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Synthesis of Carbasugar *C*-1 Phosphates via Pd-Catalyzed Cyclopropanol Ring Opening

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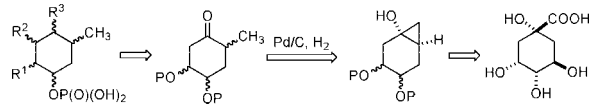
ABSTRACT



The stereoselective syntheses of 2,3-dideoxy-4-oxo-5a-carba-α-D-rhamnopyanose 1-phosphate, 2,3-dideoxy-5a-carba-α-D-rhamnopyranose 1-phosphate, 5a-carba-α-D-rhamnopyranose 1-phosphate, 5a-carba-β-D-digitoxopyranose 1-phosphate, and 5a-carba-α-L-rhamnopyranose 1-phosphate have been achieved from D-quinic acid. The routes rely upon a Simmons−Smith cyclopropanation and diastereospecific ring opening of cyclopropanol under Pd/C hydrogenation condition to set up the α-methyl ketone. A sequence of diastereoselective reduction, dihydroxylation, and/or Myers' reductive 1,3-rearrangement were used to install the desired stereochemistry.

Carbohydrates are a recurring structural motif in many bioactive natural products (e.g., antimicrobial and anticancer agents).[1] Often, the sugar portion of the molecule is a crucial element for the activities of these compounds; for instance, many aglycons of biologically active natural products are devoid of activity.[2] A cursory structure−activity relationship analysis of the carbohydrate-containing natural products points to the use of rare and deoxysugars (Figure 1).[3] The removal or

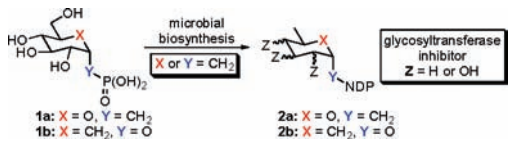


Figure 1. Biosynthesis of glycosyltransferase inhibitors.

stereochemical inversion of the various sugar hydroxyl groups can impart significant in vitro stability by lessening the abilities of naturally occurring glycosidase enzymes to degrade the structure. In fact, our ongoing interest in the de novo synthesis of carbohydrates is aimed at being able to provide new glycosylated natural products for medicinal chemistry studies.[4] An alternative approach is to alter the biosynthesis of the glycosylated natural products.[5]

In an effort to understand and ultimately alter the microbial biosynthesis of rare/deoxy-sugar containing natural products, various *C*-glycoside analogues of the NDP-sugars have been prepared.[6] Most of these efforts have been focused on the synthesis and use of *C*-glycoside analogues with exoacetal oxygen replaced with a methylene group (Y = CH_2).[6] In contrast, there is only one report that describes the use of the endoacetal oxygen *C*-glycoside (X = CH_2, cyclitol).[7] To these ends, we have initiated effort to develop an approach to these cyclitol sugar phosphates (X = CH_2) in a manner that would mimic our de novo approach to carbohydrates (i.e., one that is amenable to both enantiomers of either α- or β-isomers). Herein we report our successful efforts toward these aims from quinic acid.

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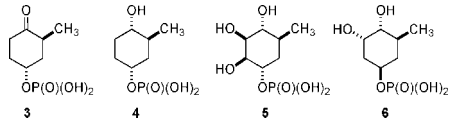
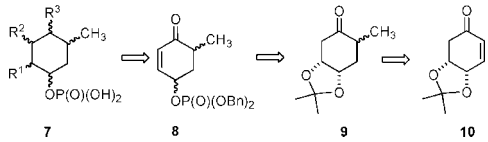


Figure 2. Target cyclitol sugar phosphates.

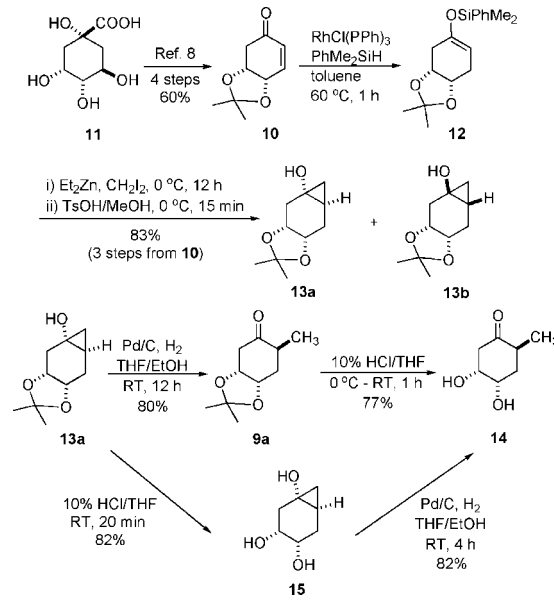
We targeted the synthesis of both enantiomers of three α-sugars and one β-sugar. These structures are outlined in Figure 2: 2,3-dideoxy-4-oxo-5a-carba-α-D-rhamnopyanose phosphate (**3**), 2,3-dideoxy-5a-carba-α-D-rhamnopyranose phosphate (**4**), 5a-carba-α-D-rhamnopyranose phosphate (**5**), 5a-carba-β-D-digitoxopyranose phosphate (**6**), and 5a-carba-α-L-rhamnopyranose phosphate (*ent*-**5**). Retrosynthetically, we envisioned that the desired carbasugar phosphate stereoisomers **7** could be synthesized from both enantiomers of the cis- and trans-diastereomers of the enone γ-phosphate **8**. We thought **8** could be derived through a β-elimination and phosphorylation from acetonide **9** (Scheme 1). The critical methyl group could be introduced by α-alkylation either through in situ generated enolate or silylenol ether from enone **10** with the acetonide-protecting group controlling the stereochemistry. The known intermediate **10** could be easily synthesized from cheap starting material D-(−)-quinic acid by known methods.[8]

Scheme 1. Retrosynthetic Analysis



Our syntheses commenced with the known four-step conversion of D-(−)-quinic acid **11** to the α,β-unsaturated ketone **10**, which was routinely accomplished on 20 g scale in 60% overall yield (Scheme 2). Application of the Tsuda−Saegusa 1,4-reduction/alkylation via the aluminum enolate with methyl iodide failed to cleanly give the desired α-methyl ketone **9**.[9] Similarly, the 1,4-hydrosilyation using Stryker's reagent and dimethylphenylsilane to form silylenol ether **12** was problematic.[10] Fortunately, the hydrosilylation occurred smoothly at 60 °C when Wilkinson's catalyst and dimethylphenyl silane were used.[11] Unfortunately, various attempts to alkylate the silylenol ether with methyl iodide via its enolate failed to cleanly provide the α-methyl ketone **9**.

Scheme 2. Cyclopropanation/Cyclopropanol Ring Opening



Alternatively, we envisioned a cyclopropanation and ring-opening process which could lead to the formation of α-methyl ketone.[12] Thus, one-pot of hydrosilylation of enone **10** (RhCl(P-Ph$_3$)$_3$/PhMe$_2$SiH, 60 °C) followed by Simmons−Smith cyclopropanation (ZnEt$_2$/CH$_2$I$_2$) of the resulting silylenol ether gave an inseparable mixture of cyclopropanol silyl ethers,[13] which when desilylated under acidic conditions (*p*-TsOH/MeOH) furnished two readily separable diastereoisomers **13a** and **13b** in 83% overall yield (Scheme 2). The diastereomeric ratio of cyclopropanes **13a** to **13b** rangedfrom 1:1 when the cyclopropanation was performed at low temperature (−20 °C) to 2:1 at 0 °C.

We next investigated the subsequent ring opening of the cyclopropanol **13a**. Unfortunately, all of our attempts to promote ring opening under acidic or basic conditions failed to give the desired ketone **9**.[14] In contrast, the stochiometric Pd(OAc)$_2$-promoted ring opening of the cyclopropanol gave an α,β-unsaturated ketone,[15] which under hydrogenation conditions resulted in an inseparable diastereomeric mixture of α-methyl ketone **9** (dr 3:1 **9a**/**9b**). We wondered if the palladium homoenolate intermediate could be trapped with hydrogen before β-hydride elimination occurred. Because we found that Pd/C also gave the same enone product, we decided to explore typical hydrogenolysis conditions.[16]

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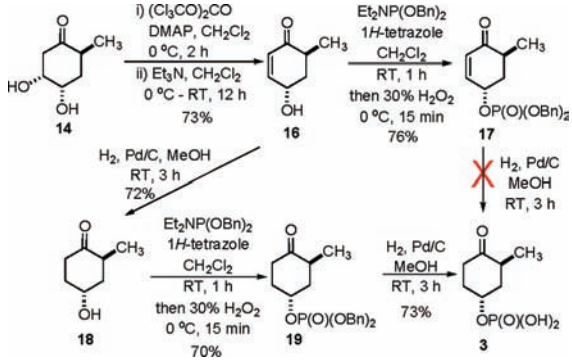
To our delight, when cyclopropanol **13a** was exposed to Pd/C under a balloon of H_2, ketone **9a** was produced in good yield (80%) and as a single diastereomer (dr >100:1, ^{1}H NMR). Next, the acetonide was removed under acidic conditions (10% HCl/THF, 0 °C to rt, 0.5−1 h) to afford diol **14** in good yield (80%). Because great care needed to be taken to avoid epimerization of either **9a** or **14** under acidic conditions, we preferred to first deprotect the acetonide **13a** to give triol **15** in 82% yield. As before, exposure of the triol **15** under hydrogenation conditions (Pd/C, H_2) afforded the diol **14** in 82% yield as a single diastereomer.

With the successful synthesis of diol **14** we next turned our attention to make phosphate targets. Carbonate formation of **14** using triphosgene followed by β-elimination under basic conditions resulted in allylic alcohol **16** in 73% yield (Scheme 3). Phosphorylation of the alcohol **16** with *N*,*N*-diethyl diben-

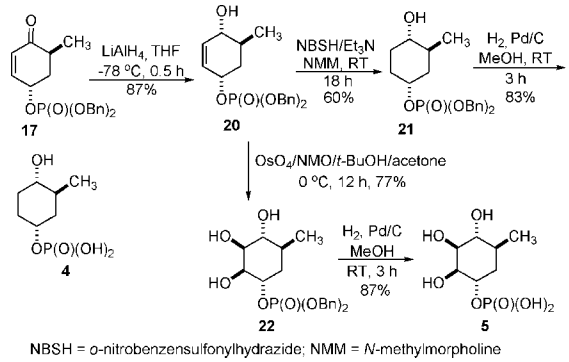
Scheme 3. 4-Keto-Sugar Phosphate **3**



zylphosphoramidite in the presence of 1*H*-tetrazole gave a phosphite intermediate which was oxidized by addition of 30% H_2O_2 to form dibenzyl phosphate **17** in 76% yield. Hydrogenative debenzylation and reduction of the double bond (H_2, Pd/C) failed to give the desired dihydrogen phosphate **3**, presumably due to hydrogenolysis of the allylic phosphate. Attempts at hydrogenation of **17** with diimide produced in situ from *o*-nitrobenzenesulfonyl hydrazide (NBSH) and Et_3N proved unsuccessful.[17] Thus, we decided to reduce the double bond before introduction of the phosphate functional group. Hydrogenation of **16** (H_2, Pd/C) gave saturated alcohol **18** in 72% yield. Phosphorylation of **18** as previously gave dibenzyl phosphate **19** in 70% yield. Debenzylation (H_2, Pd/C) afforded the 2,3-dideoxy-4-oxo-5a-carba-α-D-rhamnopyranose phosphate **3** in 73% yield. While analysis of the crude product showed diastereomerically clean material, upon sitting, the product slowly epimerized resulting in a ~2:1 mixture of methyl diastereomers.

To synthesize the phosphates **4** and **5**, we returned to enone **17** (Scheme 4). A diastereoselective reduction with $LiAlH_4$ at −78 °C gave the equatorial alcohol **20** in good yield (87%)

Scheme 4. α-D-*rhamno*-Phosphate **5** and Deoxy Analogue **4**



NBSH = *o*-nitrobenzensulfonylhydrazide; NMM = *N*-methylmorpholine

and diastereoselectivity (dr 11:1). Diimide reduction (NBSH/Et_3N) of **20** resulted in saturated alcohol **21** in 60% yield with 20% starting material back. Hydrogenation of **21** on Pd/C furnished 2,3-dideoxy-5a-carba-α-D-rhamnopyranose phosphate **4** in 83% yield. Alternatively, dihydroxylation of allylic alcohol **20** under Upjohn conditions[18] resulted in a single diastereomeric triol **22** in 86% yield, which similarly underwent hydrogenolysis to afford 5a-carba-α-D-rhamnopyranose phosphate **5** in 87% yield.

In order to achieve the β-D-digitoxose phosphate **6**, we simply switched the acetonide protecting group of the vicinal *cis*-diol of quinic acid to the bis-ketal protecting group of its *trans*-vicinal diol (Scheme 5). By reported methods,[19] α,β-unsaturated ketone **23** could be produced on a 20 g scale in five steps with high overall yield (50%). Similarly, a one-pot hydrosilylation and cyclopropanation, followed by desilylation under acidic conditions, gave a diastereomeric mixture of cyclopropanols **24a/b** (dr ~1:1) in 85% overall yield. Although in this bis-ketal case the two cyclopropanol isomers were inseparable, a direct isomerization on Pd/C of this mixture under typical hydrogenation conditions (1 atm of H_2, 6 h, rt) afforded a diastereomeric mixture of α-methyl ketones **25a/b** (63% yield, dr 2:1) along with some recovered cyclopropanol **24b** (20%, as a single diastereomer). Under equilibrating conditions, the thermodynamically more stable isomer **25b** could be prepared. Thus, treatment of a mixture **25a** and **25b** with acid (concd $HCl_{(aq.)}$/THF) resulted in a diastereomerically enriched mixture of **25b** to **25a** (dr >13:1), which after silica gel chromatography provided pure **25b**. TFA deprotection of **25b** gave crude diol (albeit with some C-5 epimerization, dr ~15:1), which underwent acylation with Boc anhydride and subsequent β-elimination to afford enone **26** (79% yield from **25b**, dr ~15:1). While the major isomer could be purified by careful chromatography, the diastereomeric mixture of **26** could be selectively reduced with $LiAlH_4$ at −78 °C to produced the allylic alcohol **27** in 82% yield with the minor diastereomers easily removed by chromatography.

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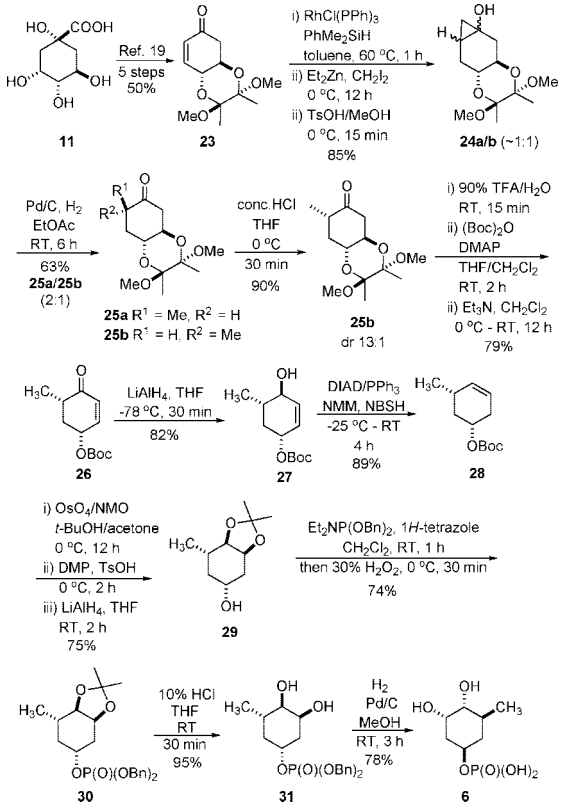
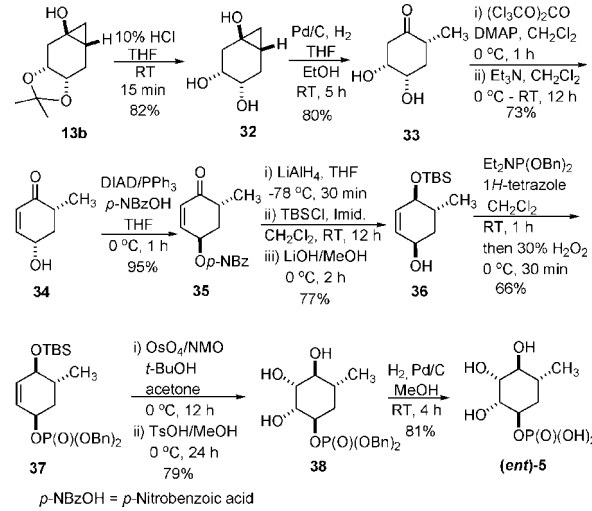
Scheme 5. β-D-Digitoxo-Phosphate **6**



Scheme 6. α-L-*rhamno*-Phosphate *ent*-**5**



With the allylic alcohol in hand, we turned our attention to the preparation of β-D-digitoxose phosphate **6**. Treatment of allylic alcohol **27** under the Myers' reductive transposition conditions provided olefin **28** in 89% yield.[17,20] The olefin was subjected to Upjohn dihydroxylation (OsO_4/NMO) and acetonide protection (dr 11:1), at which point the minor diastereomer was removed. Finally, the Boc-carbonate reduction by $LiAlH_4$ afforded alcohol **29** in 75% overall yield (three steps). Alcohol **29** was then phosphorylated to give dibenzyl phosphate **30** in 74% yield. The acetonide deprotection of **30** produced diol **31** with excellent yield (95%), which under typical hydrogenation conditions (H_2, Pd/C) resulted in 5a-carba-β-D-digitoxopyranose phosphate **6** in 78% yield.

In order to access the L-series of carbasugar phosphate (Scheme 6), we returned to the cyclopropanol **13b**, which was prepared as part of a 1:1 mixture with **13a** (Scheme 2). Deprotection of the acetonide **13b** with 10% aqueous HCl in THF furnished triol **32** with good yield (82%), which was hydrogenolytically ring opened to produce α-methyl ketone **33** in 80% yield as a single diastereomer. Dehydration of **33** via carbonate formation followed by elimination afforded allylic alcohol **34** in 73% yield over two steps. Mitsunobu reaction[21] of **34** with *p*-nitrobenzoic acid in the presence of DIAD and PPh_3 gave the ester **35** with stereochemical inversion in excellent yield (95%). Diastereoselective $LiAlH_4$ reduction of the enone **35** at −78 °C resulted in allylic alcohol with good diastereoselectivity (dr 11:1), which after TBS-protection and ester hydrolysis gave alcohol **36** in good overall yield (77% for three steps). Phosphorylation of alcohol **36** gave dibenzyl phosphate **37** in 66% yield. Dihydroxylation of **37** under Upjohn conditions produced diol in 81% yield as a single diastereomer, which after acid deprotection (*p*-TsOH/MeOH) provided triol **38** in excellent overall yield (79%, two steps). Finally hydrogenation of dibenzylphosphate **38** afforded 5a-carba-α-L-rhamnopyranose phosphate *ent*-**5** in 81% yield.

In conclusion, five carbasugar phosphates have been successfully synthesized in either D or L, α or β form from D-(−)-quinic acid. This synthesis includes a novel highly diastereospecific Pd/C-catalyzed cyclopropanol ring opening, which may be a useful alternative for the introduction of methyl groups to the α-position of ketones. Diastereoselective reduction, dihydroxylation, Mitsunobu reaction, and Myers' reductive rearrangement were also used to install the desired sugar stereochemistry. The biological evaluation of these cyclitol phosphates is ongoing.

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Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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