

# Stereoselective Synthesis of Homoneryl and Homogeranyl Triazole Bisphosphonates

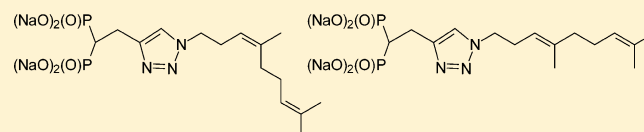
Robert A. Matthiesen,<sup>†</sup> Veronica S. Wills,<sup>†</sup> Joseph I. Metzger,<sup>†</sup> Sarah A. Holstein,<sup>‡</sup> and David F. Wiemer<sup>\*,†</sup>

<sup>†</sup>Department of Chemistry, University of Iowa, Iowa City, Iowa 52242-1294, United States

<sup>‡</sup>Division of Oncology and Hematology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska 68198-7680, United States

**S** Supporting Information

**ABSTRACT:** Isoprenoid-substituted bisphosphonates are known to serve as inhibitors of the enzyme geranylgeranyl diphosphate synthase, and their activity can be highly sensitive to olefin stereochemistry. A mixture of homogeranyl and homoneryl triazole bisphosphonates has previously demonstrated potent activity, and thus stereocontrolled syntheses of the individual isomers have been developed.



Inhibitors of the enzyme farnesyl diphosphate synthase (FDPS), including pamidronate (**1**) and zoledronate (**2**), are in clinical use for treatment of osteoporosis and diseases of the bone such as Paget's disease<sup>1</sup> and have become the standard of care for patients with multiple myeloma bone disease (Figure 1).<sup>2</sup> Inhibition of FDPS leads to depletion of the isoprenoid

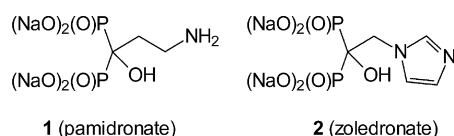


Figure 1. Inhibitors of FDPS in clinical use.

farnesyl diphosphate (FDP) as well as the downstream product geranylgeranyl diphosphate (GGDP), and there is evidence that these agents exert their pharmacological effects by virtue of the depletion of GGDP. The C<sub>20</sub> isoprenoid GGDP is formed from the C<sub>15</sub> FDP and the C<sub>5</sub> isopentenyl diphosphate (IPP) in a reaction mediated by the enzyme geranylgeranyl diphosphate synthase (GGDPS).<sup>3</sup> If depletion of GGDP is the proximate cause of the biological activity of the nitrogenous bisphosphonates, then inhibition of GGDPS may represent a more direct way to achieve the desired biological effect.

Our earliest studies of GGDPS inhibition identified several isoprenoid bisphosphonates that affect this enzyme selectively, perhaps most notably digeranyl bisphosphonate (**3**, DGBP, Figure 2) that has an IC<sub>50</sub> of approximately 260 nM against the isolated enzyme.<sup>4</sup> Several other dialkyl bisphosphonates have been reported to show comparable activity,<sup>5,6</sup> and similar activity has been found more recently in the closely related ether **4**.<sup>7</sup> While further improvements on the V-shaped motif of these compounds may yet be possible,<sup>8</sup> in our recent efforts<sup>9,10</sup> to secure more potent inhibitors we have examined bisphosphonates assembled through click chemistry.<sup>11,12</sup> In this vein, the most potent inhibitor we have identified to date is the bisphosphonate **5**.<sup>13</sup> This material is readily available via

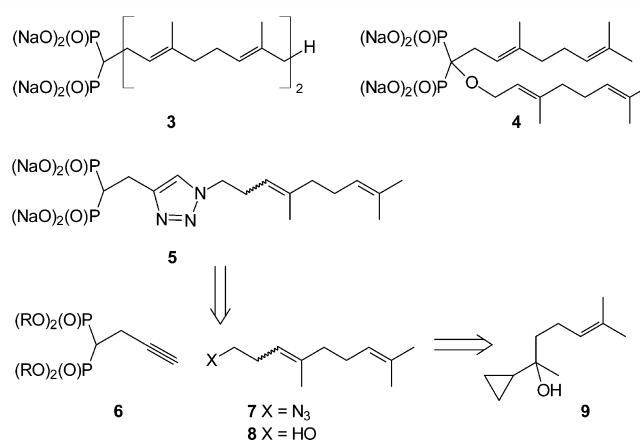


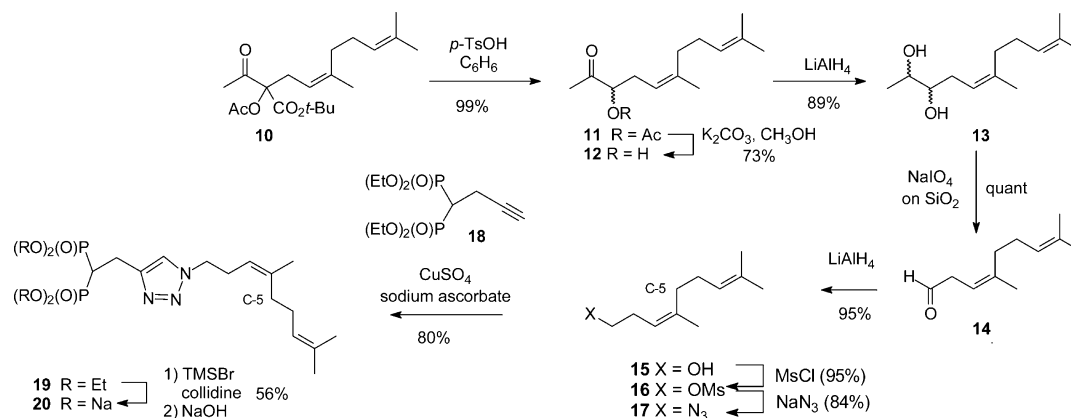
Figure 2. Bisphosphonate GGDPS inhibitors and the initial retrosynthesis of the most potent example (**5**).

cycloaddition of the acetylene **6** and the azide **7**, with the azide prepared from the alcohol **8** which in turn is readily available through a ring opening rearrangement of the cyclopropyl carbinol **9**.<sup>14</sup> Unfortunately, this rearrangement is known to give a mixture of olefin isomers in a ratio of ~3:1 (*E* to *Z*).<sup>14</sup> Variations in the reaction conditions did improve the ratio somewhat in favor of the *E*-isomer,<sup>15</sup> but the homoneryl isomer was of special interest because the neryl analogue already was known to be more active than the corresponding geranyl isomer.<sup>7</sup> As the homoallylic bromides, the olefin isomers were not readily separable and so the mixture was carried forward to provide material for initial bioassays. Those efforts were rewarded when the olefin mixture **5** was found to have an IC<sub>50</sub> of 46 nM in enzyme assays,<sup>13</sup> approximately 4-fold more potent than DGBP, and attractive activity in cellular assays as well. The increased potency of this mixture relative to earlier

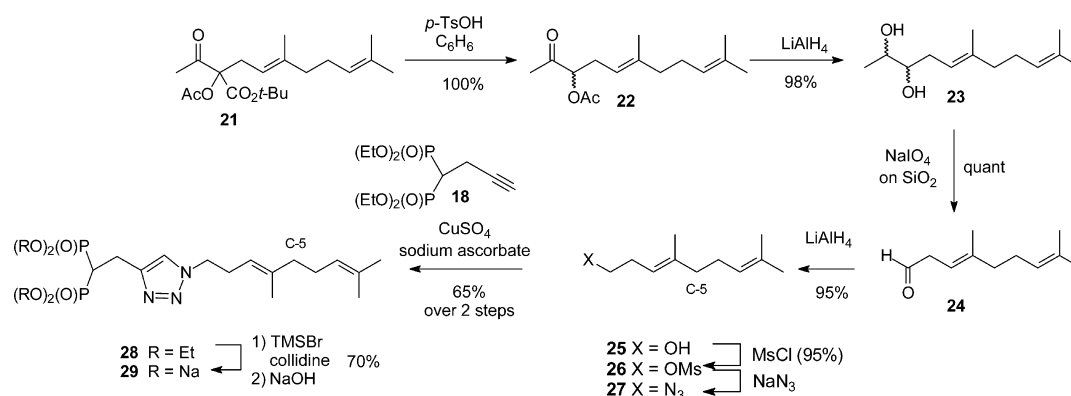
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Scheme 1. Synthesis of the Homonerol Isomer 20



Scheme 2. Synthesis of the Homogeranyl Isomer 29



compounds encouraged studies of the individual olefin isomers. In this report we describe the syntheses of both the *E*- and *Z*-olefin isomers of compound 5.

Our initial efforts<sup>15</sup> to prepare homonerol were based on use of the Wittig reagent prepared from the THP derivative of 3-bromopropanol,<sup>16</sup> which has been shown to be *Z*-selective in its reactions with aldehydes.<sup>17</sup> However, while condensation of this reagent with commercial 6-methyl-5-hepten-2-one gave the THP derivative of compound 8 as a 1.4:1 mixture of *Z*- and *E*-olefin isomers, those isomers were not readily separated either as the THP acetals or as the free alcohols.<sup>15</sup> There are several reports on preparation of homonerol and homogeraniol<sup>17–19</sup> or the corresponding carboxylic acids,<sup>20</sup> but to secure pure samples of the individual isomers a new sequence derived from research reported by Wessjohann and co-workers<sup>21</sup> appeared to be particularly attractive (Scheme 1). Their strategy relied upon classical acetoacetate chemistry and recently was employed in a clever synthesis of ephothilone D.<sup>22</sup> For that effort, the *Z* stereochemistry of a trisubstituted olefin was derived from neryl bromide and cleanly preserved throughout their reaction sequence.

For our purposes, the  $\beta$ -keto acetate derivative 10 was prepared from neryl bromide and *tert*-butyl 2-acetoxyacetoacetate according to the known procedure,<sup>22</sup> and subsequent decarboxylation upon treatment with TsOH gave racemic acetate 11 (Scheme 1).<sup>21</sup> Hydrolysis of this acetate proceeded smoothly to the acyloin 12,<sup>23</sup> but then our efforts to bring about oxidative cleavage to the carboxylic acid went unrewarded. In contrast, reduction of compound 11 proceeded smoothly upon treatment with LiAlH<sub>4</sub> to give the diol 13 as a

mixture of stereoisomers, and oxidative cleavage by treatment with sodium periodate on silica gel gave the expected aldehyde 14 in nearly quantitative yield.

Once homonerol (14) was in hand, the remaining steps in the synthetic sequence proceeded as expected. Reduction of aldehyde 14 proceeded smoothly to give the homoallylic alcohol 15 as a single olefin isomer. After conversion of this alcohol to the corresponding mesylate (16) and a subsequent reaction with sodium azide to obtain the alkyl azide 17, the click reaction with acetylene 18 gave the desired triazole 19. Hydrolysis of the tetraester 19 under standard McKenna conditions<sup>24</sup> gave the final product 20, with no apparent formation of the isomeric olefin. The final product as well as the late stage intermediates were identified as single olefin isomers on the basis of their <sup>13</sup>C NMR spectra. The C-4 methylene group of nerol and geraniol have significantly different resonances in their <sup>13</sup>C NMR spectra (32.2 and 39.7 ppm, respectively),<sup>25</sup> and the corresponding C-5 methylene resonances for homonerol (32.2 ppm) and homogeraniol (40.0 ppm) are virtually identical. In compound 19, which was soluble in CDCl<sub>3</sub>, this resonance was observed at 32.2 ppm; in compound 20, which was soluble in D<sub>2</sub>O, it was observed at 31.5 ppm. While the resonance of the  $\alpha$  carbon in the bisphosphonate also is found in this range, it can be unambiguously identified by the large coupling constant with the two phosphorus atoms (~120 Hz).

A parallel reaction sequence was employed to obtain the corresponding homogeranyl isomer (Scheme 2). In this series, the early reactions with the geranyl derivatives proceeded under parallel conditions and in nearly the same yields as those with

the neryl isomer. For experimental convenience, the mesylate **26** again was converted directly to the azide **27** and then the azide was carried immediately into the click reaction with alkyne **18** to give the triazole **28** as the tetra ethyl ester. Hydrolysis then proceeded under parallel conditions to give the desired salt **29**. This sequence also gave a single olefin isomer throughout. For the ester **28**, the resonance for the key C-5 methylene group was observed at 39.8 ppm (CDCl<sub>3</sub>) while the corresponding resonance in the salt **29** was found at 39.3 ppm (D<sub>2</sub>O).

In conclusion, isomerically pure samples of both the *Z*- and *E*-olefin isomers **20** and **29** have been prepared through short synthetic sequences based on classic acetoacetate chemistry. These sequences can be conducted on a gram scale and have provided materials appropriate for further biological investigations. Based on the initial Western blot analyses, the homoneryl isomer does appear to be more potent as an inhibitor of GGDPs than the homogeranyl isomer, which is consistent with the relative activity of the neryl/geranyl pair,<sup>7</sup> but more quantitative comparisons will require further studies.

## EXPERIMENTAL SECTION

**General Experimental Procedures.** Diethyl ether was freshly distilled from sodium and benzophenone, whereas methylene chloride was distilled from calcium hydride prior to use. All other reagents and solvents were purchased from commercial sources and used without further purification. All reactions in nonaqueous solvents were conducted in flame-dried glassware under a positive pressure of argon and with a magnetic stir bar. NMR spectra were obtained at 300 MHz for <sup>1</sup>H, 75 or 125 MHz for <sup>13</sup>C NMR, and 121 MHz for <sup>31</sup>P NMR, in CDCl<sub>3</sub> with (CH<sub>3</sub>)<sub>4</sub>Si (<sup>1</sup>H, 0.00 ppm) or CDCl<sub>3</sub> (<sup>1</sup>H, 7.26 ppm; <sup>13</sup>C NMR; 77.0 ppm) for non-aqueous samples or D<sub>2</sub>O (<sup>1</sup>H, 4.80 ppm) and 1,4-dioxane (<sup>13</sup>C, 67.19) for aqueous samples, as the internal standards. High resolution mass spectra were obtained by GC-TOF.

**(5Z)-3-Acetoxy-6,10-dimethyl-5,9-undecadien-2-one (11).** According to the published procedure,<sup>21</sup> *p*-TsOH·H<sub>2</sub>O (260 mg, 1.37 mmol) was added to a stirred solution of β-keto ester **10** (4.69 g, 13.3 mmol) in benzene (40 mL) at room temperature. The resulting solution was heated at 78 °C for 90 min and then was allowed to stir for 2 days at room temperature. The reaction mixture then was filtered through a bed of silica, the silica was rinsed with EtOAc, and the combined filtrate was concentrated *in vacuo* to afford the desired keto acetate **11** (3.34 g, 99%) as an orange oil which was used without further purification. The <sup>1</sup>H and <sup>13</sup>C NMR data were consistent with the literature data.<sup>21</sup>

**(5Z)-2,3-Dihydroxy-6,10-dimethyl-5,9-undecadiene (13).** LiAlH<sub>4</sub> (247 mg, 6.51 mmol) was added to a stirred solution of keto acetate **11** (912 mg, 3.61 mmol) in Et<sub>2</sub>O (18 mL) at 0 °C. After it was stirred for 2 h and allowed to warm slowly, the reaction then was cooled to 0 °C, quenched by slow addition of 1 N HCl followed by H<sub>2</sub>O, and extracted with Et<sub>2</sub>O (3×). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and filtered, and the filtrate was concentrated *in vacuo* to afford the desired diol **13** (685 mg, 89%) as a yellow oil. This mixture of diastereomers was used in the next step without further purification: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.23–5.05 (m, 2H), 3.89–3.31 (m, 2H), 2.28–2.16 (m, 2H), 2.12–2.04 (m, 4H), 2.02–1.98 (m, 1H), 1.94–1.88 (m, 1H), 1.74 (d, *J* = 1.2 Hz, 3H), 1.68 (s, 3H), 1.61 (d, *J* = 1.2 Hz, 3H), 1.22–1.16 (m, 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) for the major isomer δ 137.8, 131.6, 124.1, 120.7, 76.1, 70.3, 32.1, 26.5, 25.7, 23.5, 19.4, 17.6, 16.6; HRMS (ES<sup>+</sup>) *m/z* calcd for C<sub>13</sub>H<sub>24</sub>O<sub>2</sub>Na (M + Na)<sup>+</sup> 235.1674, found 235.1679.

**(Z)-4,8-Dimethylnona-3,7-dienal (14).** In a manner similar to the published procedure,<sup>26</sup> sodium periodate (2.57 g, 12.03 mmol) was dissolved in hot water (5 mL, 70 °C), and silica gel (10.04 g) was added, followed by vigorous shaking to yield sodium periodate coated silica gel. The prepared periodate reagent (510 mg, 0.35 mmol) was

suspended in CH<sub>2</sub>Cl<sub>2</sub> (2.7 mL) and allowed to stir for 10 min. To the suspension was added diol **13** (51 mg, 0.24 mmol), and the mixture was allowed to stir for 30 min, followed by filtration of the reaction mixture through diatomaceous earth, and removal of solvent using a rotary evaporator to yield the desired aldehyde **14** (39 mg, 100%) as a yellow oil that was used without further purification. The <sup>1</sup>H and <sup>13</sup>C NMR data were consistent with the literature data.<sup>27</sup>

**(Z)-4,8-Dimethylnona-3,7-dien-1-ol (15).** To a stirred suspension of LiAlH<sub>4</sub> (95%, 93 mg, 2.44 mmol) in Et<sub>2</sub>O (27 mL) at 0 °C, aldehyde **14** (677 mg, 4.07 mmol) was added as a solution in Et<sub>2</sub>O (1 mL) over 4 min. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was cooled to 0 °C, quenched by slow addition of 1 N HCl followed by H<sub>2</sub>O, and extracted with Et<sub>2</sub>O. The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and filtered, and the filtrate was concentrated *in vacuo*. Final purification by column chromatography (5% EtOAc in hexanes) afforded the desired alcohol **15** (654 mg, 95%) as a clear oil with a <sup>1</sup>H NMR spectrum in agreement with known data;<sup>28</sup> <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 139.1, 132.1, 124.3, 121.0, 62.8, 32.2, 31.6, 26.8, 25.9, 23.7, 17.9.

**(Z)-4,8-Dimethylnona-3,7-dien-1-yl Methanesulfonate (16).** In a manner similar to a published procedure,<sup>29</sup> NEt<sub>3</sub> (0.25 mL, 1.78 mmol) was added to a stirred solution of homoneryl (**15**, 178 mg, 1.06 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at 0 °C. After the reaction was allowed to stir at 0 °C for 20 min, methanesulfonyl chloride (0.13 mL, 1.68 mmol) was added dropwise to the reaction mixture. The reaction was allowed to stir for 3 h at 0 °C, followed by addition of H<sub>2</sub>O to quench the reaction mixture. The resulting mixture was washed with 1 N HCl (2×), brine (1×), and NaHCO<sub>3</sub> (2×). The combined organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and filtered, and the filtrate was concentrated *in vacuo* to afford desired mesylate **16** (247 mg, 95%) as a yellow oil that was carried immediately to the next step.

**Tetraethyl (3Z)-(2-(1-(4,8-Dimethylnon-3,7-dien-1-yl)-1H-1,2,3-triazol-4-yl)ethane-1,1-diyl)bis(phosphonate) (19).** In a manner similar to published procedures,<sup>11,30</sup> NaN<sub>3</sub> (473 mg, 7.28 mmol) was added to a stirred solution of homoneryl mesylate (**16**, 944 mg, 3.83 mmol) in DMF (20 mL) under an argon atmosphere. The mixture was heated to 40 °C and allowed to stir overnight. The reaction then was diluted with Et<sub>2</sub>O, washed with water (5×) and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and filtered, and the filtrate was concentrated *in vacuo*, to yield homoneryl azide (**17**, 626 mg, 84%) as a yellow oil. The material was used immediately in the following reaction without further purification. To a stirred solution of tetraethyl but-3-yn-1,1-diylidiphosphonate<sup>31</sup> (**18**, 770 mg, 2.36 mmol) and homoneryl azide (**17**, 616 mg, 3.19 mmol) in *t*-BuOH/H<sub>2</sub>O (4:1, 25 mL total), saturated CuSO<sub>4</sub> (0.01 mL) and sodium ascorbate (140 mg, 0.71 mmol) were added in sequence. The resulting reaction mixture was allowed to stir overnight at room temperature, and then the solvent was removed *in vacuo*. The resulting residue was dissolved in brine and extracted with EtOAc (5×). The combined organic extracts were washed with 5% NH<sub>4</sub>OH, dried (Na<sub>2</sub>SO<sub>4</sub>), and filtered, and the filtrate was concentrated *in vacuo*. Final purification by column chromatography (10% EtOH in hexanes) afforded triazole **19** (982 mg, 80%) as a yellow oil: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.46 (s, 1H), 5.12–5.03 (m, 2H), 4.26 (t, *J* = 7.5 Hz, 2H), 4.19–4.06 (m, 8H), 3.39–3.24 (td, *J*<sub>HP</sub> = 16.1 Hz, *J* = 6.4 Hz, 2H), 3.06–2.85 (m, 1H), 2.60–2.51 (m, 2H), 2.04–1.96 (m, 4H), 1.69 (s, 3H), 1.67 (s, 3H), 1.59 (s, 3H), 1.32–1.36 (m, 12H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 145.2 (t, *J*<sub>CP</sub> = 8.8 Hz), 139.6, 132.2, 124.0, 122.4, 119.6, 63.0 (d, *J*<sub>CP</sub> = 6.6 Hz, 2C), 62.7 (d, *J*<sub>CP</sub> = 6.4 Hz, 2C), 50.5, 36.9 (t, *J*<sub>CP</sub> = 133.0 Hz), 32.2, 29.2, 26.5, 25.9, 23.6, 22.3 (t, *J*<sub>CP</sub> = 4.9 Hz), 17.9, 16.6 (d, *J*<sub>CP</sub> = 3.7 Hz, 2C), 16.6 (d, *J*<sub>CP</sub> = 3.4 Hz, 2C); <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>) 22.5 ppm; HRMS (ES<sup>+</sup>) *m/z* calcd for C<sub>23</sub>H<sub>44</sub>N<sub>3</sub>O<sub>6</sub>P<sub>2</sub> (M + H)<sup>+</sup> 520.2705, found 520.2698.

**Sodium (3Z)-(2-(1-(4,8-Dimethylnon-3,7-dien-1-yl)-1H-1,2,3-triazol-4-yl)ethane-1,1-diyl)bis(phosphonate) (20).** In a manner similar to published procedures,<sup>9,24</sup> to a stirred solution of bisphosphonate ester **19** (938 mg, 1.81 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (30 mL) at 0 °C, collidine (1.67 mL, 12.6 mmol) and TMSBr (97%, 1.97 mL, 15.2 mmol) were added dropwise in succession. The reaction was allowed to stir



overnight while it warmed to room temperature, and the solvent then was removed *in vacuo*. The resulting residue was diluted with toluene (40 mL) and concentrated *in vacuo* to remove any excess TMSBr (3×). It then was treated with 2 N NaOH (6.05 mL, 12.1 mmol) and allowed to stir overnight at room temperature. Anhydrous acetone was added, and the mixture was placed in the freezer for 20 min. The resulting solid was collected by filtration, dissolved in water, and reprecipitated by addition of anhydrous acetone, and the mixture was placed in the freezer for 20 min. The resulting solid was collected by filtration, dissolved in water, and lyophilized to provide the desired salt **20** (501 mg, 56%) as a white powder: <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O) δ 7.84 (s, 1H), 5.21–5.10 (m, 2H), 4.39 (t, *J* = 6.6 Hz, 2H), 3.21 (td, *J*<sub>HP</sub> = 15.2 Hz, *J* = 6.6 Hz, 2H) 2.63–2.55 (m, 2H), 2.18–1.86 (m, 5H), 1.68 (m, 6H), 1.61 (s, 3H); <sup>13</sup>C NMR (125 MHz, D<sub>2</sub>O) δ 147.5, 140.8, 134.3, 124.8, 124.7, 120.6, 50.9, 40.1 (t, *J*<sub>CP</sub> = 116.7 Hz), 31.5, 28.9, 26.3, 25.5, 23.1, 22.3 (t, *J*<sub>CP</sub> = 4.0 Hz), 17.5; <sup>31</sup>P NMR (121 MHz, D<sub>2</sub>O) 18.7 ppm; HRMS (ES<sup>-</sup>) *m/z* calcd for C<sub>15</sub>H<sub>26</sub>N<sub>3</sub>O<sub>6</sub>P<sub>2</sub> (M - H)<sup>-</sup> 406.1297, found 406.1289.

(5*E*)-2,3-Dihydroxy-6,10-dimethyl-5,9-undecadiene (**23**). According to the procedure for preparation of diol **13**, keto ester **22** (1.26 g, 5.00 mmol) was treated with LiAlH<sub>4</sub> (595 mg, 14.9 mmol) in Et<sub>2</sub>O (34 mL) at 0 °C. A parallel workup afforded the desired diol **23** (1.04 g, 98%) as a yellow oil that was used without further purification: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 5.20–5.12 (m, 1H), 5.10–5.01 (m, 1H), 3.90–3.76 (m, 1H), 3.69–3.54 (m, 1H), 2.10–1.96 (m, 6H), 1.68 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H), 1.25 (br s 3H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 139.7, 132.1, 124.3, 113.2, 75.9, 70.6, 40.0, 29.9, 26.7, 25.9, 19.5, 17.9, 17.4; HRMS (ES<sup>+</sup>) *m/z* calcd for C<sub>13</sub>H<sub>24</sub>O<sub>2</sub>Na (M + Na)<sup>+</sup> 235.1674, found 235.1658.

(*E*)-4,8-Dimethylnona-3,7-dienal (**24**). According to the procedure for the preparation of aldehyde **14**, diol **23** (1.78 g, 8.38 mmol) was added to a stirred suspension of periodate coated silica gel (17.67 g, 12.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (56 mL). A parallel workup afforded the desired aldehyde **24** (1.39 g, 100%) as a yellow oil that was used without further purification. The <sup>1</sup>H NMR data were consistent with the literature data.<sup>27</sup>

(*E*)-4,8-Dimethylnona-3,7-dien-1-ol (**25**). According to the procedure for the preparation of homoallylic alcohol **15**, aldehyde **24** (1.39 g, 8.38 mmol) was added to a suspension of LiAlH<sub>4</sub> (180 mg, 5.03 mmol) in Et<sub>2</sub>O (55 mL) at 0 °C. A parallel workup afforded homogeraniol (**25**, 1.35 g, 96%) as a yellow oil that was used without further purification. The <sup>1</sup>H NMR data were consistent with the literature data for material prepared by a different method.<sup>32,32</sup>

(*E*)-4,8-Dimethylnona-3,7-dien-1-yl Methanesulfonate (**26**). According to the procedure for the preparation of mesylate **16**, homogeraniol (**25**, 419 mg, 2.49 mmol) was treated with NEt<sub>3</sub> (0.59 mL, 4.20 mmol) followed by MsCl (0.31 mL, 4.01 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (25 mL) at 0 °C. A parallel workup afforded the desired mesylate **26** (542 mg, 88%) as a yellow oil that was used immediately without further purification.

Tetraethyl (3*E*)-(2-(1-(4,8-Dimethylnon-3,7-dien-1-yl)-1*H*-1,2,3-triazol-4-yl)ethane-1,1-diyl)bis-(phosphonate) (**28**). According to the procedure for the preparation of triazole **19**, mesylate **26** (161 mg, 0.65 mmol) was treated with NaN<sub>3</sub> (80.1 mg, 1.23 mmol), and the resulting azide (**27**, 111 mg, 0.57 mmol) was isolated and immediately treated with acetylene bisphosphonate **18** (109 mg, 0.33 mmol), saturated CuSO<sub>4</sub> (0.01 mL), and sodium ascorbate (25 mg, 0.13 mmol) in sequence. A parallel workup and purification afforded the desired triazole **28** (112 mg, 65%) as a yellow oil: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.40 (s, 1H), 5.06–4.95 (m, 2H), 4.24–4.18 (t, *J* = 7.3 Hz, 2H), 4.12–4.04 (m, 8H), 3.32–3.19 (td, *J*<sub>HP</sub> = 16.2 Hz, *J* = 6.5 Hz, 2H), 3.00–2.80 (tt, *J*<sub>HP</sub> = 23.5 Hz, *J* = 6.3 Hz, 1H), 2.54–2.46 (dt, *J* = 7.9 Hz, 7.3 Hz, 2H), 2.00–1.88 (m, 4H), 1.61 (s, 3H), 1.53 (s, 3H), 1.48 (s, 3H), 1.26–1.19 (m, 12H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 145.0, 139.7, 131.9, 124.1, 122.5, 118.8, 63.1 (d, *J*<sub>CP</sub> = 6.5 Hz, 2C), 62.8 (d, *J*<sub>CP</sub> = 6.5 Hz, 2C), 50.3, 39.8, 36.8, 29.4, 26.7, 25.9, 22.3 (t, *J*<sub>CP</sub> = 4.9 Hz), 17.9, 16.5 (d, *J*<sub>CP</sub> = 3.4 Hz, 2C), 16.4 (d, *J*<sub>CP</sub> = 3.7 Hz, 2C), 16.3; <sup>31</sup>P NMR (121 MHz, CDCl<sub>3</sub>) 22.5 ppm; HRMS (ES<sup>+</sup>) *m/z* calcd for C<sub>23</sub>H<sub>44</sub>N<sub>3</sub>O<sub>6</sub>P<sub>2</sub> (M + H)<sup>+</sup> 520.2705, found 520.2703.

Sodium (3*E*)-(2-(1-(4,8-Dimethylnon-3,7-dien-1-yl)-1*H*-1,2,3-triazol-4-yl)ethane-1,1-diyl)bis-(phosphonate) (**29**). According to the procedure for the preparation of sodium salt **20**, the bisphosphonate ester **28** (1.10 g, 2.12 mmol) was treated with TMSBr (97%, 2.30 mL, 17.7 mmol), collidine (1.95 mL, 14.6 mmol), and then 2 N NaOH (7.2 mL). A parallel workup and precipitation provided the desired sodium salt **29** (1.05 g, 70%) as a white powder: <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O) δ 7.71 (s, 1H), 5.08–4.98 (m, 2H), 4.27–4.20 (t, *J* = 6.8 Hz, 2H), 3.10–2.95 (td, *J*<sub>HP</sub> = 15.0 Hz, *J* = 6.8 Hz, 2H), 2.52–2.42 (m, 2H), 2.10–1.80 (m, 5H), 1.56 (s, 3H), 1.48 (s, 3H), 1.36 (s, 3H); <sup>13</sup>C NMR (75 MHz, D<sub>2</sub>O) δ 150.5 (t, *J*<sub>CP</sub> = 7.3 Hz), 140.4, 134.0, 124.8, 124.4, 119.6, 50.5, 41.8 (t, *J*<sub>CP</sub> = 118.1 Hz), 39.3, 28.8, 26.2, 25.4, 24.3, 17.5, 15.6; <sup>31</sup>P NMR (121 MHz, D<sub>2</sub>O) 18.7 ppm; HRMS (ES<sup>-</sup>) *m/z* calcd for C<sub>15</sub>H<sub>26</sub>N<sub>3</sub>O<sub>6</sub>P<sub>2</sub> (M - H)<sup>-</sup> 406.1297, found 406.1304.

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01693.

The <sup>1</sup>H and <sup>13</sup>C NMR spectra of compounds **13**, **19**, **20**, **23**, **28**, and **29** and the <sup>1</sup>H NMR spectra of compounds **15** and **25** (PDF)

## ■ AUTHOR INFORMATION

### ✉ Corresponding Author

\*E-mail: david-wiemer@uiowa.edu.

### Notes

The authors declare the following competing financial interest(s): D.F.W. is a named inventor of intellectual property related to digeranyl bisphosphonate that is owned by the University of Iowa Research Foundation. He is a founder of Terpenoid Therapeutics, Inc., which has licensed this property.

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