First Synthesis of Subelliptenone F, an Inhibitor of Topoisomerase II

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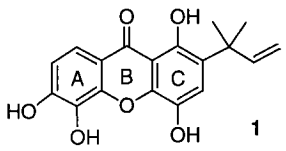
Subelliptenone F, a potent inhibitor of topoisomerase II, was synthesized for the first time via coupling of A and C ring components and B ring formation, followed by Claisen rearrangement of the 3-methyl-2-butenyl ether.

Subelliptenone F (**1**) was isolated from root bark of the Guttifereae plant *Garcinia subelliptica* and characterized by spectroscopic analysis in 1994.[1] Thereafter, **1** was found to show a potent topoisomerase II inhibitory activity as well as the other xanthones isolated from Guttiferaeous plants.[2] It exhibited higher activity than etopside that is already used as a clinical drug. For further study of the biological activity of **1** and the structure-activity relationship, we planned to develop an effective approach to **1** and its analogues. Described here is the first total synthesis of subelliptenone F through coupling of A and C ring components, and then B-ring formation followed by Claisen rearrangement to introduce the 1,1-dimethyl-2-propenyl substituent.



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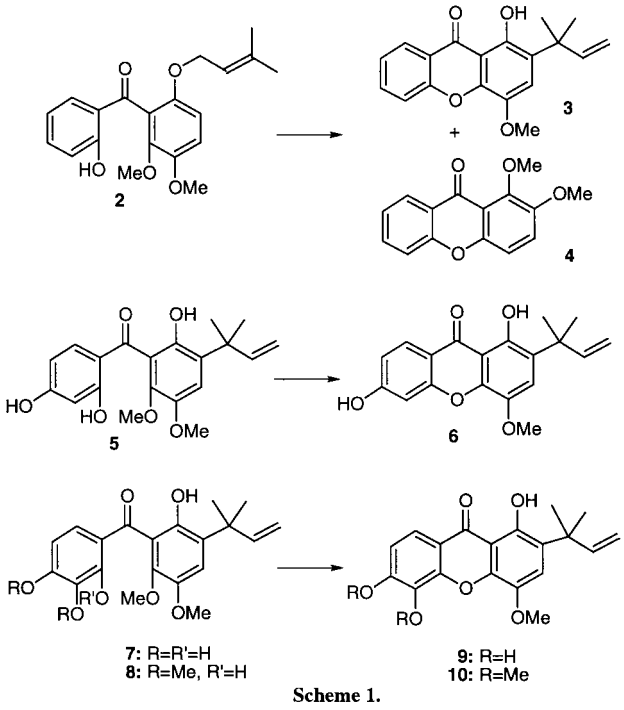
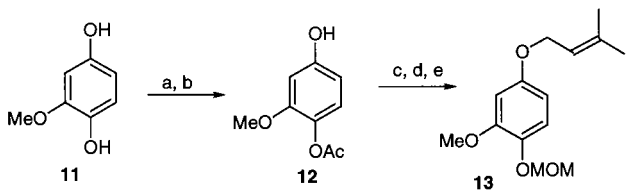
In preliminary studies toward synthesis of **1** and its analogues, we had already gained some insights (Scheme 1). On treatment of **2** with tetramethylammonium hydroxide in pyridine-water (1:1) at refluxing temperature,[3] cyclization on the desired mode and simultaneous Claisen rearrangement occurred, giving **3** in 56% yield. Dimethyl ether **4**, which arose from the attack of the phenoxide to the other site, was produced in 15% yield. Demethylation of **3** was successful using excess lithium diphenylphosphide,[4] although use of BBr_3 or BCl_3 destroyed the vinyl substituent of **3** with liberated hydrogen halide. In the synthesis of the xanthone **6**, Claisen rearrangement at an earlier stage followed by B ring formation was effective, since the 3-methyl-2-butenyl group on C ring was totally eliminated under the acidic condition to liberate two hydroxyl groups of A ring. Cyclization of 5 and demethylation of the resultant **6** gave the corresponding phenol in moderate yield. This methodology, however, did not work at all on the synthesis of **9**. Similar treatment of tetrahydroxy benzophenone derivative **7** gave no desired product **9** but a mixture of unknown products. On the contrary, suitably protected phenol **8** gave the cyclized product **10** in good yield. In this case, however, removal of all the methyl protecting groups of **10** was unsuccessful under various conditions.

Given those results, we finally decided to use methoxymethyl (MOM) group instead of methyl group, and trimethylsilylethoxymethyl (SEM) group[5] for protection of 2-hydroxyl group of A ring. It was expected that fluoride anion mediated deprotection of SEM group would produce the phenoxy anion that undergoes simultaneous cyclization.



Scheme 1.

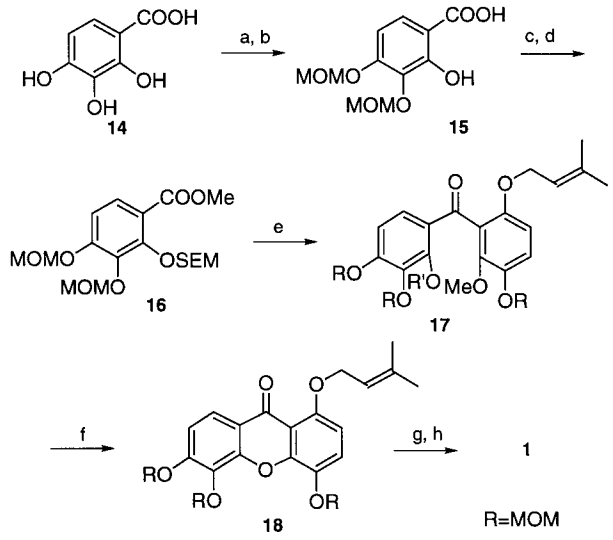
Thus, C ring component **13** was synthesized as shown in Scheme 2. Methoxyhydroquinone **11** was acetylated to diacetate, whose less hindered site was selectively hydrolyzed to give monoacetate **12**. The relationship of acetyl group and methoxy group of **12** was confirmed by NOE experiment.[6] The hydroxyl group of **12** was alkylated with 1-chloro-3-methyl-2-



Scheme 2. (a) Ac_2O, Py, DMAP, rt ; (b) KOH, MeOH, 0 °C (74% in 2 steps); (c) 1-chloro-3-methyl-2-butene, K_2CO_3, DMF, rt (74%); (d) KOH, MeOH, rt (97%); (e) MOMCl, NaH, DMF, rt (92%).

butene using potassium carbonate as the base, and then MOM group was introduced after deacetylation. Direct alkylation of less hindered hydroxyl group of **11** was unsuccessful.

The A ring component **16** was efficiently delivered from 2,3,4-trihydroxybenzoic acid **14** (Scheme 3). All the hydroxyl groups of **14** including carboxyl group were protected as MOM ether and ester. Basic hydrolysis of the ester group and acidic workup induced selective removal of MOM group adjacent to carboxyl group to give bis MOM ether **15** in good yield. Selective methylation of carboxyl group was achieved with iodomethane and sodium hydrogencarbonate and the free hydroxyl group was protected as SEM ether **16**.



Scheme 3. (a) MOMCl, NaH, rt, DMF (98%); (b) KOH, MeOH, H_2O, rt, then acidic workup (86%); (c) MeI, $NaHCO_3$, DMF, rt (98%); (d) SEMCl, NaH, DMF, rt (92%); (e) **13**, n-BuLi, TMEDA, THF -15 °C (43%); (f) TBAF, THF 80 °C, (70%); (g) *N,N*-diethylaniline, 150 °C (47%); (h)HCl, MeOH, rt (71%).

Lithiation[7] of **13** with BuLi in the presence of *N,N,N',N'*-tetramethylethylendiamine followed by reaction with **16** afforded the coupling product **17** in moderate yield. Deprotection of SEM group using tetrabutylammonium fluoride in THF induced the expected cyclization to give the desired product **18** in good yield. In contrast to the cyclization of model compound **2**, no side product was obtained under these conditions. Attempted Claisen rearrangement in the same vessel was unsuccessful at 150 °C using HMPA as a solvent. The rearrangement occurred smoothly in *N,N*-diethylaniline[8] at 150 °C giving MOM ether of **1**, which was converted to the final compound in acidic methanol. IR, ^{1}H- and ^{13}C-NMR spectra of synthetic subelliptenone F were identical with those of the natural product.

With this establishment of the efficient pathway to **1**, we are now preparing the analogues using this way. Full detail of synthetic studies and the relation between the structure and biological activity will be described in the future.

References and Notes

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6 In the NOESY spectrum of the alkylation product of **12**, cross peaks between methylene protons of alkyl group and both aromatic protons at ortho positions were observed.
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