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Synthesis of 1α-Pyrophosphoryl-2α,3α-dihydroxy-4β-cyclopentanemethanol-5-phosphate, a Carbocyclic Analog of 5-Phosphoribosyl-1-pyrophosphate (PRPP)

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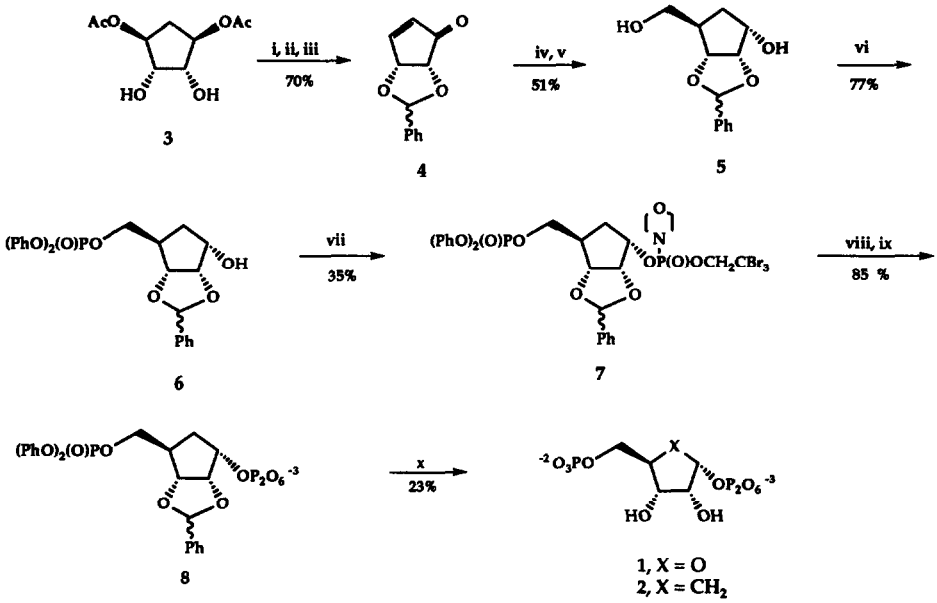
Abstract: 5-Phosphoribosyl-1-pyrophosphate (PRPP) is a key intermediate in a variety of important metabolic pathways. A total synthesis of the cyclopentyl analog of PRPP has been accomplished. A formal total synthesis of the enantiomer of this analog whose absolute configuration corresponds to that of PRPP is also reported.

In most organisms the biosynthesis of pyridine, pyrimidine, and purine nucleotides, as well as the biosynthesis of the aromatic amino acids histidine and tryptophan, involves a group of ten enzymes which are known as phosphoribosyltransferases.[1] Each of these enzymes catalyzes a reaction between α–D-5-phosphoribosyl-1-pyrophosphate (PRPP) (**1**) (Scheme I) and a second substrate which contains nitrogen. In every case, the reaction involves displacement of the pyrophosphate group by a nitrogen atom of the substrate with inversion of configuration at C-1 of PRPP.[1] The transition-state for the reaction is believed to involve an enzyme-stabilized carbonium ion.[1] Because of the key role played by the phosphoribosyltransferases, inhibitors of some of these enzymes can possess antiparasitic or anticancer activity.[2] For this reason, we would like to report the first total synthesis of 1α-pyrophosphoryl-2α,3α-4β-cyclopentanemethanol-5-phosphate (**2**), which is the cyclopentyl analog of PRPP. It is anticipated that the analog **2** will be much less reactive than PRPP because no oxygen atom is present to stabilize the carbonium ion generated by the departure of the pyrophosphate moiety. The compound should therefore be of interest for mechanistic and inhibitory studies of many of the phosphoribosyltransferases. Furthermore, investigations[3] of the biosynthesis of the carbocyclic nucleoside antibiotic aristeromycin have suggested that the PRPP analog **2** may be involved in aristeromycin biosynthesis. The availability of **2** may therefore facilitate studies of the biosynthesis of carbocyclic nucleosides.

A synthesis of (±)-**2** was carried out (Scheme I) beginning with the known[4] diacetoxydiol **3** which was protected as its O-benzylidene derivative and subsequently converted into the O-benzylidene cyclopentenone **4**, using chemistry similar to that employed in the O-isopropylidene series.[4] By carrying out the benzylidene protection reaction at low temperature, it was found that the benzylidene derivative consisted mostly of one epimer, a result which simplified the ^{1}H NMR spectra of all the intermediates bearing the benzylidene group. Photochemical addition of methanol[3b] to the cyclopentenone **4** yielded the corresponding cyclopentanone. The next stage of the synthesis required the generation of a hydroxyl group with the α-configuration at C-1. In order to obtain a completely stereospecific reduction in the desired sense, it was found necessary to carry out the reaction using sodium triacetoxyborohydride[5] and to leave the C-5 hydroxyl group free. The resulting diol **5** was shown to posssess the correct stereochemistry at C-1 by means of NOE experiments. Selective phosphorylation of the diol **5** with diphenyl chlorophosphate was accomplished by using N,N-diisopropyl-ethylamine in CH_2Cl_2. Various other bases including pyridine, DMAP, and triethylamine failed to give

Scheme I[a]

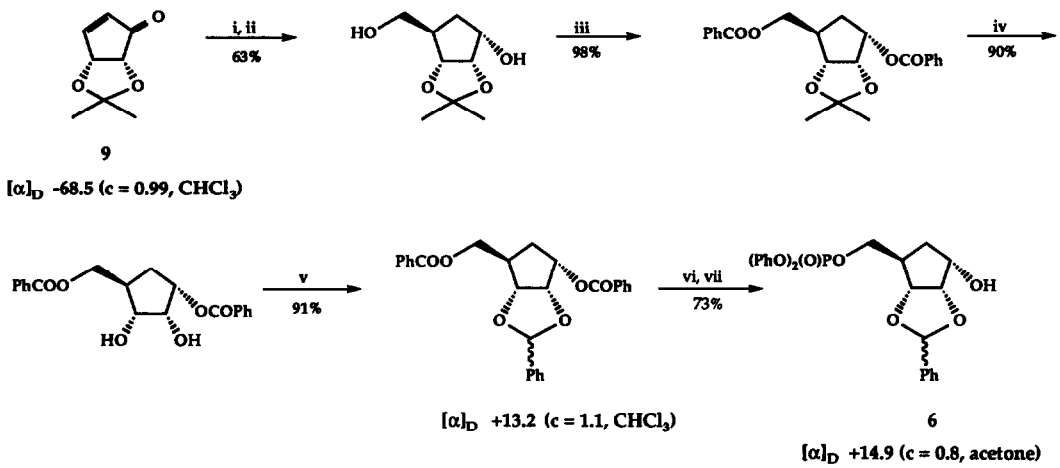


[a]Key: (i) PhCH(OMe)$_2$, p-TsOH, CH_2Cl_2, -15 - 0°; (ii) KOH, MeOH, rt; (iii) DCC, DMSO, TFA, pyridine, rt; (iv) Ph_2CO, MeOH, hv 350nm, rt; (v) $NaBH(OAc)_3$, PhH, rt; (vi) $(PhO)_2(O)PCl$, $EtN(iPr)_2$, rt; (vii) 2, 2 ,2-tribromoethyl phosphoromorpholinochloridate, pyridine, 45°; (viii) Cu, Zn, DMF, rt; (ix) $(n\text{-}Bu)_3NH^+$ $H_2PO_4^-$, pyridine, rt; (x) PtO_2, H_2, EtOH, rt.

selective phosphorylation. The resulting phosphate ester **6** was then treated with 2,2,2-tribromoethyl phosphoromorpholinochloridate[6] and pyridine to yield the morpholidate derivative **7**. Due to the hindered nature of the hydroxy group in **7**, the reaction with the phosphoromorpholinochloridate reagent was quite slow, even in pyridine at 45°. Attempts to speed up the reaction by using other bases, increasing the reaction temperature, or the in situ generation of the bromidate or iodidate forms of the reagent were unsuccessful. The tribromoethyl group was removed from **7** using Cu/Zn dust in DMF[6] and the excess Cu/Zn removed by filtration before reaction between the deblocked morpholidate and excess tri-n-butylammonium phosphate[7] to give the pyrophosphate **8**. In order to facilitate the subsequent purification steps, the tri-n-butylammonium phosphate was prepared from [^{32}P]phosphoric acid. The pyrophosphate **8** was purified by gel filtration on LH-20 using 40% ethyl acetate in chloroform and then deprotected using Adam's catalyst and H_2 at atmospheric pressure to yield **2** in the form of its tri-n-butylammonium salt.[8] This salt was purified by chromatography on polyethyleneimine cellulose using a triethylammonium bicarbonate gradient to yield **2** as its triethylammonium salt. The triethylammonium salt of **2** was characterized by ^{1}H, ^{13}C, and ^{31}P NMR analysis and by a Bird-pulsed ^{13}C-^{1}H reverse HETCOR experiment.[9] All of the spectral data were consistent with the assigned structure.[10] The triethylammonium salt of **2** was converted into the sodium salt using the method of Khorana et

al.[11, 12] For some biological studies, it may be desirable to employ the enantiomer of 2 whose absolute configuration corresponds to that of PRPP. The appropriate enantiomer of 2 can be obtained from the correct enantiomer of the intermediate 6 (Scheme I). In order to complete a formal total synthesis of optically active 2, intermediate 6 of the correct absolute configuration has been prepared from the known[13] optically active ketone 9 by the route shown in Scheme II. Investigations of the biological activity of 2 are in progress.

Scheme II[a]



9

$[\alpha]_D$ -68.5 (c = 0.99, $CHCl_3$)

$[\alpha]_D$ +13.2 (c = 1.1, $CHCl_3$)

6

$[\alpha]_D$ +14.9 (c = 0.8, acetone)

[a]Key: (i) Ph_2CO, MeOH, hv 350 nm, rt; (ii) $NaBH(OAc)_3$, PhH, rt; (iii) PhCOCl, pyridine, rt; (iv) 85% HOAc, cat. TFA, rt; (v) $PhCH(OMe)_2$, p-TsOH, -15 - 0°; (vi) NaOH, MeOH, rt; (vii) $(PhO)_2(O)PCl$, $EtN(iPr)_2$, rt.

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10. ^{1}H NMR (250 MHz, D_2O), δ 2.1-2.4 (m, 2H, CH_2, correlates to ^{13}C resonance at 24.6 ppm), 2.5 (m, 1H, CH, correlates to ^{13}C resonance at 41.2 ppm), 3.8 (m, 2H, CH_2, correlates to ^{13}C resonance at 65.5 ppm), 4.7 (m, 1H, CH, correlates to ^{13}C resonance at 74.6 ppm), 4.8 (m, 1H, CH, correlates to ^{13}C resonance at 79.5 ppm), 4.9 (m, 1H, CH, correlates to ^{13}C resonance at 105.4 ppm); ^{31}P NMR (101.25 MHz, D_2O, H_3PO_4 as external reference, $\delta_{H3PO4} = 0.0$) δ 0.6 (s, 1P), -10.4 (d, 1P, $^{2}J_{PP}$ = 21.3 Hz), -11.2 (d, 1P, $^{2}J_{PP}$ = 21.3 Hz); ^{13}C (62.9 MHz, D_2O) 24.6 (C-6, d, $^{3}J_{CP}$ = 8.3 Hz), 41.2 (C-4, d, $^{3}J_{CP}$ = 8.3 Hz), 65.5 (C-5, d, $^{2}J_{CP}$ = 5.3 Hz), 74.6 (C-3, d, $^{4}J_{CP}$ = 4.8 Hz), 79.5 (C-2, $^{3}J_{CP}$ = 4.5 Hz), 105.4 (C-1, d, $^{2}J_{CP}$ = 6.7 Hz).
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12. FABMS (p-nitrobenzyl alcohol, TFA): 317 (M - PO_3 - $2H_2O$ + 2Na), 307 (M - PO_3 + 3H), 289 (M - PO_3 + 3H - H_2O). Both FABMS and NMR data indicate that traces of unexchanged triethylammonium ions are present in the sodium salt.
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