A Concise Synthesis of Pawhuskin A

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Pawhuskin A is an isoprenylated stilbene that was isolated from *Dalea purpurea* and reported to have affinity for the opioid receptor *in vitro*. It has been synthesized through a convergent sequence that joins a prenylated aldehyde with a geranylated phosphonate in a stereoselective Horner−Wadsworth−Emmons condensation to afford the target *E* olefin isomer. This synthesis confirms the structure assigned to the natural product and establishes a route that may be used to explore its biological activity and to prepare more active analogues.

Early in 2004, Belofsky and co-workers reported the isolation of several compounds from *Dalea purpurea*, including three new isoprenylated stilbenes that they named pawhuskins A−C (Figure 1, **1**−**3**).[1] These three compounds were shown to have affinity for the opioid receptor in bioassays that quantified displacement of ^{3}H-naloxone from a preparation of rat striatal tissue that included the α, κ, and μ receptors.[2] Our earlier work on synthesis of the schweinfurthins,[3] also doubly prenylated stilbenes, allowed a rapid synthesis of pawhuskin C.[4] Because it bears an acyclic isoprenoid substituent on just one of the arene rings, pawhuskin C can be viewed as the simplest member of its family. However, pawhuskin A is the most active with respect to opioid receptor binding, and its substitution pattern differs from that of pawhuskin C or the natural[5,6] (e.g., **4** or **5**) or synthetic[3,7] schweinfurthins.

Within the past few years, it has been recognized that non-nitrogenous compounds can bind at the opioid receptors and demonstrate activity or block the binding of active agents.[8] The diterpenoid salvinorin A[9] was found to be a κ selective agonist, and then more recently the pawhuskins have been reported to bind at opioid receptors, although their specificity has not been established. Whether the pawhuskins bind at hitherto unrecognized sites or bind at known sites in these receptors is not yet clear, and whether they can serve as agonists or antagonists has not yet been determined. However, there are compelling needs for new analgesics for treatment of pain, as well as for compounds that block opiate binding for use in pharmacological interventions in cases of stimulant abuse.[10]

The combination of interesting biological activity and the need for different protocols for introduction of the isoprenoid substituents led to an interest in the preparation of this compound. In this paper, we report an efficient synthesis of pawhuskin A that confirms the structure assigned to the natural product and paves the way for exploration of structure−activity relationships.

Retrosynthesis of pawhuskin A (Figure 2) through disconnection of the central stilbene olefin to intermediates appropriate for Horner−Wadsworth−Emmons (HWE) condensation leads to either the aryl aldehyde **6** as the left half and a benzylic phosphonate **7** as the right half, which we chose to pursue, or to the opposite pairing. The aldehyde **6** could then be recognized in commercial 3,4-dihydroxybenzaldehyde (**8**), while the phosphonate **7** might be derived from commercial methyl 3,5-dihydroxybenzoate (**9**).

In a synthetic sense, preparation of the phosphonate appeared to require the longer sequence. Initially, conversion of ester **9** to the protected benzylic alcohol **10** was accomplished by variations on literature methods (Scheme 1).[11] After formation of the TBS ether

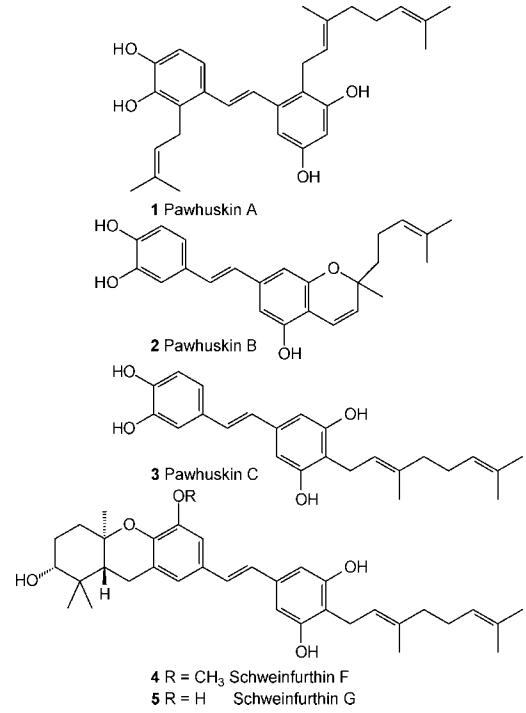

Figure 1. The natural pawhuskins and two related schweinfurthins.

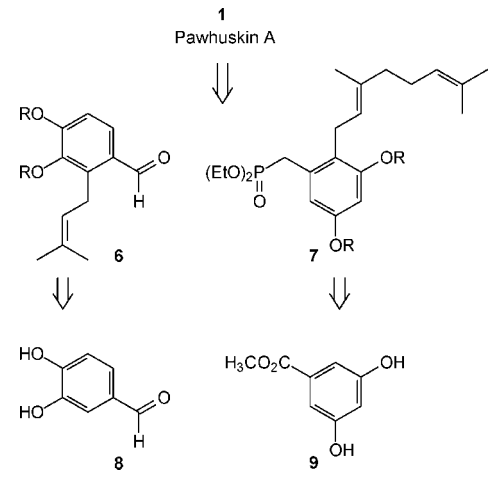

Figure 2. Retrosynthesis of pawhuskin A.

10, bromination with NBS provided the aryl bromide **11** in good yield.[12] Halogen−metal exchange and reaction with geranyl

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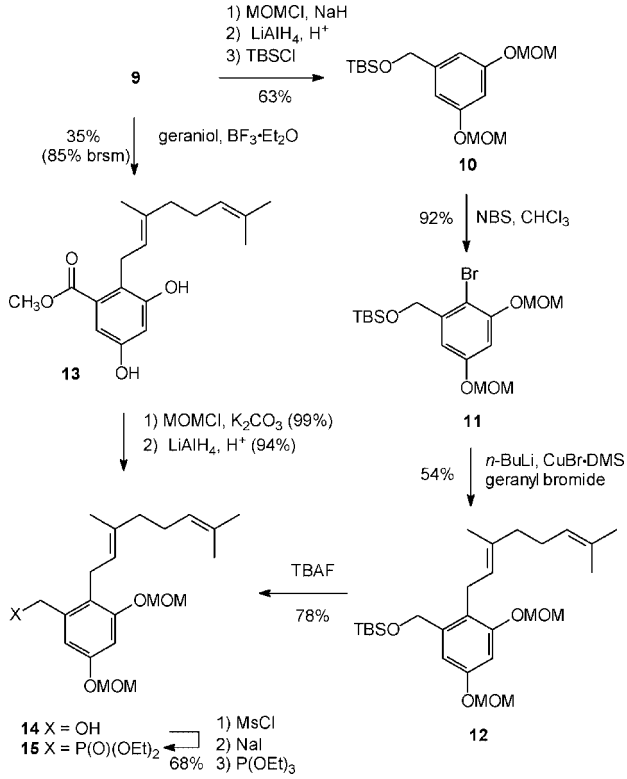
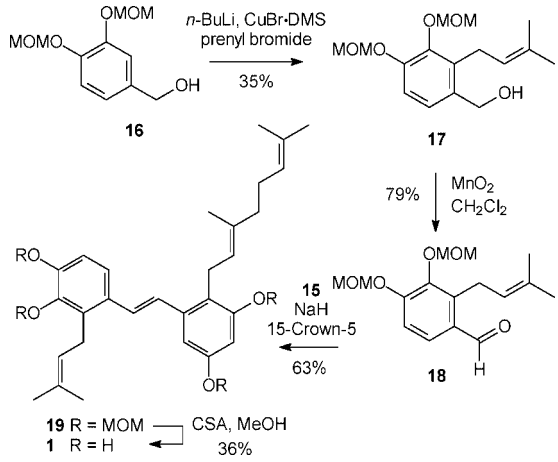
Scheme 1. Synthesis of Phosphonate **15**



Scheme 2. Synthesis of Pawhuskin A



bromide in the presence of CuBr·DMS gave the target carbon skeleton **12** in moderate yield, and treatment of this silyl ether with TBAF afforded the benzylic alcohol **14**. An alternate route to compound **14** through the resorcinol derivative **13** was explored and proved significantly more efficient. For this sequence the ester **9** was treated with geraniol and $BF_3 \cdot OEt_2$ to obtain the target carbon skeleton directly.[13] While the yield for this reaction was modest (35%), a substantial amount of the starting material was recovered and the yield based on recovered starting material was very attractive (85%). Subsequent introduction of the MOM groups and reduction with $LiAlH_4$ proceeded smoothly to afford the benzylic alcohol **14** in a very direct fashion. Conversion of alcohol **14** to the corresponding phosphonate **15** also proceeded smoothly through formation of the mesylate, displacement with NaI, and a final reaction with $P(OEt)_3$.

Synthesis of the complementary benzaldehyde required for the anticipated HWE condensation is shown in Scheme 2. Commercial 3,4-dihydroxybenzaldehyde (**8**) was readily converted to the MOM-protected benzyl alcohol **16**.[14] After treatment of this alcohol with excess *n*-BuLi to induce directed *ortho* metalation and CuBr·DMS, reaction with prenyl bromide afforded the substituted arene **17**. Oxidation of the benzylic alcohol **17** to the corresponding aldehyde **18** occurred readily upon treatment with MnO_2. The HWE condensation of aldehyde **18** and phosphonate **15** was straightforward, providing the *trans*-stilbene **19** with no trace of the isomeric *cis* product. Hydrolysis of the four MOM groups was accomplished with CSA in MeOH to afford pawhuskin A (**1**). While the yield for this last step is somewhat disappointing, it does reflect cleavage of four separate protecting groups and is consistent with yields observed in other such highly protected systems.[15] The final product gave ^1H and ^{13}C NMR data identical to those of the natural product.

In conclusion, the natural product pawhuskin A has been prepared by a convergent sequence ending in formation of the central stilbene and deprotection of the MOM groups. The required phosphonate intermediate **15** can be prepared in a straightforward fashion from the corresponding alcohol **14**. This key alcohol **14** was prepared through two different sequences, a more traditional approach that required six steps from commercial methyl 3,5-dihydroxybenzoate and gave the desired product in ~25% overall yield, and a new strategy that required only three steps and provided this key intermediate in ~33% overall yield (and almost 80% overall yield based on recovered starting material). By means of this new sequence, the synthesis reported here should provide sufficient material to explore the biological properties of pawhuskin A in more detail and allow synthesis of analogues for more extensive structure−activity relationship studies.

Experimental Section

General Experimental Procedures. Tetrahydrofuran (THF) and Et_2O were distilled from Na and benzophenone and used immediately, while CH_2Cl_2 was distilled from CaH_2. Anhydrous DMF was used directly without further purification. All nonaqueous reactions were done under an Ar atmosphere, in oven- or flame-dried glassware, and with magnetic stirring. Flash chromatography was done on silica gel with an average of 40−63 μm particle size. The ^1H and ^{13}C NMR spectra were recorded at 300 MHz with $CDCl_3$ as solvent and $(CH_3)_4Si$ as internal standard unless otherwise noted. High-resolution and electrospray (ES) mass spectra were obtained at the University of Iowa Mass Spectrometry Facility. The elemental analyses were conducted by Atlantic Microlab, Inc. (Norcross, GA).

Synthesis of Aryl Bromide 11. To a stirred solution of silyl ether **10**[15] (5.38 g, 15.7 mmol) in $CHCl_3$ was added NBS (2.82 g, 15.8 mmol) at room temperature, and the reaction was heated to reflux for 2 h and then allowed to cool to room temperature. The reaction mixture was quenched by addition of H_2O and extracted into $CHCl_3$. The combined organic layers were washed twice with H_2O, dried ($MgSO_4$), and concentrated *in vacuo* to afford a yellow oil. Final purification by flash chromatography (17% EtOAc in hexanes) gave aryl bromide **11** as a clear oil (6.06 g, 92%) having spectral properties identical to the known compound.[12]

***tert*-Butyl[{2-(2*E*-3,7-dimethyl-2,6-octadienyl)-3,5-bis(methoxymethoxy)benzyl}oxy]dimethylsilane (12).** To a solution of aryl bromide **11** (0.52 g, 1.31 mmol) in THF (10 mL) at −78 °C was added *n*-BuLi (0.60 mL, 1.44 mmol, 2.4 M hexanes), and the resulting solution was stirred for 1 h. After CuBr·DMS (0.30 g, 1.45 mmol) was added and the reaction was stirred for 30 min, geranyl bromide (0.29 mL, 1.45 mmol) was added and the reaction mixture was allowed to warm to room temperature and stirred for 10 h. The reaction was quenched by addition of saturated NH_4Cl and extracted with EtOAc, and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to afford a yellow oil. Final purification by column chromatography (8% to 18% EtOAc in hexanes) afforded the geranylated arene **12** (340 mg, 54%) as a clear oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 6.91 (d, J = 2.5 Hz, 1H), 6.71 (d, J = 2.6 Hz, 1H), 5.16 (s, 2H), 5.15 (s, 2H), 5.08−5.02 (m, 2H), 4.69 (s, 2H), 3.47 (s, 3H), 3.46 (s, 3H), 3.28 (d, J = 6.6 Hz, 2H), 2.08−1.93 (m, 4H), 1.76 (s, 3H), 1.65 (s, 3H), 1.57 (s, 3H), 0.95 (s, 9H), 0.09 (s, 6H); ^{13}C NMR δ 156.1, 155.3, 141.5, 134.6, 131.3, 124.2, 122.8, 120.8, 107.4, 102.0, 94.6, 94.6, 62.6, 56.0, 55.9, 39.7, 26.7, 25.9 (3C), 25.7, 23.9, 18.4, 17.6, 16.1, −5.3(2C); *anal*. C 67.95%, H 9.71%, calcd for $C_{27}H_{46}O_5Si$, C 67.74%, H 9.68%.

2-[(2*E*)-3,7-Dimethyl-2,6-octadienyl]-3,5-bis(methoxymethoxy-)benzyl Alcohol (13). The silyl ether **12** (107 mg, 0.23 mmol) was dissolved in THF (10 mL), and the solution was cooled to 0 °C. To this solution was added TBAF (0.26 mL, 1.00 M in THF), the reaction was allowed to warm to room temperature, and after 1.5 h it was quenched by addition of saturated NH_4Cl. After extraction with EtOAc, the combined organic extract was washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow oil. Final purification by flash chromatography (30% EtOAc in hexanes) gave the benzylic alcohol **13** (65 mg, 78%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.79 (d, J = 2.4 Hz, 1H), 6.76 (d, J = 2.4 Hz, 1H), 5.17 (s, 2H), 5.15 (s, 2H), 5.11−5.02 (m, 2H), 4.64 (s, 2H), 3.47 (s, 3H), 3.47 (s, 3H), 3.38 (d, J = 6.6 Hz, 2H), 2.08−1.94 (m, 4H), 1.77 (s, 3H), 1.65 (s, 3H), 1.57 (s, 3H); ^{13}C NMR δ 156.2, 155.9, 140.9, 135.1, 131.4, 124.1, 123.4, 122.4, 108.8, 103.0, 94.6, 94.6, 63.3, 56.0, 56.0, 39.7, 26.6, 25.6, 24.1, 17.6, 16.1; HRMS(FAB) calcd for $C_{21}H_{33}O_5$ $(M + H)^+$ 365.2328, found 365.2319.

Methyl 2-(3,7-Dimethylocta-2,6-dienyl)-3,5-dihydroxybenzoate (13). To a solution of benzoate **9** (4.00 g, 23.8 mmol) in dioxane (100 mL) was added $BF_3 \cdot OEt_2$ (1.2 mL, 9.5 mmol). The reaction was heated to 50 °C, and geraniol (2.08 mL, 11.9 mmol) in dioxane (20 mL) was added dropwise over 50 min. After the reaction was allowed to stir for an additional 2 h, it was poured into H_2O and extracted with Et_2O (300 mL). The combined organic fractions were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Final purification by flash column chromatography (25−35% EtOAc in hexanes) gave the geranylated compound **13** (1.27 g, 35%) as a light yellow oil as well as recovered benzoate **9** (2.35 g, 59%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.86 (d, J = 2.7 Hz, 1H), 6.53 (d, J = 2.7 Hz, 1H), 5.20 (t, J = 6.6 Hz, 1H), 5.07−5.00 (m, 1H), 4.83 (s, 2H), 3.86 (s, 3H), 3.59 (d, J = 6.5 Hz, 2H), 2.12−1.99 (m, 4H), 1.78 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H); ^{13}C NMR δ 169.1, 156.9, 154.9, 138.6, 132.34, 132.31, 124.1, 122.5, 120.5, 109.8, 107.5, 52.6, 40.0, 26.7, 26.1, 26.0, 18.0, 16.5; HRMS *m*/*z* 304.1675 (calcd for $C_{18}H_{24}O_4$, 304.1673).

Methyl2-(3,7-Dimethylocta-2,6-dienyl)-3,5-bis(methoxymethoxy)benzoate. To a solution of compound **13** (272 mg, 0.89 mmol) in acetone (50 mL) was added anhydrous K_2CO_3 (1.23 g, 8.94 mmol). After the reaction was allowed to stir for 15 min, MOMCl (0.34 mL, 4.47 mmol) was added and the solution was heated to 60 °C for 6 h. The reaction was allowed to cool to room temperature, the acetone was removed *in vacuo*, and EtOAc (100 mL) was added. The solution then was washed with saturated NH_4Cl, H_2O, and brine, dried ($MgSO_4$), and finally concentrated *in vacuo* to give the protected ester (348 mg, 99%) as a yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.09 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 2.5 Hz, 1H), 5.17 (s, 2H), 5.15 (s, 2H), 5.12 (m, 1H), 5.05 (t, J = 6.6 Hz, 1H), 3.85 (s, 3H), 3.59 (d, J = 6.9, 2H), 3.46 (s, 3H), 3.45 (s, 3H), 2.08−1.90 (m, 4H), 1.74 (s, 3H), 1.63 (s, 3H), 1.56 (s, 3H); ^{13}C NMR δ 168.6, 156.6, 155.9, 135.0, 132.4, 131.5, 126.0, 124.6, 123.5, 110.2, 107.1, 94.8 (2C), 56.4, 56.3, 52.4, 40.1, 27.0, 25.9, 25.6, 17.9, 16.5; HRMS *m*/*z* 392.2204 (calcd for $C_{22}H_{32}O_6$, 392.2199).

[2-(3,7-Dimethylocta-2,6-dienyl)-3,5-bis(methoxymethoxy)phenyl-]methanol (14). To a suspension of $LiAlH_4$ (29 mg, 0.75 mmol) in THF (5 mL) at 0 °C was added the intermediate ester (151 mg, 0.38 mmol) in THF (2 mL) dropwise. The reaction was allowed to stir for 1 h and then quenched by addition of H_2O. The reaction mixture was acidified with 1 M HCl (5 mL) and then diluted with EtOAc, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Final purification by flash column chromatography (25% EtOAc in hexanes) gave alcohol **14** (130 mg, 94%). Both ^{1}H and ^{13}C NMR data matched those reported above.

Diethyl [2-{(2*E*)-3,7-Dimethyl-2,6-octadienyl}-3,5-bis-(methoxymethoxy)benzyl]phosphonate (15). Methanesulfonyl chloride (0.26 mL, 3.4 mmol) was added dropwise to a solution of alcohol **14** (302 mg, 0.83 mmol) and Et_3N (0.20 mL 1.4 mmol) in CH_2Cl_2 (8 mL) at 0 °C, and the reaction mixture was allowed to warm to room temperature over 1.5 h, quenched by addition of H_2O, and extracted with EtOAc. The combined organic layers were washed with saturated NH_4Cl and brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting residue and NaI (135 mg, 0.90 mmol) were stirred in acetone (9 mL) for 16 h. This reaction mixture was concentrated *in vacuo* to afford a red solid, which was dissolved in EtOAc. After the resulting yellow solution was washed once with $NaHCO_3$ and then with $Na_2S_2O_3$ (10% aqueous) until the color faded, it was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The resulting yellow oil was added to triethyl phosphite (1 mL), and the mixture was heated at 100 °C for 10 h. After the solution was allowed to cool to room temperature, the excess phosphite was removed under high vacuum. The initial yellow oil was purified by flash chromatography (50% EtOAc in hexanes) to afford phosphonate **15** (274 mg, 68%) as a clear oil: ^{1}H NMR (CDCl3, 300 MHz) δ 6.70−6.68 (m, 2H), 5.15 (s, 2H), 5.13 (s, 2H), 5.07−5.00 (m, 2H), 4.07−3.98 (m, 4H), 3.46−3.45 (m, 2H), 3.46 (s, 3H), 3.45 (s, 3H), 3.13 (d, J_{HP} = 22 Hz, 2H), 2.09−1.95 (m, 4H), 1.78 (s, 3H), 1.65 (s, 3H), 1.57 (s, 3H), 1.26 (t, J_{HP} = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 155.9, 155.7 (d, J_{CP} = 3.8 Hz), 134.8, 132.0 (d, J_{CP} = 9.1 Hz), 131.2, 124.0,124.2, 122.9, 111.4, 102.4 (d, J_{CP} = 3.7 Hz), 94.6, 94.6, 62.0 (d, J_{CP} = 6.17, 2C), 56.0, 55.9, 39.6, 30.4 (d, J_{CP} = 137 Hz), 26.6, 25.6, 24.6, 17.6, 16.3, 16.3, 16.1; ^{31}P NMR δ 27.3; HRMS (ESI) calcd for $C_{25}H_{41}O_7P$ 484.2590, found 484.2595.

Synthesis of [3,4-Bis(methoxymethoxy)-2-(3-methylbut-2-enyl)phenyl]methanol (17). To a stirred solution of alcohol **16**[4,14] (203 mg, 0.92 mmol) in THF (4 L) was added *n*-BuLi (0.78 mL of a 2.48 M solution in hexanes) at 0 °C, and the mixture was stirred for 30 min at 0 °C. To this mixture was added CuBr as its dimethyl sulfide complex (201 mg, 0.98 mmol), and the reaction was allowed to stir for 30 min at 0 °C. After prenyl bromide (0.11 mL, 0.98 mmol) was added dropwise at 0 °C, the mixture was stirred for 2 h at 0 °C, then quenched by addition of H_2O and extracted with Et_2O. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a dark yellow oil. The oil was purified by flash chromatography (15−20% EtOAc in hexanes) to give the prenylated arene **17** as a light yellow oil (92 mg, 35%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.10 (d, J = 8.4 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 5.19 (s, 2H), 5.15 (t, J = 1.5, 1H), 5.11 (s, 2H), 4.60 (s, 2H), 3.59 (s, 3H), 3.54 (s, 1H), 3.52 (d, J = 1.8 Hz, 2H), 3.50 (s, 3H) 1.80 (s, 3H), 1.69 (s, 3H); ^{13}C NMR δ 149.9, 145.3, 135.0, 134.1, 132.4, 125.1, 123.8, 114.3, 99.6, 96.4, 63.6, 57.9, 56.6, 26.0, 25.7, 18.3; *anal.* C 65.13%, H 8.44%, calcd for $C_{16}H_{24}O_5$, C 64.84%, H 8.16%.

3,4-Bis(methoxymethoxy)-2-(3-methylbut-2-enyl)benzaldehyde (18). To a stirred solution of benzyl alcohol **17** (116 mg, 0.39 mmol) in CH_2Cl_2 (10 mL) was added MnO_2 (0.80 g, 7.80 mmol) at 0 °C, and the resulting mixture was stirred for 22 h while it was allowed to warm to room temperature. The reaction mixture was filtered through Celite, and the pad was rinsed with EtOAc, Et_2O, hexanes, and MeOH. After the combined filtrate was concentrated *in vacuo* to afford a yellow oil, final purification by flash chromatography (30% EtOAc in hexanes) gave the aldehyde **18** as a pale yellow oil (91 mg, 79%). The ^{1}H and ^{13}C NMR data were identical to reported data.[16]

Tetra(methoxymethyl)pawhuskin A (19). NaH (as a 60% dispersion in mineral oil, 46 mg, 1.15 mmol) and 15-crown-5 (0.03 mL, 0.12 mmol) were dissolved in THF (5 mL), and the solution was cooled to 0 °C. Aldehyde **18** (32 mg, 0.11 mmol) and phosphonate **15** (106 mg, 0.22 mmol) were dissolved in THF (3 mL) and transferred via syringe to the NaH suspension. The mixture was stirred for 22 h while it was allowed to warm to room temperature. The reaction mixture was quenched by addition of H_2O (10 mL) and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a yellow oil. The yellow oil was purified by flash chromatography (25% EtOAc in hexanes) to afford stilbene **19** as a yellow oil (44 mg, 63%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29 (d, J = 8.7 Hz, 1H), 7.10 (s, 2H), 7.02 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 2.4 Hz, 1H), 6.74 (d, J = 2.1 Hz, 1H), 5.21 (s, 2H), 5.18 (s, 2H), 5.17 (s, 2H), 5.15 (t, J = 1.5 Hz, 1H), 5.13 (t, J = 0.9 Hz, 1H), 5.11 (s, 2H), 5.05 (tt, J = 6.6, 1.2 Hz, 1H), 3.60 (s, 3H), 3.56 (d, J = 6.3 Hz, 2H), 3.51 (s, 3H), 3.49 (s, 3H), 3.48 (s, 3H), 3.45 (d, J = 6.9 Hz, 2H), 2.05−1.97 (m, 4H), 1.80 (s, 3H), 1.79 (s, 3H), 1.69 (s, 3H), 1.62 (s, 3H), 1.55 (s, 3H); ^{13}C NMR δ 156.3, 156.0, 149.5, 144.8, 138.8, 134.9, 134.7, 132.3, 131.9, 131.6, 128.7, 127.5, 124.6, 123.7, 123.4, 123.2, 122.3, 114.5, 106.9, 103.1, 99.6, 95.4, 95.0, 95.0, 57.9, 56.6, 56.3, 56.3, 40.1, 27.1, 26.2, 25.9, 25.9, 25.0, 18.5, 18.0, 16.7; HRMS calcd for $C_{37}H_{52}O_8$ (M^+) 624.3662, found 624.3657.

Pawhuskin A (1). To a stirred solution of stilbene **19** (42 mg, 0.06 mmol) was added camphorsulphonic acid (4 mg, 0.02 mmol), in MeOH, and the mixture was stirred at 55 °C for 24 h. The reaction mixture was quenched by addition of saturated NH_4Cl and extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to afford a yellow oil. Final purification by flash chromatography (30% EtOAc in hexanes) gave pawhuskin A (**1**) as a

yellow oil (11 mg, 36%). Both ^{1}H and ^{13}C NMR spectra were identical to published data.[1]

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