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The total synthesis of eupomatilones 2 and 5

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Abstract—Efficient and diastereocontrolled syntheses of natural lignans eupomatilone 2 (**1**) and 5 (**2**) are described. Biaryl coupling was achieved using Suzuki chemistry. The lactone moiety was constructed using allylmetal reagents, which were synthesized from Baylis–Hillman adducts. Allylindium reagents were found to be most effective.

The α-methylene-γ-lactone moiety is widely found in naturally occurring compounds.[1] The ability of the unsaturated lactone functionality to act as a highly reactive Michael acceptor is the basis of its role as a physiologically important building block[2] Eupomatilones are structurally novel lignans, first isolated in 1991 by Carrol and Taylor from the shrub *eupomatia bennettii* and are characterized by a biaryl system with a substituted γ-lactone ring system attached to one of the aryl rings.[3] Three synthetic approaches to eupomatilone-6 (**3**) (in which the olefin on the lactone moiety is hydrogenated) have been reported; however there are no reports relating to the syntheses of eupomatilones that contain an α-methylene-γ-lactone.[4] We wish to report the first total syntheses of eupomatilones 2 (**1**) and 5 (**2**) (Fig. 1) using Baylis–Hillman adducts as synthetic precursors.

The Baylis–Hillman reaction is an attractive method for forming carbon–carbon bonds because it yields highly functionalized products.[5] In a continuation of our study of reactions involving organoborane reagents,[6] we reported the cross-coupling of Baylis–Hillman adducts and bis(pinacoloto)diboron in the presence of palladium catalysts to generate 3-substituted-2-alkoxycarbonylallylboronates.[7] Reaction of these allylboronates with aldehydes required relatively long reaction times. However, we recently observed that the allylation reaction is accelerated in the presence of Lewis acids to generate functionalized homoallylic alcohols, which can be cyclized to α-methylene-γ-lactones.[8] These results encouraged us to investigate new approaches to the synthesis of eupomatilones 2 (**1**) and 5 (**2**).

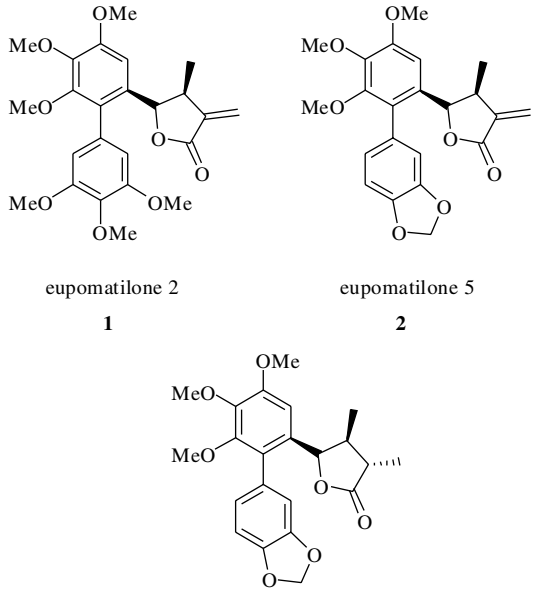

Figure 1. Eupomatilone structures.

The synthesis is initiated with the synthesis of **5** from commercially available **4**.[9] The key reaction involves coupling an arylboronic acid **6** with 2-bromo-3,4,5-trimethoxybenzaldehyde (**5**) in the presence of 4 mol %

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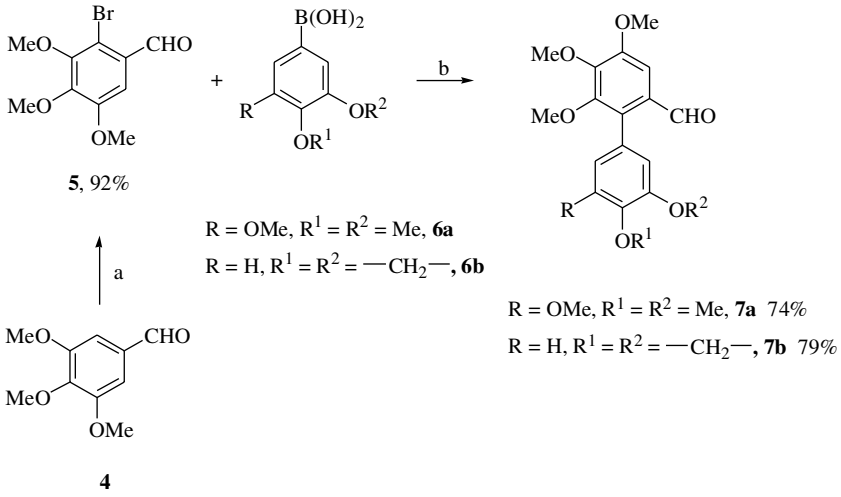


Scheme 1. Reagents and conditions: (a) NBS, $CHCl_3$, reflux, 2 h; (b) $PdCl_2(PPh_3)_2$ (4 mol %), toluene: H_2O (10:1), KF (2 equiv).

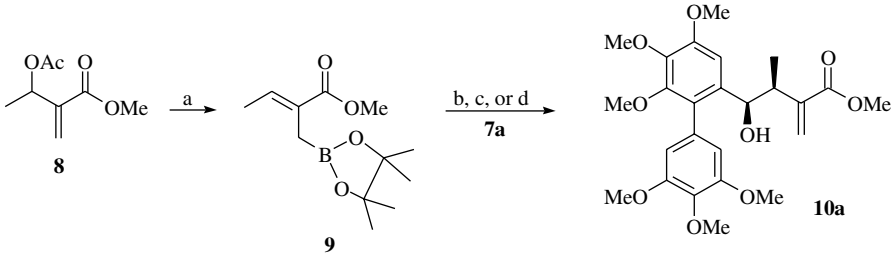
of $PdCl_2(PPh_3)_2$ (Scheme 1). The cross-coupling was achieved without the use of an external ligand (KF was used as the base) to obtain biaryl aldehydes **7a** and **7b** in high yield.

The lactone ring of eupomatilone 2 (**1**) was constructed by the addition of 3-methyl-2-methoxycarbonylallylboronate (**9**) to the biaryl aldehyde **7a**. Allylboronate **9** was prepared via reaction of Baylis–Hillman acetate adduct **8** with bis(pinacoloto)diboron in the presence of a palladium catalyst as shown in Scheme 2.[7] Since allylboronates are moisture sensitive and can be difficult to purify, allylboronate **9** was used directly in the preparation of **10a**. A variety of conditions were employed but the reaction yields were poor presumably due to steric factors and the presence of the electron donating methoxy groups on the aromatic ring of the aldehyde.

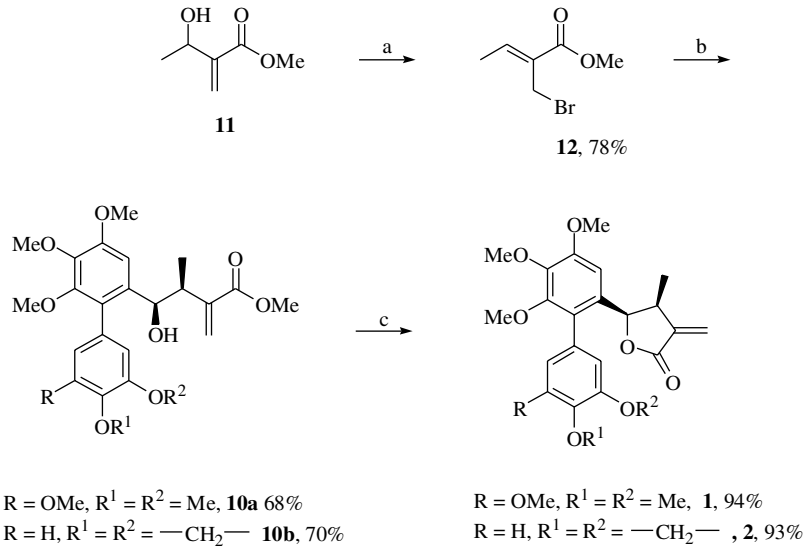
Since the boronate-based coupling reactions generated only modest yields of the desired products, we investigated the use of indium moderated reactions developed by Paquette and others.[10] Allylbromide **12** was synthesized from Baylis–Hillman adduct **11**.[11] Bromination using *N*-bromosuccinimide and triphenylphosphine in CH_2Cl_2 at room temperature occurred regioselectively (with allylic rearrangement) to afford the thermodynamically favored *Z*-isomer. The allylation of **7a** and **7b** with **12** was most efficiently carried out using powdered indium in a mixture of water and tetrahydrofuran (1:1).[10a] Homoallylic alcohols **10a** and **10b** formed as the desired *syn* isomers (95:5) (minor amounts of the *anti* isomers were observed, however, they were easily separated from the desired product). Cyclization of alcohols **10a** and **10b** was achieved under mild acidic conditions (PTSA, CH_2Cl_2) to form products **1** and **2** (Scheme 3). The ^1H NMR and ^{13}C NMR spectra[12] of **1** proved identical with those published for eupomatilone 2.[3] The spectra[13] of **2** revealed the presence of a mixture of non-separable atropisomers, which were identical to natural eupomatilone 5.[3]

After successfully completing the total synthesis of the two natural eupomatilones 2 (**1**) and 5 (**2**), reaction of **1** and **2** with 10% Pd/C and H_2 in ethanol gave olefin isomerized products **13a** and **13b**, respectively (Scheme 4). The conjugated unsaturated lactone **13b** is an intermediate in the Gurjar approach to the synthesis of 3-*epi*-eupomatilone 6 (**14**) and on further hydrogenation in the presence of Rh/Al_2O_3 in ethyl acetate at 60 psi produces 3-*epi*-eupomatilone 6 (**14**).[4c]

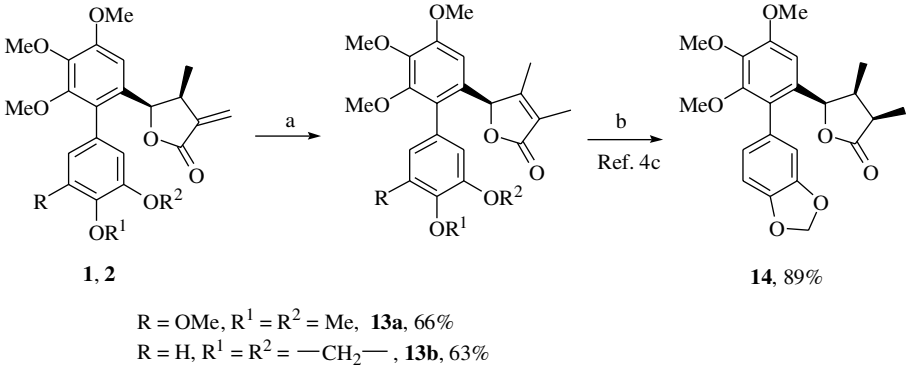
In conclusion, we have successfully completed the syntheses of eupomatilones 2 and 5 using Suzuki coupling and allylation reactions as the key steps. We have demonstrated that eupomatilone 5 can be hydrogenated to synthesize another biaryllignan 3-*epi*-eupomatilone 6. Although no reports have appeared describing the biological activity of eupomatilones, our short and efficient



Scheme 2. Reagents and conditions: (a) bis(pinacoloto)diboron (1.1 equiv), $Pd_2(dba)_3$ (3 mol %), toluene, 50 °C, 5 h; (b) $Sc(OTf)_3$ (10 mol %), rt, 3 days, 12%; (c) $BF_3{\cdot}SiO_2$,[8d] (300 mg) rt, 3 days, 15%; (d) 90 °C, 3 days, 19%.



Scheme 3. Reagents and conditions: (a) NBS, PPh_3, rt, 12 h; (b) In, THF/H_2O (1:1), 2 h; (c) PTSA (10 mol %), DCM, rt, 12 h.



Scheme 4. Reagents and conditions: (a) Pd/C, H_2, EtOH, rt, 18 h; (b) Rh/Al_2O_3, H_2, 60 psi, 20 h, Ref. 4c.

strategy could serve as a catalyst for research in this area.

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12. Eupomatilone 2 (**1**): ^{1}H NMR ($CDCl_3$); ^{1}H NMR ($CDCl_3$); 0.85 (d, $J = 7.5$, 3H), 2.87 (m, 1H), 3.70 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 5.52 (d, $J = 7.2$ Hz, 1H), 5.56 (d, $J = 2.0$ Hz, 1H), 6.24 (d, $J = 2.0$ Hz, 1H), 6.36 (d, $J = 1.5$ Hz, 1H), 6.47 (d, $J = 1.5$ Hz, 1H), 6.69 (s, 1H); ^{13}C NMR ($CDCl_3$); 16.6, 38.1, 55.9, 60.6, 61.1, 79.0, 104.4, 104.7, 106.3, 107.3, 121.7, 127.5, 129.7, 130.8, 137.1, 140.7, 141.7, 151.0, 152.7, 152.8, 169.8.
13. Eupomatilone 5 (**2**): mixture of non-separable atropisomers. ^{1}H NMR ($CDCl_3$); 0.80 (d, $J = 7.5$, 3H), 0.83 (d, $J = 7.6$, 3H), 2.87 (m, 2H), 3.64 (s, 3H), 3.65 (s, 3H), 3.88 (s, 6H), 3.91 (s, 6H), 5.44 (d, $J = 7$ Hz, 1H), 5.54 (d, $J = 2$ Hz, 2H), 6.02 (m, 4H), 6.23 (d, $J = 2$ Hz, 2H), 6.58–6.74 (m, 6H), 6.68 (d $J = 8$ Hz, 2H); ^{13}C NMR ($CDCl_3$) 17.2, 38.1, 38.3, 56.0, 60.8, 61.0, 79.3, 101.2, 104.8, 108.1, 108.4, 109.9, 110.5, 121.9, 122.7, 123.3, 127.1, 128.9, 130.0, 141.1, 141.8, 146.9, 147.0, 147.7, 151.4, 152.8, 169.9.