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Stereocontrolled regeneration of olefins from epoxides

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Abstract

Through treatment with NaI and trifluoroacetic anhydride, which presumably forms trifluoroacetyl iodide *in situ*, epoxides can be converted to olefins. This reaction now has been shown to tolerate remote olefins without loss of their individual stereochemistry. A reaction sequence involving regiospecific epoxidation of an isoprenoid alcohol, conversion of the alcohol to an azide, and cycloaddition with an acetylene, followed by conversion of the epoxide back to the original olefin, has allowed stereocontrolled preparation of triazole bisphosphonates with a farnesyl or a geranylgeranyl substituent. This strategy may be applicable selective protection of an alkene in other polyolefins, including substrates for metathesis reactions.

Graphical Abstract

Keywords

epoxide; deoxygenation; phosphonate; triazole

The carbon-carbon double bond of an olefin is not often described as the central functional group of organic synthesis, but perhaps it should be. On the one hand, it is found within an enormous number of natural products including the majority of terpenoids and steroids. On the other hand, it can be transformed into alcohols, amines, diols, and epoxides among other functional groups, and participate in reactions including oxidative cleavage, the Diels-Alder reaction, and the Heck reaction. The tremendous interest in olefin metathesis further

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Supplementary data

Experimental procedures and/or spectral data for compounds **10** and **12–19** are available as well as additional bioassay data.

Supplementary data associated with this article can be found in the online version at doi:

amplifies its value. An assortment of protecting groups has been developed for various other functional groups, and epoxides can be a convenient protecting group for olefins. But in order for this protecting group to be practical, it is important that it be removable in good yield and with a predictable impact on the original olefin stereochemistry.

Our interest in the utilization of epoxides as an olefin protecting group stems from work we have done with click chemistry^{1,2,3} to make isoprenoid triazole bisphosphonates as potential inhibitors of downstream enzymes in the isoprenoid biosynthetic pathway, especially geranylgeranyl diphosphate synthase (GGDPS).^{4,5} For example, the geranyl (**1**) and neryl (**2**) triazoles can be prepared easily by a click reaction of an acetylenic bisphosphonate⁶ with an isoprenoid azide. However, whether the geranyl or neryl azide is employed, the resulting triazole is obtained as a ~2:1 mixture of olefin isomers due to an allylic azide rearrangement that equilibrates the olefin stereochemistry.⁷ After bioactivity was observed in a mixture of geranyl and neryl isomers,¹ it became important to avoid the allylic azide rearrangement and prepare each individually. We recently reported the activity of bisphosphonates **1** and **2** as single olefin isomers and, perhaps surprisingly, the neryl isomer **2** was the more potent inhibitor of GGDPS.² The individual olefins were prepared via their corresponding epoxides, and those epoxides were not active in our bioassays. An attempt to reduce the epoxide to the olefin after the click reaction using Caputo's conditions of TMSCl and NaI⁸ only returned starting material. However, deoxygenation to furnish compounds **1** and **2** was achieved upon treatment with trifluoroacetic anhydride (TFAA) and NaI under conditions first reported by Sonnet,⁹ which is thought to form trifluoroacetyl iodide *in situ*. In this case it was important to note that the olefin was regenerated with stereochemistry present in the original alcohol. However, because the terminal olefin in compounds **1** and **2** does not have stereochemistry, it was unclear whether this strategy could be used to prepare individual isomers of triazoles derived from longer isoprenoids. We now report that this strategy has been applied successfully to preparation of farnesyl and geranylgeranyl derivatives, and that the remote olefins are tolerated by the necessary reaction conditions.

To explore the viability of this strategy with larger isoprenoids, initially the C₁₅ derivatives were prepared from commercially available (2*E*, 6*E*)-farnesol (**3**, Scheme 1). The reaction sequence begins with treatment of the alcohol **3** with VO(C₅H₇O₂)₂ and TBHP to afford epoxyfarnesol (**4**, Scheme 1). The resulting primary alcohol then was converted to bromide **5**¹⁰ through a mesylate intermediate.

As outlined in Scheme 2, preparation of the C₂₀ azide required a somewhat longer sequence because pure (2*E*, 6*E*, 10*E*)-geranylgeraniol is not commercially available. Therefore alcohol **8** was prepared from farnesyl acetone (**6**).¹¹ A Horner-Wadsworth-Emmons (HWE) condensation of triethyl phosphonoacetate and farnesyl acetone (**6**) provided ester **7** as a mixture of olefin isomers (approximately 10:1 *E* : *Z*). Because the *E*- and *Z*-isomers were not readily separable by column chromatography at this stage, they were carried forward as a mixture. After the esters were reduced to alcohols by treatment with LiAlH₄, the individual isomers were obtained by column chromatography to afford pure (2*E*, 6*E*, 10*E*)-geranylgeraniol (**8**) in 61% yield.¹¹ Regioselective formation of epoxygeranylgeraniol (**9**) was accomplished by treatment of alcohol **8** with vanadyl acetylacetonate and TBHP.^{12,13}

The resulting epoxide then was allowed to react with MsCl, followed by LiBr to afford the primary bromide **10**.

In anticipation of a click reaction with the acetylene bisphosphonate **11**,⁶ the bromide **5** was allowed to react with NaN₃. Out of concern for the stability of the resulting azide (**12**), once this intermediate was formed it was subjected to standard click reaction conditions with only minimal purification. Reaction of the primary azide **12** and acetylene bisphosphonate **11** under standard click reaction conditions⁶ gave the desired triazole bisphosphonate **13**. The critical deoxygenation was accomplished through formation of trifluoroacetyl iodide *in situ* from NaI and TFAA, and the olefin was regenerated to provide the farnesyl triazole bisphosphonate **14** as a single isomer. The geometry of the olefin was confirmed by observation of the diagnostic signal at 39.6 ppm in the ¹³C NMR spectrum corresponding to the methylene adjacent to the newly formed olefin. This is comparable to the resonance reported for the corresponding carbon in (2*E*, 6*E*)-farnesol (39.8 ppm) and certainly distinct from the signal for the same carbon in (2*Z*, 6*E*)-farnesol (32.7 ppm).^{11,14} Furthermore there was no detectable scrambling of the central olefin stereochemistry, as determined by the presence of a second resonance at 39.8 ppm, and comparison of the ¹³C NMR resonances with those of other linear isoprenoids.^{11,14} The target farnesyl triazole bisphosphonate sodium salt **15** finally was obtained by hydrolysis of bisphosphonate ester **14** under standard conditions.¹⁵

In a parallel fashion, bromide **10** was treated with NaN₃ to form the primary azide **16**, which then was subjected to click reaction conditions (CuSO₄, sodium ascorbate, and acetylene bisphosphonate **11**)⁶ to provide the triazole bisphosphonate **17**. The next step was to reduce the epoxide, and stereospecific regeneration of the olefin and was accomplished by treatment of the epoxide with NaI and TFAA under Sonnet's conditions⁹ to provide triazole bisphosphonate **18** as a single isomer. The ¹³C NMR spectrum confirmed that that the regenerated olefin was the *E*-isomer. Specifically, the resonance at 39.7 ppm could be attributed to the methylene adjacent to the more substituted carbon of the newly formed olefin, and was compared to the corresponding carbon in (2*E*, 6*E*, 10*E*)-geranylgeraniol (39.8 ppm). This signal is much different from the methylene carbon of the (2*Z*, 6*E*, 10*E*)-isomer, which would have a resonance at 32.1 ppm for the same carbon.^{11,16} Once again there was no apparent scrambling of the two central olefins' stereochemistry based on the ¹³C NMR spectrum. For compound **18** a total of three resonances were observed ~39 ppm, as expected for the all-trans isomer based on literature data for other linear isoprenoids.^{11,14} Furthermore, the spectrum of epoxide **17** showed just two resonances in this region. Finally, the tetraethyl ester of bisphosphonate **18** was hydrolyzed under standard conditions by treatment with TMSBr and collidine followed by NaOH¹⁵ to afford the corresponding sodium salt **19**.

Triazole bisphosphonates **15** and **19** have been tested for their activity as inhibitors of several enzymes in the isoprenoid biosynthetic pathway. These enzyme assay results, as well as those from an assay for cellular activity, are summarized in Table 1 below. In enzyme assays, these two compounds showed only very modest activity as GGDPS inhibitors and they were not as active as the C₁₀ isoprenoid triazole bisphosphonates we already have reported.² Compounds **15** and **19** showed no activity in the cell assays (Table 1 and SI).

In conclusion, the new farnesyl and geranylgeranyl triazole bisphosphonates, **15** and **19** respectively, have been synthesized as single olefin isomers via click chemistry. In order to avoid an allylic azide rearrangement that results in olefin isomerization, the C-2 olefin was protected as an epoxide and then reduced to the olefin after the click reaction. The deoxygenation proceeded smoothly upon treatment with NaI and TFAA, and the olefin regenerated after removal of the epoxide was a single isomer of the same geometry present in the original allylic alcohol. While compounds **15** and **19** did not have potent biological activity, these syntheses not only broaden the substrate scope of the original report⁹ on deoxygenation beyond epoxides with no additional functionality, but they also illustrate the stability of remote olefins to these reaction conditions. The insight gained from this work can be applied in the synthesis of similar compounds as well as in other uses of an epoxide as an olefin protecting group. For example, synthetic strategies including olefin metathesis have become common in organic chemistry, and recent examples conducted in the presence of a remote epoxide can be found based on cross metathesis with electron deficient olefins,¹⁷ ring-closing olefin metathesis,^{18,19} and ene-yne metathesis.²⁰ Given the ability to regenerate an olefin from an epoxide in the presence of additional olefins while preserving their stereochemistry, one can easily imagine application through sequences involving epoxidation, metathesis, and conversion of the epoxide back to an olefin.

Supplementary Material

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Figure 1.
Isoprenoid triazole bisphosphonates that inhibit GGDPS.

Scheme 1.
Synthesis of racemic epoxide **5**.

Scheme 2.
Synthesis of racemic epoxide **10**.

Scheme 3.
Synthesis of triazole bisphosphonates.

Table 1

Enzyme and cellular assay data.

Compound	GGDPS IC ₅₀ (μM)	FDPS IC ₅₀ (μM)	GGTase II IC ₅₀ (μM)	Cellular activity at 100 μM [*]
15	40	58	1000	None
19	123	103	>1000	None

* Cellular activity was assessed by immunoblot analysis for unmodified Rap1a and Rab6 (SI) as well as intracellular light chain levels (data not shown).