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Application of benzyl protecting groups in the synthesis of prenylated aromatic compounds

Sina I. Odejinmi and David F. Wiemer*

Department of Chemistry, University of Iowa, Iowa City, IA 52242-1294, USA

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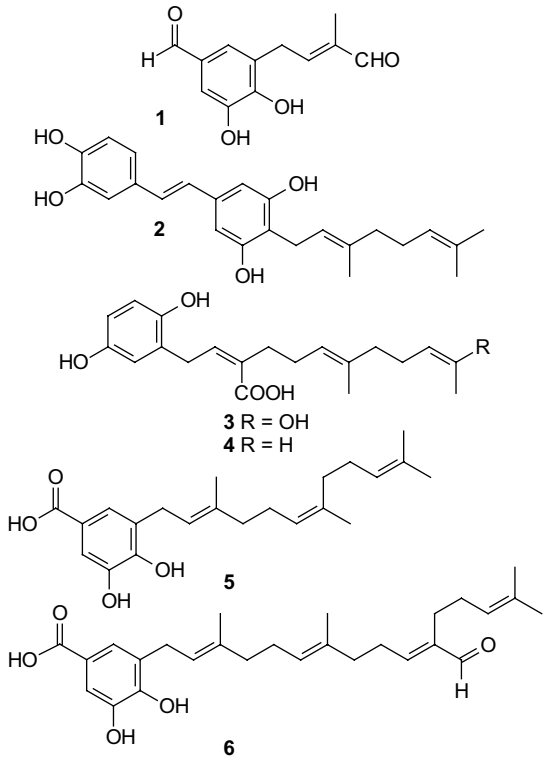
Abstract—Benzyl ethers have proven to be useful protecting groups for synthesis of phenols bearing isoprenoid chains because the benzyl groups can tolerate the conditions of halogen–metal exchange used to introduce the side chains yet are cleaved in good yields upon treatment with sodium *s*-butanol.

Prenylated aromatic compounds often have been found as natural products, and they have displayed a wide range of biological activities. Various compounds have shown antiviral, anticancer,[1] antimicrobial,[2,3] and antifungal properties.[4] Others have been reported to function as insect repellents,[5] immunosuppressive agents,[6] and opioid receptor modulators.[7] Representative examples, illustrating isoprenoid chains of different lengths and varied oxidation patterns, include montadial (**1**),[8] pawhuskin C (**2**)[7] the ganomycins (**3**, **4**),[3] piperoic acid (**5**)[9] and arieianal (**6**).[10]

Recently we have become interested in the synthesis of prenylated aromatic compounds because of their interesting structures and novel bioactivities.[11] One feature common to both the compounds we have targeted and many others is the presence of at least one phenolic group on the aromatic ring *ortho* to the isoprenoid substituent. In addition, functionality such as phenol or hydroxyl groups, aldehydes, and/or carboxylic acids commonly can be found on the aromatic ring and/or the isoprenoid chain. Thus while there are many strategies that can be employed to attach an isoprenoid chain to an aromatic ring, these generally require phenol protection and the protection/deprotection strategy must be compatible with other functional groups found on the ring and on the side chain.

Many different protecting groups might be employed for phenol protection,[12] but the abundance of functionality encountered in these systems and the demanding conditions often employed to attach the isoprenoid chain



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* Corresponding author. Tel.: +1 319 335 1365; fax: +1 319 335 1270; e-mail: david-wiemer@uiowa.edu

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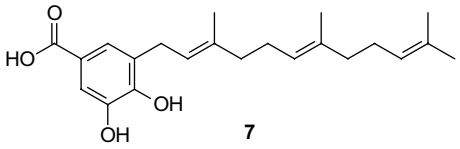
make this a delicate choice. If the side chain is attached via an intermediate anion, the chosen protecting groups must endure conditions for directed *ortho* metallation or halogenation followed by halogen–metal exchange. Conditions required for these reactions limit use of phenolic silyl ethers because they may undergo a Brook rearrangement and esters which might be halogenated or deprotonated. Further limitations arise because deprotection must be conducted in the presence of the olefins of a terpenoid side chain. This limits use of strongly acidic reagents as a means of deprotection because undesired cyclized products might result from cyclization via addition of the phenolic group to the side chain olefin(s).[13] Benzyl ethers are attractive in many ways, but cleavage by catalytic hydrogenolysis can be problematic because simple olefins may undergo hydrogenation under these reaction conditions.[14,15] The cleavage of phenolic benzyl ethers was explored during the course of our efforts to prepare two prenylated aromatic compounds, and is the subject of this report.

Our two initial targets were montadial A (**1**) and the *E*,*E*-isomer of piperoic acid, compound **7**. Montadial A was isolated from the white rot fungus *Bondarzewia montana* that grows at the base of the Abies tree and other conifers, and has been reported to have significant activity against lymphocytic leukemia of mice as well as promyelocytic human leukemia.[8] Piperoic acid (**5**) was isolated during the course of our own studies of plant defense against insects and fungi, and incorporates the *E*,*Z*-olefin stereochemistry. For this study we chose to target the *E*,*E*-isomer **7** based on the assumption that it could be derived from commercial *E*,*E*-farnesyl bromide.



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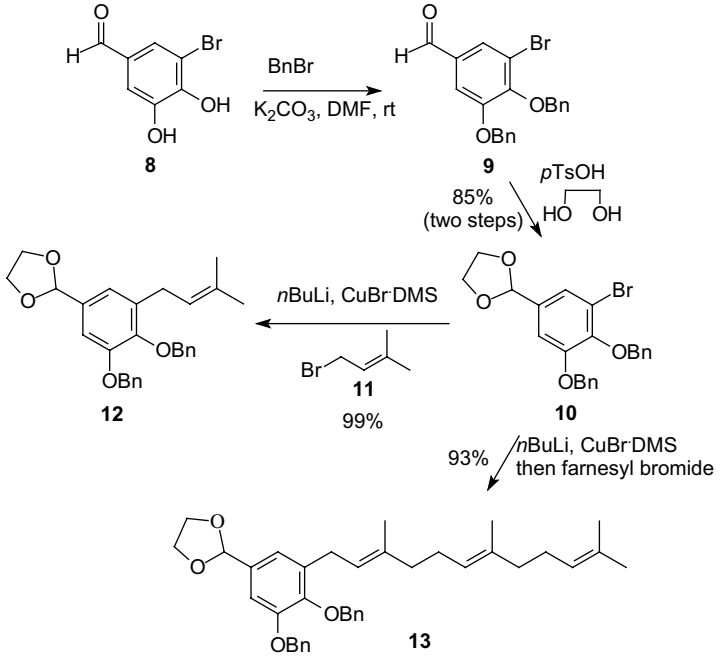
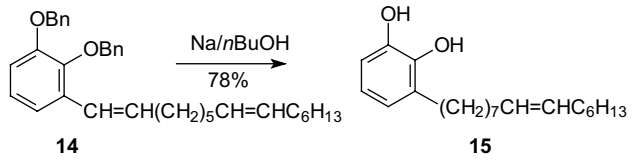
Synthesis of the two prenylated aromatic skeletons is shown in Scheme 1. The known catechol **8** was protected as its benzyl ether[16] and the resulting aldehyde **9** then was converted to the acetal **10**. Direct coupling of the organolithium reagent derived from compound **10** with prenyl bromide (**11**) in THF was not attractive because significant decomposition was observed after the addition of *n*BuLi. Reaction temperatures from room temperature to −78 °C were explored without significant success. However, when a mixture of benzene and ether was used as the solvent for the halogen metal exchange and CuBr was added as its dimethyl sulfide complex (CuBr·DMS), reaction with prenyl bromide **8** was nearly quantitative. In a similar fashion, reaction of compound **10** with *n*BuLi and farnesyl bromide, in the presence of CuBr·DMS, gave the desired product **13** in very good yield.[17]

Cleavage of the benzyl ethers of compound **13** was attempted by catalytic hydrogenolysis over Pd/C but reduction of the olefins proved to be more facile.[14,15] A second possibility for removal of the benzyl protecting groups was suggested by an early report that described deprotection of aromatic benzyl ethers during synthesis of alkyl and alkenyl phenols (e.g. Scheme 2).[18] In those investigations, compound **14** was treated with metallic



Scheme 1.



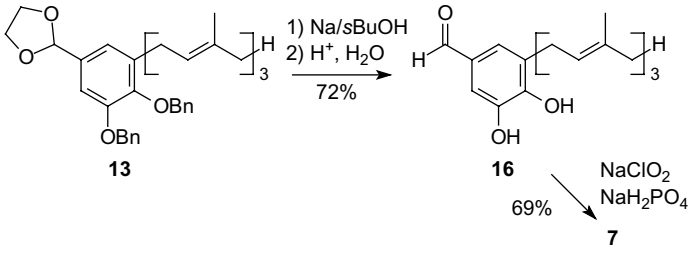
Scheme 2.

sodium in *n*-butanol to obtain catechol **15**, where two benzyl ethers were cleaved and the conjugated olefin was reduced but the isolated olefin was not affected.[18b] Given the reduction of the conjugated olefin, the authors assumed reductive cleavage of the benzyl ether as well. Even if an exact mechanism is not entirely clear, the fact that an isolated olefin survived these conditions suggested that deprotection of compounds **12** and **13** under similar conditions might be viable.

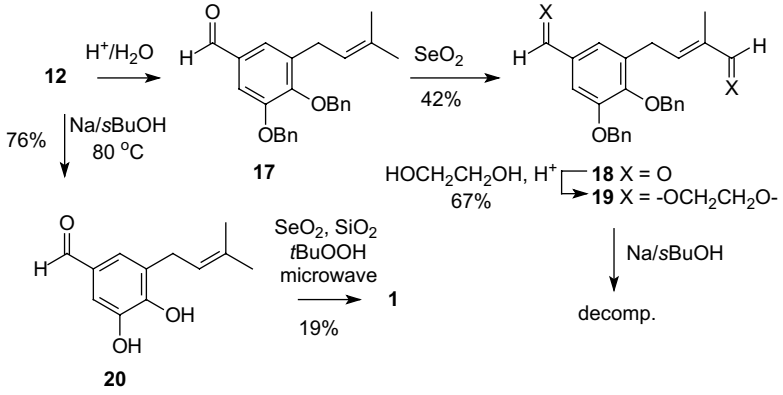
While the original literature procedure described piecemeal addition of metallic Na to a hot solution of compound **14**, this appeared unwise because the subsequent reaction is exothermic. Instead, after addition of sodium metal to a solution of acetal **13** in *s*BuOH at room temperature, the reaction mixture was heated to 80 °C for 2 h and the desired aldehyde **16** was obtained in good yield after work-up with aqueous acid.[19] It was apparent from the NMR spectra[19] of the product that the olefins of the farnesyl side chain survived these reaction conditions. Final oxidation of the aldehyde **16** with sodium chlorite gave the desired carboxylic acid **7**[20] (Scheme 3).

A reasonable mechanism for cleavage of the benzyl protecting groups under these conditions would involve nucleophilic attack of *s*BuONa at the benzylic carbon of each benzyl ether. This is similar to the regioselective cleavage of a methylenedioxy ring through reaction with sodium alkoxides in dipolar aprotic solvents,[16] but may be more facile because attack occurs at an activated (i.e. benzylic) position. However, the reductive process suggested earlier[18] might also be involved.

A similar strategy was used to prepare the natural product montadial A (Scheme 4). In this case, after hydrolysis of the acetal **12** to the corresponding aldehyde **17**, oxidation with SeO_2 proceeded as expected to afford the dialdehyde **18** in moderate yield. Standard reaction with ethylene glycol in the presence of *p*TsOH gave the desired acetal **19**, but attempted cleavage of the benzyl ethers gave only decomposition. As an alternate strategy, the acetal **12** first was treated with Na/*s*BuOH to afford the aldehyde **20** after work-up with aqueous acetic acid. To complete the synthesis of montadial A, the aliphatic aldehyde was introduced through reaction of compound **20** with SeO_2 and *t*BuOOH on silica gel under brief microwave irradiation.[21] This procedure gave the desired product in low yield, perhaps because of the sensitivity of the aromatic aldehyde and/or the catechol to further oxidation. However, the spectral data of the synthetic material were identical to that published for the natural product and the brevity of the reaction sequence compensates in some measure for the low yield of the final transformation.



Scheme 3.



Scheme 4.

In conclusion, benzyl ethers have proven to be useful protecting groups for synthesis of the prenylated aromatic compounds montadial A (**1**) and the piperoic acid isomer **7**. In both cases, benzyl ethers have proven stable to the process of halogen–metal exchange, which presumably involves an intermediate of considerable base strength, yet they are cleaved in good yield upon treatment with sodium in *s*BuOH. Application of this protecting group in synthesis of other more complex prenylated aromatic compounds will be reported in due course.

Acknowledgements

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17. Preparation of compound **13**. An oven-dried sample of compound **10** (3.40 g, 7.72 mmol) was dissolved in hot benzene (10 mL), the resulting solution was allowed to cool to room temperature, and anhydrous ether (20 mL) and molecular sieves were added. After addition of *n*BuLi (3.50 mL, 2.30 M in hexanes, 8.05 mmol), the reaction mixture was stirred for 5 min and then solid CuBr·DMS (791 mg, 3.85 mmol) was added. (CAUTION: This reaction is exothermic and on a larger scale should be moderated with a water bath.) The reaction mixture was allowed to stir for 30 min and then farnesyl bromide was added. After the reaction mixture was stirred for 4.5 h, it was quenched by addition of saturated NH_4Cl (20 mL). The aqueous layer was extracted with ether, washed with brine, dried ($MgSO_4$), and then concentrated in vacuo. The initial oil was purified by flash chromatography to afford compound **13** (1.81 g, 93%) as a clear light yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.47–7.25 (m, 10H), 7.04 (d, J = 1.8 Hz, 1H), 6.93 (d, J = 1.9 Hz, 1H), 5.72 (s, 1H), 5.26 (m, 1H), 5.13–5.05 (m, 4H), 4.99 (s, 2H), 4.14–3.98 (m, 4H), 3.35 (d, J = 7.1 Hz, 2H), 2.12–1.94 (m, 8H), 1.71 (s, 3H), 1.67 (s, 3H), 1.58 (s, 6H); ^{13}C NMR δ 152.2, 147.2, 138.1, 137.2, 136.4, 136.3, 135.2, 133.4, 131.4, 128.7–127.7 (10C), 124.6, 124.4, 122.8, 120.7, 109.8, 103.9, 74.9, 71.1, 65.5 (2C), 40.0 (2C), 28.7, 27.0, 26.9, 25.9, 17.9, 16.5, 16.2; HRMS (EI) *m*/*z* calcd for $C_{38}H_{46}O_4$ $(M)^+$ 566.3396, found 566.3399.
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19. Representative procedure. Sodium metal (102 mg, 4.44 mmol) was added to a solution of acetal **13** (100 mg, 0.178 mmol) in anhydrous *s*BuOH (2.0 mL) at room temperature. The resulting mixture was heated to 76 °C until all the solids were dissolved completely and reaction mixture was stirred for 2 h at 76–80 °C. The reaction was quenched by addition of aqueous AcOH (20%, 2.0 mL). After hexane was added to this mixture, it was heated at reflux and the aqueous layer was removed with a Dean Stark trap overnight. The organic layer then was filtered and concentrated in vacuo. The crude product was purified by flash chromatography (3:1 hexane:EtOAc) to yield compound **16** (44 mg, 72%): ^{1}H NMR ($CDCl_3$) δ 9.75 (s, 1H), 7.38 (d, J = 1.8 Hz, 1H), 7.26 (d, J = 1.2 Hz, 1H), 5.35 (t, J = 6.2 Hz, 1H), 5.10–5.05 9 (m, 2H), 3.44 (d, J = 7.2 Hz, 2H), 2.19–1.98 (m, 8H), 1.80 (s, 3H), 1.67 (s, 3H), 1.62 (s, 3H), 1.60 (s, 3H); ^{13}C δ 192.2, 149.1, 144.4, 139.4, 135.9, 131.7, 129.5, 128.1, 126.8, 124.5, 123.9, 121.0, 112.7, 40.0 (2C), 29.1, 27.0, 26.9, 25.9, 17.9, 16.5, 16.3.
20. For the carboxylic acid **7**: ^{1}H NMR ($CDCl_3$) ^{1}H NMR δ 7.52 (d, J = 1.7 Hz, 1H), 7.5 (d, J = 1.7 Hz, 1H), 5.34 (t, J = 6.2, 1H), 5.10–5.06 (m, 2H), 3.41 (d, J = 3.41, 2H), 2.14–1.97 (m, 8H), 1.78 (s, 3H), 1.67 (s, 3H), 1.60 (s, 6H); ^{13}C δ 172.3, 148.0, 143.5, 139.2, 135.9, 131.6, 127.7, 125.1, 124.6, 123.9, 121.2, 121.1, 115.2, 39.9, 29.4, 26.9, 26.6, 25.9, 21.1, 17.9, 16.5, 16.3. HRMS (EI) *m*/*z* calcd for $C_{22}H_{30}O_4$ $(M)^+$ 358.2144, found 358.2151.
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