



Total synthesis of (±)-megistophylline I

Yuko Nishihama, Yuichi Ishikawa, Shigeru Nishiyama *

Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi 3-14-1, Kohoku-ku, Yokohama 223-8522, Japan

ARTICLE INFO

Article history:

Received 21 February 2009

Revised 21 March 2009

Accepted 24 March 2009

Available online 27 March 2009

Keywords:

Sarcomelicope megistophylla Hartley

(Rutaceae)

Acridone

Claisen rearrangement

Ullmann reaction

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.

© 2009 Elsevier Ltd. All rights reserved.

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 activity² 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-

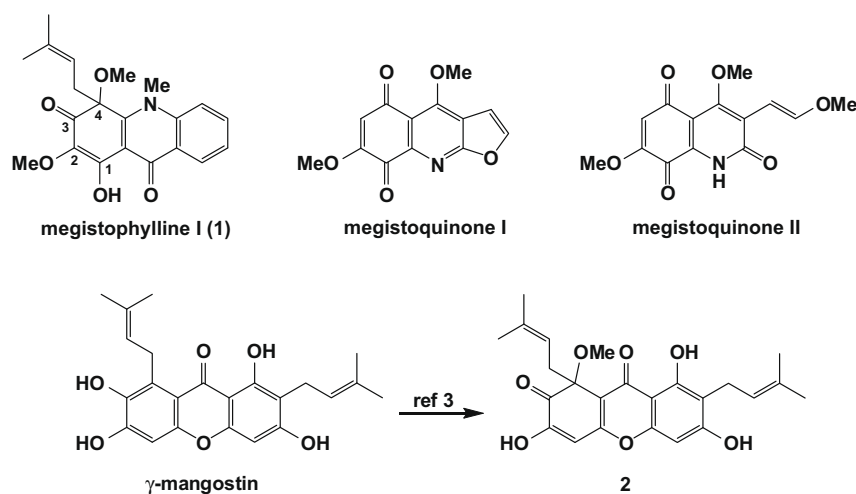
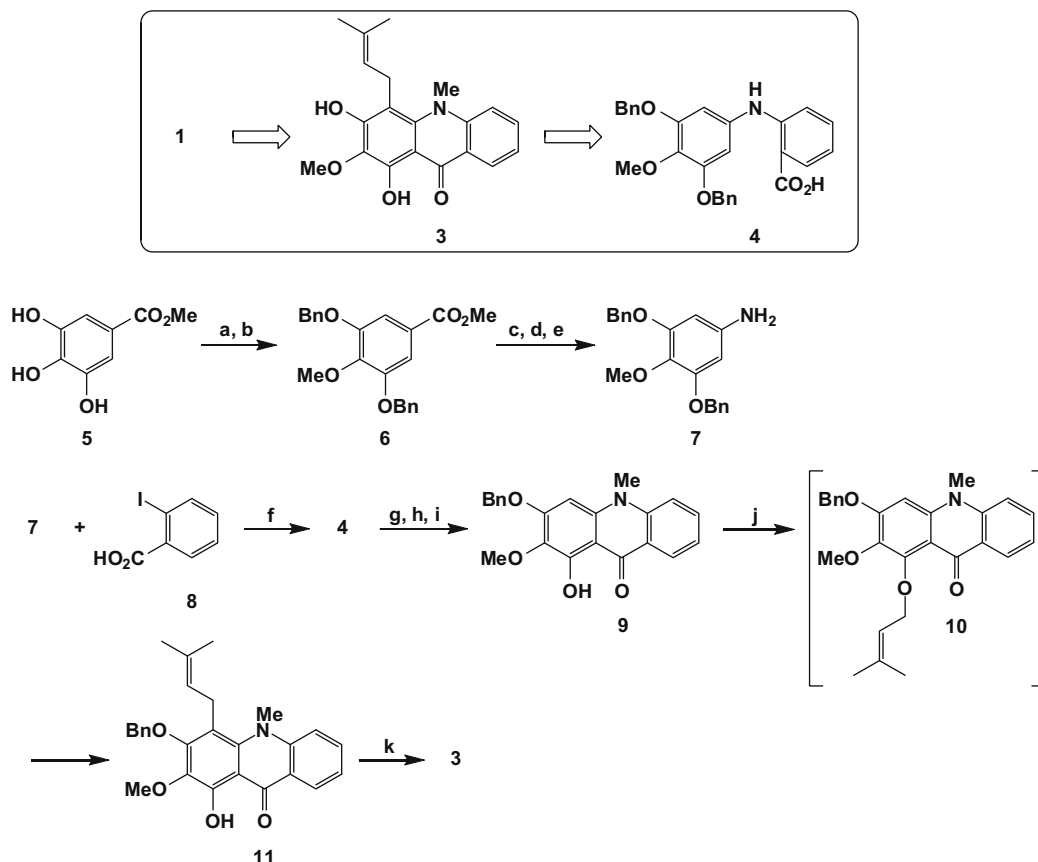


Figure 1.

* Corresponding author. Tel./fax: +81 45 566 1717.

E-mail address: nishiyama@chem.keio.ac.jp (S. Nishiyama).



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, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, DMF, 80%; (g) TFAA, CH_2Cl_2 , 91%; (h) NaH, MeI, DMF, 82%; (i) $\text{MgBr}_2 \cdot \text{Et}_2\text{O}$, 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 methyl⁴ and benzyl groups to give fully protected **6**. Compound **6** was subsequently subjected to alkaline hydrolysis, Curtius rearrangement, and removal of a benzyl-oxycarbonyl 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 $\text{Pb}(\text{OAc})_4$ 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.

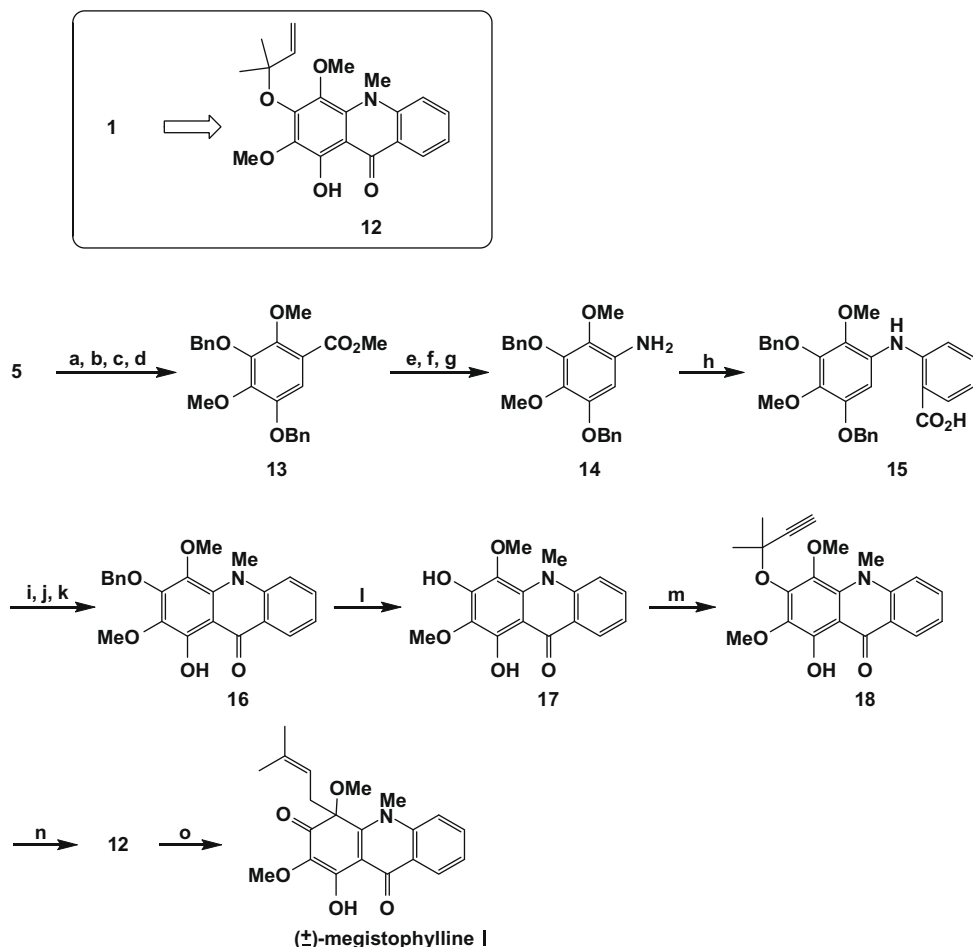
Claisen rearrangement approach: After elaboration of synthetic approaches to **1**, we turned our attention to the Claisen rearrangement of a prenyl group (**12**→**1**), as shown in Scheme 2.

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	$\text{PhI}(\text{OCH}_2\text{CF}_3)_2$, ⁵ MeOH	Unknown
4	Me	FeCl_3 , MeOH	n.r.
5	Me	PbO_2 , MeOH	n.r.
6	Ac	Ac $\text{Pb}(\text{OAc})_4$, 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, $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, DMF; (i) TFAA, CH_2Cl_2 , 73% in two steps; (j) 35% HCHO, NaCNBH₃, 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 atmosphere⁷ 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.

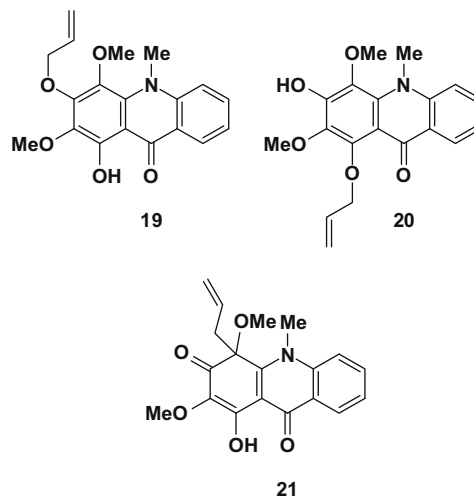
Acknowledgments

This work was supported by Scientific Research C (20510203) from MEXT, High-Tech Research Center Project for Private Universities matching fund subsidy from MEXT, 2006–2011, and Keio Leading-edge Laboratory of Science and Technology (Y.N.).

References and notes

- Papageorgiou, M.; Fokialakis, N.; Mitaku, S.; Skaltsounis, A.-L.; Tillequin, F.; Sévenet, T. *J. Nat. Prod.* **2000**, *63*, 385–386.
- Fokialakis, N.; Magiatis, P.; Chinou, I.; Mitaku, S.; Tillequin, F. *Chem. Pharm. Bull.* **2002**, *50*, 413–414.
- Nishihama, Y.; Amano, Y.; Ogami, T.; Nishiyama, S. *Electrochemistry* **2006**, *74*, 609–611.
- Alam, A.; Takaguchi, Y.; Ito, H.; Yoshida, T.; Tsuboi, S. *Tetrahedron* **2005**, *61*, 1909–1918.
- Amano, Y.; Nishiyama, S. *Tetrahedron Lett.* **2006**, *47*, 6505–6507.
- 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.
- 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 $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in CH_2Cl_2 (–40 °C). (3) Compound **19** was heated at 200 °C (neat) to give the desired product **21**



- 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.