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Biomimetically Inspired Total Synthesis and Structure Activity Relationships of 1-*O*-Methyllateriflorone. 6π Electrocyclizations in Organic Synthesis

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Abstract: The total synthesis of 1-*O*-methyllateriflorone (**2**) is described. The construction of the cage-like domain of the molecule involved a biomimetic Claisen/Diels−Alder cascade, whereas the novel spiroxalactone framework was generated by an intramolecular Michael reaction within precursor **16a** involving the carboxylate residue as the nucleophile. This finding might bear on the biosynthetic pathway by which nature forms lateriflorone. Described herein is also an interesting cascade sequence involving facile 6π electrocyclizations which leads to complex benzopyran systems. The biological evaluation of a small library of lateriflorone analogues and related systems establishing the first SAR within this class of compounds is also included. Among the most active compounds against tumor cells are **2**, **16b**, **56**, **58**, and **59**.

Introduction

The continuing phytochemical studies of *Garcinia* species (belonging to the Guttiferae family of tropical plants) led to the isolation of several xanthone-derived natural products, which possess unusual molecular architectures and diverse biological properties. Thus, some of these compounds exhibit noteworthy cytotoxic and antibacterial properties, and the plant sources from this family have been used by natives as folk medicines for centuries.[1] The signature structural motif of many of these compounds is an intriguing 4-oxatricyclo[4.3.1.0]decan-2-one scaffold attached onto a common xanthonoid ring system. Figure 1 displays a number of representative members of this class of cage-like xanthonoids, including lateriflorone (**1**),[2] morellin (**3**),[3] desoxymorellin (**4**),[3] morellic acid (**5**),[3] bractatin (**6**),[4] 1-*O*-methylbractatin (**7**),[4] 1-*O*-methylneobractatin (**8**),[4] forbesione (**9**),[5] gaudichaudione H (**10**),[6] scortechinone A (**11**),[7] and scortechinone B (**12**).[7] Among all, lateriflorone (**1**), isolated from the stem bark of *Garcinia Lateriflora Bl* (*Guttiferae*),[2] is the most interesting in that it possesses the additional complexity of a unique spiroxalactone moiety, making its total synthesis the ultimate challenge within this group of natural products.

Based on some scattered speculations, the biogenetic pathway[8] for the formation of the xanthonoid ring system of these compounds might involve an intramolecular oxidative coupling of benzephenone or benzophenone-like intermediates, which, in turn, are formed by the condensation of shikimate and acetate-derived moieties. In case of lateriflorone (**1**), it is hypothesized[2] that the unique spiroxalactone could be formed either by an oxidative cyclization of **13** (Scheme 1) or by the spiroketalization between the two fragments **14** and **15**. In the later case, the C7-keto functionality of **14** could react with the C7-hydroxyl group of **15** to form a hemiketal, which could subsequently undergo lactonization in a Michael fashion to generate the novel spiroxalactone system. Lateriflorone (**1**) exhibits potent cytotoxicity against the P388 cancer cells (ED$_{50}$ 5.4 μg/mL). Like with all other xanthonoids of this family, the mechanism of action of this compound is not known, although it is assumed that the intriguing cage domain of the molecule plays a role in their biological action. In this Article, we describe full details of our investigations in this area which culminated to the total synthesis of 1-*O*-methyllateriflorone (**2**), the application of 6π electrocyclizations in the synthesis of novel benzopyran systems, and the synthesis of several lateriflorone analogues and precursors and their biological evaluation.

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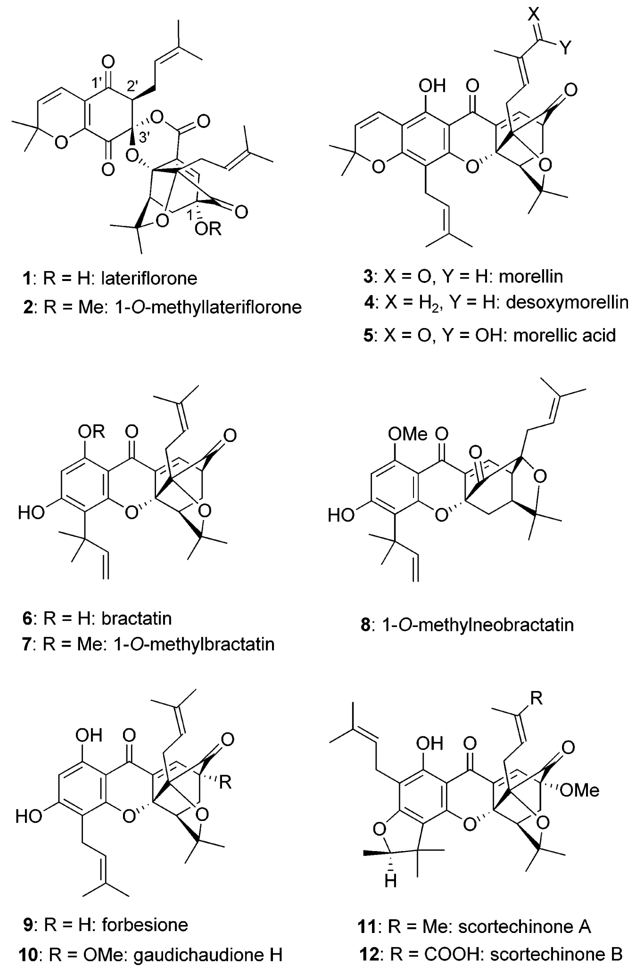
10.1021/ja040037+ CCC: $27.50



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

3: X = O, Y = H: morellin
4: X = H_2, Y = H: desoxymorellin
5: X = O, Y = OH: morellic acid

6: R = H: bractatin
7: R = Me: 1-*O*-methylbractatin

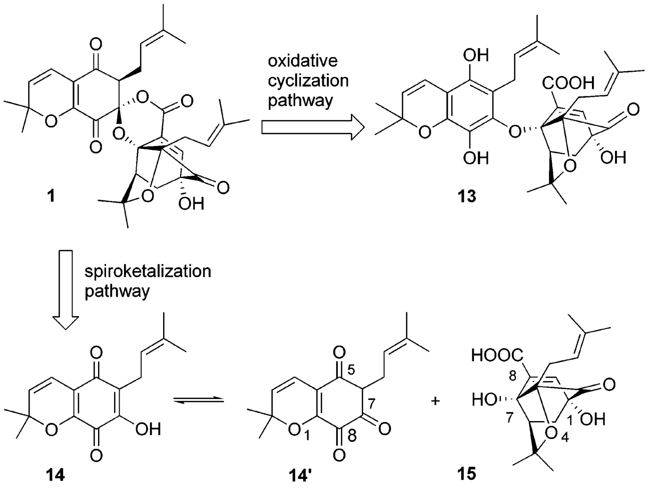
8: 1-*O*-methylneobractatin

9: R = H: forbesione
10: R = OMe: gaudichaudione H

11: R = Me: scortechinone A
12: R = COOH: scortechinone B

Figure 1. Selected natural products from the *Garcinia* family of plants.

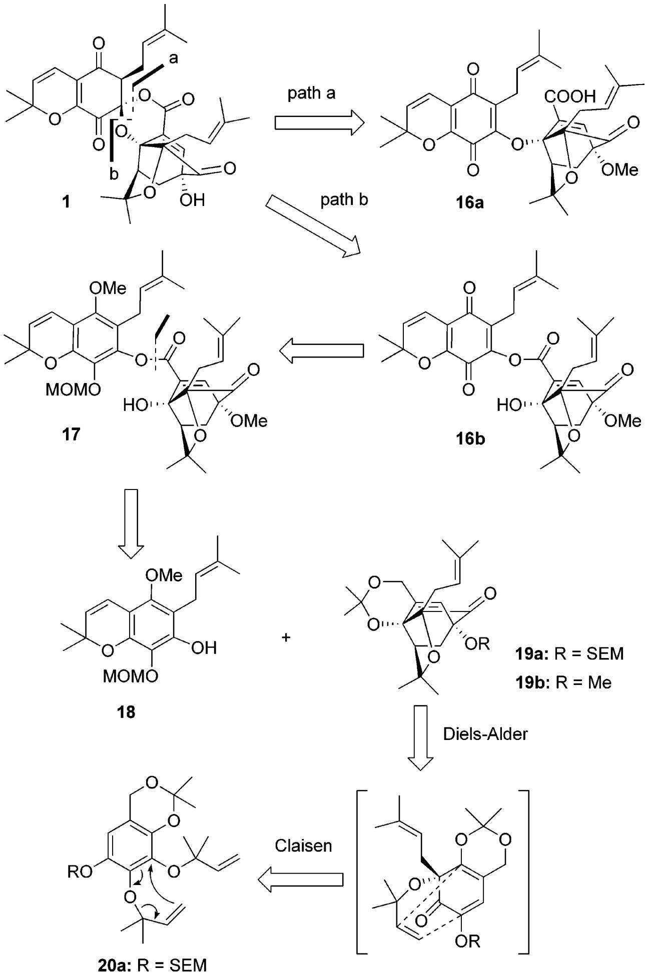
Scheme 1. Proposed Biosynthesis of Lateriflorone (**1**)



Results and Discussion

1. Retrosynthetic Analysis. Inspection of the structure of lateriflorone (**1**)[9] leads to the identification of the spirolactone-ketal moiety as the most appropriate strategic site for retrosynthetic disconnection. Not only are the two C−O bonds among the easiest to form in the molecule, but, most significantly, such disconnections would lead to a convergent strategy in the synthetic direction. Scheme 2 depicts the logic of the initial retrosynthetic analysis of **1**. Thus, rupturing bond **a** generates quinone-ether carboxylic acid **16a**. Intramolecular conjugate addition (path **a**) of the carboxyl group onto the closest enone carbon atom may be expected to lead to **1** − granted with an unknown stereochemical outcome. Alternatively, cleavage of the ether C−O bond of the spiroketal system leads to quinone-ester **16b**, whose similar intramolecular collapse (path **b**) may form the target molecule, again with the uncertainty of the stereochemical outcome at the two generated centers looming over the ring closure. In contemplating the choice between the two paths (**a** and **b**), the ease of construction of the required precursor (**16a** or **16b**) favored path **b**, because forming an ester bond was considered so much easier than casting an ether linkage as needed for path **a**. Having defined **16b** as the next target, its quinone moiety was then retrosynthetically transformed into the benzenoid system **17** whose disconnection at the ester bond led to fragments **18** and **19a**. Our previous study with forbesione (**9**)[10] pointed to the cascade approach to the cage intermediate **19a** from the aromatic system **20a** via one Claisen rearrangements and one Diels−Alder reaction (intramolecular) as shown in Scheme 2.

Scheme 2. Retrosynthetic Analysis of Lateriflorone (**1**)



SEM = $-CH_2OCH_2CH_2SiMe_3$

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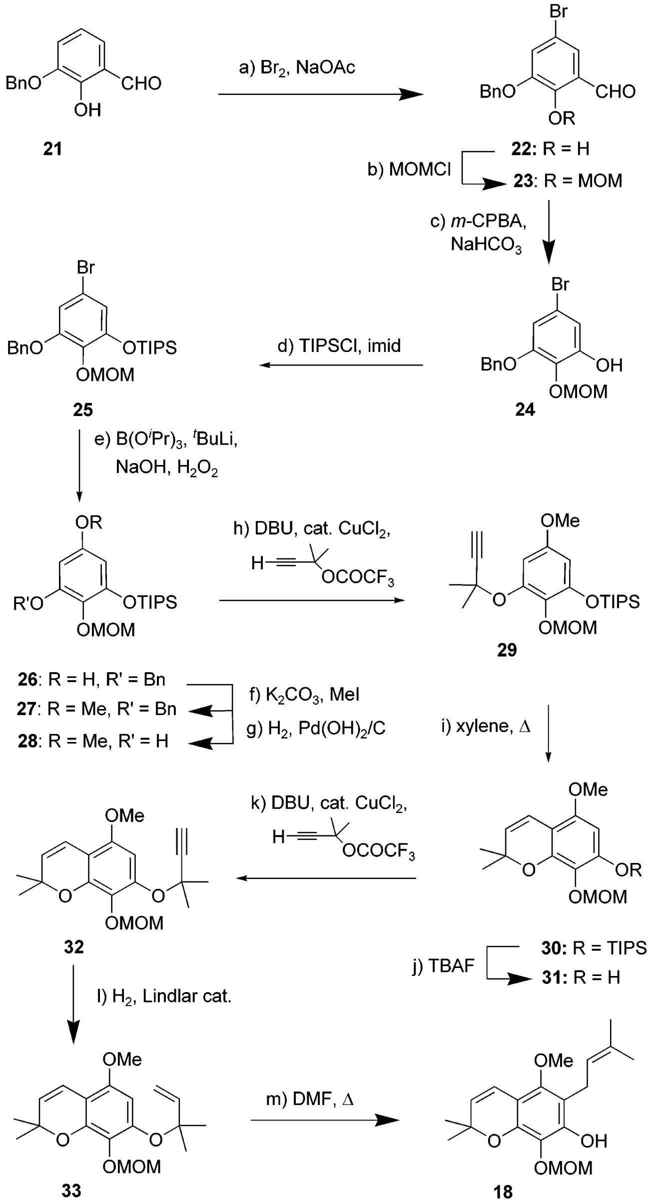
(9) (a) For a preliminary communication, see: Nicolaou, K. C.; Sasmal, P. K.; Xu, H.; Namoto, K.; Ritzen, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4225−4229. (b) For the synthesis of *seco*-lateriflorone, see: Tisdale, E. J.; Vong, B. J.; Li, H.; Kim, S. H.; Chowdhury, C.; Theodorakis, E. A. *Tetrahedron* **2003**, *59*, 6873−6887.

(10) For the total synthesis of 1-*O*-methyl forbesione, see: Nicolaou, K. C.; Li, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4264−4268.

2. Construction of the Benzopyran Domain. The synthesis of the required prenylated 2,2′-dimethybenzopyran fragment **18** is summarized in Scheme 3. Thus, the known compound **21**[11] was smoothly and selectively brominated at the *para* position with bromine in the presence of NaOAc to afford *p*-bromophenol **22** (92% yield) whose exposure to MOMCl−Et$_3$N led to MOM ether **23** (93% yield). Dakin oxidation (*m*-CPBA) of aldehyde **23** followed by in situ cleavage of the intermediate formate ester with NaHCO$_3$ furnished the new bromophenol **24** in 71% overall yield, which was protected as a TIPS ether by treatment with TIPSCl in the presence of imidazole, leading to compound **25** in 96% yield. Combining bromide **25** with B(O^{i}Pr)$_3$ in ether followed by sequential addition of ^{t}BuLi at −78 °C and NaOH−H$_2$O$_2$ at 0 °C furnished phenol **26** (86% yield) via the corresponding borate derivative.[12] The phenol (**26**) was then methylated (K$_2$CO$_3$−MeI) to afford methoxy compound **27** in 88% yield. Subsequent hydrogenolysis at the benzyl group in **27** (H$_2$, 10% Pd(OH)$_2$/C) afforded phenolic compound **28** in quantitative yield. Propargylation[13] of **28** using in situ generated HC≡CC(Me)$_2$OCOCF$_3$ in the presence of DBU and catalytic amounts of CuCl$_2$ afforded propargylic ether **29** in 76% yield (90% yield based on 84% conversion). Compound **29** underwent Claisen rearrangement[14] in refluxing xylene to furnish benzopyran system **30**. Removal of the solvent followed by treatment of the crude product with TBAF in THF gave desilylated product **31** in 93% overall yield from **29**. Finally, a second propargylation employing the same reaction conditions as mentioned above afforded benzopyran system **32** in 80% yield (91% based on 88% conversion). Selective reduction (H$_2$) of the acetylenic moiety in **32** in the presence of Lindlar catalyst generated the corresponding olefin (**33**) in 95% yield. A second Claisen rearrangement under thermal conditions (DMF, 120 °C) converted **33** to the targeted benzopyran fragment **18** in 70% yield.

Scheme 3. Construction of Benzopyran Fragment **18**[a]



[a] (a) Br$_2$ (1.1 equiv), NaOAc (1.2 equiv), AcOH, 25 °C, 2 h, 92%; (b) Et$_3$N (5.0 equiv), 4-DMAP (0.1 equiv), MOMCl (3.0 equiv), 25 °C, 16 h, 93%; (c) *m*-CPBA (1.1 equiv), 0 → 25 °C, CH$_2$Cl$_2$, 6 h; then saturated aqueous NaHCO$_3$, 16 h, 71%; (d) TIPSCl (1.5 equiv), imid (2.0 equiv), DMF, 25 °C, 2 h, 96%; (e) premix **25** and B(O^{i}Pr)$_3$ (2.2 equiv) in ether; then ^{t}BuLi (2.2 equiv) at −78 °C, 2 h, −78 → 0 °C, 1 h; then MeOH, 10% aqueous NaOH (4.8 equiv), H$_2$O$_2$ (5.0 equiv), 0 °C, 0.5 h, 86%; (f) K$_2$CO$_3$ (10 equiv), MeI (10 equiv), acetone, 25 °C, 16 h, 88%; (g) 10% Pd(OH)$_2$/C (10 wt %), H$_2$ (1 atm), EtOAc/EtOH (1:1), 25 °C, 0.5 h, 100%; (h) propargyl alcohol (1.3 equiv), DBU (1.5 equiv), TFAA (1.2 equiv), MeCN, 0 °C, 0.5 h; DBU (1.35 equiv), CuCl$_2$ (0.01 equiv), 10 min; then TFA propargyl ester was added, 4 h, 0 °C, 76% (90% based on 84% conversion); (i) xylene, 140 °C, 0.5 h; (j) TBAF (1.5 equiv), THF, 0 °C, 5 min, 93% for two steps; (k) propargyl alcohol (1.3 equiv), DBU (1.5 equiv), TFAA (1.2 equiv), MeCN, 0 °C, 0.5 h; DBU (1.35 equiv), CuCl$_2$ (0.01 equiv), 10 min; then TFA propargyl ester was added, 4 h, 0 °C, 80% (91% based on 88% conversion); (l) Lindlar catalyst (10 wt %), H$_2$ (1 atm), quinoline (3.0 equiv), EtOAc, 25 °C, 2 h, 95%; (m) DMF, 120 °C, 1 h, 70%. Bn = benzyl, 4-DMAP = 4-(dimethylamino)pyridine, MOM = methoxymethyl, *m*-CPBA = *m*-chloroperbenzoic acid, TIPS = triisopropylsilyl, imid = imidazole, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TFAA = trifluoracetic anhydride, TBAF = tetra-*n*-butylammonium fluoride.

3. Construction of the Caged Domain and Coupling of the Two Fragments. The sequence devised and executed for the synthesis of the initially designed precursor **20a** is shown in Scheme 4. Thus, commercially available 2,3,4-trihydroxybenzaldehyde (**34**) was perbenzylated with BnBr in the presence of K$_2$CO$_3$ and catalytic amounts of KI in DMF, generating the known aldehyde **35**[15] in 85% yield. Selective debenzylation of the phenolic group adjacent to the aldehyde moiety was achieved by the action of MgBr$_2$·Et$_2$O in ether, leading to *o*-hydroxybenzaldehyde derivative **36** in 83% yield. Bromination with molecular bromine in acetic acid of the later compound (**36**) resulted in the formation of *p*-bromophenol **37** in 89% yield. NaBH$_4$ reduction of aldehyde **37** afforded diol **38** (91% yield), which was subjected to acetonide formation, furnishing ketal **39** in 95% yield. This bromo compound (**39**) was then converted to phenolic substrate **40** in 90% overall yield following the standard protocol mentioned above via the borate intermediate. Thus, lithium−halogen exchange (^{n}BuLi), borate formation [B(OMe)$_3$], and oxidation with alkaline (NaOH) hydrogen peroxide resulted in **40** whose phenolic group was protected as

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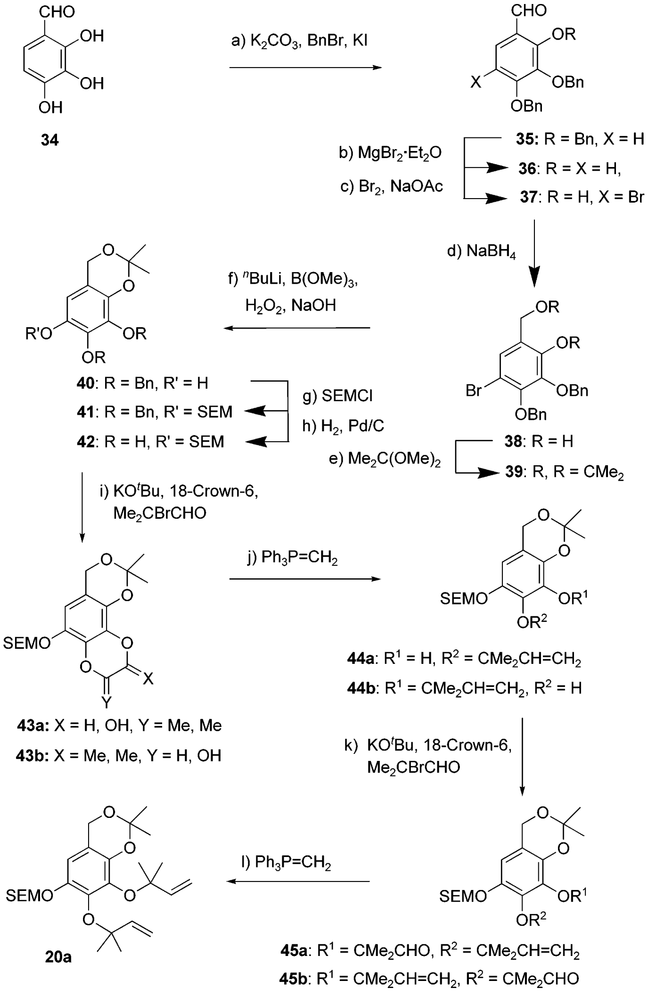
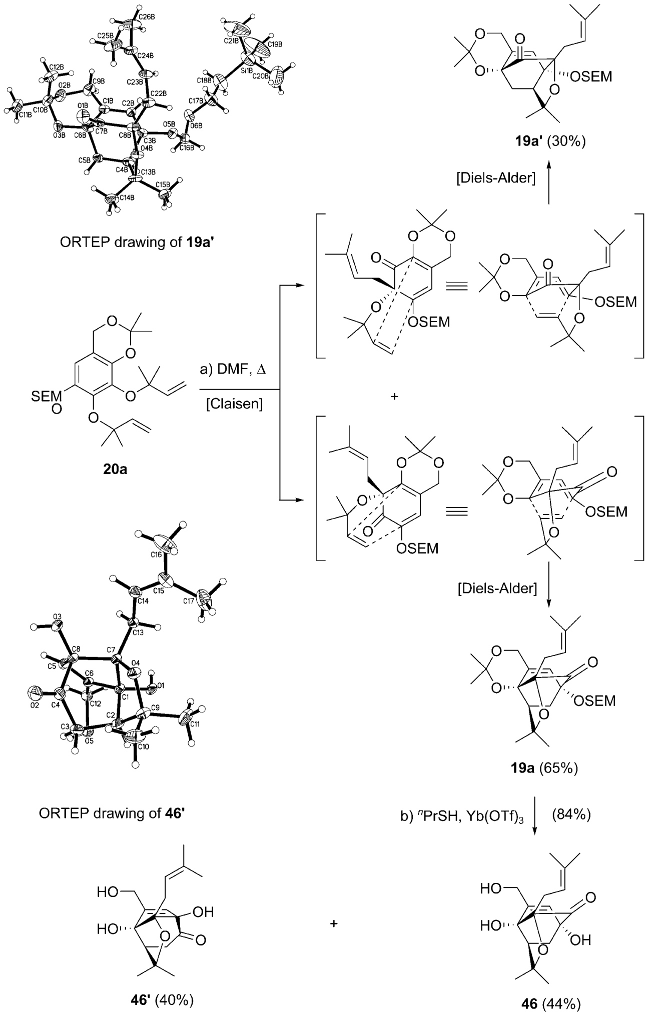
Scheme 4. Construction of Intermediate **20**[a]



[a] (a) K_2CO_3 (5.0 equiv), BnBr (5.0 equiv), KI (0.1 equiv), DMF, 25 °C, 24 h, 85%; (b) $MgBr_2{\cdot}OEt_2$ (1.1 equiv), 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, 0.5 h, 91%; (e) 2,2-dimethoxypropane (5.0 equiv), *p*-TsOH (0.01 equiv), CH_2Cl_2, 1 h, 95%; (f) ^nBuLi (1.1 equiv), ether, −78 °C, 2 h; then $B(OMe)_3$ (3.0 equiv), 1 h, −78 → 0 °C; then 10% aqueous NaOH (4.8 equiv), H_2O_2 (5.0 equiv), 0 °C, 0.5 h, 90%; (g) SEMCl (1.5 equiv), $(^iPr)_2$ NEt (2.0 equiv), CH_2Cl_2, 0 → 25 °C, 2h, 70%; (h) 10% Pd/C (10 wt %), H_2 (1 atm), EtOAc, 25 °C, 45 min, 95%; (i) ^tBuOK (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) ^tBuOK (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, 75%. Ts = *p*-toluenesulfonyl, HMDS = hexamethyldisilazane.

Scheme 5. First Attempt To Prepare the Cage-like Domain of Lateriflorone[a]



[a] (a) DMF, 120 °C, 2 h, **19a** (65%) and **19a′** (30%); (b) ^nPrSH (9.0 equiv), $Yb(OTf)_3$ (0.1 equiv), CH_2Cl_2, 25 °C, 1.5 h, 84%.

a SEM ether (SEMCl, Et_3N) to afford **41** (70% yield). Subsequent hydrogenolysis of the benzyl groups (H_2, 10% Pd/C, 95% yield) in **41** led to the formation of dihydroxy compound **42**. The di-potassium salt of **42**, generated by addition of KO^tBu, was then suspended in acetonitrile and reacted with bromoisobutyraldehyde[16] in the presense of 18-Crown-6 to afford an unseparable mixture of regioisomeric lactols (**43a**:**43b**, ca. 1.7:1 ratio,70% yield) which reacted with methylene phosphorane (generated from $MeP^+Ph_3Br^-$ and NaHMDS), leading to olefins **44a**:**44b** (ca. 1.7:1 ratio of the regioisomers, 75% yield). The phenolic group within **44** was alkylated with bromoisobutyraldehyde under the same reaction conditions as mentioned above to afford regioisomeric aldehydes **45a** and **45b** in 75% combined yield. A second Wittig reaction on the latter mixture then furnished the required di-olefin **20a** in 75% yield.

Having constructed the aromatic precursor **20a**, we then proceeded to the next stage which aimed at the rearrangement of this substrate to the desired cage-like intermediate via the projected Claisen/Diels−Alder cascade.[10,17] Thus, heating **20a** in DMF at 120 °C for 2 h led to the expected product **19a** (65% yield) and its regioisomer **19a′** (30% yield), presumably via the shown intermediates (see Scheme 5). The structures of these products were based on both spectroscopic and X-ray crystallographic techniques (see ORTEP drawing[18] of **19a′**, Scheme 5). Attempts to selectively remove the acetonide group from **19a**, however, were unsuccessful; instead, the various conditions tried led to unwanted products, including triol **46** (44% yield) and rearranged triol **46′** (40% yield), both of which were

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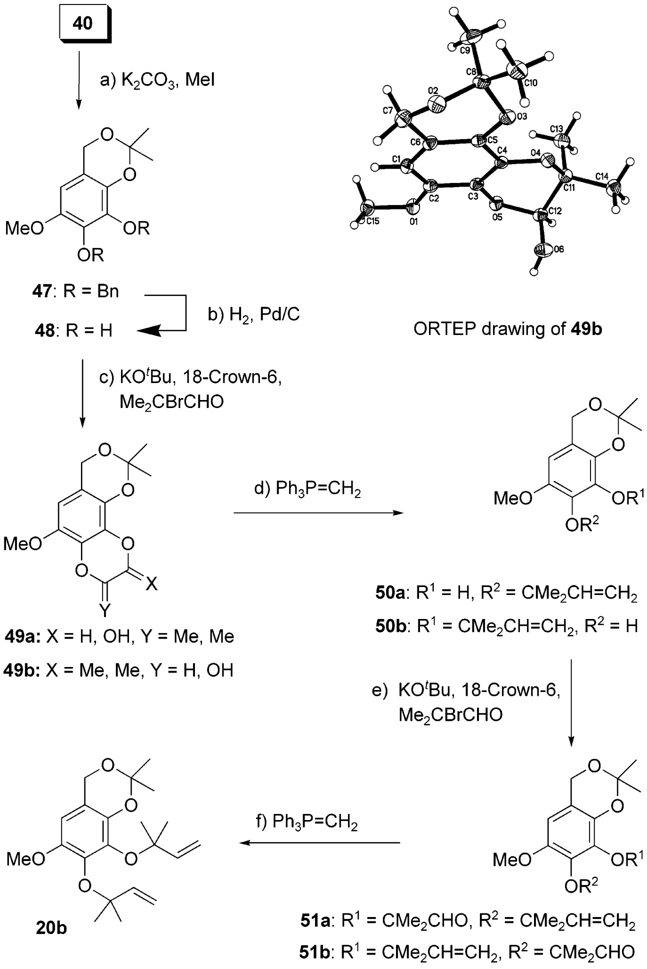
(16) Beckwith, A. L. J.; Thomas, C. B. *J. Chem. Soc., Perkin Trans. 2* **1972**, 861.

(17) (a) Quillinan, A. J.; Scheinmann, F. *Chem. Commun.* **1971**, 966−967. (b) Tisdale, E. J.; Chowdhury, C. Vong, B. G.; Li, H.; Theodorakis, E. A. *Org. Lett.* **2002**, *4*, 909−912.

(18) See the Supporting Information for crystallographic data of compounds **19a′**, **46′**, **49b**, **19b′**, **17**, **58**, and **2**.

Scheme 6. Construction of Key Building Block **20b**[a]



[a] (a) K_2CO_3 (5.0 equiv), MeI (10 equiv), DMF, 25 °C, 16 h, 99%; (b) 10% Pd/C (10 wt %), H_2 (1 atm), EtOAc, 25 °C, 45 min, 98%; (c) ^{t}BuOK (2.2 equiv), THF, 0 °C; then reaction mixture concentrated and suspended in MeCN; then 18-Crown-6 (2.2 equiv), 15 min, bromoisobutyraldehyde (5.0 equiv), 0 → 25 °C, 1 h, 70%; (d) $CH_3P^+Ph_3Br^-$ (3.0 equiv), NaHMDS (3.0 equiv), THF, 0 °C, 1 h, 75%; (e) ^{t}BuOK (1.1 equiv), THF, 0 °C; then reaction mixture concentrated and suspended in MeCN; then 18-Crown-6 (1.1 equiv), 15 min, bromoisobutyraldehyde (5.0 equiv), 0 → 25 °C, 1 h, 75%; (f) $CH_3P^+Ph_3Br^-$ (2.0 equiv), NaHMDS (2.0 equiv), THF, 0 °C, 1 h, 80%.

obtained upon exposure to ^{n}PrSH−Yb(OTf)$_3$.[19] Apparently, the rearranged keto-triol **46′** is formed by the Lewis acid-induced α-ketol rearrangement[20] of the parent triol **46**. Although these two triols were chromatographically unseparable, the rearranged compound (**46′**) crystallized preferentially from an ether/hexane solution of the mixture, thus enabling its X-ray crystallographic analysis[18] (see ORTEP drawing of **46′**, Scheme 5).

In the face of this rather unexpected circumstance, we decided to target lateriflorone's 1-*O*-methyl derivative (**2**) to avoid the complications arising from the deacetonization step. We, therefore, adopted the methoxy derivative **20b** (Scheme 6) as the substrate for the Claisen/Diels−Alder cascade sequence. Its construction proceeded along lines similar to those already described above for compound **20a** and is summarized in Scheme 6. Thus, phenolic compound **40** was methylated (K_2CO_3, MeI) to afford methoxy derivative **47** (99% yield), and the latter compound was debenzylated (H_2, 10% Pd/C, 98% yield), leading to bis-phenol **48**. This compound was found to be quite sensitive on standing and was, therefore, taken immediately to the next step which involved generation of the di-potassium salt (KO^{t}Bu−18-Crown-6) followed by quenching with bromoisobutyraldehyde to afford a mixture of regioisomeric lactols (**49a**:**49b**, ca. 1:1 ratio, 70% yield). These two lactols were separated by chromatography, allowing the X-ray crystallographic analysis[18] of the one that crystallized (**49b**) from its ether−hexane solution (see ORTEP drawing of **49b**, Scheme 6). Each of the two lactols (**49a** and **49b**) was subjected to Wittig olefination ($Ph_3P{=}CH_2$) to afford the corresponding phenolic olefin (**50a** and **50b**) in 70% yield. Reiteration of the last two-step sequence furnished the targeted di-olefin **20b**, via **51a** and **51b** (60% overall yield).

Upon heating in DMF at 120 °C for 1 h, the methoxy derivative **20b** entered into the expected Claisen Diels−Alder cascade channel, leading to the indicated intermediate products **19b** and **19b′** in 47% and 42% yields, respectively (see Scheme 7). An X-ray crystallographic analysis[18] of **19b′** revealed its structure, and by extension that of **19b**. Both structures **19b** and **19b′** were also supported by nOe studies. Selective removal of the acetonide group from **19b** was achieved by treatment of **20b** with catalytic amounts of *p*-TsOH in methanol, furnishing diol **52** in 98% yield. A two-step oxidation protocol (DMP;[21] $NaClO_2$[22]) then was employed to convert diol **52** to the required hydroxy carboxylic acid **54** in 93% overall yield via intermediate aldehyde **53**. The crucial coupling of carboxylic acid **54** with phenol **18** (see Scheme 3) was brought about by EDC and 4-DMAP, leading to advanced intermediate ester **17** in 64% yield. Crystalline **17** yielded to X-ray crystallographic analysis (see ORTEP drawing of **17**, Scheme 7).

4. Final Stages of the Synthesis. Having constructed the ester bridge between the two domains, the next task called for oxidation of the molecule's aromatic nucleus to a quinone and ring closure to lateriflorone's spirolactone skeleton. To this end, compound **17** was exposed to the action of 0.25 N HCl in MeOH:Et$_2$O (1:1) solution, leading to a spontaneously equilibrating mixture[23] of phenolic esters (**55a**:**55b**, ca. 1:1, 96% yield) (see Scheme 8). Careful separation of the two components of this mixture by HPLC revealed the rapid equilibration of each back to the original ca. 1:1 composition. It was, however, decided to proceed to the next step in the hopes that at least some of the desired oxidation product, or even the targeted lateriflorone derivative, might result. Oxidation of this mixture (**55a**:**55b**) under a variety of conditions[24] did not lead, however, to the desired outcome, but rather to an array of other products,

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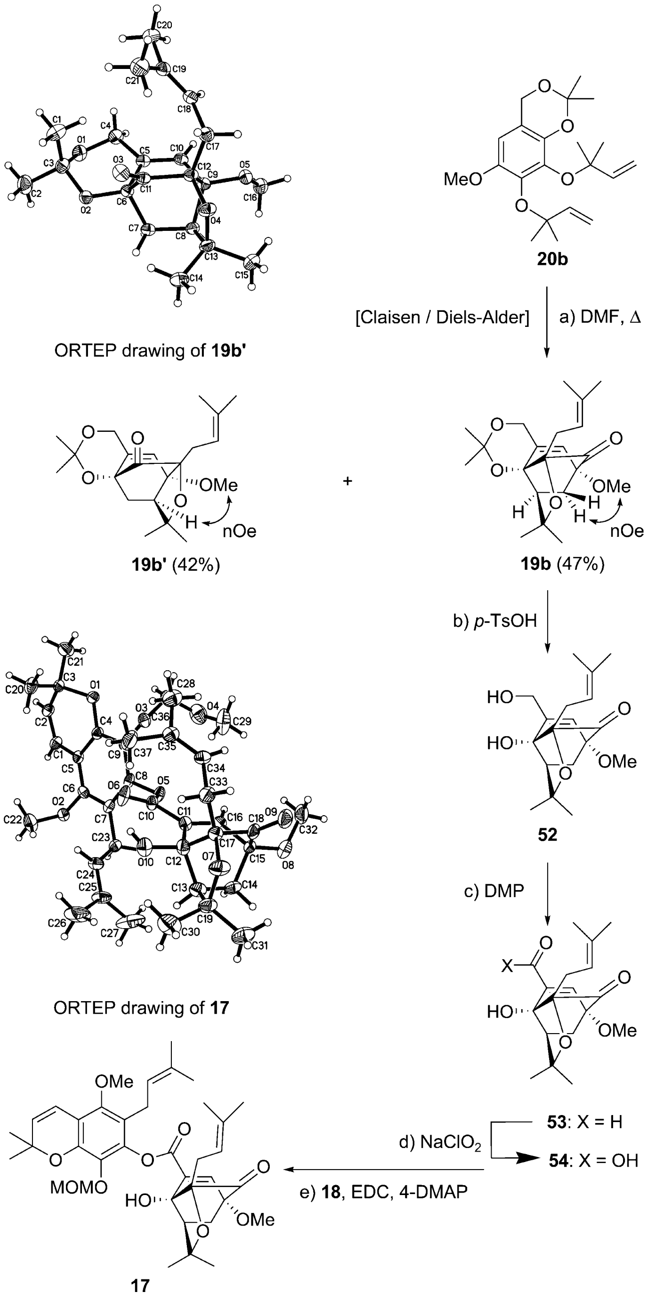
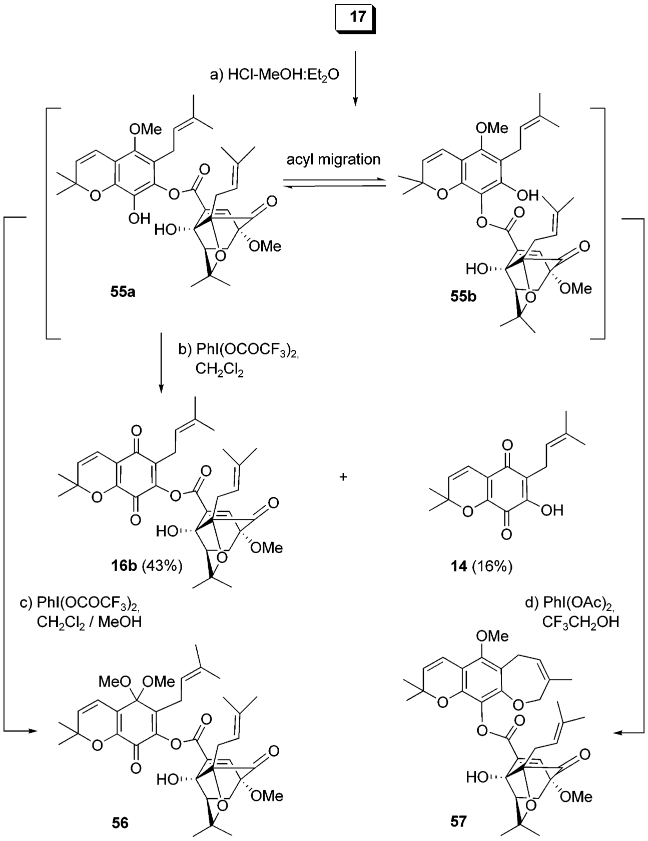
Scheme 7. Synthesis of Advanced Intermediate **17**[a]



[a] (a) DMF, 120 °C, 1 h, **19b** (47%) and **19b′** (42%); (b) *p*-TsOH (20 mol %), MeOH, 25 °C, 16 h, 98%; (c) DMP (2.0 equiv), $NaHCO_3$ (2.0 equiv), CH_2Cl_2, 25 °C, 0.5 h, 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), 0.5 h, 100%; (e) EDC (1.5 equiv), 4-DMAP (1.5 equiv), **18** (2.0 equiv), CH_2Cl_2, 0 to 25 °C, 16 h, 64%. DMP = Dess−Martin periodinane, EDC = 1-ethyl-(3-dimethylaminopropyl)carbodiimide hydrochloride.

Scheme 8. Oxidation of Phenols **55ab** with Hypervalent Iodine Reagents[a]



[a] (a) 0.25 M HCl in MeOH:ether (1:1), 0 → 25 °C, 1 h, 96%; (b) $PhI(OCOCF_3)_2$ (1.2 equiv), CH_2Cl_2, −78 → 25 °C, 2 h, **16b** (43%) and **14** (16%); (c) $PhI(OCOCF_3)_2$ (1.2 equiv), CH_2Cl_2:MeOH (1:1), −78 → 25 °C, 2 h, 60%; (d) $PhI(OAc)_2$ (1.2 equiv), pyridine (cat.), CF_3CH_2OH, −20 → 0 °C, 30 min, 15%.

among which the most interesting are those shown in Scheme 8. Thus, exposure to $PhI(OAc)_2$ in CF_3CH_2OH afforded a complex mixture from which was isolated novel benzo-oxepene ring system **57** (15% yield), presumably formed from **55b** via radical chemistry.[25] On the other hand, reaction of **55a**:**55b** with $PhI(OCOCF_3)_2$ in MeOH:CH_2Cl_2 (1:1) led to benzoquinone monoketal **56** (60% yield) through the participation of a molecule of methanol.[26] Hydroxyquinones **16b** (43% yield) and **14**[9b] (16% yield) were obtained as the only characterizable products from **55a**:**55b** upon treatment with $PhI(OCOCF_3)_2$ in CH_2Cl_2 (see Scheme 8).

The failure to obtain the lateriflorone structure directly from the oxidation of **55a**:**55b** did not end the chase for lateriflorone, because the newly formed hydroxyquinone **16b** held considerable promise as a potential precursor to the coveted architecture. Toward this goal, several attempts were made, including protocols involving acidic conditions (e.g., PPTS, *p*-TsOH, TFA, amberlyst 15), basic conditions (e.g., Et_3N, DBU, LiHMDS, NaH), sealed tube high temperature (180 °C), and high pressure (100 psi) treatment in xylene under microwave irradiation, as well as silica supported (both acidic and basic) microwave irradiation. In all cases, decomposition and/or recovery of starting material was observed with no evidence of spiroxalactone formation.

At this juncture, we reasoned that the poor nucleophilicity of the tertiary hydroxyl group was responsible for the failure to obtain the desired spiroxalactone moiety from hydroxyquinone **16b**, and we proceeded to design a more electrophilic Michael acceptor to enhance the chances for ring closure involving the same tertiary hydroxyl group. Toward this purpose, hydroxy dimethyl ketal **56** was treated with PPTS in refluxing benzene, and, according to our expectation, spiroxalactone compound **58**

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(25) For a precedent of radical generation with $PhI(OAc)_2$, see: Dorta, R. L.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez, E. *J. Chem. Res., Synop.* **1990**, 240−241.

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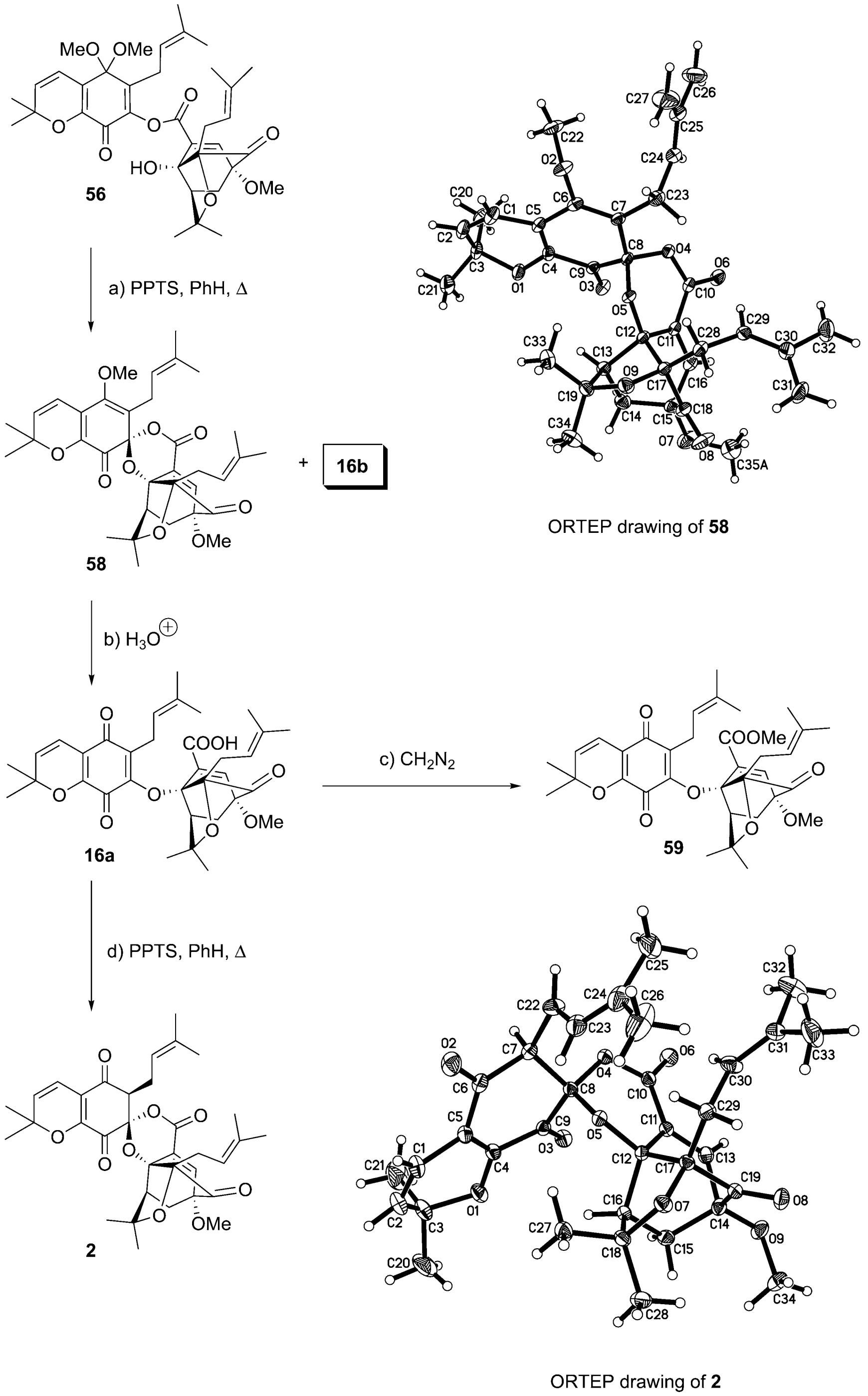
Scheme 9. Synthesis of 1-*O*-Methyllateriflorone (**2**)[a]



[a] (a) PPTS (1.0 equiv), benzene, reflux, 4 h, **58** (69%) and **16b** (11%); (b) 1 N aqueous HCl, THF, 0 → 25 °C, 16 h, 80%; (c) excess CH_2N_2, ether, 0 °C, 0.5 h, 81%; (d) PPTS (1.0 equiv), benzene, reflux, 4 h, 83%. PPTS = pyridinium *p*-toluene sulfonate.

was formed in 69% yield, together with quinone **16b** (11% yield) (see Scheme 9). The latter compound might be formed by simple rupture of the ketal moiety prior to cyclization. Compound **58** crystallized in beautiful yellow crystals, whose X-ray crystallographic analysis[18] revealed its lateriflorone-like molecular architecture, including the correct stereochemistry at C-3′ (see ORTEP drawing, Scheme 9). From compound **58**, 1-*O*-methyllateriflorone (**2**) was in sight, the two compounds separated only by ketal hydrolysis. While mild acidic conditions employing PPTS or TFA left **58** unchanged, an attempt to hydrolyze the enol methyl ether within **58** employing aqueous HCl in THF at room temperature led to red quinone ether carboxylic acid **16a** in 80% yield. This acid was derivatized and characterized as its methyl ester **59**, a red colored substance, obtained in 81% yield upon methylation with diazomethane.

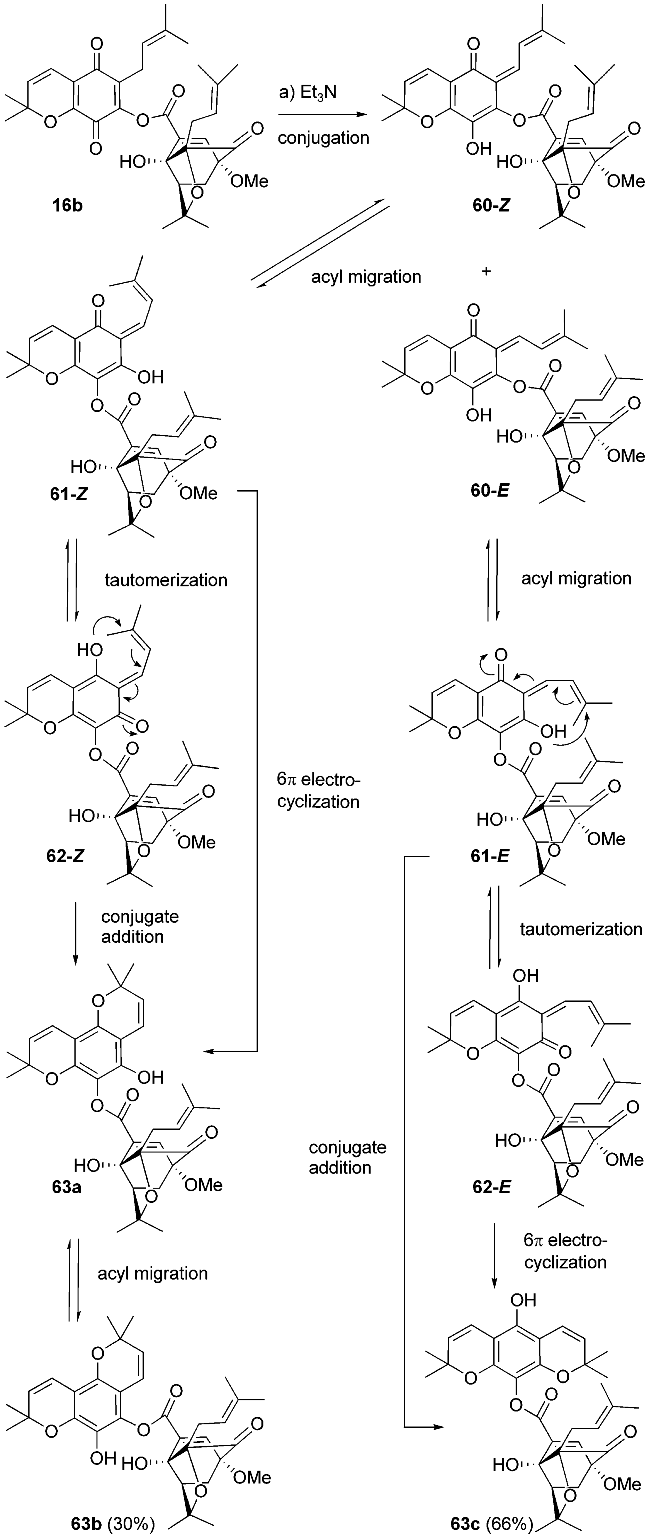
Compound **16a** presented yet another opportunity to effect the long-sought ring closure to the lateriflorone framework, the expectation being that acid treatment would initiate the required conjugate addition. Indeed, exposure of **16a** to PPTS in refluxing benzene led to the formation of a single yellow substance whose spectral data were consistent with the expected, lateriflorone-like structure **2**. Also, upon crystallizing fron an ether−hexane solution in beautiful yellow crystals, this compound yielded to X-ray crystallographic analysis[18] (see ORTEP drawing, Scheme 9), which confirmed beyond doubt its structure (**2**). Thus, the quest for this unusual molecular architecture was complete. Attempts to remove the methyl group from the C-20 oxygen were not successful, presumably due to the inherent instability of the labile α-ketol moiety, especially under the Lewis acid conditions employed in the attempts.

The exclusively regio- and stereoselective manner by which both substrates **16a** and **56** cyclize under acid conditions to form the spirolactone framework is noteworthy. In both cases, the reaction may proceed under thermodynamic control, leading to the natural stereochemistry at C-3′. In the case of **16a**, the cyclization leads to what might actually be the thermodynamically most stable configuration at both C-2′ and C-3′, which also happens to be the natural arrangement at those centers.

5. Synthetic Technology for the Construction of Benzopyrans via Facile 6π Electrocyclizations. From the several attempts to accomplish the required ring closure to the spirolactone fragments, the one involving Et_3N led to the most interesting results, even though it, too, like the others failed to produce the desired outcome. Thus, exposure of **16b** to Et_3N in CH_2Cl_2 at room temperature (the red solution turned immediately to yellow) followed by concentration and chromatographic purification led to isolation of compounds **63a**:**63b** (30%, equilibrium mixture of regioisomers due to internal acyl migration, yellow) and **63c** (66%, colorless) (see Scheme 10). To explain the formation of these intriguing structures from **16b**, we propose initial conjugation of **16b** to its two geometrical isomers **60-*Z*** and **60-*E***, which then follow different reaction paths, leading to the observed products via a series of bond reorganizations, including a 6π electrocyclization[14b,27](or a conjugate addition, **62-*Z*** → **63a** and **61-*E*** → **63c**) as the key ring-forming process.

The mild conditions and high yield associated with this cascade sequence[28] boded well for its further exploitation to generate benzopyran-type[29] compounds from the corresponding quinonoid systems. As shown in Table 1, this entry into this series of compounds (**64** → **67a**−**c**; **65** → **68a**−**c**; and **66** → **69a**−**c**) is quite general and holds promise for the construction of a variety of natural-product-like structures.

Scheme 10. Cascade Sequence Leading from Quinone **16b** to Benzopyrans **63a**−**c**[a]



[a] (a) Et_3N (10 equiv), CH_2Cl_2, 25 °C, 1 h, **63ab** (30%) and **63c** (66%).

6. Biological Investigations. The campaign toward lateriflorone produced a number of key building blocks and advanced intermediates which were considered worthy of biological evaluation. Following the lead of the natural substance, we proceeded to screen such compounds (see Table 2) as cytotoxic agents against ovarian cancer cells 1A9 (parental), A2780, and AD10 (transformed 1A9, producing drug transporter pgp). The first noteworthy observation was that these compounds are not substrates for pgp because the IC_{50} values are not so different in the two assays as shown in Table 2. Second, it was noted that compound **58** is the most potent of the series, being 4−5 times more potent than 1-*O*-methyllateriflorone (**2**). Interestingly, the benzoquinone monoketal **56**, which lacks the spiro-

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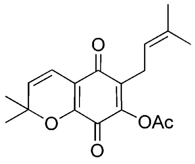
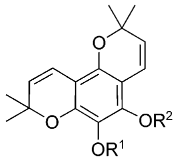
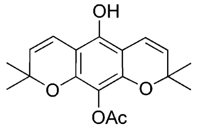
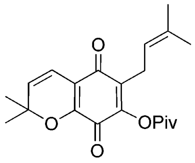
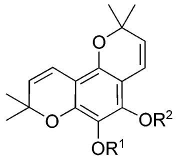
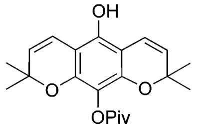
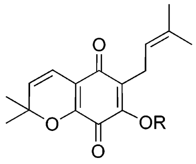
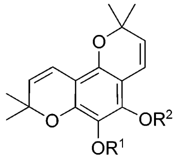
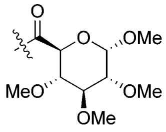
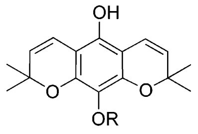
(28) For recent reviews on cascade reactions in organic synthesis, see: (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. E. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698. (b) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551−564.

(29) For recent advances in benzopyran synthesis, see: (a) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. *J. Am. Chem. Soc.* **2000**, *122*, 9939−9953. (b) Nicolaou, K. C.; Pfefferkorn, J. A.; Mitchell, H. J.; Roecker, A. J.; Barluenga, S.; Cao, G.-Q.; Affleck, R. L.; Lillig, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 9954−9967. (c) Nicolaou, K. C.; Pfefferkorn, J. A.; Barluenga, S.; Mitchell, H. J.; Roecker, A. J.; Cao, G.-Q. *J. Am. Chem. Soc.* **2000**, *122*, 9968−9976.

(30) Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. *J. Natl. Cancer Inst.* **1990**, *82*, 1107−1112.

Table 1. Synthesis of Benzopyran System via 6π Electrocyclizations[a]

Entry	Substrate	Product(s)	Yield (%)
1	 **64**	 **67a**: R^1 = Ac, R^2 = H **67b**: R^1 = H, R^2 = Ac	36^b
		 **67c**	54
2	 **65**	 **68a**: R^1 = Piv, R^2 = H **68b**: R^1 = H, R^2 = Piv	43^c
		 **68c**	52
3	 **66**	 **69a**: R^1 = R, R^2 = H **69b**: R^1 = H, R^2 = R	41^d
	R = 	 **69c**	50

[a] Reactions were carried out on 1.0 mmol scale in dichloromethane with 10 equiv of Et_3N at room temperature for 1 h. [b] 2:1 equilibrium mixture. [c] 1:1 equilibrium mixture. [d] 10:1 equilibrium mixture.

Table 2. Cytotoxicity of Selected Compounds against 1A9, A2780, and AD10 Human Carcinoma Cells[a]

entry	compounds	1A9 (IC_{50} in μM)	A2780/AD10 (pgp expresser)
1	**52**	150	150
2	**54**	87	136
3	**17**	63	99
4	**57**	28	63
5	**18**	56	81
6	**14**	96	104
7	**16b**	17	25
8	**16a**	37	49
9	**56**	9	10
10	**58**	5	5
11	**59**	17	23
12	**2**	25	37

[a] The antiproliferative effects of the tested compounds against the parental 1A9 and resistant clones (A2780 and AD10) were determined in a 72 h growth inhibition exposure using the SRB (sulforhodamine-B) assay.[30]

lactone moiety, exhibited approximately 2.5 times the activity of **2**. It is also of interest to note that the seco-analogues (open forms) **16a** and **16b** were found to be more or less equipotent to their cyclized counterpart, compound **2**. Finally, the two precursor domains of lateriflorone, building blocks chromene quinone **14** and hydroxy acid **54**, showed poor activity against these cell lines.

Conclusion

Described herein is a convergent strategy for the synthesis of the unprecedented and highly unusual structure of 1-*O*-methyllateriflorone (**2**). The synthetic journey to this target required several redesigns and attempts to cast the final C−O bond of the novel spirolactone moiety. The successful final fusion turned out to be that involving the carboxylate residue, and not the tertiary alcohol, a finding that may bear on the biosynthetic pathway through which nature is generating this structure. On the way to the final destination, we also uncovered a number of interesting cascade sequences to complex benzopyran systems involving facile 6π electrocyclizations which may find applications in complex molecule constructions. We were also able to produce and biologically evaluate a small library of lateriflorone analogues and related systems. These chemical biology investigations established the first structure activity relationships within this class of compounds.

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Supporting Information Available: Experimental procedures, compound characterization, and selected ^{1}H and ^{13}C NMR spectral data (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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