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Total synthesis of pawhuskin C: a directed *ortho* metalation approach

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Abstract—The total synthesis of the opioid modulator pawhuskin C has been accomplished in eight steps from methyl 3,5-dihydroxybenzoate. The key step in this sequence is a directed *ortho* metalation reaction conducted without protection of a benzylic alcohol and thus presumed to involve a formal dianion intermediate.

Earlier this year, Belofsky et al. reported isolation of a small set of natural opioid receptor modulators named pawhuskin A–C (**1**–**3**, Fig. 1) from *Dalea purpurea*,[1] a plant once used by Plains Indians in North America. These compounds are prenylated stilbenes and as such display structural similiarity to the schweinfurthins, a family of natural products with anticancer activity.[2] Indeed pawhuskin C (**3**) includes a geranylated resorcinol also found in three of the natural schweinfurthins as well as the synthetic analogue 3-deoxyschweinfurthin B (**4**, Fig. 2).[3] As an initial step toward the pawhuskin family of natural products, the phosphonate **5** was identified as a synthon for the right half of compound **3**. A first generation synthesis of phosphonate **5** was disclosed in connection with the total synthesis of schweinfurthin C,[4] and allowed use of a late stage Horner–Wadworth–Emmons (HWE) condensation to establish the central

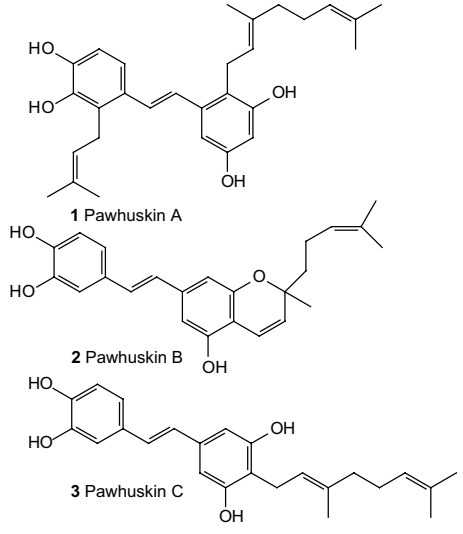

Figure 1. The pawhuskins.

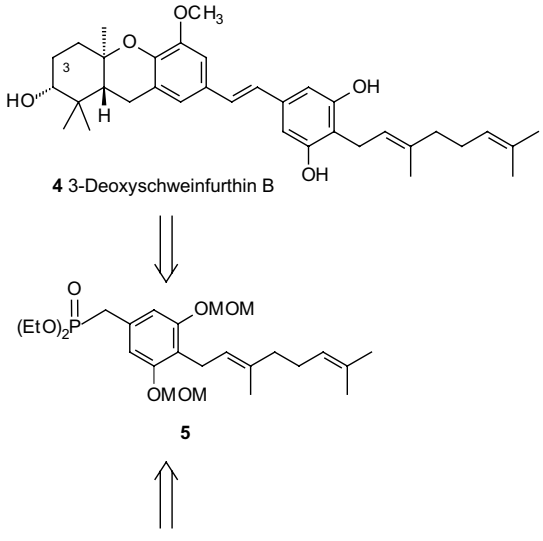

Figure 2. Retrosynthetic analysis.

Keywords: Pawhuskin; Directed *ortho* metalation.
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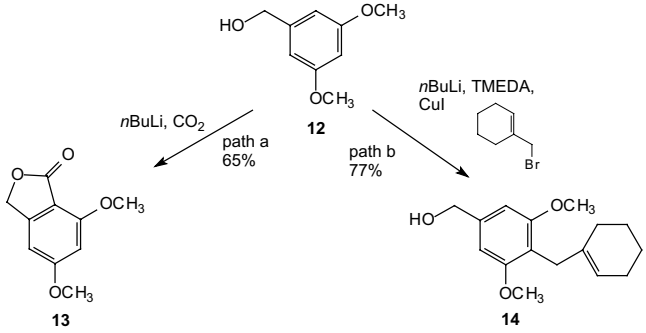
stilbene olefin. While a similar strategy might be used to prepare pawhuskin C, a more efficient synthesis of the phosphonate intermediate **5** would make this route more attractive.

The initial route to phosphonate **5** (Scheme 1) commenced with the commercial resorcinol **6**. The resorcinol hydroxyl groups were protected as methoxymethyl (MOM) ethers followed by reduction of the ester to give benzylic alcohol **7**. Protection of the benzylic alcohol as a silyl ether gave arene **8**. This compound was subjected to directed *ortho* metalation (D*o*M) conditions followed by lithium–copper exchange and alkylation to install the geranyl chain and set the entire carbon skeleton for the right half of pawhuskin C in silyl ether **9**. Removal of the silyl ether and functional group manipulation at the benzylic position afforded the required phosphonate **5** in eight steps and 34% overall yield from ester **6**.

This series of reactions gives access to the desired reagent **5**, but a more efficient synthesis would be attractive.[5] Studies by several groups[6] suggested that this route could be improved through use of D*o*M methodology to generate a formal dianion. Specifically, if the bis-MOM ether **7** could be regioselectively metalated at the C-4 position without introduction of the silyl ether protecting group, both the silylation and the later deprotection could be avoided. There is some literature precedent, which suggested that a selective D*o*M reaction could be accomplished. Treatment of the dimethoxy compound **12** with *n*BuLi in hexanes affords the product of metalation at the C-2 position, compound **13** (Scheme 2, path a),[7] whereas use of *n*BuLi with TMEDA and lithium–copper exchange gives the product where metalation has been directed to the C-4 position **14** (path b).[8]

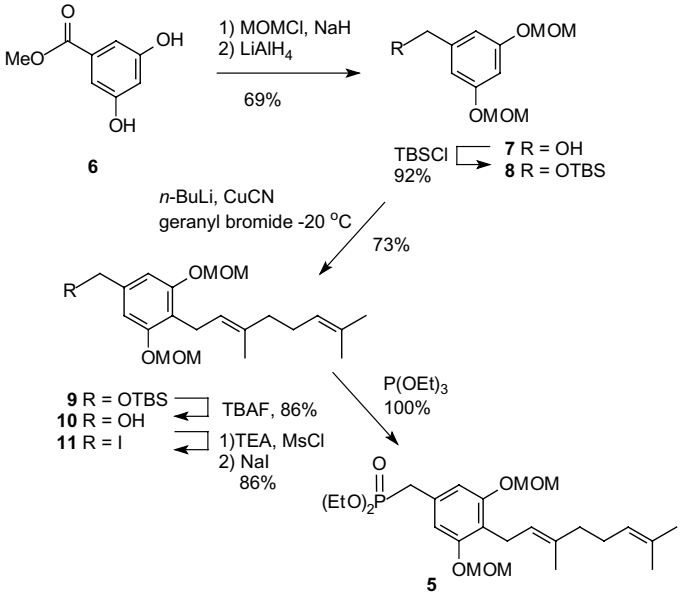
It might be possible to alkylate the dimethoxy compound **12** with geranyl bromide, and subsequently cleave the methyl ethers to phenols. However, we chose



Scheme 2.

instead to explore alkylation of the protected resorcinol **7** because the MOM ethers would be easier to remove. After some experimentation (Table 1), it was found that reaction of the MOM protected resorcinol **7** with *s*BuLi and TMEDA, followed by treatment with copper bromide–dimethyl sulfide and geranyl bromide at −20 °C, gave the alkylated benzylic alcohol **10** in yields comparable to those observed with the protected analogue **8** (Scheme 3).[10] This route allows access to the phosphonate **5** in just six steps and 37% yield. This represents several improvements over the first generation route, notably in the removal of a protection/deprotection sequence. This strategy saves significant time and effort, while also allowing use of the less toxic CuBr reagent in place of the CuCN used in the first generation approach.

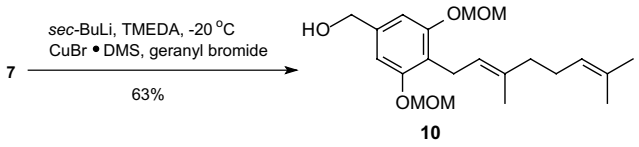
To complete the synthesis of pawhuskin C, the known benzaldehyde **15**[9] (Scheme 4) was treated with phosphonate **5** and sodium hydride in the presence of catalytic 15-crown-5 to initiate an HWE condensation and afford the stilbene **16** in good yield.[11] This stilbene bearing four MOM protecting groups was subjected to acidic hydro-



Scheme 1.

Table 1. Conditions explored for dianion D*o*M reaction of arene **7** and geranyl bromide (RX) in the presence of TMEDA (2 equiv)

Trial	Base, equiv, addition *T*	CuBr·DMS (equiv, *T*)	Addition *T* for RX	Yield (%)
1	*n*BuLi, 2.5 equiv, −20 °C	—	−78 °C	NR
2	*n*BuLi, 2.5 equiv, −20 °C	2.0 equiv, −20 °C	−78 °C	NR
3	KH (excess), *n*BuLi, 3.3 equiv, −78 °C	—	−78 °C	NR
4	KH (excess), *n*BuLi, 2.7 equiv, −20 °C	—	−78 °C	13
5	KH (excess), *n*BuLi, 3.0 equiv, −20 °C	—	−20 °C	17
6	KH (excess), *n*BuLi, 3.0 equiv, −20 °C	2.0 equiv, −20 °C	−20 °C	41
7	*n*BuLi, 3.3 equiv, −20 °C	2.0 equiv, −20 °C	−20 °C	57
8	*s*BuLi, 2.4 equiv, −20 °C	2.0 equiv, −20 °C	−20 °C	63



Scheme 3.

lysis with camphorsulfonic acid (CSA) to give the natural product pawhuskin C (**3**) in moderate yield.[12] The synthetic material was identical to the natural product in all respects including ^{1}H and ^{13}C NMR as well as TLC comparison with an authentic sample ($R_r = 0.10$ in 2:1 hexanes/ethyl acetate).

The current studies confirm the structure of the natural product pawhuskin C through total synthesis, and expand the utility of the dianion D*o*M type approach in alkylation of suitably functionalized benzylic alcohols. Through elimination of two steps from the previous synthetic sequence to phosphonate **5**, this route facilitates the large scale access to this phosphonate and advances efforts directed at synthesis of other pawhuskin or schweinfurthin analogues. This phosphonate also can be used in synthetic and medicinal chemistry efforts aimed at other prenylated or geranylated stilbenes. The current effort required just eight steps to achieve the synthesis of the opioid modulator pawhuskin C in 15% overall yield, and provides an excellent example of this potential. Further work in these areas will be disclosed in due course.

Acknowledgements

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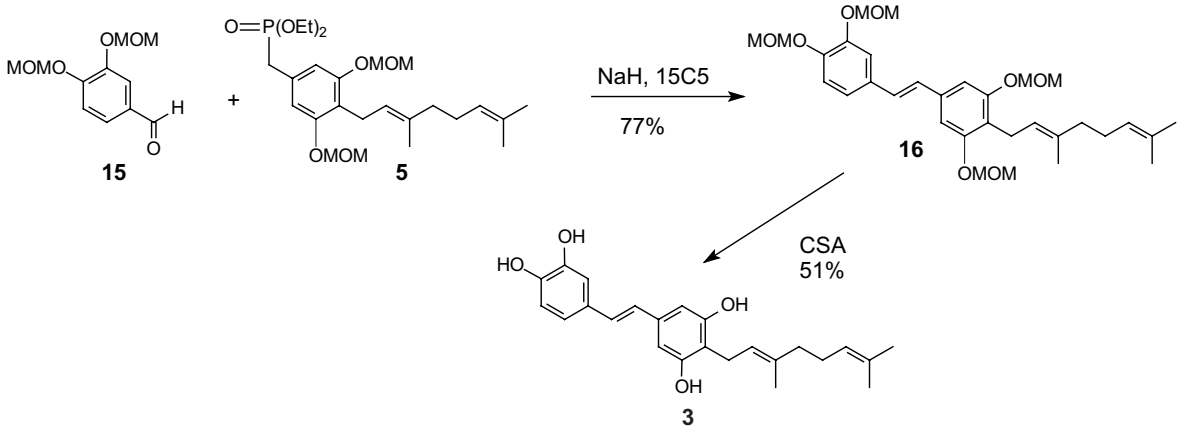

Scheme 4.

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10. [4-(3,7-Dimethyl-octa-2,6-dienyl)-3,5-dimethoxymethoxy-phenyl]-methanol (**10**). *sec*-BuLi (8.0 mL, 1.00 M in hexanes) was added dropwise to a solution of benzylic alcohol **7** (772 mg, 3.37 mmol) and TMEDA (1.10 mL, 7.28 mmol) in THF (20 mL) at −20 °C. After this solution was stirred for 1 h at −20 °C, CuBr as its DMS complex (1.39 mg, 6.76 mmol) was added in one portion and the mixture was stirred for 1 h at −20 °C. Geranyl bromide (0.75 mL, 3.77 mmol) was added dropwise and the reaction mixture was stirred for 2 h at −20 °C. The reaction was quenched by addition of 1 N NH_4Cl, the aqueous layer was neutralized to pH 7 with 1 N HCl, and then was extracted with EtOAc. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. Final purification by flash column chromatography (40% EtOAc in hexanes) afforded compound **10**[4] (773 mg, 63%) as a clear yellow oil.
11. Tetra-MOM ether **16**. A suspension of NaH (36 mg, 1.5 mmol) and 15-crown-5 (4 μL, 0.02 mmol) in THF (10 mL) was cooled to 0 °C. Aldehyde **15** (32 mg, 0.14 mmol) and phosphonate **5** (94 mg, 0.19 mmol) in THF (2 mL) were added, and the mixture was allowed to warm to rt and stirred for a total of 18 h. Water was added dropwise, and the solution was extracted with EtOAc. The resulting organic phase was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Final purification by column chromatography (4:1 hexanes/EtOAc) gave the stilbene **16** (60 mg, 77%) as a clear oil: ^{1}H NMR ($CDCl_3$) δ 7.33–7.32 (m, 1H), 7.15–7.08 (m, 2H), 7.03–6.88 (m, 4H), 5.28 (s, 2H), 5.24 (s, 2H), 5.23 (s, 4H), 5.22–5.19 (m, 1H), 5.11–5.04 (m, 1H), 3.56 (s, 3H), 3.53 (s, 3H), 3.50 (s, 6H), 3.40 (d, J = 7.2 Hz, 2H), 2.08–2.01 (m, 2H), 1.98–1.93 (m, 2H), 1.79 (s, 3H), 1.64 (s, 3H), 1.57 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.9 (2C), 147.4, 146.8, 136.4, 134.6, 132.2, 131.2, 127.7, 127.7, 124.4, 122.6, 121.0, 119.8, 116.6, 114.3, 106.1 (2C), 95.4, 95.4, 94.5 (2C), 56.2, 56.2, 56.0 (2C), 39.8, 26.7, 25.6, 22.7, 17.6, 16.1; HRMS calcd for $C_{32}H_{45}O_8$ $(M+H)^+$ 557.3114, found 557.3130.
12. Pawhuskin C (**3**). To a solution of stilbene **16** (60 mg, 0.11 mmol) in MeOH (10 mL) was added a catalytic amount of camphorsulfonic acid, and the resulting solution was stirred at rt for 24 h. The reaction was quenched by addition of satd $NaHCO_3$, extracted with ethyl acetate, and the organic phase was washed with brine and dried ($MgSO_4$). Concentration in vacuo, followed by final purification by column chromatography (1:1, hexanes/ethyl acetate) afforded pawhuskin C (**3**, 21 mg, 51%) as a yellow solid: all spectral characteristics matched the published data.[1]