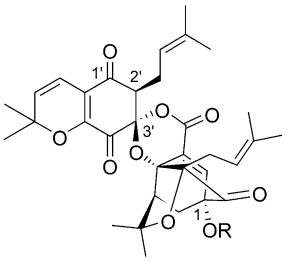
Natural Product Synthesis

Total Synthesis of 1-*O*-Methyllateriflorone**

K. C. Nicolaou, Pradip K. Sasmal, Hao Xu, Kenji Namoto, and Andreas Ritzén*

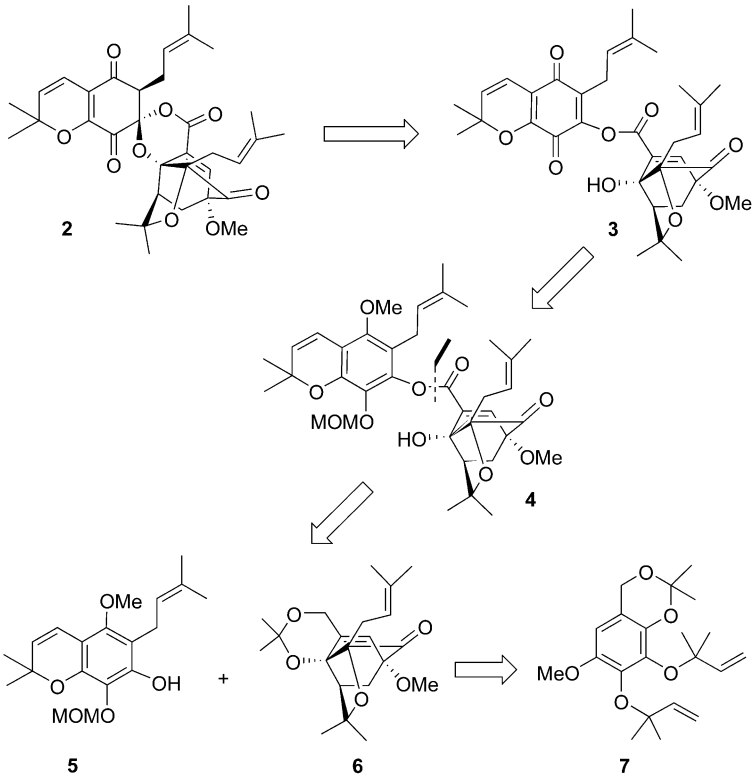
With its unique spiroxalactone framework carrying a prenylated dihydrobenzoquinone moiety and a trioxatetracyclo[7.4.1.$0^{2,7}$.$0^{2,11}$]tetradecane system, lateriflorone (**1**) represents an unusual synthetic challenge. Reported in 1999, this



1 (R = H): lateriflorone
2 (R = Me): 1-*O*-methyllateriflorone

novel natural product[1] was isolated from the stem bark of *Garcinia Lateriflora Bl* (*Guttiferae*) collected from Indonesia, and it exhibits potent cytotoxicity against the P388 cancer cell line ($ED_{50} = 5.4\ \mu g\,mL^{-1}$). Its seemingly fragile structure was secured by spectroscopic and X-ray crystallographic analysis. The secret of its stability, particularly at the spiroxalactone–dihydroquinone junction, is probably due to the *syn* arrangement between the C2′ proton and the C3′ ester grouping which locks the leaving group in place, avoiding the β-elimination pathway that may lead to its rupture. The intriguing structural features of lateriflorone, coupled with its biological activity, prompted us to seek a possible pathway for its construction in the laboratory. Herein we report our findings thus far in this project, including the first total synthesis of 1-*O*-methyllateriflorone (**2**).

We planned our synthesis of 1-*O*-methyllateriflorone (**2**) based on the expectation that the ester bond would be the easier bridge to forge between the two domains of the molecules. The retrosynthetic analysis began with the disconnection of the spiroxalactone moiety by rupturing its ethereal C–O bond, thus unraveling prenylated quinone **3** as a possible precursor (Scheme 1). The next rational disconnections, namely retro-aromatization of **3** and disassembly of its precursor **4** at the ester bond led to fragments **5** and **6** as suitable starting materials. Given our previous studies on forbesione,[2,3] a naturally occurring substance related to the present target, the cage ring system **6**[4] can be traced to the benzenoid compound **7**. The coupling partner **5** can be obtained from a simple benzene derivative.



Scheme 1. Retrosynthetic analysis of lateriflorone (**1**).

The required prenylated 2,2′-dimethybenzopyran fragment **5** was synthesized as summarized in Scheme 2. Thus, 2,3-dihydroxybenzaldehyde (**8**) was selectively benzylated at the 3-position according to a literature procedure[5] to afford compound **9**, which was converted into bromophenol **10** in 61% overall yield by the following sequence: a) bromination *para* to the phenolic group; b) protection as a MOM ether, c) oxidation with *m*-CPBA; and d) cleavage of the resulting formate ester with $NaHCO_3$ (for abbreviations of reagents and protecting groups, see legends in schemes). Protection of the phenolic group in **10** as a TIPS ether to form **11** proceeded smoothly under standard conditions (TIPSCl, imid, 96%). Boronation of **11** required premixing of the substrate with $B(OiPr)_3$ prior to addition of *t*BuLi in Et_2O at −78 °C. The resulting borate derivative was then oxidized with H_2O_2 under basic conditions (NaOH), and the resulting phenolic product was methylated to afford **12** in 76% overall yield from **11**.

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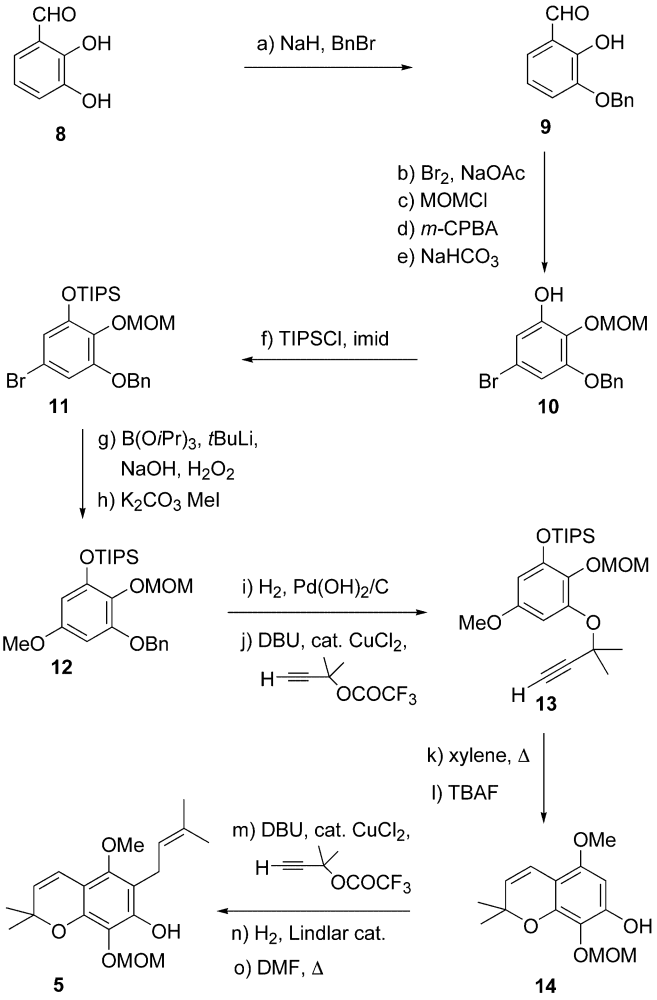


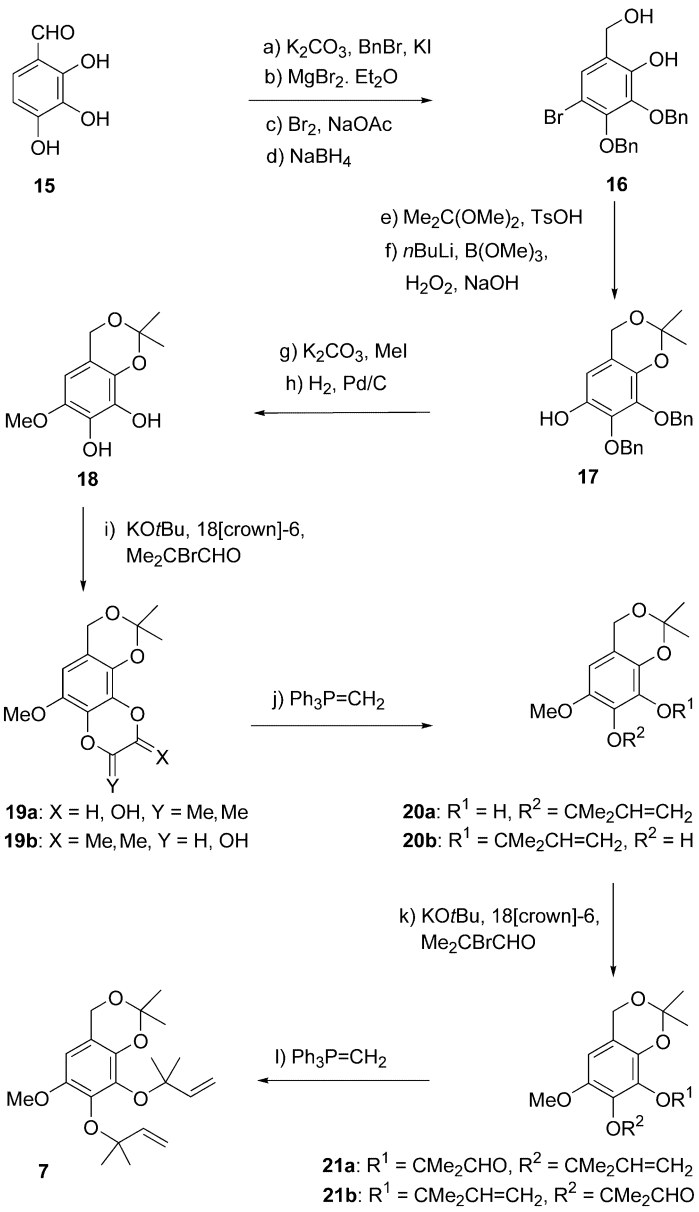
Scheme 2. Synthesis of prenylated 2,2′-dimethylbenzopyran fragment **5**: a) NaH (2.5 equiv), BnBr (1.0 equiv), THF, 25 °C, 48 h, 72%; b) Br_2 (1.1 equiv), NaOAc (1.2 equiv), AcOH, 25 °C, 2 h; c) Et_3N (5.0 equiv), 4-DMAP (0.1 equiv), MOMCl (3.0 equiv), 25 °C, 16 h; d) *m*-CPBA (1.1 equiv), 0→25 °C, CH_2Cl_2, 6 h; e) aqueous saturated $NaHCO_3$, 16 h, 61% for four steps; f) TIPSCl (1.5 equiv), imid (2.0 equiv), DMF, 25 °C, 2 h, 96%; g) premix **11** and $B(OiPr)_3$ (2.2 equiv) in diethyl ether; then *t*BuLi (2.2 equiv) at −78 °C, 2 h, −78→0 °C, 1 h; then MeOH, aqueous NaOH (10%; 4.8 equiv), H_2O_2 (5.0 equiv), 0 °C, 30 min, 86%; h) K_2CO_3 (10 equiv), MeI (10 equiv), acetone, 25 °C, 16 h, 88%; i) $Pd(OH)_2/C$ (10 wt%; 10%), H_2 (1 atm), EtOAc/EtOH (1:1), 25 °C, 30 min, 100%; j) propargyl alcohol (1.3 equiv), DBU (1.5 equiv), TFAA (1.2 equiv), MeCN, 0 °C, 30 min; DBU (1.35 equiv), $CuCl_2$ (0.01% equiv), 10 min; then TFA propargyl ester, 4 h, 0 °C, 76% (90% based on 84% conversion); k) xylene, 140 °C, 30 min; l) TBAF (1.5 equiv), THF, 0 °C, 5 min, 93% for two steps; m) propargyl alcohol (1.3 equiv), DBU (1.5 equiv), TFAA (1.2 equiv), MeCN, 0 °C, 30 min; DBU (1.35 equiv), $CuCl_2$ (0.01% equiv), 10 min; then TFA propargyl ester, 4 h, 0 °C, 80% (90% based on 86% conversion); n) Lindlar catalyst (10 wt%), H_2 (1 atm), EtOAc, quinoline (3 equiv), 25 °C, 2 h, 95%; o) DMF, 120 °C, 1 h, 70%. Bn = benzyl, 4-DMAP = 4-dimethylaminopyridine, MOM = methoxymethyl, *m*-CPBA = *m*-chloroperbenzoic acid, TIPS = triisopropylsilyl, imid = imidazole, DMF = *N*,*N*-dimethylformamide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TFAA = trifluoracetic anhydride, TBAF = tetra-*n*-butylammonium fluoride.

Hydrogenolysis of the benzyl group in this new product followed by reaction with $CH{\equiv}CC(Me)_2OCOCF_3$[6] in the presence of DBU and $CuCl_2$ resulted in the formation of propargylic ether **13** in 76% overall yield. Heating of the latter compound in refluxing xylene induced a Claisen rearrangement,[7] furnishing, after desilylation with TBAF, benzopyran derivative **14** in 93% overall yield. Finally, a second propargyl ether was introduced in **14**; selective reduction (H_2, Lindlar catalyst) of the acetylenic group to the corresponding olefin and Claisen rearrangement under thermal conditions provided the targeted prenylated benzopyran segment **5** in 53% overall yield.

The sequence devised and executed for the synthesis of precursor **7** is shown in Scheme 3. Thus, 2,3,4-trihydroxybenzaldehyde (**15**) was perbenzylated (K_2CO_3, BnBr, KI) and then selectively debenzylated at the position adjacent to the aldehyde group by the action of $MgBr_2{\cdot}Et_2O$. Subsequent *para* bromination (Br_2, NaOAc) and reduction of the aldehyde with $NaBH_4$ afforded dihydroxy compound **16** in 57% overall yield. Acetonide formation ($Me_2C(OMe)_2$, TsOH) followed by lithium–halogen exchange (*n*BuLi), borate formation ($B(OMe)_3$), and oxidation (H_2O_2, NaOH) led to phenolic substrate **17** in 86% overall yield. Methylation of **17** followed by hydrogenolysis of its benzyl ethers led to dihydroxy derivative **18** in 97% overall yield. The dipotassium salt of **18**, generated by addition of KO*t*Bu, was suspended in acetonitrile and treated with bromoisobutyraldehyde in the presence of 18[crown]-6 to afford a mixture of regioisomeric lactols **19a**,**b** (ca. 1:1, 70% yield), which reacted with methylene phosphorane ($MeP^+Ph_3Br^-$, NaHMDS) to provide olefins **20a**,**b** (ca. 1:1, 75% yield). Reiteration of the last two steps furnished, via **21a**,**b**, the required dialkene **7** in 60% overall yield.

Upon heating in DMF at 120 °C, the methoxy derivative **7** entered into the expected Claisen rearrangement/Diels–Alder cascade[3,8] leading through the indicated intermediate products to **6** and **6′** in 47 and 42% yields, respectively (Scheme 4). X-ray crystallographic analysis of **6′**[9] (see ORTEP drawing, Scheme 4) revealed its structure, and, by extension, that of **6**; both structures **6** and **6′** were also supported by NOE studies (see Scheme 4). Selective removal of the acetonide group from **6** (TsOH, MeOH), followed by a two-step oxidation protocol (1) DMP, 2) $NaClO_2$), led to hydroxy carboxylic acid **22** in 91% overall yield. An analogous sequence to that shown in Schemes 3 and 4 was originally employed to construct the dihydroxy acid **22a**. Attempted coupling of this fragment, **22a**), with the phenolic domain **5** (see Scheme 2), however, proved futile, presumably as a result of complications instigated by the free hydroxy group adjacent to the ketone moiety. Thus, this problem led to the targeting and adoption of the methoxy counterpart of this compound, substrate **22**, for our subsequent studies. The coupling of **22** with benzopyran system **5** (see Scheme 2) was smoothly realized under the influence of EDC and 4-DMAP (64% yield) to furnish the required advanced intermediate **4** as shown in Scheme 4.

Having assembled the entire lateriflorone carbon skeleton as expressed in compound **4**, its MOM group was selectively cleaved upon exposure to acidic conditions (HCl, MeOH/Et_2O) leading to a rapidly and spontaneously equilibrating mixture of phenolic esters **23a**,**b** (ca. 1:1, 96% yield) (Scheme 4). Oxidation of this mixture under a variety of



Scheme 3. Synthesis of intermediate **7**: a) K_2CO_3 (5.0 equiv), BnBr (5.0 equiv), KI (0.1 equiv), DMF, 25 °C, 24 h, 85 %; b) $MgBr_2{\cdot}Et_2O$ (1.1 equiv), diethyl ether, 25 °C, 10 h, 83 %; c) Br_2 (1.1 equiv), NaOAc (1.15 equiv), AcOH, 25 °C, 2 h, 89 %; d) $NaBH_4$ (1.5 equiv), EtOH, 0→25 °C, 30 min, 91 %; e) 2,2-dimethoxypropane (5.0 equiv), TsOH (0.01 equiv), CH_2Cl_2, 1 h, 95 %; f) *n*BuLi (1.1 equiv), diethyl ether, −78 °C, 2 h; then $B(OMe)_3$ (3.0 equiv), 1 h, −78→0 °C; then aqueous NaOH (10 %; 4.8 equiv), H_2O_2 (5.0 equiv), 0 °C, 30 min, 90 %; g) K_2CO_3 (5.0 equiv), MeI (10.0 equiv), DMF, 0→25 °C, 16 h, 99 %; h) Pd/C (10 wt %; 10 %), H_2 (1 atm), EtOAc, 25 °C, 45 min, 98 %; i) *t*BuOK (2.2 equiv), THF, 0 °C; then concentrated and suspended in MeCN; then 18[crown]-6 (2.2 equiv), 15 min, bromoisobutyraldehyde (5.0 equiv), 0→25 °C, 1 h, 70 %; j) $CH_3P^+Ph_3Br^-$ (3.0 equiv), NaHMDS (3.0 equiv), THF, 0 °C, 1 h, 75 %; k) *t*BuOK (1.1 equiv), THF, 0 °C; then concentrated and suspended in MeCN; then 18[crown]-6 (1.1 equiv), 15 min, bromoisobutyraldehyde (5.0 equiv), 0→25 °C, 1 h, 75 %; l) $CH_3P^+Ph_3Br^-$ (2.0 equiv), NaHMDS (2.0 equiv), THF, 0 °C, 1 h, 80 %. Ts = *p*-toluenesulfonyl, HMDS = hexamethyldisilazane.

conditions[10] did not lead directly to the desired lateriflorone molecular framework, but rather to an array of other products, among which the most interesting were those shown in Scheme 5. Thus, exposure of **23a,b** to $PhI(OCOCF_3)_2$ in CH_2Cl_2 led to benzoquinone **3** (Table 1) in 43 % yield. Attempts to cyclize this substance under

Table 1: Selected data for compounds **2**, **3**, and **25**.

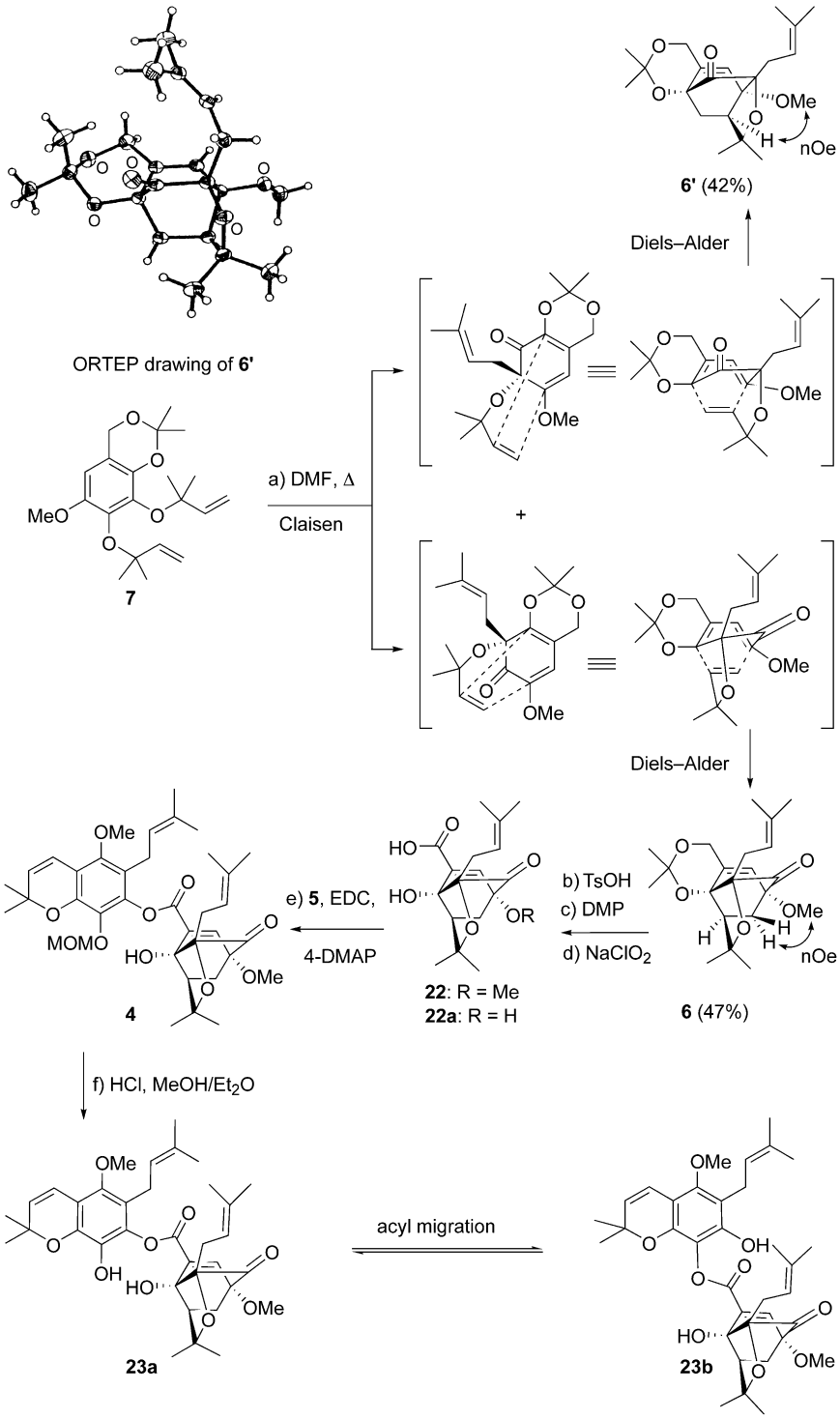
2: R_f = 0.19 (silica gel, EtOAc/hexanes 3:7); m.p. = 173–174 °C (Et_2O/hexane, uncorrected); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.50 (s, 1 H), 6.49 (d, J = 9.8 Hz, 1 H), 5.78 (d, J = 9.8 Hz, 1 H), 5.32 (br t, J = 7.0 Hz, 1 H), 4.66 (br t, J = 7.0 Hz, 1 H), 3.53 (s, 3 H), 3.20 (dd, J = 8.3, 3.1 Hz, 1 H) 2.83 (m, 1 H), 2.79 (m, 1 H), 2.56 (m, 1 H), 2.39 (dd, J = 14.5, 7.0 Hz, 1 H), 2.16 (d, J = 13.0 Hz, 1 H), 1.89 (d, J = 9.9 Hz, 1 H), 1.69 (s, 3 H), 1.68 (s, 3 H), 1.60 (dd, J = 13.0, 9.9 Hz, 1 H), 1.56 (s, 3 H), 1.55 (s, 3 H), 1.48 (s, 3 H), 1.45 (s, 3 H), 1.16 ppm (s, 3 H), 1.14 ppm (s, 3 H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 200.7, 189.0, 186.7, 158.0, 150.9, 139.0, 136.5, 133.6, 134.0, 125.2, 123.0, 121.6, 116.0, 115.4, 101.3, 85.6, 84.7, 84.0, 82.8, 81.3, 57.4, 54.1, 48.6, 31.9, 30.0, 29.1, 28.3, 28.2, 27.8, 25.9, 25.8, 21.6, 18.1, 17.9 ppm; HRMS (MALDI): calcd for $C_{34}H_{40}O_9Na^+$: 615.2564 [M+Na^+], found 615.2549

3: R_f = 0.32 (silica gel, EtOAc/hexanes 3:7); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.50 (s, 1 H), 6.45 (d, J = 10.1 Hz, 1 H), 5.63 (d, J = 10.1 Hz, 1 H), 5.43 (s, 1 H, OH, D_2O exchangeable), 4.99 (br t, J = 7.5 Hz, 1 H), 4.84 (br t, J = 7.2 Hz, 1 H), 3.57 (s, 3 H), 3.09–3.17 (m, 2 H), 2.68 (dd, J = 14.0, 6.9 Hz, 1 H), 2.61 (dd, J = 14.0, 7.9 Hz, 1 H), 2.37 (d, J = 13.0 Hz, 1 H), 2.35 (d, J = 10.1 Hz, 1 H), 1.69 (s, 3 H), 1.68 (dd, J = 13.0, 10.1, Hz, 1 H), 1.67 (s, 3 H), 1.61 (s, 3 H), 1.60 (s, 3 H), 1.59 (s, 3 H), 1.51 (s, 3 H), 1.50 (s, 3 H), 1.27 ppm (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.8, 182.8, 174.7, 162.5, 149.7, 146.7, 144.2, 135.6, 135.4, 135.3, 130.6, 128.7, 118.4, 117.2, 116.1, 115.0, 84.6, 84.2, 83.5, 82.7, 81.2, 54.0, 50.1, 31.4, 30.1, 29.2, 28.54, 28.53, 28.3, 26.1, 25.9, 23.5, 18.1, 17.9 ppm; HRMS (MALDI): calcd for $C_{34}H_{40}O_9Na^+$: 615.2564 [M+Na^+], found 615.2594

25: R_f = 0.24 (silica gel, EtOAc/hexanes 3:7); m.p. = 154 °C (Et_2O/hexane, uncorrected); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47 (s, 1 H), 6.25 (d, J = 10.0 Hz, 1 H), 5.84 (d, J = 10.0 Hz, 1 H), 5.24 (br t, J = 6.5 Hz, 1 H), 4.75 (br t, J = 8.0 Hz, 1 H), 3.60 (s, 3 H), 3.53 (s, 3 H), 3.24 (dd, J = 15.0, 8.0 Hz, 1 H), 2.99 (dd, J = 15.0, 6.5 Hz, 1 H), 2.84 (dd, J = 13.5, 8.0 Hz, 1 H), 2.40 (dd, J = 13.5, 6.0 Hz, 1 H), 2.13 (d, J = 13.0 Hz, 1 H), 2.08 (d, J = 9.5 Hz, 1 H), 1.75 (dd, J = 13.0, 9.5 Hz, 1 H), 1.68 (s, 6 H), 1.56 (s, 3 H), 1.49 (s, 3 H), 1.48 (s, 3 H), 1.44 (s, 3 H), 1.34 (s, 3 H), 1.16 ppm (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 201.5, 188.7, 159.0, 149.2, 140.4, 136.6, 136.1, 135.6, 132.6, 126.2, 124.7, 123.4, 121.7, 117.1, 116.2, 97.3, 85.2, 84.9, 84.0, 82.8, 78.0, 60.4, 54.0, 48.4, 31.9, 29.9, 28.3, 28.0, 27.7, 27.2, 26.0, 25.8, 24.5, 17.9, 17.8 ppm; HRMS (MALDI): calcd for $C_{35}H_{43}O_9$: 607.2901 [M+H^+], found 607.2886

a variety of conditions failed to produce the desired lateriflorone skeleton, leading instead to a number of other compounds whose description will have to await the full account of this work.

Having failed to construct the desired 1-*O*-methyllateriflorone (**2**) from quinone **3**, we then proceeded to investigate the possibility of casting this structural motif from **23a,b** via benzoquinone monoketal **24**. To this end, **23a,b** was exposed to $PhI(OCOCF_3)_2$ in $MeOH/CH_2Cl_2$ (1:1), which led to the formation of **24** (60 % yield) through the participation of a molecule of methanol. Upon subsequent treatment with PPTS in refluxing benzene under azeotropic conditions, **24** led to **25**



Scheme 4. Construction of advanced intermediate **23a,b**: a) DMF, 120 °C, 1 h, **6′** (42%) and **6** (47%); b) TsOH (20 mol%), MeOH, 25 °C, 16 h, 98%; c) DMP (2.0 equiv), $NaHCO_3$ (2.0 equiv), CH_2Cl_2, 25 °C, 30 min, 93%; d) $NaClO_2$ (6.0 equiv), NaH_2PO_4 (6.0 equiv), 2-methyl-2-butene (75.0 equiv), THF/*t*BuOH/H_2O (2:4:1), 30 min, 100%; e) EDC (1.5 equiv), 4-DMAP (1.5 equiv), **5** (2.0 equiv), CH_2Cl_2, 0→25 °C, 16 h, 64%; f) HCl (0.25 M) in MeOH/Et_2O (1:1), 0→25 °C, 1 h, 96%. DMP = Dess–Martin periodinane, EDC = 1-ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride.

(Table 1) in 69% yield, together with quinone **3**, which was obtained in 11% yield (Scheme 5). Pleasantly, compound **25** crystallized as beautiful yellow crystals whose X-ray crystallographic analysis[9] revealed its lateriflorone-like molecular architecture, including the correct stereochemistry at C3′ (see ORTEP drawing, Scheme 5). However, an attempt to hydrolyze the enol methyl ether within **25** under acidic conditions (HCl (aq.)/THF) led to red quinone ether carboxylic acid **3′** (80%), which after methylation with diazomethane, afforded red quinone methyl ester **26** (81%, Scheme 6). The structurally intriguing isomeric quinones **3** (Scheme 5) and **3′** (Scheme 6) may well be related to biogenetic precursors and/or in vivo degradation products of lateriflorone. As such, these novel compounds, **3** and **3′**, may exhibit biological activity, and so could 1,1′-*O*,*O*-dimethyllateriflorone (**25**).

At this juncture, we felt that benzoquinone carboxylic acid **3′** presented a new opportunity for a final attempt to reach the lateriflorone framework. Indeed, exposure of **3′** to PPTS in refluxing benzene under anhydrous conditions led, in 83% yield, to a single yellow substance whose spectral data strongly suggested the lateriflorone-like structure **2** (Scheme 6). Pleasingly, X-ray crystallographic analysis[9] of the crystalline **2** (Table 1) confirmed its identity as 1-*O*-methyllateriflorone, ending the quest for this highly unusual molecular architecture. The completely stereoselective manner in which both **3′** and **24** cyclize to the corresponding lateriflorone frameworks is noteworthy. It is not impossible that both reactions are under thermodynamic control, leading to the natural stereochemistry, which may represent the most stable configuration of this system.

The described chemistry opens a facile entry into the novel lateriflorone molecular architecture and underscores the importance of careful strategy design for its construction. Future studies in the field will include further methodological explorations and chemical biology investigations with the synthesized compounds.

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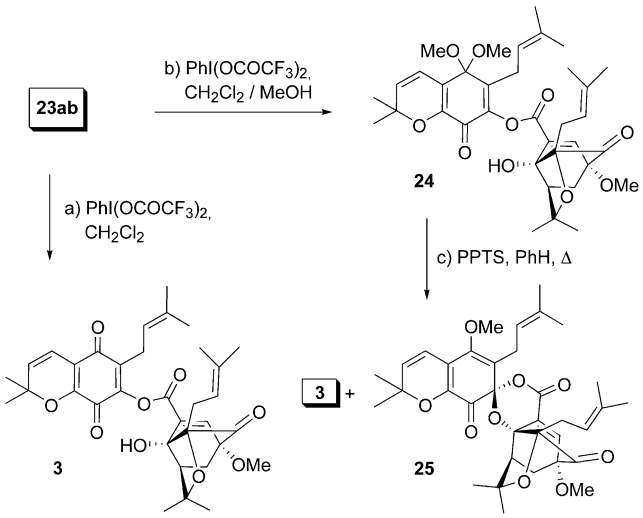
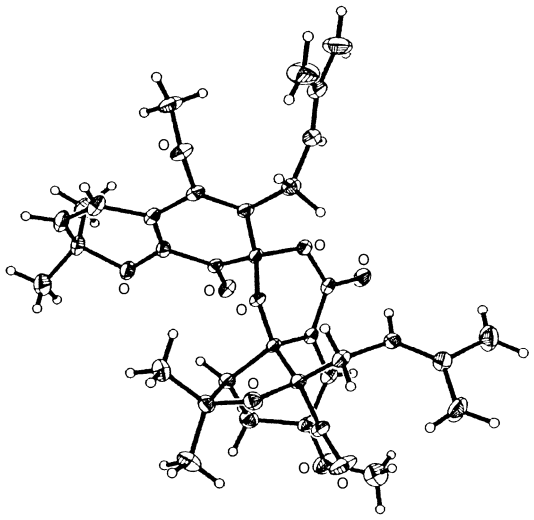
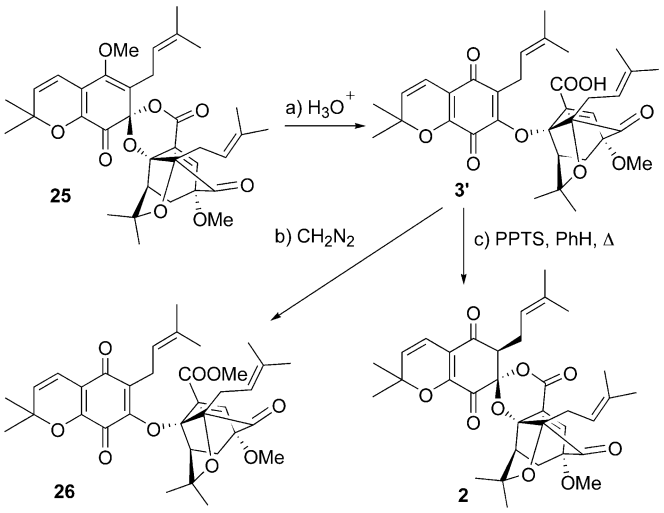
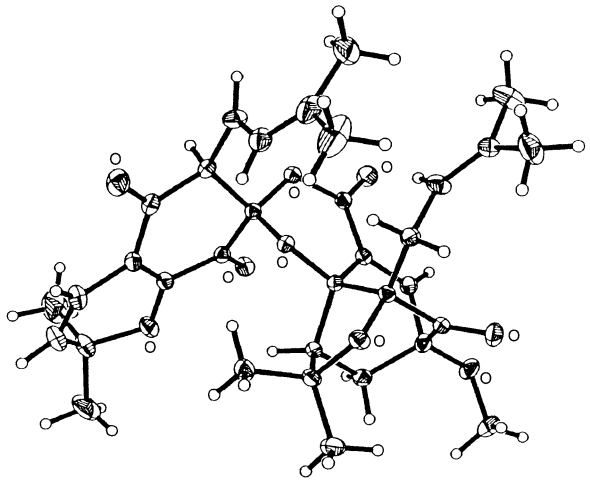




ORTEP drawing of **25**

Scheme 5. Synthesis and ORTEP drawing of 1,1′-*O*,*O*-dimethyllateriflorone (**25**): a) $PhI(OCOCF_3)_2$ (1.2 equiv), CH_2Cl_2, −78→25 °C, 2 h, 43%; b) $PhI(OCOCF_3)_2$ (1.2 equiv), CH_2Cl_2/MeOH (1:1), −78→25 °C, 2 h, 60%; c) PPTS (1.0 equiv), benzene, reflux, 4 h, **3** (11%) and **25** (69%). PPTS = pyridinium *p*-toluenesulfonate.





ORTEP drawing of **2**

Scheme 6. Synthesis and ORTEP drawing of 1-*O*-methyllateriflorone (**2**): a) aqueous HCl (1 N), THF, 0→25 °C, 16 h, 80%; b) CH_2N_2, diethyl ether, 0 °C, 30 min, 81%; c) PPTS (1.0 equiv), benzene, reflux, 4 h, 83%.

Keywords: cascade reactions · Claisen rearrangement · Diels–Alder reactions · electrocyclic reactions · natural products · quinones

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