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Synthesis of (sulfonyl)methylphosphonate analogs of prenyl diphosphates

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ABSTRACT

Syntheses of several (sulfonyl)methylphosphonate analogs of geranyl, neryl, and farnesyl diphosphates are described. Key steps include utilization of an (*E*)-selective Horner–Wadsworth–Emmons olefination which couples an aldehyde to the sulfone phosphonate moiety, and a selective reduction of the resulting dienyl sulfone phosphonate substrates.

Analogs of prenyl diphosphates (e.g., Chart 1) have received much attention over the years for their ability to bind to and competitively inhibit prenyl transferase enzymes.[1–3] Disruption of the prenylation process has been shown to inhibit the growth of malignant tumor cells, for which prenylation is key for various cell signaling and regulatory processes, thus leading to significant anticancer activities.[1]

Prenyl diphosphate analogs can also bind to terpene synthase enzymes, which utilize prenyl diphosphates as substrates for complex reactions that produce the varied and complicated molecular architectures of terpene natural products.[4–6] Beyond inhibition activity, prenyl diphosphate analogs could be exploited for crystallographic studies of terpene synthase enzymes.[4–6] To date, relatively few terpene synthase crystal structures have been reported, and although there is occasionally a prenyl diphosphate or analog in these structures, most have ammonium ion analogs of putative carbocation intermediates or no discernable organic molecule bound.[4–6] It is our hope that binding with one or more of our analogs may not only facilitate crystallization of the enzyme but may also produce complexes that reveal important details of the folding adopted by the substrate upon binding, since the analogs should not be processed by the enzyme (prenyl diphosphates are rapidly ionized in the enzyme active site).

Additionally, prenyl diphosphates have been reported to serve as substrates for soluble epoxide hydrolase (sEH), which displays lipid phosphate phosphatase activity that is linked to sterol synthesis and inflammation.[7–9] Not surprisingly, compounds that mimic the substrates of this enzyme are often potent inhibitors.[7–9] Furthermore, farnesyl diphosphate is a substrate for squalene synthase, which has been targeted for cholesterol-lowering activity.[10–14] Finally, farnesyl diphosphate is also a reported substrate for dehydrosqualene synthase (CrtM), which is involved in the biosynthesis of the carotenoid staphyloxanthin, a known virulence factor in *Staphylococcus aureus*.[15] Inhibitors with structures based on that of farnesyl diphosphate have shown potent activities and may serve as the basis for new therapies for bacterial infections.[15]

In this Letter, we report the synthesis and characterization of several compounds (Chart 2) lacking an ionizable group, which we believe are excellent mimics of geranyl, neryl, and farnesyl diphosphates, and which therefore have a strong potential for the applications discussed above. Chart 2 shows both free phosphonic acids and their isopropyl-protected precursors. While the phosphonic acids are expected to be closer mimics to the diphosphates in Chart 1, their isopropyl ester counterparts may have useful applications as well.[10–12,16] As one measure of the similarity between these mimics and the diphosphates, electrostatic potential maps (Fig. 1) of geranyl diphosphate and deprotonated forms of **1b** and **2b** were generated (see Supplementary data for details).

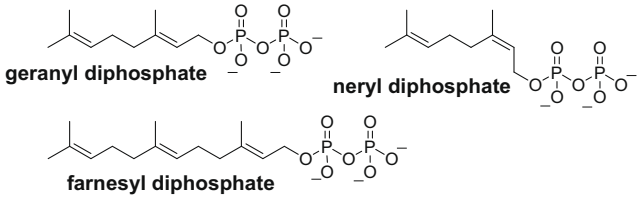

Chart 1.

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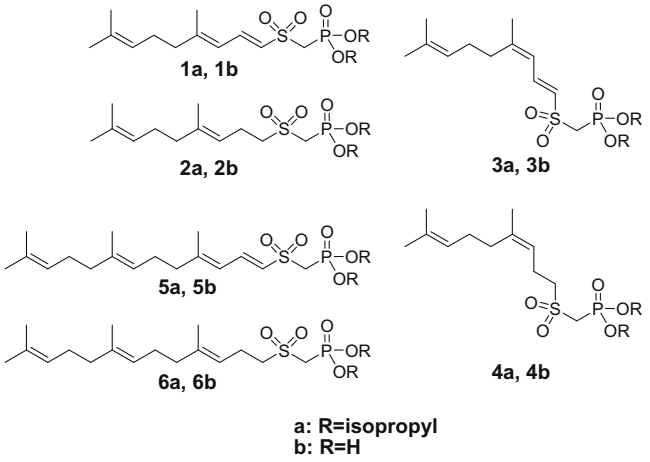


Chart 2.

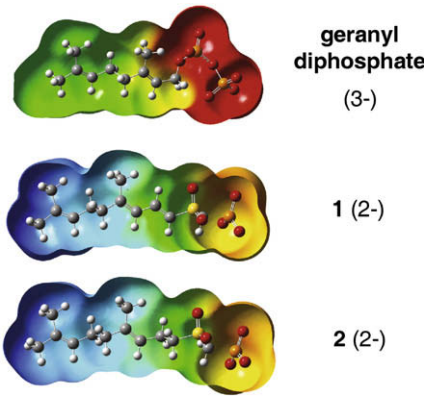


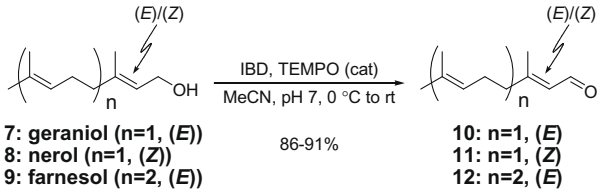
Figure 1. Computed electrostatic potential maps of fully anionic geranyl diphosphate and compounds **1** and **2**.

These images suggest that, despite the difference in overall charge, the charge distributions in the mimic structures are quite similar to those of the diphosphate compound itself.

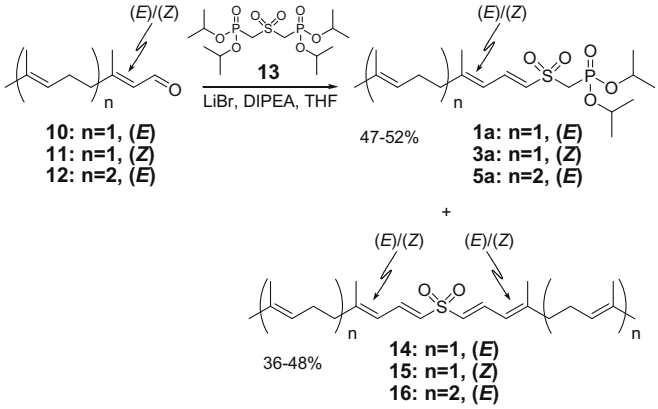
Some of our analogs are rigid in the vicinity of the sulfone group, while others are not. If the preferred conformation of a bound natural prenyl diphosphate is effectively mimicked by an (*E*) double bond,[4–6] then the rigidity of compounds **1**, **3**, or **5** should enhance binding. However, the flexibility of compounds **2**, **4**, and **6** will allow for a more thorough sampling of conformational space. Our synthetic scheme allows for the production of both types of prenyl diphosphate analogs.

Our syntheses began with commercially-available geraniol, nerol, and farnesol. These alcohols were oxidized to the corresponding aldehydes in high yields via a catalytic TEMPO oxidation with iodosobenzene diacetate (IBD) as the stoichiometric oxidant (Scheme 1).[17] Initial attempts to oxidize these substrates using either PDC[18] or hydrogen peroxide and platinum[19] resulted in the formation of a significant amount (~10–25%) of (*E*)/(*Z*) isomerization of the α–β alkene. In contrast, the TEMPO oxidation proved highly reliable for the clean conversion of the alcohols to the aldehydes and had the additional benefits of being procedurally simple and avoiding the use of heavy metals.

The next step involved a Horner–Wadsworth–Emmons coupling of the aldehydes to a diisopropoxyphosphonate sulfone reagent (**13**, Scheme 2) developed by Gervay-Hague and coworkers, which was synthesized in three steps without intermediate purification from commercially-available materials.[16,20–22] The



Scheme 1.



Scheme 2.

coupling reactions (Scheme 2) proceeded smoothly to produce the desired (dienylsulfonyl)methylphosphonate products in approximately 50% yield and with complete (*E*) selectivity,[23] along with the formation of the bis-coupled adducts **14**–**16**, approximately 40%). It was observed that the yield of the desired product could be increased, along with a concomitant decrease in bis-coupled adduct formation, through the use of a larger excess of sulfone-phosphonate reagent (as reported for other systems).[16,20–22] However, consideration of the time and cost associated with synthesizing this reagent, along with the relative ease by which the two products could be isolated, led us to use, in general, only a two-fold excess. The highly acidic methylene protons situated between the sulfone and phosphonate ester, along with the susceptibility of the conjugated diene to (*E*)/(*Z*) isomerization necessitated extra caution during the workup procedure. Here, the THF solvent was removed and replaced with $CHCl_3$ prior to the addition of 1 N HCl at 0 °C. The remainder of the workup steps were also rigorously carried out at this temperature.

At this point, a portion of each of the three intermediates was subjected to further transformation via a reduction of the α–β double bond of the dienyl sulfone moiety. There are only scattered reports in the literature of α–β unsaturated sulfone reductions[24–35] and, to our knowledge, no reports of the reduction of an α–β/γ–δ dienyl sulfone, selective or otherwise. While we expected that this would be a challenging transformation, we were optimistic that a larger LUMO coefficient on the β carbon (relative to the δ carbon), along with the greater steric accessibility of this site would favor α,β-reduction with a hydride-donor reagent. Figure 2, which includes the computed LUMO, highlights these two features for a model dienyl sulfone (see the Supplementary data for details).

Consistent with this prediction, numerous trials with various conditions involving the use of $NaBH_4$ with $InCl_3$,[36] $CoCl_2$,[37] and $RuCl_3$[38] catalysts, along with uncatalyzed $NaBH_4$, super hydride,[25,35] and bulky K-Selectride all led to the predominant formation of the desired product. Unfortunately, none of these reactions were highly selective, and each was accompanied by significant

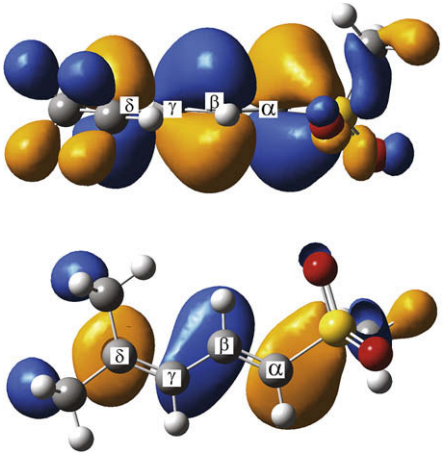


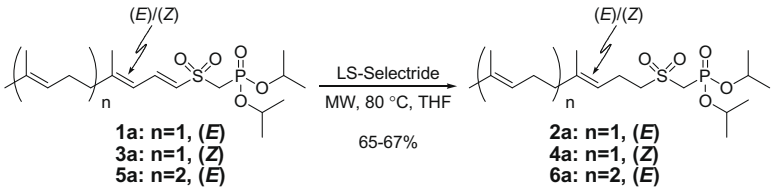
Figure 2. Computed LUMO for a model dienyl sulfone. Shown are two orthogonal views, with the front half of the orbital removed from the lower image for clarity.

amounts of the α,δ-reduced, and/or over-reduced products. Furthermore, these mixtures proved to be inseparable under standard chromatographic conditions. It was not until we resorted to the extremely bulky LS-Selectride reagent that we observed complete selectivity for the formation of the desired products, albeit in moderate yields (Scheme 3). This selectivity, however, came at the price of a very sluggish reaction. At temperatures ranging from −78 °C to 40 °C, TLC analysis showed some initial product formation, but the reaction did not progress even over the course of several days with the addition of excess equivalents of reagent. In hopes of accelerating this reaction, we utilized microwave heating at 80 °C, but obtained similar results. On occasion, however, we observed an apparent modest increase in product formation (via TLC) upon workup of the reaction. This prompted an approach where, after initial addition of 2 equiv of reagent at 0 °C and microwave heating for 25 min, 1–2 equiv of H_2O was added to the reaction at 0 °C. After the reaction was allowed to gradually warm up to room temperature, this cycle was repeated three additional times using 2 equiv of reagent and 1–2 equiv of H_2O each time. At this point, the starting material was virtually undetectable by TLC analysis, and the reaction was subjected to a standard oxidative workup procedure ($NaOH/H_2O_2/H_2O$) to ultimately yield up to 67% of the desired products after flash chromatography purification.

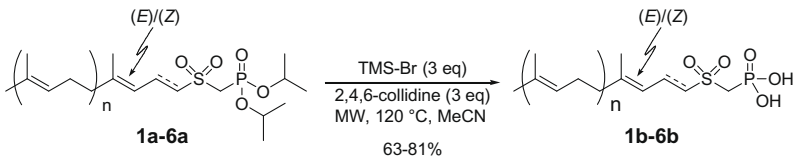
The final step in the synthesis of compounds **1b**–**6b** was deprotection of the isopropyl phosphonate ester to produce the free phosphonic acids. This transformation was effected (Scheme 4) using TMS–Br,[39] and inclusion of 2,4,6-collidine as a non-nucleophilic base proved essential for the success of these reactions.[40] Furthermore, microwave heating promoted rapid and efficient conversion to product with 21 min reaction times.[41] The crude products were evaporated to dryness and then subjected directly to HPLC purification to yield the products in approximately 60–80% yields (likely representing nearly quantitative conversion prior to purification).

Spectral analysis of the expected nerol-derived products (**3b** and **4b**), however, showed some peculiarities. Examination of the NMR and high resolution mass spectra for expected product **3b** revealed that a mixture of the expected product and a covalent hydrate of **3b** was isolated. This is evidenced by the presence of a C–O–H proton (at $\delta = 4.43$ ppm) and a decreased integration value for one of the vinyl signals in the ^1H NMR spectrum, as well as the presence of a mass + H_2O peak in the high resolution mass spectrum. However, prior LC–MS analysis completed immediately after purification but before concentration strongly suggested the presence of only the desired compound at this stage. Thus it appears that the observed covalent hydrate was likely formed upon concentration (lyophilization of the H_2O/MeCN solvent mixture). Examination of the spectra for expected product **4b** also revealed similar peculiarities. In this case, initial LC–MS analysis following purification again suggested the presence of only the desired compound, but NMR analysis completed after concentration showed highly cluttered spectra which were not readily interpretable. Furthermore, LC–MS analysis of a portion of the NMR sample itself then revealed the presence of an additional unknown compound of mass 372. Therefore it is clear that although initially formed, the (*Z*)-configured free phosphonic acid products were susceptible to further reaction, an observation which likely reflects the increased reactivity of these alkenes under somewhat acidic conditions. In contrast, all four reactions on the geraniol- and farnesol-derived intermediates proceeded cleanly to form the expected products **1b**, **2b**, **5b**, and **6b**.

In summary, we have completed the synthesis of a number of prenyl diphosphates which we believe are likely to show activity toward enzymes that utilize these substrates in important biological contexts. Efforts to assess the utility of these compounds as inhibitors and mechanistic probes (through crystallography) are currently underway.



Scheme 3.



Scheme 4.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, analytical data, and computational details related to the figures) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.119.

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