ORGANIC LETTERS

2003
Vol. 5, No. 9
1491−1494

Regioselective Synthesis of the Tricyclic Core of Lateriflorone

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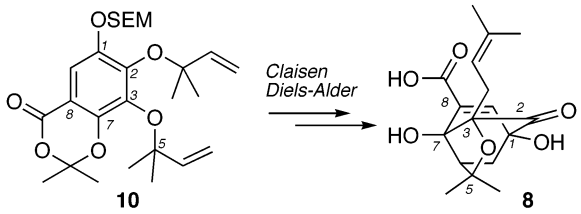
Received February 17, 2003

ABSTRACT



An efficient synthetic approach to the tricyclic core 8 of lateriflorone is described. Essential to the synthesis was the implementation of a biomimetic tandem Claisen/Diels–Alder reaction that produced the desired tricyclic scaffold as a single isomer. A rationalization of the excellent regio and stereoselectivity of this transformation is also proposed.

Plants of the genus *Garcinia* (Guttiferae) are encountered largely in the tropical rainforests of Indo China, Malaysia, and Borneo and have been used in traditional medicine for their wound healing, antibacterial, and cytotoxic activities.[1] Efforts to isolate and structurally identify the bioactive components of these plants have led to a new family of caged xanthonoids that include morellin (**1**),[2] morellic acid (**2**),[3] scortechinones A and B (**3**, **4**),[4] 1-*O*-methylneobractatin (**5**),[5] and lateriflorone (**6**)[6] (Figure 1). The chemical structure of these natural products is distinguished by the presence of a remarkable 4-oxa-tricyclo[4.3.1.0^{3,7}]decan-2-one scaffold, in which a highly substituted tetrahydrofuran core with three quaternary carbon centers is featured. This uncommon caged structure constitutes an intriguing synthetic target and may account for the reported biological activities.[7] An additional level of architectural complexity is found in the structure of lateriflorone (**6**), in which the tricyclic motif is attached to an unprecedented spiroxalactone core.

From a biosynthetic point of view,[8] the caged scaffold of these natural products is presumed to derive from a tandem Claisen/Diels−Alder rearrangement,[9,10] implying polyprenylated aromatic rings as plausible biosynthetic precursors. Moreover, two related biosynthetic scenarios were proposed for the unique spiroxalactone core of lateriflorone (**6**). The first is based on an oxidative rearrangement of a xanthone precursor, while the second rests upon condensation of two

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10.1021/ol034276y CCC: $25.00
Published on Web 04/01/2003

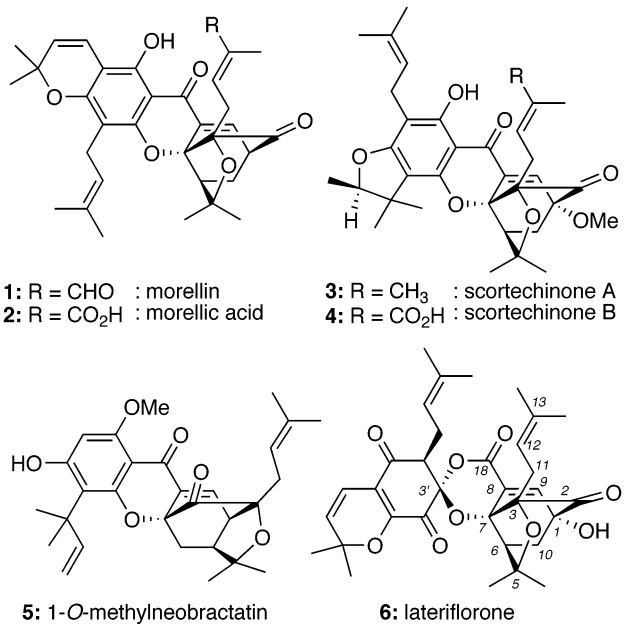

Figure 1. Selected natural products from *Garcinia* plants.

fully functionalized fragments such as **7** and **8** (Figure 2). In the synthetic direction, these two fragments are envisioned to combine at the C3′ center of **7** (lateriflorone numbering) through a biomimetic type of condensation, i.e., spirolactonization, to produce **6**. The tricyclic motif of **8** was projected to be formed via Diels−Alder cycloaddition of intermediate **9**, which in turn could arise from aryl ether **10** by a Claisen rearrangement.[11] Further disconnection of benzodioxanone **10** reveals benzopyran **11** as a synthetic precursor, the aromatic ring of which, can be traced back to commercially available 4-hydroxysalicylic acid (**12**). Herein, we disclose the results of our studies based on these retrosynthetic considerations.

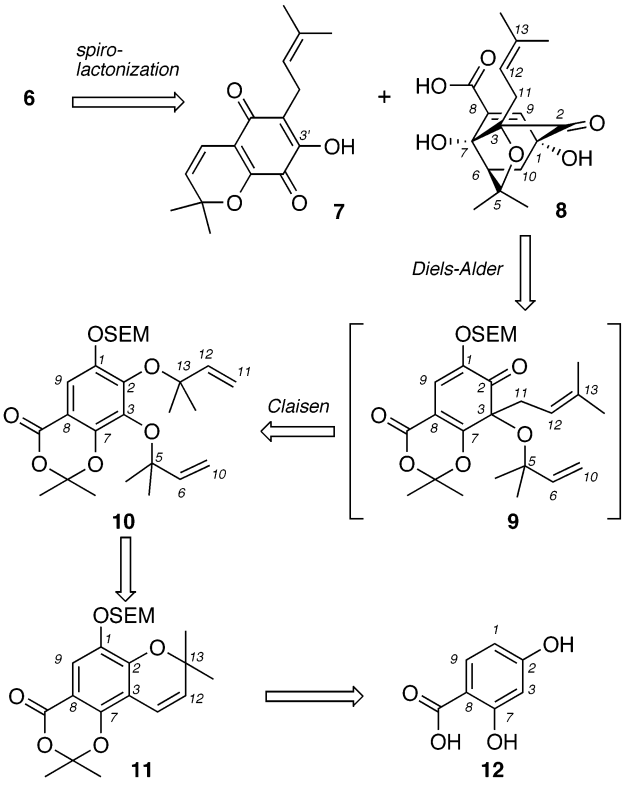

Figure 2. Retrosynthetic analysis of lateriflorone (**6**).

Our studies commenced with 4-hydroxysalicylic acid (**12**) that, upon regioselective bromination, afforded 5-bromo-4-hydroxysalicylic acid (**13**) in 75% yield (Scheme 1).[12] This compound was selectively protected in the presence of acetone and TFAA/TFA to furnish dioxanone **14** in 61% yield.[13] Alkylation of **14** with 3-chloro-3-methyl-butyne (**15**) in the presence of K_2CO_3, KI, and catalytic CuI in refluxing acetone gave rise to alkyne **16**,[14] which upon heating at 140 °C overnight produced benzopyran **17** in 90% combined yield. Conversion of **17** to phenol **18** was accomplished in 36% yield via treatment with *t*-Buli, quenching of the resulting anion with trimethyl borate, and one-pot oxidation with H_2O_2.[15] The resulting phenol **18** was subsequently protected with SEMCl and DIPEA to afford SEM ether **11** in 77% yield.[16]

Dihydroxylation of chromene **11** in the presence of catalytic amounts of OsO_4 and NMO,[17] followed by oxidative cleavage with LTA,[18] gave dialdehyde **19** in 86% combined yield. Formation of lactol **20** from **19** through Baeyer−Villiger oxidation[19] and subsequent saponification proved to be more problematic than expected, presumably due to the steric encumbrance imposed by the acetonide group on the adjacent aldehyde. After several attemps, it was found that treatment of a dilute solution of **19** at 0 °C with 0.5 equiv of *m*CPBA in CH_2Cl_2 every 0.5 h was the key to success. Careful saponification of the resulting formate ester with 1 N NaOH in MeOH gave lactol **20**, albeit in only 25% yield. This compound was subjected to a Wittig olefination reaction[20] to form phenol **21** in 43% yield. Treatment of the

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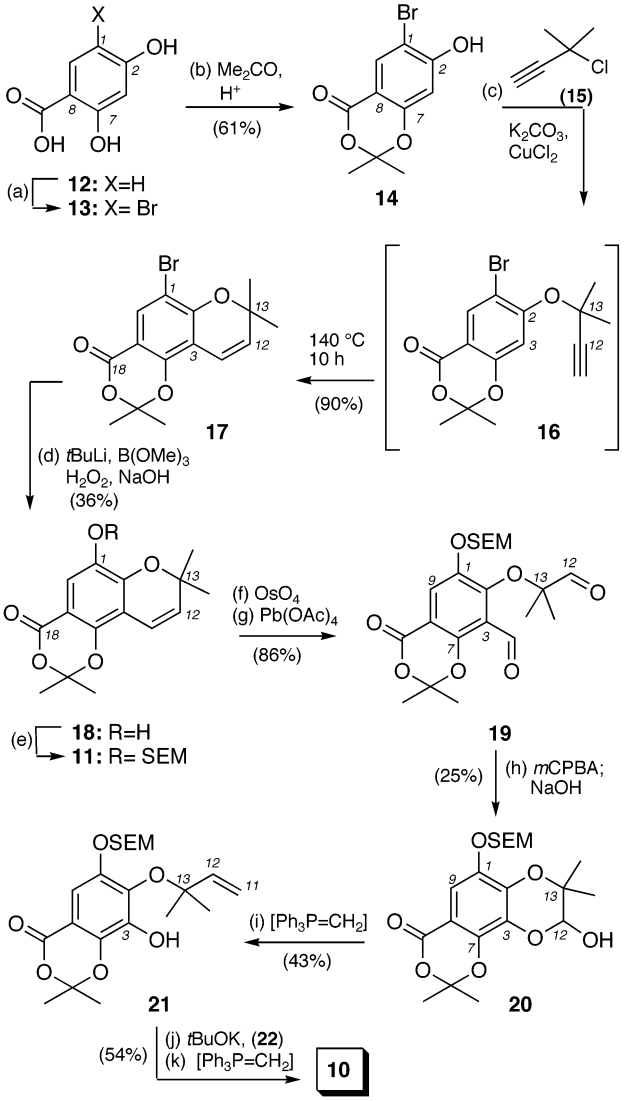
Scheme 1. Synthesis of Fragment **10**[a]

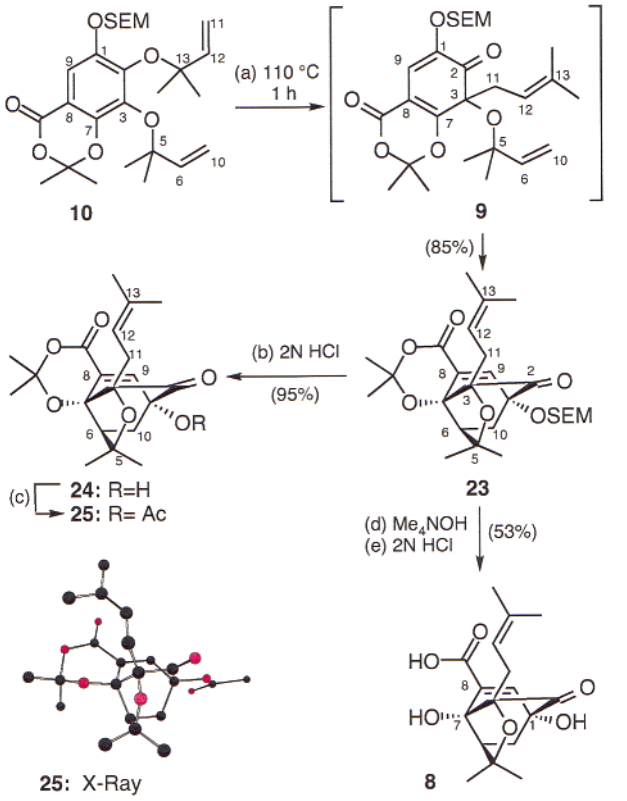


[a] Reagents and conditions: (a) 1.1 equiv of Br_2, HOAc, 5 h, 25 °C, 75%; (b) 3.0 equiv of $(CH_3)_2CO$, 3.0 equiv of TFAA, TFA, 10 h, 0 to 25 °C, 61%; (c) 2.0 equiv of 3-chloro-3-methyl-1-butyne (**15**), 1.1 equiv of K_2CO_3, 1.1 equiv of KI, 0.1 mol % CuI, $(CH_3)_2CO$, 0.5 h, reflux, then DMF, 10 h, 140 °C, 90%; (d) 2.2 equiv of *t*-BuLi, 3.0 equiv of $B(OMe)_3$, THF, 0.5 h, −78 to −30 °C, then excess 30% H_2O_2 (aq), 1 N NaOH (aq), 10 h, −30 to 25 °C, 36%; (e) 3.0 equiv of SEMCl, 4.0 equiv of DIPEA, 10 h, 0 to 25 °C, 77%; (f) 1.6 equiv of NMO, 0.3 mol % OsO_4, H_2O/THF/*t*-BuOH, 12 h, 25 °C; (g) 1.2 equiv of $Pb(OAc)_4$, CH_2Cl_2, 0.3 h, 25 °C, 86% (over two steps); (h) 0.5 equiv of *m*CPBA per 0.5 h, CH_2Cl_2, 6 h, 0 °C, then 0.3 equiv of 1 N NaOH (aq) per 0.2 h, MeOH, 1 h, 25 °C, 25%; (i) 3.0 equiv of methyltriphenylphosphonium bromide, 2.5 equiv of NaHMDS, THF, 1 h, 0 to 25 °C, 43%; (j) 1.0 equiv of *t*-BuOK, THF, 0.5 h, 0 to 25 °C, then 1.5 equiv of α-bromoisobutyraldehyde (**22**), 1.0 equiv of 18-C-6, CH_3CN, 1.0 h, 0 to 60 °C; (k) 2.0 equiv of methyltriphenylphosphonium bromide, 1.5 equiv of NaHMDS, THF, 1 h, 0 to 25 °C, 54% (over two steps).

potassium salt of **21** with α-bromoisobutyraldehyde (**22**) in the presence of 18-C-6 produced the corresponding α-phenoxycarboxaldehyde that was subsequently converted to alkene **10** using Wittig olefination (54% combined yield).[10]

With alkene **10** in hand, the stage was set for the implementation of a tandem Claisen/Diels−Alder reaction. Along these lines, heating of bis-(α,α-dimethylallyl) aryl ether **10** in toluene at 110 °C gave rise to a single product, **23**, in 85% yield (Scheme 2). The structure and composition

Scheme 2. Synthesis of Tricyclic Fragment **8**[a]



[a] Reagents and conditions: (a) $PhCH_3$, 1 h, 110 °C, 85%; (b) excess 2 N HCl (aq), MeOH, 0.5 h, 25 °C, 95%; (c) 5.0 equiv of pyridine, 4.0 equiv of CH_3COCl, 0.2 equiv of DMAP, $CHCl_3$, 80 °C (sealed tube), 10 h, 92%; (d) excess 5% NMe_4OH (aq), MeOH, 2.5 h, 25 °C, 56%; (e) excess 2 N HCl (aq), MeOH, 0.5 h, 25 °C, 95%.

of **23** were ultimately confirmed by crystallographic analysis of derivative **25**, which divulged that the tandem rearrangement produced exclusively the desired tricyclic scaffold. Subsequent studies also showed that compound **10** can be converted to **23** simply upon sitting at room temperature for a number of days. Such facile rearrangement could be attributed to a cumulative electron-donating effect of the four oxygens attached to the aromatic ring of **10**, prompting its dearomatization through a tandem Claisen/Diels−Alder reaction cascade.

Having confirmed the structure of **23**, we turned our attention to deprotection of both the silyl ether and the acetonide units. To this end, exposure of **23** to 5% NMe_4-OH (aq) in MeOH was found to provide the optimum saponification conditions and produced the desired *β*-hydroxy carboxylic acid in 56% yield.[21] Finally, desilylation of the O1-silyl ether was best accomplished in the presence of 2 N

HCl in MeOH[22] and gave rise to desired compound **8** in 94% yield.

The excellent regioselectivity observed during the tandem Claisen/Diels−Alder reaction deserves some additional comments. In principle, compound **10** can undergo two different *ortho*-Claisen rearrangements giving rise to structures **9** and **26**, which after the sequential Diels−Alder reaction can produce adducts **23** and **27**, respectively (Figure 3).[23] The

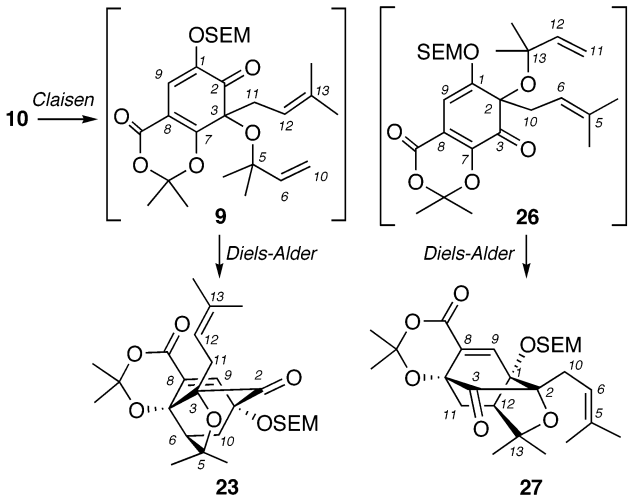


Figure 3. Possible isomers anticipated from the tandem Claisen/Diels−Alder reaction of compound **10**.

absence of **27** and complete conversion of compound **10** to desired regioisomer **23** could be due to an intrinsic preference of **10** to form Claisen adduct **9**. This preference may be attributed to the substitution pattern and the electronic effects of the substituents on the aromatic ring.[11,24,25] With this in mind, it appears that having preinstalled all functionalities at the correct oxidation state in compound **10** triggers the desired rearrangement, producing tricycle **23** exclusively. Such regiochemical preference during this tandem rearrangement is also manifested in the vast majority of the *Garcinia* natural products, the structure of which is highlighted by the same homochiral scaffold (Figure 1). The sole exception to this trend is found in the structure of *O*-methylneobractatin (**5**), which as one would expect has been isolated only as a minor product.

In conclusion, we present herein an efficient synthetic strategy for the synthesis of tricyclic fragment **8** of lateriflorone (**6**). Essential to our strategy is the implementation of a biomimetic and completely regioselective Claisen/Diels−Alder cascade reaction. Application of this process to a biomimetic synthesis of lateriflorone and related natural products is currently in progress in our laboratories.

Acknowledgment. Financial support from the NIH (CA086079) is gratefully acknowledged. We thank Dr. P. Gantzel (UCSD, X-ray Facility) for the reported crystallographic structure and the San Diego Chapter of the ARCS Foundation and the Department of Education for their support through graduate student fellowships to E.J.T. and B.G.V., respectively.

Supporting Information Available: Spectroscopic and analytical data available for compounds **10**, **11**, **17**, **18**, **20**, **23**, and **25** and X-ray data for compound **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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