An Expeditious Synthesis of (±)-Mimosifoliol Utilizing a Cascade Involving an *o*-Quinone Methide Intermediate

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Abstract: An efficient synthesis of (±)-mimosifoliol is reported. The key transformation involves a domino sequence leading to an *o*-quinone methide and its subsequent consumption in 1,4-conjugate addition with a vinyl Grignard reagent.

Key words: alcohols, aldehydes, domino reactions, natural products, Michael additions, Grignard reactions, enones, eliminations, protecting groups, quinones, regioselectivity, tandem reactions, total synthesis

(+)-Mimosifoliol (**1**) was recently isolated from the rootwood of *Aeschynomene mimosifolia* Vatke (Leguminosae) along with (+)-mimosifolenone (**2**) (Figure 1).[1] (+)-Mimosifoliol (**1**) demonstrated weak activity in a DNA-strand scission assay. A concentration of 25 μg/mL of **1** was approximately equal in activity with a 0.1 μg/mL of bleomycin sulfate. On the other hand (+)-**2** proved to be inactive in this assay. Despite its activity in the assay, (+)-mimosifoliol (**1**) proved to be inactive against several human cancer cell lines. Nevertheless, we felt that it might serve as a nice target to showcase a recent method developed by our group.

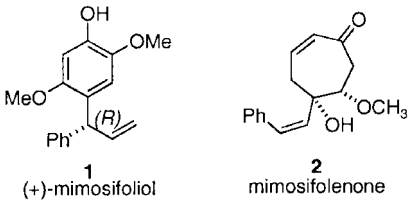

Figure 1 Rootwood constituents of *Aeschynomene mimosifolia*

Upon first glance (+)-mimosifoliol (**1**) appears to be a simple molecule that can be readily synthesized by allylation of a 1,2,4-trihydroxyaromatic ring using a Claisen rearrangement or DoM reaction. However, appearances can be deceiving. Such strategies overlook many subtle issues of regioselectivity such as distinguishing between similar hydroxyl residues on an aromatic ring.[2]

We recently disclosed a solution to the problem of regioselective functionalization of phenols.[3] We address the question of regioselectivity through the accessibility of a starting -OBOC salicylaldehyde. In general, salicylaldehydes are more accessible in various regiochemical motifs than their *ortho*-substituted phenol counterparts. The -OBOC salicylaldehyde serves as a precursor for an *o*-quinone methide intermediate that can be functionalized through a number of reactions including 1,4-conjugate additions of organomagnesium reagents; a reaction that as yet had not been demonstrated in connection with a total synthesis.[4]

The essence of our allylation strategy ultimately used for the synthesis of **1** is shown in Scheme 1. The salicylaldehyde (**i**) undergoes addition with various organometallic reagents (Mg, Li, Al, Na) to produce the corresponding benzyloxy anion **ii**. The fate of **ii** depends on the counterion associated with it. In the case of aluminum reagents the reaction stops; presumably a consequence of the O–Al bond strength. Lithium and magnesium reagents proceed through intermediate **iii** to the corresponding phenoxide **iv**. Lithium derivatives of the phenoxide **iv** are stable from –78 °C to 0 °C for considerable time. Organomagenium derivatives, on the other hand, proceed to the *o*-quinone methide **v** by expelling the carbonate **vii**. The difference in reactivity between the lithium and magnesium intermediate **iv** may be a consequence of the Lewis acidity of Mg^{2+}, which facilitates elimination of carbonate **vii** through chelation. The most useful conclusion supported by experiment is that the addition of a Li-reagent can be followed by the addition of a Mg-reagent, such as **viii**, resulting in the addition of two different nucleophiles to the benzylic carbon atom.

To demonstrate this transformation within the context of a total synthesis of **1** we began with the commercially available trimethoxyaldehyde **3**. Following DeKimpe's procedure, the aryl ether **3** (0.3 M in CH_2Cl_2) was slowly added to 3.5 equivalents of $AlCl_3$ (1.1 M in CH_2Cl_2) at room temperature to afford the dihydroxyaldehyde **4** in 73% yield after 3 hours.[5] Presumably, ethers leading to the most stable alkoxides are cleaved first. Subjecting **4** (0.1 M in CH_2Cl_2, r.t.) to 2.2 equivalents of BOC_2O, 0.5 equivalents $(i\text{-Pr})_2NEt$ and a catalytic quantity of DMAP (0.05 equiv) afforded the *bis*-OBOC aldehyde **5** after 12 h in 82%. The stage was set for the one-pot generation and consumption of the *o*-quinone methide intermediate. The aldehyde **5** (0.1 M in THF) was cooled to –30 °C and then phenyl lithium (1.5 equiv, 1.4 M in Et_2O) was added. The reaction was slowly warmed to 0 °C over 1 hour and then cooled to –78 °C, whereupon freshly prepared vinyl magnesium bromide (2.5 equiv, 1M in THF) was added

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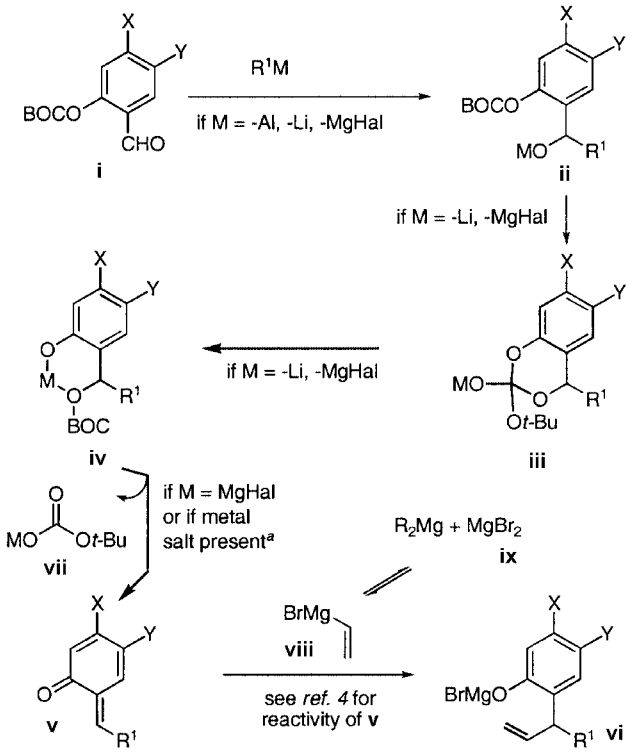
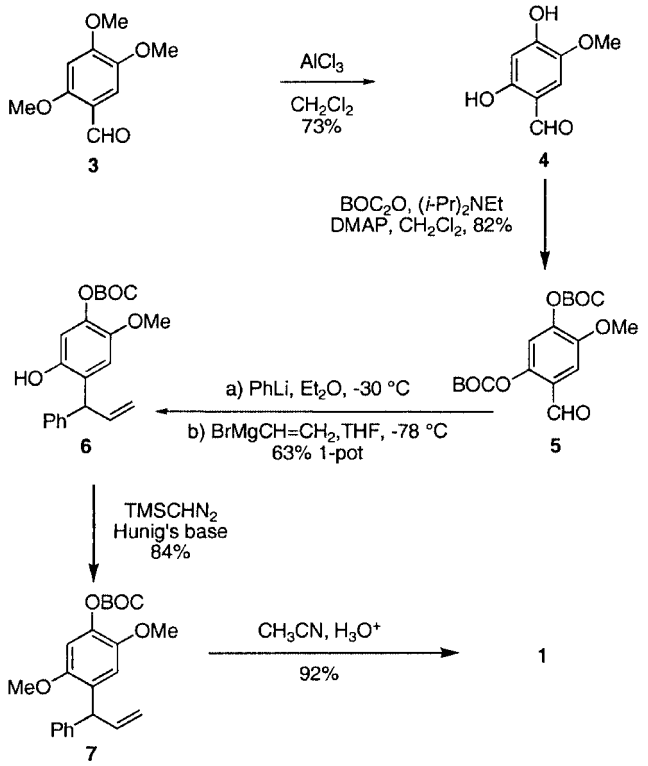


Scheme 1 The metal-cation mediated cascade leading to the generation of an *o*-quinone methide and the subsequent consumption by 1,4-conjugate addition. (a) Large amounts of metal salts, such as Li-Br, in the reaction mixture can facilitate the elimination of **iv** to **v**.



Scheme 2 Total synthesis of (±)-mimosifoliol (**1**).

dropwise. Upon warming to room temperature the reaction was quenched (1 M NH_4Cl) and chromatographed to afford the phenol **6** in 63%. Methylation of **6** (0.1 M in 9:1 CH_3CN–MeOH) with $TMSCHN_2$ (10.0 equiv) and DIPEA (1.0 equiv) afforded the aryl ether **7** in 84%. The OBOC residue in **7** can be cleaved in comparable yields by several methods. Deprotection by addition of either a) LiOH (10 equiv) in MeOH, b) $ZnBr_2$ (10 equiv) in CH_3NO_2, or c) 3 M aq HCl and dioxane, afforded mimosifoliol **1** in yields ranging from 84–92%. Thus, the overall yield of **1** from **3** via this 5-pot protocol can be as high as a 29% (Scheme 2).

Synthetic (+)-mimosifoliol (**1**) proved identical in all spectroscopic respects to that obtained from natural sources excepting the specific rotation.[1]

Resorcinol **4**: Constructed as reported.[5] Slow recrystallization from benzene yields **4** as a single regioisomers in 73% yield.

OBOC-salicylaldehyde **5**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.17 (s, 1 H), 7.44 (s, 1 H), 7.17 (s, 1 H), 3.91 (s, 3 H), 1.57 (s, 9 H), 1.55 (s, 9 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 187.4, 151.4, 150.3, 149.8, 146.8, 145.3, 126.1, 117.9, 111.1, 85.0, 84.6, 56.6, 27.8, 27.8. IR (CH_2Cl_2): 2985, 1765, 1691, 1614, 1507, 1397, 1372, 1257, 1207, 1143, 1117 cm^{-1}. HRMS (CI): *m/z* [M + H]$^+$ calcd for $C_{18}H_{24}O_8$: 369.1563, found: 369.1549.

Phenol **6**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.21 (m, 5 H), 6.68 (s, 1 H), 6.66 (s, 1 H), 6.34–6.25 (m, 1 H), 5.33–5.29 (m, 1 H), 5.05–5.00 (m, 1 H), 4.93 (d, *J* = 6.6 Hz, 1 H), 4.75 (s, 1 H), 3.73 (s, 3 H), 1.56 (s, 9 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 151.8, 147.3, 145.5, 141.3, 139.3, 128.9, 128.8, 127.5, 127.2, 127.1, 117.5, 114.4, 111.6, 83.8, 56.8, 49.2, 27.8. IR (CH_2Cl_2): 3569, 3087, 2985, 2926, 1760, 1638, 1601, 1506, 1371, 1277, 1252, 1206, 1141 cm^{-1}. HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{21}H_{24}O_5$: 379.1514, found: 379.1521.

Methyl ether **7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.17 (m, 5 H), 6.77 (s, 1 H), 6.71 (s, 1 H), 6.30–6.22 (m, 1 H), 5.23–5.20 (m, 1 H), 5.13 (d, *J* = 6.5 Hz, 1 H), 4.96–4.91 (m, 1 H), 3.75 (s, 3 H), 3.70 (s, 3 H), 1.57 (s, 9 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 151.9, 151.1, 145.1, 142.9, 140.3, 139.1, 129.9, 128.9, 128.4, 126.4, 116.7, 114.7, 106.8, 83.6, 56.9, 56.5, 47.6, 27.9. IR (CH_2Cl_2): 3006, 2971, 2920, 1758, 1507, 1401, 1372, 1272, 1268, 1260, 1211, 1144 cm^{-1}. HRMS (ESI) *m/z* [M + Na]$^+$ calcd for $C_{22}H_{26}O_5$: 393.1661, found: 393.1678.

Synthetic (±)-mimosifoliol (**1**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.17 (m, 5 H), 6.65 (s, 1 H), 6.57 (s, 1 H), 6.32–6.23 (m, 1 H), 5.55 (s, 1 H), 5.22–5.18 (m, 1 H), 5.10 (d, *J* = 6.6 Hz, 1 H), 4.95–4.90 (m, 1 H), 3.79, (s, 3 H), 3.70 (s, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 151.8, 144.9, 143.5, 140.7, 140.4, 128.7, 128.3, 126.2, 122.8, 116.2, 112.7, 99.9, 56.9, 56.5, 47.3. IR (CH_2Cl_2) 3532, 3065, 3005, 2937, 2843, 1602, 1509, 1256, 1194 cm^{-1}. HRMS (EI) *m/z* [M]$^+$ calcd for $C_{17}H_{18}O_3$: 270.1248, found: 270.1255.

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