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Preparation of Aromatic Farnesol Analogues via a Cu(I)-Mediated Grignard Coupling of THP Ethers

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Abstract: A Cu(I)-mediated reaction of aromatic Grignard reagents with allylic tetrahydropyranyl ethers results in formation of the coupled products in good yields. This methodology allows facile synthetic manipulation of compounds with two reactive allylic positions.

Mammalian *ras* genes encode guanosine triphosphate-binding proteins that play an essential role in the signal transduction pathways which regulate cell proliferation.[1-4] Mutations in RAS proteins are associated with approximately 30% of all human cancers[1] and the demonstration that RAS farnesylation is essential for RAS-induced cellular transformations has aroused an intense interest in farnesyl pyrophosphate analogues as potential chemotherapeutic agents.[5-7] Most of these compounds have been designed with similar terpenoid "tails" and variations limited to mimics of the polar diphosphate "heads".[8-13] The recent publication of a crystal structure for farnesyl protein transferase (FPTase),[14] the enzyme that catalyzes reaction of farnesyl pyrophosphate with RAS, revealed a hydrophobic pocket lined with ten aromatic amino acids that presumably accepts the terpenoid chain. The crystal data lends credibility to the design of novel farnesyl "tails" incorporating aromatic rings, compounds that may illuminate the importance of non-bonding interactions in recognition of the farnesyl chain.[15] Synthesis of such compounds could be approached through displacement of an allylic leaving group by an aromatic nucleophile, but constructing farnesol analogues (e.g. **1**) would require reaction at one allylic position of a geraniol derivative (**2**) in the presence of a second functional group that also might be displaced. One solution to this problem is the subject of this report.

1 **2**

Selenium dioxide is routinely employed for oxidation of terminal prenyl units at the E methyl group.[16] For example, oxidation of geranyl acetate (**3**) with SeO_2 gives the alcohol **4**, and this compound has been converted to the corresponding bromide **5** by reaction with NBS/DMS.[17] Treatment of compound **5** with phenyl magnesium bromide in

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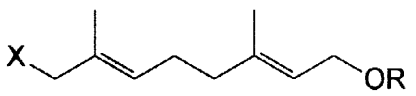
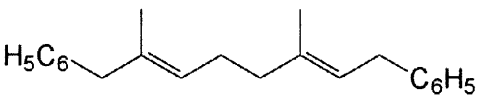
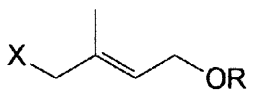
the presence of CuI revealed that both the bromide and the acetate were displaced at roughly equivalent rates to give the diaryl compound **6**. Converting acetate **5** to the corresponding alcohol (**7**) also proved difficult. Attempted hydrolysis by treatment with KOH/MeOH[18] gave primarily the methyl ether **8** while reductive cleavage of the acetate was accompanied by reduction of the allylic bromide. An alternative strategy, utilizing a different geraniol protecting group prior to the SeO_2 oxidation, was limited by the impact of many potential protecting groups on the yield of the oxidation step.[16] However, compound **9** was prepared by reaction of the THP ether derived from geraniol with SeO_2 and subsequent reaction with acetic anhydride. Attempted use of compound **9** in a coupling reaction with C_6H_5MgBr initially was disappointing because again both the THP and acetate groups were displaced under mild conditions. However, this unexpectedly facile displacement[19] of the THP ether suggested an alternate reaction sequence that did allow the desired Grignard coupling.



3 X = H R = Ac
4 X = OH R = Ac
5 X = Br R = Ac
7 X = Br R = H
8 X = OCH_3 R = H
9 X = OAc R = THP
10 X = OTHP R = Ac
11 X = OTHP R = H

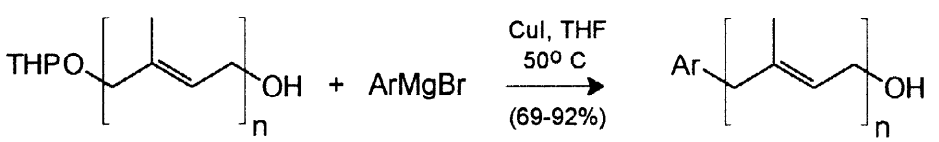


6



12 X = H R = Ac
13 X = OH R = Ac
14 X = OTHP R = Ac
15 X = OTHP R = H

The known THP ether **10**[20] was prepared in quantitative yield by reaction of dihydropyran with the product (**4**) of selenium dioxide oxidation of geranyl acetate. As expected, no problems were encountered cleaving the acetate **10** to the alcohol **11** by reduction or hydrolysis in the presence of the THP-protected allylic alcohol. A parallel series of reactions was used to convert prenyl acetate (**12**) to the known alcohol **13**, and then to the desired THP ethers **14** and **15**.[21] Both compounds **11** and **15** were examined in Grignard coupling reactions with several different organometallic

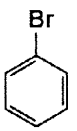
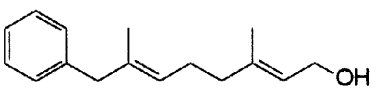
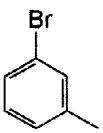
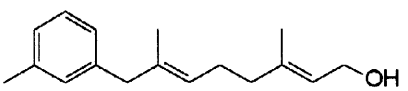
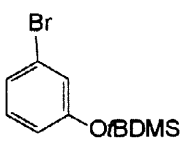
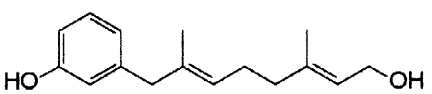
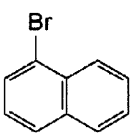
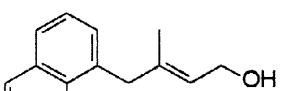
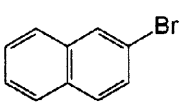
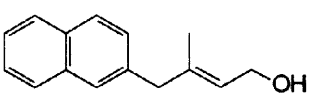
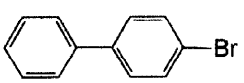
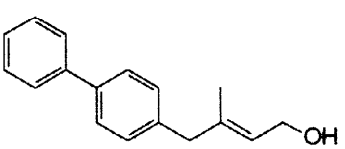


11 n = 2; **15** n = 1 **16-21**

species and all pairings provided efficient coupling (Table 1). When compound **11** was treated with an excess of the reagents derived from bromobenzene or *m*-bromotoluene, the coupled products **16** and **17** were obtained in high yield. With the tBDMS-protected *m*-bromophenol, coupling also proceeds smoothly, and treatment of the initial product with TBAF gave the phenol **18** in 92% overall yield. Coupling of the smaller THP ether **15** was examined with larger naphthyl and biphenyl reagents to obtain coupled products approximating the length of the farnesyl chain. In this series, the desired compounds (**19**, **20**, and **21**) were always the major reaction products and each was obtained in good yield, but in all three cases a small amount of S_N2' coupling was observed. The S_N2 and S_N2' products were

readily separable by column chromatography and easily identified by their ^{1}H NMR spectra. Presumably, the larger terpenoid chain of compound **11** provides sufficient steric hindrance to minimize S_N2' coupling in that series.[19a]

Table 1. Cu(I)-Mediated Grignard Couplings with THP Ethers.[22]

entry	substrate	aryl halide	product	yield
1	**11**		 **16**	81%
2	**11**		 **17**	91%
3	**11**		 **18**	92%
4	**15**		 **19**	69% (12%)[a]
5	**15**		 **20**	75% (16%)[a]
6	**15**		 **21**	77% (15%)[a]

a) Yield of the S_N2' product.

In conclusion, the displacement of THP ethers in Cu(I)-mediated Grignard reactions is an effective strategy for coupling aromatic compounds with allylic alcohols. While the basis of the special reactivity of the THP group is not completely clear, a simple comparison of parallel reactions showed that the THP derivative of geraniol undergoes this displacement at least 10-fold faster than the corresponding methyl or phenyl ethers. Because allylic THP ethers can be prepared in high yields from allylic alcohols, and are more stable to many conditions than the corresponding allylic halides, it is possible to view this moiety as both a protecting group and

a reactive center. Further studies on the scope of Cu(I)-mediated THP displacements, as well as on the biological activity of these farnesol analogues, will be reported in due course.

ACKNOWLEDGMENTS

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