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First synthesis of antimalarial Machaeriols A and B

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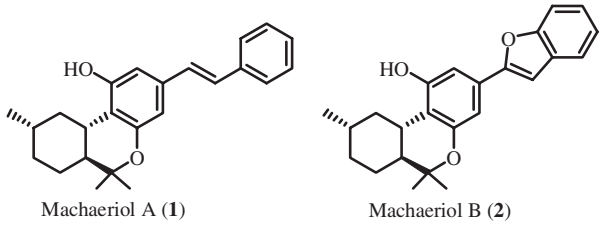
Abstract—A short and efficient synthesis of the naturally occurring antimalarial compounds, Machaeriols A and B, from commercially available citronellal via hetero-Diels–Alder cycloaddition and Suzuki coupling in 33% overall yield is described.

Increasing resistance of the malarial parasite *Plasmodium falciparum* to conventional drugs such as chloroquine or mefloquine warrants the development of new and effective drugs to combat this parasitic disease. Machaeriol A (**1**) and Machaeriol B (**2**) are (+)-*trans*-hexahydrodibenzopyran derivatives isolated from *Machaerium multiflorum* spruce by Muhammad et al. in 2001 (Fig. 1).[1] Machaeriol B showed growth inhibition of the chloroquine-resistant *P. falciparum* W-2 clone ($IC_{50} = 120$ ng/mL; SI = >40); while Machaeriol A was found to be only weakly active. They also reported that these compounds showed good antibacterial activity against *Staphylococcus aureus* and methicillin-resistant *S. aureus*, with IC_{50} values of 5 and 4.5 μg/mL, respectively. Unfortunately, their low natural abundance (16 mg of each from 500 g of plant material) has limited further studies. Furthermore, no synthesis of **1** or **2** has been reported in the literature to date.



Machaeriol A (**1**) Machaeriol B (**2**)

Figure 1.

In connection with our ongoing efforts to discover novel natural products for the treatment of malaria, we herein report the first syntheses of the hexahydrodibenzopyran derivatives **1** and **2** from commercially available *S*-(−)-citronellal. Our synthetic approach to Machaeriols A and B involves condensation of protected, lithiated phloroglucinol with *S*-citronellal. Upon mild acid hydrolysis of the protecting groups, a hetero-Diels–Alder cycloaddition ensues. The resultant diphenol then undergoes chemoselective Suzuki coupling of the monotriflate[2] with an aryl or alkenyl boronic acid to afford the natural products.

Murphy et al.[3] reported that heating mixtures of phenols and citronellal in the presence of an organic base, such as quinoline, leads directly to the formation of a hexahydro dibenzopyran derivative. Phloroglucinol **3** was subjected to hetero-Diels–Alder reaction with (*S*)-citronellal in the presence of quinoline as a base under refluxing conditions, resulting in the formation of an inseparable diastereomeric mixture (87:13) of hexahydrodibenzopyran deriavatives **6** in 45% yield. A major side product formed in 38% was isopulegol, produced presumably via Prins reaction.[4] Extended reaction times at elevated temperatures and poor chemoselectivity prompted us to develop an enantioselective route for the formation of the tricyclic hexahydrodibenzopyran derivative **6**.

Within the literature,[5] precedent existed for the condensation of (*S*)-citronellal with an aryl anion, generating an appropriate benzylic alcohol precursor for our IMDA approach. Thus, we selected to orthometallate the tris-(*O*-methoxymethyl)ether of phloroglucinol (**4**)[6] with *n*-butyl lithium rather than attempt the generation of a di- or tri-anion. Hence, on treatment of **4** with

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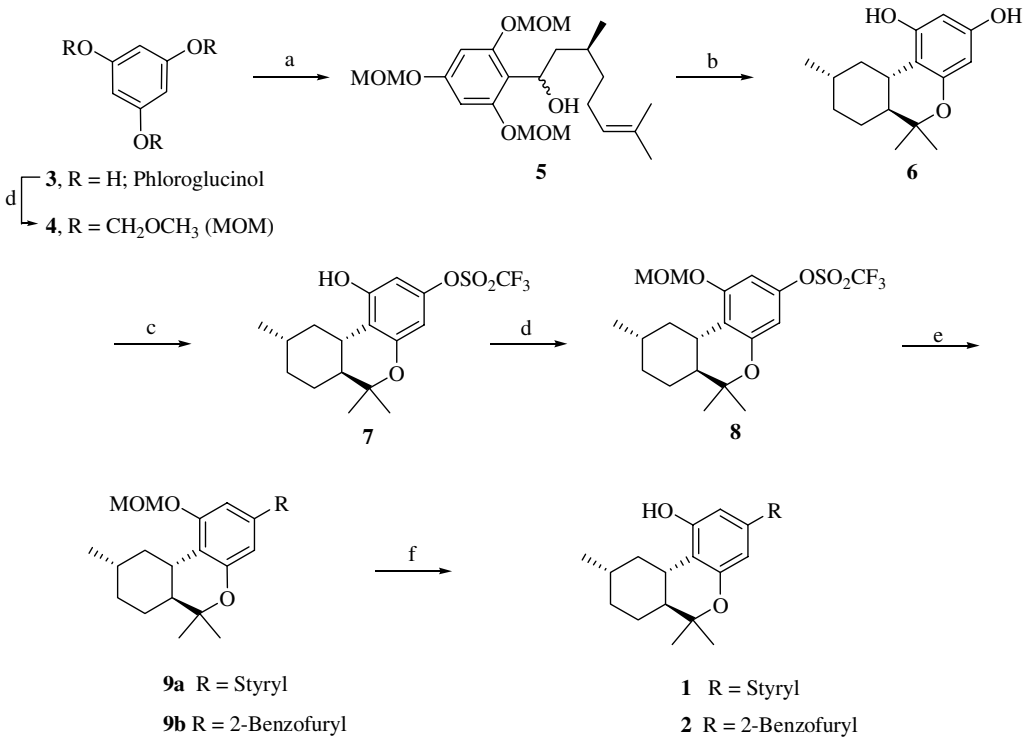

Scheme 1. Reagents and conditions: (a) *n*-BuLi, TMEDA, 0 °C, (*S*)-citronellal, 30 min, 85%; (b) 4% aqueous HCl in MeOH, rt, 12 h, 65%; (c) $PhNTf_2$, Et_3N, CH_2Cl_2, 3 h, 74%; (d) NaH, MOMCl, THF, 30 min, 97%; (e) boronic acid (*trans*-phenylvinyl or 2-benzofuryl) (1.5 equiv), $Pd(PPh_3)_4$ (1 mol %)/2 M aq Na_2CO_3 (1.5 equiv)/MeOH/toluene, reflux, 2 h (**9a**, 90%; **9b**, 86%); (f) 1% aqueous HCl in MeOH, reflux, 30 min (**1**, 95%; **2**, 97%).

1.2 equiv of *n*-butyl lithium and 1.2 equiv of *N*,*N*,*N*′,*N*′-tetramethylethylene diamine (TMEDA) followed by condensation with (*S*)-citronellal led to facile formation of a 1:1 mixture of diasteromers (**5**) in 85% purified yield (Scheme 1). Initially, we planned to remove the methoxymethyl (MOM) protecting groups to produce the triphenol corresponding to **5**. Surprisingly, with 4% aqueous HCl in methanol (v/v) at room temperature, the product of IMDA reaction, hexahydrodibenzopyran derivative **6** was produced instead in 65% isolated yield with >98% diastereoselectivity. Regioselective triflation of **6** was then readily performed with 1 equiv of $PhNTf_2$[7] and triethylamine at 0 °C to give the monotriflate **7** in 74% yield. The exclusive formation of monotriflate **7** was confirmed by 2D NMR experiments. The monotriflate **7**, when further subjected to methoxymethylation[8] (NaH, MOMCl) gave the MOM-protected triflate **8** in 97% yield. Introduction of the requisite styryl or benzofuran moieties of the Machaeriols into the MOM-triflate **8** was readily accomplished by Suzuki coupling.

Using 1.5 equiv of the appropriate boronic acid with 1 mol % tetrakis(triphenylphosphine) palladium in a 2 M aqueous solution of Na_2CO_3 (1.5 equiv) together with toluene–methanol (8:1) at 100 °C, lead to the coupled products **9a** or **9b** in 90% or 86% yields, respectively. Finally removal of the MOM group was achieved by mild acid treatment[9] to provide **1** and **2** in 95% and 97% yields, respectively. The spectral[10] and physical properties of **1** and **2** were in agreement with those of natural **1** and **2**, confirming the earlier absolute stereochemical assignment.[1]

In summary, the first syntheses of Machaeriols A (**1**) and B (**2**) have been accomplished efficiently from commercially available phloroglucinol and *S*-citronellal, giving natural products ultimately in 33% overall yield (without optimization). This synthetic process lends itself quite readily to the development of parallel or combinatorial libraries. Presently both solid phase and solution phase chemistries are being investigated to allow facile construction of such libraries. Of course, these libraries can then be examined for antimalarial and other antiinfective activities in vitro and have QSAR developed. Assessment and understanding of cannabinoid activity, if any, of these analogs will be important eventually in relationship to clinical development. However, based on known cannabinoid SAR, and a lack of cannabinoid activity for Machaeriols A and B, it seems unlikely that this will represent a substantial obstacle to this research.[1]

Studies are underway using gene microarrays to understand potential mechanisms of action of this exciting and novel class of antiinfective natural products.

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10. Spectral data for new compounds:
7: ^{1}H NMR ($CDCl_3$, 500 MHz): 6.35 (d, 1H, $J = 2.5$ Hz); 6.25 (d, 1H, $J = 2.5$ Hz); 5.42 (br s, 1H); 3.00 (br d, 1H, $J = 12.5$ Hz); 2.46 (ddd, 1H, $J = 2.5$, 11.5, 14.0 Hz); 1.88 (m, 2H); 1.62 (m, 1H); 1.46 (m, 1H); 1.39 (s, 3H); 1.17 (m, 2H); 1.08 (s, 3H); 0.97 (d, 3H, $J = 6.5$ Hz); 0.78 (dd, 1H, $J = 11.5$, 24.5 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): 156.0, 155.8, 148.0, 117.1, 113.5, 103.2, 100.6, 78.3, 48.7, 38.4, 35.3(2), 32.8, 27.9, 27.5, 22.5, 19.0. HRMS (ESI): calcd for $C_{17}H_{21}F_3O_5S$: 395.1140 $[M+H]^+$, found: 395.1146.
8: ^{1}H NMR ($CDCl_3$, 400 MHz): 6.55 (d, 1H, $J = 2.0$ Hz); 6.40 (d, 1H, $J = 1.9$ Hz); 5.17 (dd, 2H, $J = 21$ Hz); 3.49 (s, 3H); 2.95 (br d, 1H, $J = 12.0$ Hz); 2.43 (ddd, 1H, $J = 2.5$, 11.0, 14.2 Hz); 1.85 (m, 2H); 1.63 (m, 1H); 1.46 (m, 1H); 1.37 (s, 3H); 1.10 (m, 2H); 1.05 (s, 3H); 0.94 (d, 3H, $J = 6.4$ Hz); 0.74 (dd, 1H, $J = 11.5$, 23.5 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): 157.3, 155.4, 148.4, 117.1, 115.3, 104.3, 99.5, 94.6, 78.0, 56.4, 48.8, 38.8, 35.6, 35.3, 32.9, 27.9, 27.5, 22.6, 18.9. HRMS (ESI): calcd for $C_{19}H_{25}F_3O_6S$: 477.0961 $[M+K]^+$, found: 477.0974.
9a: ^{1}H NMR ($CDCl_3$, 400 MHz): 7.50 (d, 2H, $J = 7.6$ Hz); 7.36 (t, 2H, $J = 7.6$, 7.2 Hz) 7.26 (t, 1H, $J = 7.2$ Hz); 7.06 (d, 1H, $J = 16.4$ Hz); 6.99 (d, 1H, $J = 16.4$ Hz); 6.80 (d, 1H, $J = 1.7$ Hz); 6.71 (d, 1H, $J = 1.9$ Hz); 5.26 (dd, 2H, $J = 20.6$ Hz); 3.55 (s, 3H); 3.05 (br d, 1H, $J = 12.4$ Hz); 2.51 (ddd, 1H, $J = 2.5$, 11.5, 14.0 Hz); 1.89 (m, 2H); 1.67 (m, 1H); 1.47 (m, 1H); 1.42 (s, 3H); 1.16 (m, 2H); 1.10 (s, 3H); 0.95 (d, 3H, $J = 6.4$ Hz); 0.83 (dd, 1H, $J = 12$, 24.5 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): 157.0, 154.9, 137.4, 136.7, 128.6(2), 128.5, 128.4, 127.5, 126.5, 126.0, 115.2, 109.4, 104.4, 94.4, 77.1, 56.3, 49.2, 39.3, 36.0, 35.5, 33.0, 28.1, 27.7, 22.7, 19.0. HRMS (ESI): calcd for $C_{26}H_{32}O_3$: 393.2430 $[M+H]^+$, found: 393.2425.
9b: ^{1}H NMR ($CDCl_3$, 400 MHz): 7.60 (d, 1H, $J = 7.2$ Hz); 7.55 (d, 1H, $J = 7.6$ Hz); 7.29 (m, 2H); 7.19 (d, 1H, $J = 1.2$ Hz); 7.08 (d, 1H, $J = 1.2$ Hz); 7.00 (s, 1H); 5.34 (dd, 2H, $J = 20.8$ Hz); 3.60 (s, 3H); 3.11 (br d, 1H, $J = 12.4$ Hz); 2.57 (ddd, 1H, $J = 2.5$, 11.5, 14.0 Hz); 1.92 (m, 2H); 1.70 (m, 1H); 1.58 (m, 1H); 1.46 (s, 3H); 1.15 (m, 2H); 1.15 (s, 3H); 1.02 (d, 3H, $J = 6.4$ Hz); 0.9 (dd, 1H, $J = 12$, 24 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): 157.2, 155.9, 155.1, 154.8, 129.6, 129.3, 124.1, 122.8, 120.8, 116.1, 111.2, 108.2, 102.5, 101.2, 94.6, 77.3, 56.4, 49.2, 39.2, 36.1, 35.5, 33.0, 28.1, 27.7, 22.7, 19.0. HRMS (ESI): calcd for $C_{26}H_{30}O_4$: 407.2222 $[M+H]^+$, found: 407.2242.