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Total synthesis of (±)-megistophylline I

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ABSTRACT

(±)-Megistophylline I (**1**), carrying a dienone residue in the acridone framework, was synthesized using the Claisen rearrangement to introduce a prenyl group as a key step.

Megistophylline I (**1**), isolated from the bark of *Sarcomelicope megistophylla* Hartley (Rutaceae) by Papageorgiou et al.,[1] possesses the acridone framework with a prenylated dienone residue, which may be produced by biogenetic oxidation of the corresponding phenol precursor (Fig. 1).

Megistoquinones I and II exhibiting antibacterial activity[2] were also isolated from the same plant species. In our previous studies on mangostins, the dienone derivative **2**, which is very similar to **1**, was synthesized under anodic oxidation conditions.[3] As **2** showed several biological activities, the structural similarity of **1** to **2** suggested that **1** may also show similar antibacterial activity. As information of new biological activity may contribute to the development of efficient chemotherapeutic agents, we planned to synthesize **1** using a similar phenolic oxidation ap-

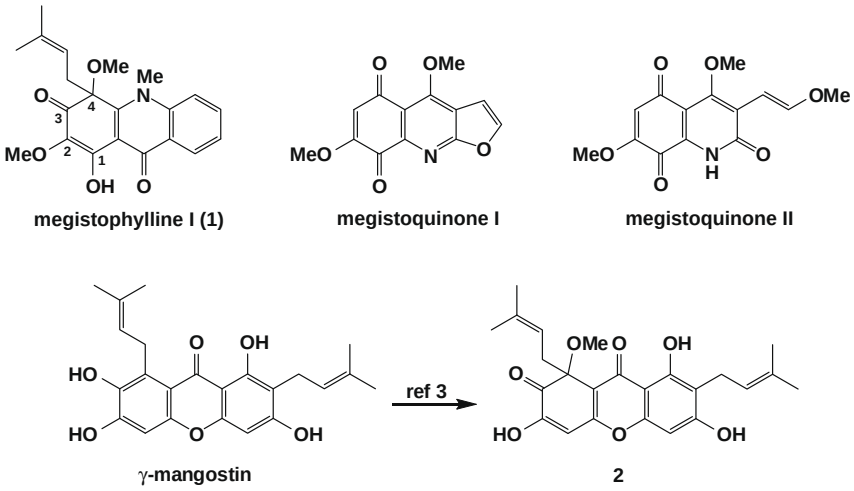

Figure 1.

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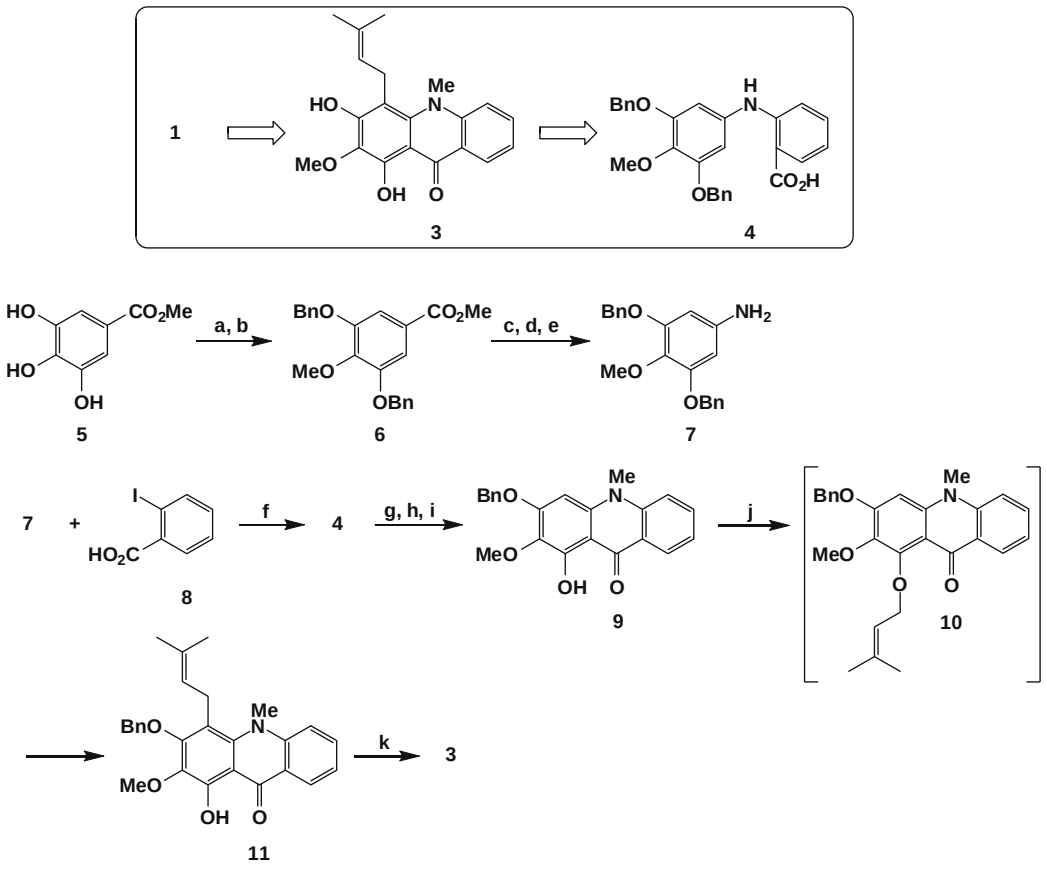


Scheme 1. Reagents and conditions: (a) Li_2CO_3, MeI, DMF, 57%; (b) K_2CO_3, BnBr, acetone, 95%; (c) 20% NaOH, THF, 91%; (d) DPPA, Et_3N, BnOH, PhMe, quant.; (e) 40% KOH, MeOH, 90%; (f) KOAc, $Cu(OAc)_2{\cdot}H_2O$, DMF, 80%; (g) TFAA, CH_2Cl_2, 91%; (h) NaH, MeI, DMF, 82%; (i) $MgBr_2{\cdot}Et_2O$, PhH, Et_2O, 97%; (j) prenyl bromide, NaH, THF, then silica gel, 40%; (k) Pd Black, 1,4-cyclohexadiene, MeOH, 71%.

proach to **2**, as depicted in the retrosynthetic analysis (Scheme 1).

Phenolic oxidation approach: According to the analysis mentioned above, the synthesis was commenced by selective protection of methyl gallate **5** by methyl[4] and benzyl groups to give fully protected **6**. Compound **6** was subsequently subjected to alkaline hydrolysis, Curtius rearrangement, and removal of a benzyloxycarbonyl group generated to give the amine **7**. Condensation of **7** with 2-iodobenzoic acid by the Ullmann protocol provided the expected diarylamine **4** in 80% yield (Scheme 1). Cyclization of **4** with trifluoroacetic anhydride (TFAA) proceeded smoothly to give an acridone, which was subjected to successive N-methylation and selective removal of a benzyl group at the C-1 position to give **9**.[8] Prenylation by the standard procedure produced not only **10**, but also the automatically rearranged product **11** in 40% yield, after chromatographic separation. Removal of a benzyl group in **11** under hydrogen transfer conditions provided **3**,[8] without undesired over-reduction, which will give a saturated alkyl chain.

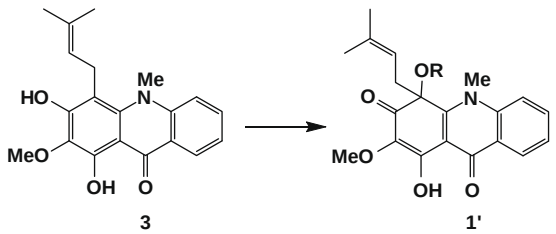
Among the oxidation conditions examined, clear reaction to the target molecule was unsuccessful as shown in Table 1. When $Pb(OAc)_4$ in PhH was used as an oxidant, acetylated megistophylline I (**1'**), was obtained in 72% yield. However removal of the acetyl group was unsuccessful under acidic or basic deprotection conditions, involving 0.05 M KOH aq or 6 M HCl aq.

Claisen rearrangement approach: After elaboration of synthetic approaches to **1**, we turned our attention to the Claisen rearrangement of a prenyl group (**12**→**1**), as shown in Scheme 2.

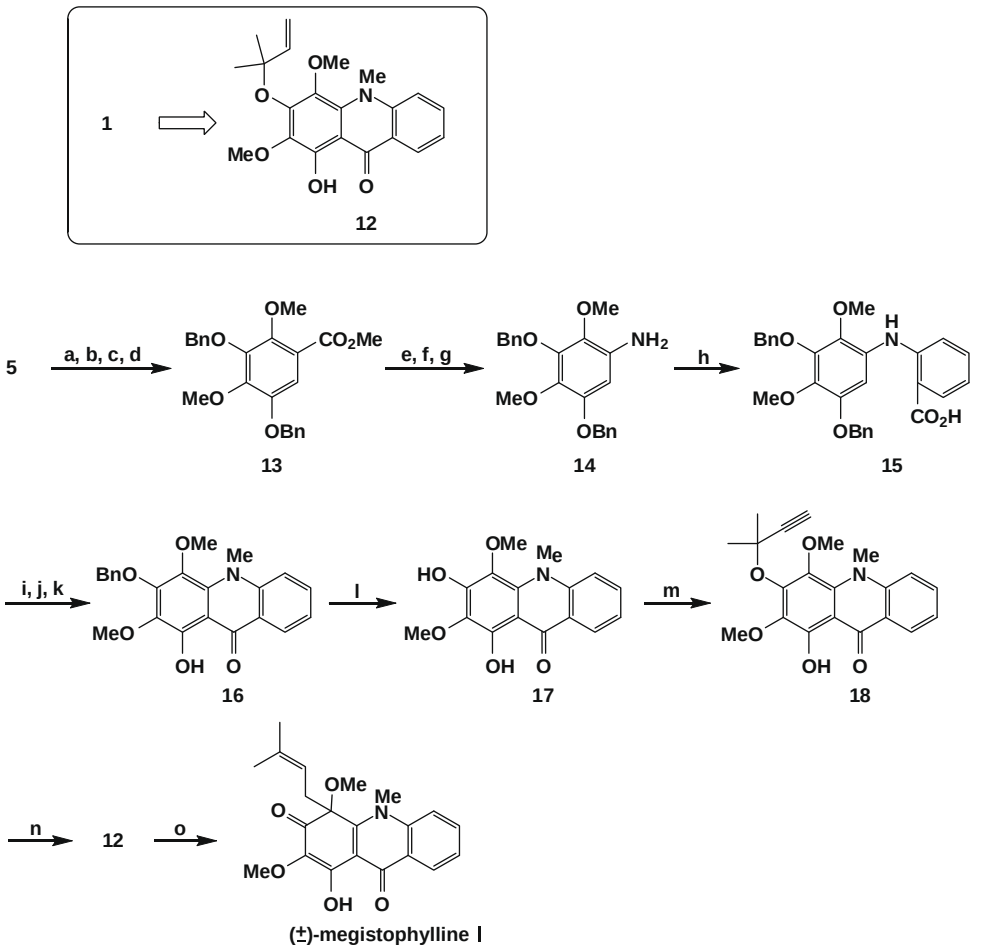
Thus, selective methylation was followed by bromination using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH),[4] protection as a benzyl ether, and then Ullmann reaction of the bromine leading to a methoxy group to give **13**. Alkaline hydrolysis of the ester function in **13**, Curtius rearrangement, and removal of the generated benzyloxycarbonyl group yielded **14**, which on condensation with **8** and subsequent cyclization, followed by N-methylation, gave the acridone **16**.

Removal of a benzyl group afforded the phenol **17**, which on reaction with 3-chloro-3-methylbut-1-yne and selective reduction gave the desired product **12**, through **18**.[6,8] At the final stage, **12**

Table 1
Oxidation conditions of **3**



Entry	R	Conditions	Result
1	Me	C.C.E. (0.7 mA/cm^2, 2 F/mol), MeOH	Unknown
2	Me	PIFA, MeOH	Unknown
3	Me	$PhI(OCH_2CF_3)_2$,[5] MeOH	Unknown
4	Me	$FeCl_3$, MeOH	n.r.
5	Me	PbO_2, MeOH	n.r.
6	Ac	Ac $Pb(OAc)_4$, PhH	1' (72%)



Scheme 2. Reagents and conditions: (a) Li_2CO_3, MeI, DMF, 57%; (b) DBDMH, $CHCl_3$; (c) K_2CO_3, BnBr, DMF; (d) NaOMe, CuI, DMF, 38% in three steps; (e) 20% NaOH, THF, 88%; (f) DPPA, Et_3N, BnOH, PhMe, 81%; (g) 40% KOH, MeOH, 89%; (h) **8**, KOAc, $Cu(OAc)_2{\cdot}H_2O$, DMF; (i) TFAA, CH_2Cl_2, 73% in two steps; (j) 35% HCHO, $NaCNBH_3$, AcOH, MeCN; (k) K_2CO_3, MeI, acetone, 70% in two steps; (l) Pd black, 1,4-cyclohexadiene, MeOH, 93%; (m) K_2CO_3, KI, CuI, 3-chloro-3-methylbut-1-yne, acetone, 75%; (n) H_2, Lindlar cat., quinoline, PhH–hexane (1:5), **12**: 41%, **17**: 28%; (o) neat, 200 °C, 65%.

was heated at 200 °C (neat) under an argon atmosphere[7] to give (±)-megistophylline I (**1**), spectroscopic data of which were identical to those reported previously.[1] Assessments of biological activity of synthetic samples will be performed in due course.

Acknowledgments

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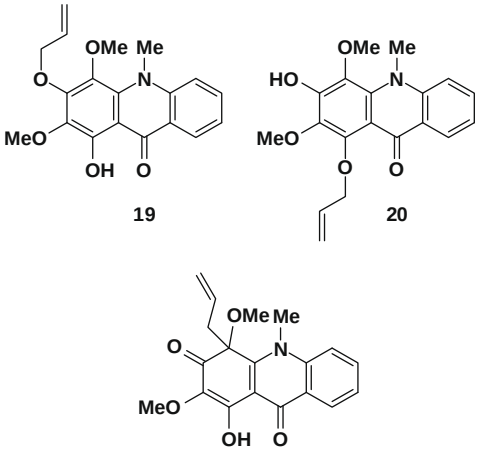
6. In this reduction, **17** was also produced by undesired deprenylation with Pd catalysts. Although this process has not been optimized, deprenylation proceeded preferentially without hexane as a co-solvent.
7. Reaction conditions of the Claisen rearrangement were elaborated using **19**, which was synthesized by direct allylation of **17**. (1) Heating at 140 °C in xylene caused decomposition of the substrate. (2) Compound **19** was converted to the regio-isomer **20** under $BF_3{\cdot}Et_2O$ in CH_2Cl_2 (−40 °C). (3) Compound **19** was heated at 200 °C (neat) to give the desired product **21**



8. *Selected spectroscopic data* **3**: δ_H ($CDCl_3$) 1.75 (3H, s), 1.76 (3H, s), 3.48 (2H, d, J = 4.9 Hz), 3.83 (3H, s), 4.03 (3H, s), 5.36 (1H, t, J = 4.9 Hz), 6.75 (1H, s), 7.25 (1H, t, J = 8.8 Hz), 7.39 (1H, d, J = 8.8 Hz), 7.68 (1H, t, J = 7.8 Hz), 8.34 (1H, d, J = 7.8 Hz); δ_C ($CDCl_3$) 18.2, 25.7, 27.2, 43.6, 60.8, 104.5, 107.1, 116.2, 121.0, 121.4, 123.5, 125.9, 128.3, 132.5, 133.7, 143.0, 145.5, 152.8, 155.3, 182.0.

Compound **9**: δ_H ($CDCl_3$) 3.62 (3H, s), 3.91 (3H, s), 5.21 (2H, s), 6.17 (1H, s), 7.12-7.64 (8H, m), 8.25 (1H, d, *J* = 7.6 Hz), 14.72 (1H, s); δ_C ($CDCl_3$) 29.8, 34.0. 60.8, 70.7, 88.6, 105.6, 114.4, 120.3, 121.2, 126.2, 127.1, 128.1, 128.6, 133.7, 136.1, 139.9, 141.6, 156.0, 158.1, 180.4. Compound **18**: δ_H ($CDCl_3$) 1.82 (6H, s), 2.46 (1H, s), 3.74 (3H, s), 3.96 (3H, s), 4.05 (3H, s), 7.27 (1H, t, *J* = 8.0 Hz), 7.49 (1H, d, *J* = 8.0 Hz), 7.73 (1H, s, *J* = 8.0 Hz), 8.39 (1H, s, *J* = 8.0 Hz), 14.37 (1H, s); δ_C ($CDCl_3$) 30.3, 40.8, 60.6, 61.3, 73.2, 76.7, 77.9, 85.5, 108.9, 115.5, 120.9, 121.3, 126.3, 128.1, 128.4, 134.2, 144.9, 150.7, 152.2, 180.2. Compound **12**: δ_H ($CDCl_3$) 1.59 (6H, s), 3.70 (3H, s), 3.91 (3H, s), 4.01 (3H, s), 5.15 (1H, dd, *J* = 10.8, 1 Hz), 5.22 (1H, dd, *J* = 17.4, 1 Hz), 6.30 (1H, dd, *J* = 10.8, 17.4 Hz) 7.28 (1H, t, *J* = 8.8 Hz), 7.48 (1H, d, *J* = 8.8 Hz), 7.73 (1H, td, *J* = 8.8, 1.6 Hz), 8.39 (1H, dd, *J* = 8.8, 1.6 Hz), 14.33 (1H, s); δ_C ($CDCl_3$) 9.2, 25.7, 26.7, 35.5, 40.9, 60.36, 60.4, 61.1, 113.0, 115.6, 121.4, 126.4, 134.2, 134.8, 137.0, 143.3, 145.1, 151.3, 152.5, 182.2.