOH (22 mL) was hydrogenated (H_2, 1 atm, −10 °C, 1 h) using 10% Pd/C catalyst (66 mg). The reaction mixture was filtered, the filtrate was evaporated under reduced pressure, and the residue was coevaporated three times with dry THF (2 × 5 mL) to give 1,3-*O*-benzylidene-2-*C*-methyl-D-erythritol 2,4-bis(phosphoric acid, mono-ester) as a colorless oil: ^{1}H NMR (500 MHz, THF-d_8) δ 1.65 (s, 3H), 3.99 (dd, 1H, J = 8.1, 10.4 Hz), 4.08 and 4.16 (ABdd, 2H, J_{AB} = 10.4 Hz), 4.29 (d, 1H, J = 8.1 Hz), 4.60 (dd, 1H, J = 7.8, 10.4 Hz), 5.59 (s, 1H), 7.28−7.32 (m, 3H), 7.46−7.48 (m, 2H), 8.91 (br, 4H); ^{13}C NMR (125 MHz, THF-d_8) δ 18.1, 65.7, 74.9, 76.2, 82.8, 102.5, 117.2, 128.6, 129.3, 139.1; ^{31}P NMR (202 MHz, THF-d_8) δ −1.44, 2.51. A solution of the crude bis(monophosphate) in anhydrous DMSO (3 mL) was added dropwise over 5 min at rt to a stirred solution of 1,1′-carbonyldiimidazole (81 mg, 0.49 mmol) in DMSO (10 mL).[39] Stirring was continued for an additional 4 h after which DMSO was removed under reduced pressure (0.1 Torr, 40 °C). The yellowish oily residue was dissolved in 0.2% NH_4HCO_3 (5 mL) and loaded onto a column of Dowex 50WX8-200 (35 mL, ammonium form). Elution with 0.2% NH_4HCO_3 followed by silica gel chromatography (MeCN:*i*-PrOH:10%NH_4OH 3:3:1, 2:2:1) and lyophilization afforded 86 mg (62%) of cyclic phosphate **19** as a flocculent white solid: mp 220−222 °C (dec); TLC R_f 0.2 (MeCN:*i*-PrOH:10%NH_4OH 2:2:1); ^{1}H NMR (500 MHz, D_2O) δ 1.75 (s, 3H), 3.98 (ν_B of ABq, 1H, J = 10.9 Hz), 4.07 (ddd, 1H, J = 3.7, 10.1, 11.0 Hz), 4.15−4.22 (m, 2H), 4.59 (dd, 1H, J = 3.7, 10.1 Hz), 5.76 (s, 1H), 7.45−7.47 (m, 3H), 7.52−7.53 (m, 2H); ^{13}C NMR and DEPT (126 MHz, D_2O) δ 19.3 (d, J = 6.4 Hz), 66.2 (d, J = 6.4 Hz, CH_2), 76.2 (d, J = 8.3 Hz, CH_2), 77.3 (d, J = 5.5 Hz, quat C), 80.5 (CH), 104.7 (CH), 129.0, 131.4, 132.7, 138.7; ^{31}P NMR (202 MHz, D_2O) δ −15.80 (d, J = 25 Hz), −11.09 (d, J = 25 Hz); MS (FAB) m/z 384 (M + 1 − NH_3), 367 (M + 1 − 2NH_3). Anal. Calcd for $C_{12}H_{22}N_2O_9P_2 \cdot 1.5H_2O$: C, 33.73; H, 5.90; N, 6.56. Found: C, 33.63; H, 5.14; N, 6.40.

2-*C*-Methyl-D-erythritol 2,4-Cyclodiphosphate, Ammonium Salt (5, ME-2,4-cycloPP). Deprotection of the benzylidene acetal (**19**, 160 mg, 0.40 mmol) was accomplished by hydrogenation (H_2, 1 atm, 48 h, rt) using 20% $Pd(OH)_2$/C (70 mg) in absolute MeOH (10 mL) and HCOOH (0.3 mL). The mixture was filtered to remove the catalyst, the solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography on silica gel (MeCN:*i*-PrOH:1% NH_4HCO_3 4:2:1). Lyophilization afforded 121 mg (97%) of the ammonium salt of cyclodiphosphate **5**: TLC R_f 0.14 (MeCN:*i*-PrOH:1%NH_4HCO_3 4:2:1); $[\alpha]^{25}_D$ +1.8° (c = 1.00, H_2O, l = 0.5 dm); ^{1}H NMR (500 MHz, D_2O) δ 1.23 (s, 3H), 3.43 and 3.58 (ABq, 2H, J = 12.4 Hz), 3.91−4.03 (m, 3H); ^{13}C NMR (125 MHz, D_2O) δ 18.9, 68.4 (d, J = 6.4), 69.6, 71.1, 86.6 (d, J = 8.6 Hz); ^{31}P NMR (202 MHz, D_2O) δ −14.30 (d, J = 23 Hz), −10.22 (d, J = 23 Hz); MS (FAB) m/z 296 (M + 1 − NH_3), 279 (M + 1 − 2NH_3). The NMR data are similar to those reported in the literature.[15e,41,63] The somewhat greater chemical shifts of the ^{13}C NMR signals above ($\Delta\delta$ +2 to +3 ppm) are attributable to differences in reference standards and concentrations.

1,3-Benzylidene-2-*C*-methylthreitol (27). A solution of cis,cis epoxide **25** (250 mg, 0.74 mmol) in dry THF (3.0 mL) was stirred and cooled at 0 °C as $LiAlH_4$ (28 mg, 0.74 mmol) was added in portions. After 1 h at 0 °C, the reaction was quenched with cold water (2 mL). The resulting solids were filtered through celite, and the filter cake was washed with ethyl acetate (3 × 10 mL). The filtrate was dried over $MgSO_4$ and evaporated to give the crude product as oil. Purification by flash chromatography (60:40 ethyl acetate:hexane) gave 150 mg (90%) of pure 1,3-benzylidene 2-*C*-methylthreitol (**27**) as a white solid: mp 137−138 °C; TLC R_f 0.15 (30:70 ethyl acetate:hexane); $[\alpha]^{25}_D$ +16.9° (c = 1.20, MeOH); ^{1}H NMR (400 MHz, benzene-d_6) δ 0.65 (bs, 3H), 1.81 (app dd, 1H, J = 8.5, 2.5 Hz), 2.94 (s, 1H), 3.06 and 3.48 (ABdd, 2H, J = 11.3 Hz), 3.21 (dd, 1H, J = 6.6, 3.4 Hz), 3.65−3.77 (m, 2H), 5.15 (s, 1H), 7.12−7.18 (m, 3H), 7.14−7.18 (m, 2H); ^{13}C NMR (100 MHz, benzene-d_6) δ 18.6, 61.4, 66.5, 76.6, 83.7, 101.5, 126.4, 127.7, 128.8, 128.9; IR (neat film) ν 3477, 2977, 2961, 2875, 1449, 1405, 1376, 1290, 1130 cm^{-1}; HRMS (FAB) m/z calcd for $C_{12}H_{16}O_4$ (M + 1)$^+$, 225.1128; found, 225.1126.

1,3-Benzylidene-2-*C*-methylthreitol, 4-Dibenzylphosphate (29). A solution of diol **27** (75 mg, 0.33 mmol) in dry THF (3.0 mL) was stirred and cooled at −75 °C, as 0.31 mL of *n*-BuLi (1.6 *M* in hexane, 0.5 mmol) was added dropwise. After 10 min, the dibenzyl phosphorochloridate [prepared from dibenzyl phosphite (131 mg, 0.5 mmol) and *N*-chlorosuccinamide (67 mg, 0.5 mmol) in benzene][60] in benzene was added. The resulting solution was stirred for 10 min at −75 °C and 15 min at 25 °C. Water (1 mL) and ether (25 mL) were added, and the organic layer was dried over $MgSO_4$. Evaporation of the solvent and purification by flash chromatography (50:50 EtOAc:hexane) provided 130 mg (80%) of monodibenzyl phosphate **29** as a white solid: mp 99−100 °C; TLC R_f 0.5 (70:30 ethyl acetate:hexane); $[\alpha]^{25}_D$ +18.7° (c = 0.8, MeOH); ^{1}H NMR (500 MHz, benzene-d_6) δ 0.68 (bd, 3H, J = 2.3 Hz), 3.08 (dd, 1H, J = 11.2, 3.2 Hz), 3.45 (dd, 1H, J = 11.4, 3.6 Hz), 3.65 (m, 1H), 4.33 (m, 2H), 4.89−4.96 (m, 4H), 5.15 (bs, 1H), 6.97−7.02 (m, 5H), 7.07−7.16 (m, 8H), 7.52 (m, 2H); ^{13}C NMR (125 MHz, benzene-d_6) δ 18.6, 65.8, 66.5 (d, J = 5.5 Hz), 69.1 (d, J = 5.5 Hz), 69.2 (d, J = 1.8 Hz), 76.4, 82.4 (d, J = 6.4 Hz), 101.2, 126.4, 128.1, 128.2, 128.4, 128.6, 128.9, 136.5, 136.6, 138.2; ^{31}P NMR (202 MHz, benzene-d_6) δ 1.4 (s); IR (neat film) ν 3414, 3034, 2966, 1497, 1455, 1382, 1275, 1215 cm^{-1}; HRMS (FAB) m/z calcd for $C_{26}H_{29}O_7P$ (M + 1)$^+$, 485.1729; found, 485.1729.

2-*C*-Methylthreitol 4-Phosphate, Ammonium Salt (30). To a solution of the dibenzyl phosphate (**29**, 45 mg, 0.09 mmol) in ethanol (2 mL) containing HCO_2H (1 drop) was added 20% $Pd(OH)_2$/C (20 mg). The resulting heterogeneous mixture was allowed to stir under an H_2 atmosphere for 12 h. The mixture was diluted with MeOH (5 mL) and filtered, and the filtrate was cooled to 0 °C. A slow stream of NH_3 gas was bubbled through the solution for ∼2 min. Evaporation of the solvent under reduced pressure gave 21 mg (91%) of ammonium phosphate **30** as a white solid: ^{1}H NMR (500 MHz, D_2O) δ 0.96 (s, 3H), 3.35 (s, 2H), 3.56−3.62 (m, 2H), 3.73−3.77 (m, 2H); ^{13}C NMR (125 MHz, D_2O) δ 19.3, 64.8 (d, J = 4.6 Hz), 66.3, 74.1 (d, J = 7.3 Hz), 74.3; ^{31}P NMR (202 MHz, D_2O) δ 4.76; negative ion FAB MS: m/z 215.1 ($C_5H_{12}O_7P$−H); HRMS (ESI) m/z calcd for ($C_5H_{13}O_7P$ + H)$^+$, 217.0477; found, 217.0483.

(2*R*,3*S*)-4-Amino-3-methylbutane-1,2,3-triol (41). A solution of azido triol **40** (12.0 mg, 0.07 mmol) in ethanol (1.5 mL) was stirred under nitrogen as 10% Pd/C (5 mg) was added. The suspension was allowed to stir under hydrogen for 12 h at rt. Methanol was added, the solids were removed by filtration through Celite, and the filter cake was washed thoroughly with methanol (3 × 5 mL). Concentration of the filtrate under reduced pressure gave 7.1 mg (70%) of amino triol **41** as viscous oil: ^{1}H NMR (400 MHz, D_2O) δ 1.07 (s, 3H), 2.57 and 2.68 (Abdd, 2H, J_{AB} = 13.4 Hz), 3.48−3.56 (m, 2H), 3.76 (dd, 1H, J = 1.5, 10.5 Hz); ^{13}C NMR (125 MHz, D_2O) δ 19.2, 46.6, 61.7, 74.8, 76.4; HRMS (CI) m/z calcd for $C_5H_{13}NO_3$ (M + 1)$^+$, 136.0975; found, 136.0937.

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Supporting Information Available: Part 1: General aspects and experimental procedures, characterization data, and references for compounds **10**, **11**, **24**, **25**, **26**, **15** (from **26**), **28**, **31**−**35**, tosylate intermediate, **38**, **39**, and **40**. Part 2: Reproductions of selected ^{1}H, ^{13}C, and ^{31}P NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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