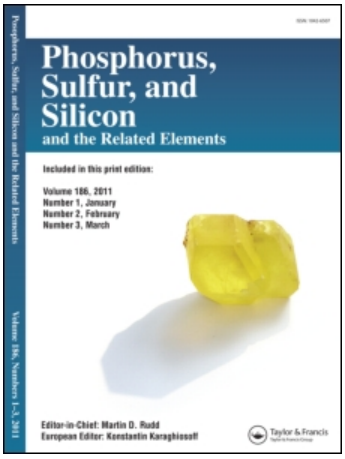

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Approaches to the Syntheses of 2- and 3-Phosphonomethyl Derivatives of Arabinose Via Pentacovalent Oxaphospholene Methodology

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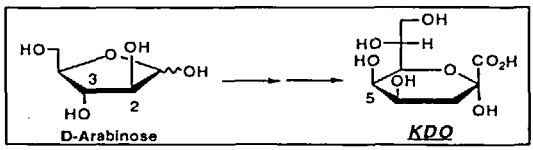
Approaches to the syntheses of 2- and 3-phosphonomethyl derivatives of arabinose via pentacovalent oxaphospholene methodology are outlined. Condensation of the requisite pentacovalent oxaphospholenes with either a mono-protected glyoxal derivative or glyceraldehyde acetonide were highly stereoselective, producing the syn aldol product as the major isomer in both cases. The reduction of **4a** to the diol did not give the expected stereoselectivity. Stereochemical correlation of **5** and **6** were via the carbonates.

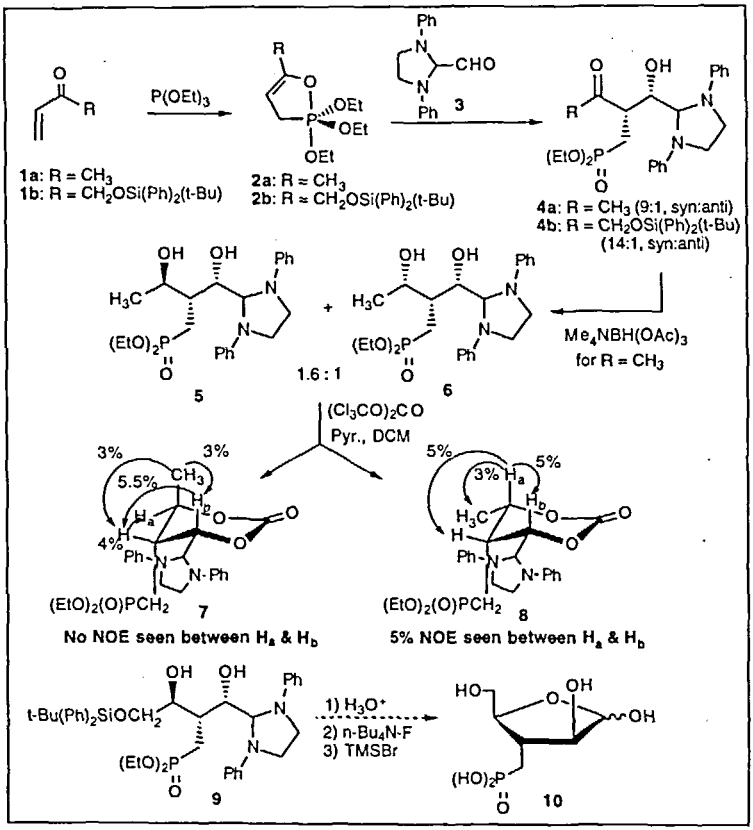
Keywords: pentacovalent oxaphospholene; arabinose; phosphonate analogs; KDO

We are interested in producing carbohydrate analogs that target the enzymes in the biosynthetic pathway that produces 3-deoxy-D-manno-2-octulosonic acid (KDO), the major component of the outer membrane lipopolysaccharides (LPS) of all Gram-negative bacteria.[1] As KDO is unique to Gram-negative bacteria, agents targeting its biosynthesis would disrupt the formation of the bacterial outer membrane, and hence exhibit antibacterial activity without affecting mammalian cells. The 3-deoxy-3-phosphonomethyl D-arabinose, **10**, would most likely be an effective inhibitor of KDO synthetase, as it is the hydroxyl group at the 3 position in D-arabinose that eventually becomes the ring oxygen in the pyranose form of KDO. Submitting the 2-phosphonomethyl derivative of arabinose, **16**, to the KDO biosynthetic pathway would produce the 5-phosphonomethyl KDO, **17**. This compound would then inhibit the biosynthesis of LPS, as it is through this 5 position that the KDO monomers link to form the KDO trimer found in the LPS.



The synthetic approach to 3-deoxy-3-phosphonomethyl D-arabinose, **8**, via our pentacovalent oxaphospholene methodology[2] is shown in **Scheme 1**. We have initially investigated the condensation of the known aldehyde-aminal 3[3] with the P(V) **2a** derived from methyl vinyl ketone and triethyl phosphite. An excellent ratio (9:1, syn:anti) of the condensation products were obtained either at r.t. (72 hr) or at 0°C in 30 min. with $MgBr_2 \cdot OEt_2$ (1 eq.) Lewis acid assistance. Directed reduction utilizing the Gribble reagent, tetramethylammonium triacetoxyborohydride[4], gave disappointing ratios of product, with or without Lewis acid assistance. In earlier work, we obtained 95:5 ratios of the anti diol when smaller groups on the aldehyde condensation partner

Scheme 1



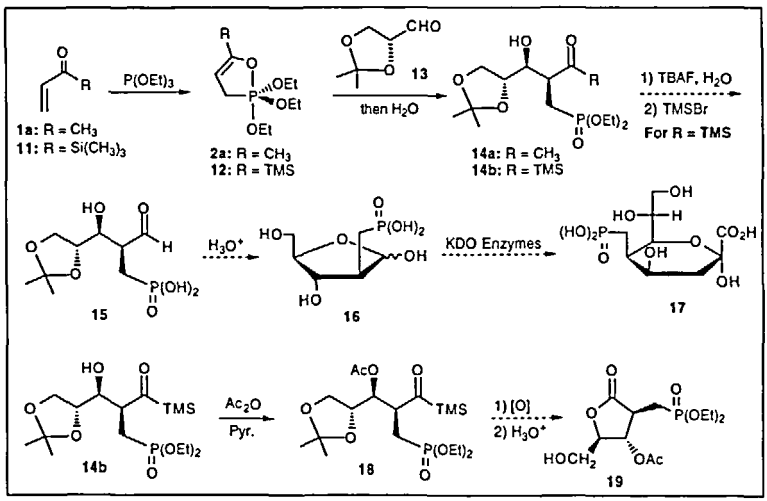
were used.[1e,5] L- or K-Selectride, as well as sodium borohydride, produced the cyclic phosphonate formed from cyclization of the newly formed alkoxide onto the phosphonate. Zinc borohydride has produced the diols in a ratio of 6:1 anti:syn (5:6), but in low yields. We are currently screening other reducing agents, as well as other glyoxal derivatives for the condensation. It is assumed that the bulk of the groups on the aldehyde **3** is inhibiting the chelation needed for stereocontrol in the reduction.

The carbonates, **7** and **8**, were readily formed from the mixture of diols **5** and **6**, and the compounds were separated at this point. Proton NMR Nuclear Overhauser experiments on the two diastereomers confirmed their relative stereochemistries.

The enone, **1b**, needed for the synthesis of **10** has been prepared in three steps from ethyl glycolate (via Weinreb's amide procedure[6]), and was reacted with triethyl phosphite to produce the P(V) **2b** in quantitative yield. Condensation of this P(V) **2b** with the aldehyde **3** produced the aldol product **4b** in an excellent syn:anti ratio of 14:1. The directed reduction of the ketone in **4b** is currently being investigated.

The synthesis to date of the 2-phosphonomethyl arabinose derivative **16** is illustrated in **Scheme 2**. The known acyl silane[7] **11** is being utilized in lieu of acrolein, as the P(V) derived from acrolein is produced only in low yields, and the condensation products of this P(V) with aldehydes are also unstable, and readily undergo retro-aldol reactions.[5] We have initially investigated the condensation of the

Scheme 2



chiral aldehyde **13** with our standard P(V) **2a**. All four diastereomers were produced in an isolated ratio of 14 : 3.3: 1 : trace, with **14a** being the major isomer.[8] Condensation of the TMS P(V) **12** with this aldehyde in methylene chloride at room temperature was *highly* stereoselective, producing the desired aldol product in a syn:anti ratio of 15-20:1 (^{31}P NMR). We are currently performing a further stereochemical correlation by producing the lactone, **19**.[8] The complete synthesis of the 2-phosphonomethyl derivative **16** will be reported shortly.

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