

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/10789486>

Regioselective Synthesis of the Tricyclic Core of Lateriflorone

ARTICLE *in* ORGANIC LETTERS · JUNE 2003

Impact Factor: 6.36 · DOI: 10.1021/ol034276y · Source: PubMed

CITATIONS

19

READS

21

5 AUTHORS, INCLUDING:



Eric J. Tisdale

University of California, San Diego

10 PUBLICATIONS 220 CITATIONS

SEE PROFILE



Binh Vong

Senomyx

11 PUBLICATIONS 324 CITATIONS

SEE PROFILE



Sun Hee Kim

Arena Pharmaceuticals, Inc.

56 PUBLICATIONS 1,017 CITATIONS

SEE PROFILE



Emmanuel A Theodorakis

University of California, San Diego

164 PUBLICATIONS 3,788 CITATIONS

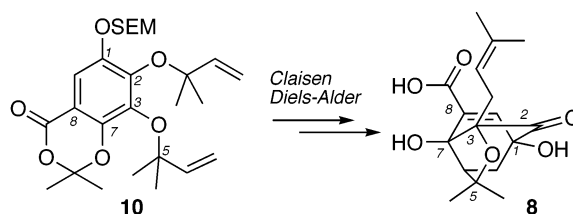
SEE PROFILE

Regioselective Synthesis of the Tricyclic
Core of LaterifloroneEric J. Tisdale, Hongmei Li, Binh G. Vong, Sun Hee Kim, and
Emmanuel A. Theodorakis*Department of Chemistry and Biochemistry, University of California, San Diego,
9500 Gilman Drive, La Jolla, California 92093-0358

etheodor@chem.ucsd.edu

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

(1) For selected general references on this topic, see: Ollis, W. D.; Redman, B. T.; Sutherland, I. O.; Jewers, K. *J. Chem. Soc., Chem. Commun.* **1969**, 879–880. Kumar, P.; Baslas, R. K. *Herba Hungarica* **1980**, *19*, 81–91. Thoison, O.; Fahy, J.; Dumontet, V.; Chiaroni, A.; Riche, C.; Tri, M. V.; Sevenet, T. *J. Nat. Prod.* **2000**, *63*, 441–446.

(2) Rao, B. S. *J. Chem. Soc. C* **1937**, 853–857. Kartha, G.; Ramachandran, G. N.; Bhat, H. B.; Nair, P. M.; Raghavan, V. K. V.; Venkataraman, K. *Tetrahedron Lett.* **1963**, *4*, 459–472.

(3) Karanjgaongar, C. G.; Nair, P. M.; Venkataraman, K. *Tetrahedron Lett.* **1966**, *7*, 687–691.

(4) Rukachaisirikul, V.; Kaewnok, W.; Koysomboon, S.; Phongpaichit, S.; Taylor, W. C. *Tetrahedron* **2000**, *56*, 8539–8543.

(5) Thoison, O.; Fahy, J.; Dumontet, V.; Chiaroni, A.; Riche, C.; Tri, M. V.; Sevenet, T. *J. Nat. Prod.* **2000**, *63*, 441–446.

(6) Kosela, S.; Cao, S.-G.; Wu, X.-H.; Vittal, J. J.; Sukri, T.; Masdianto; Goh, S.-H.; Sim, K.-Y. *Tetrahedron Lett.* **1999**, *40*, 157–160.

(7) Cao, S.-G.; Sng, V. H. L.; Wu, X.-H.; Sim, K.-Y.; Tan, B. H. K.; Pereira, J. T.; Goh, S. H. *Tetrahedron* **1998**, *54*, 10915–10924. For related gaudichaudiones, see: Cao, S.-G.; Wu, X.-H.; Sim, K.-Y.; Tan, B. K. H.; Pereira, J. T.; Wong, W. H.; Hew, N. F.; Goh, S. H. *Tetrahedron Lett.* **1998**, *39*, 3353–3356. Wu, X.-H.; Tan, B. K. H.; Cao, S.-G.; Sim, K.-Y.; Goh, S. H. *Nat. Prod. Lett.* **2000**, *14*, 453–458.

(8) Bennett, G. J.; Lee, H.-H. *J. Chem. Soc., Chem. Commun.* **1988**, 619–620. Roberts, J. C. *Chem. Rev.* **1961**, *61*, 591–605.

(9) Quillinan, A. J.; Scheinmann, F. *J. Chem. Soc., Chem. Commun.* **1971**, 966–967.

(10) For a recent demonstration of this tandem rearrangement, see: Nicolaou, K. C.; Li, J.; *Angew. Chem., Int. Ed.* **2001**, *40*, 4264–4268.

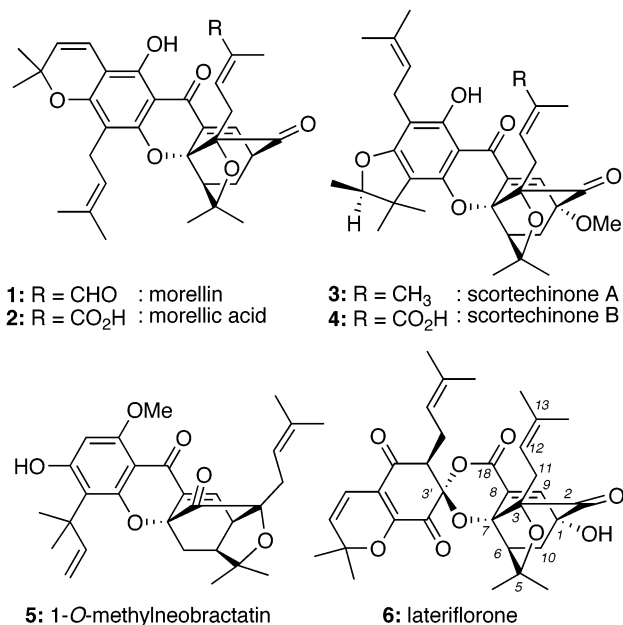


Figure 1. Selected natural products from *Garcinia* plants.

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., spiroac-

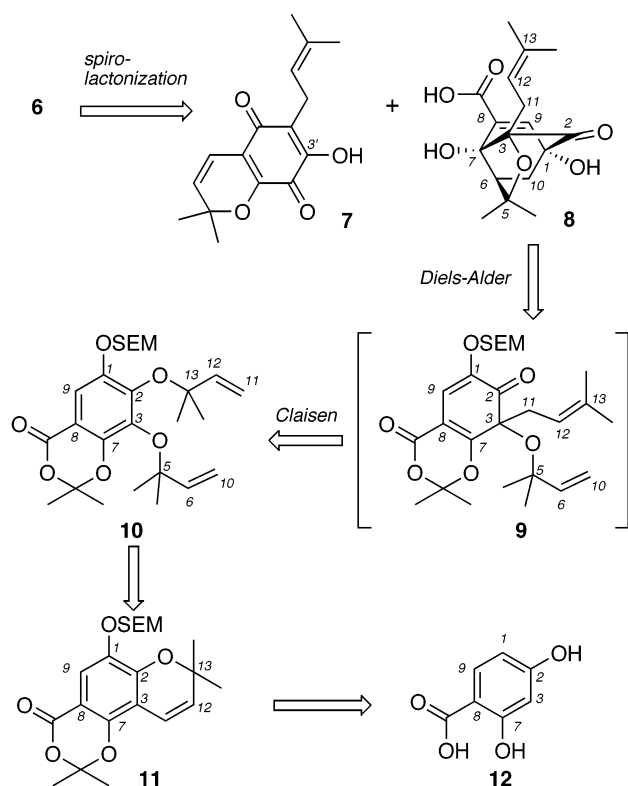


Figure 2. Retrosynthetic analysis of lateriflorone (**6**).

tonization, 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.

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 K₂CO₃, 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 H₂O₂.¹⁵ 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 OsO₄ 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 oxidation¹⁹ 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 attempts, it was found that treatment of a dilute solution of **19** at 0 °C with 0.5 equiv of *m*CPBA in CH₂Cl₂ 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 reaction²⁰ to form phenol **21** in 43% yield. Treatment of the

(11) Claisen, L. *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 3157. For recent and selected reviews on Claisen rearrangement, see: Nowicki, J. *Molecules* **2000**, *5*, 1033–1050. Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43–50. Gajewski, J. J. *Acc. Chem. Res.* **1997**, *30*, 219–225. Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423–1452. Rhoads, S. J.; Raulins, N. R. In *Organic Reactions*; Dauben, W. G., Ed.; John Wiley & Sons: New York, 1975; Vol. 22, Chapter 1, pp 1–252. Wipf, P. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; 1991; Vol. 5, p 827.

(12) Under these conditions, a minor byproduct identified as 3,5-dibromohydroxysalicylic acid was formed and was easily separated from the monobrominated adduct by column chromatography.

(13) Rheinheimer, J.; Vogelbacher, U. J.; Bauman, E.; König, H.; Gerber, M.; Westphalen, K.-O.; Walter, H. U.S. Patent 5,569,640, Oct. 29, 1996.

(14) Pernin, R.; Muiyard, F.; Bévalot, F.; Tillequin, F.; Vaquette, J. J. *Nat. Prod.* **2000**, *63*, 245–247. Pettus, T. R.; Hoarau, C. *Synlett.* **2003**, 127–137.

(15) Moody, C. J.; Shah, P. J. *Chem. Soc., Perkin Trans. 1* **1989**, 2463–2471.

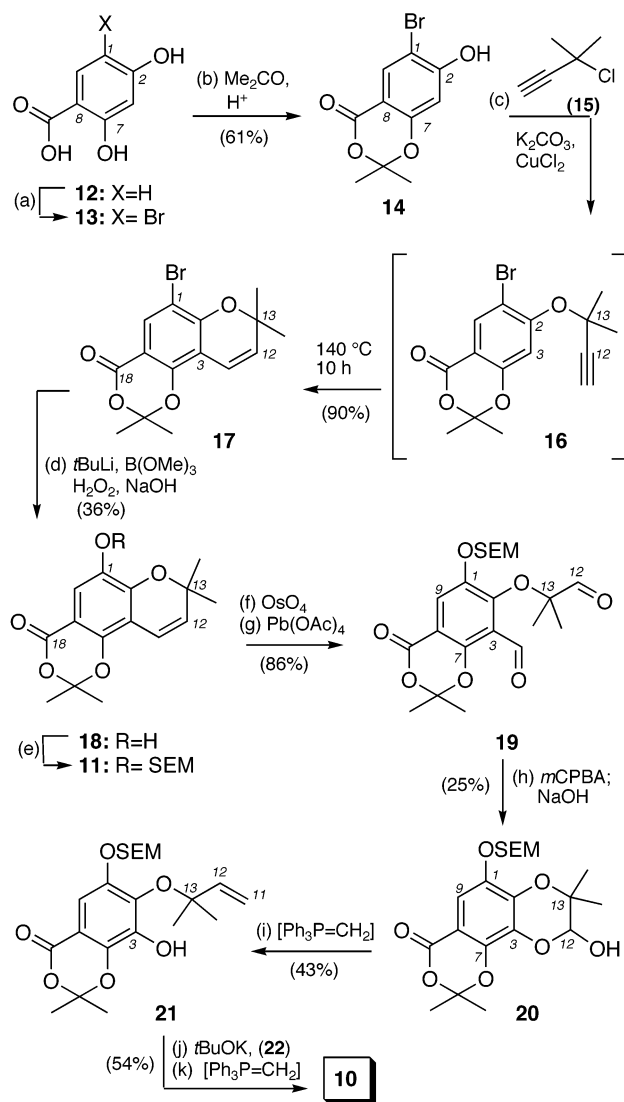
(16) Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343.

(17) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *23*, 1973–1976. Trost, B. M.; Crawley, M. L.; Lee, C. B. *J. Am. Chem. Soc.* **2000**, *122*, 6120–6121.

(18) Chauret, D. C.; Chong, J. M.; Ye, Q. *Tetrahedron: Asymmetry* **1999**, *10*, 3601–3614.

(19) For a review of the Baeyer–Villiger reaction, see: Krow, G. R. *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1993; Vol. 43, Chapter 3, pp 251–798.

Scheme 1. Synthesis of Fragment 10^a

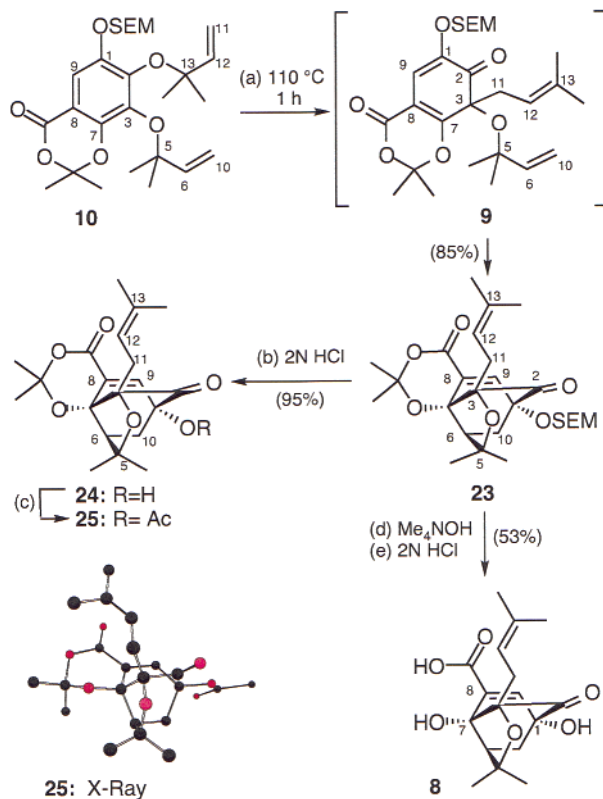


^a Reagents and conditions: (a) 1.1 equiv of Br₂, HOAc, 5 h, 25 °C, 75%; (b) 3.0 equiv of (CH₃)₂CO, 3.0 equiv of TFAA, TFA, 10 h, 0 to 25 °C, 61%; (c) 2.0 equiv of 3-chloro-3-methyl-1-butyne (15), 1.1 equiv of K₂CO₃, 1.1 equiv of KI, 0.1 mol % CuI, (CH₃)₂CO, 0.5 h, reflux, then DMF, 10 h, 140 °C, 90%; (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% H₂O₂ (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 % OsO₄, H₂O/THF/*t*-BuOH, 12 h, 25 °C; (g) 1.2 equiv of Pb(OAc)₄, CH₂Cl₂, 0.3 h, 25 °C, 86% (over two steps); (h) 0.5 equiv of *m*CPBA per 0.5 h, CH₂Cl₂, 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, CH₃CN, 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) PhCH₃, 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 CH₃COCl, 0.2 equiv of DMAP, CHCl₃, 80 °C (sealed tube), 10 h, 92%; (d) excess 5% NMe₄OH (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% NMe₄-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 MeOH²² 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

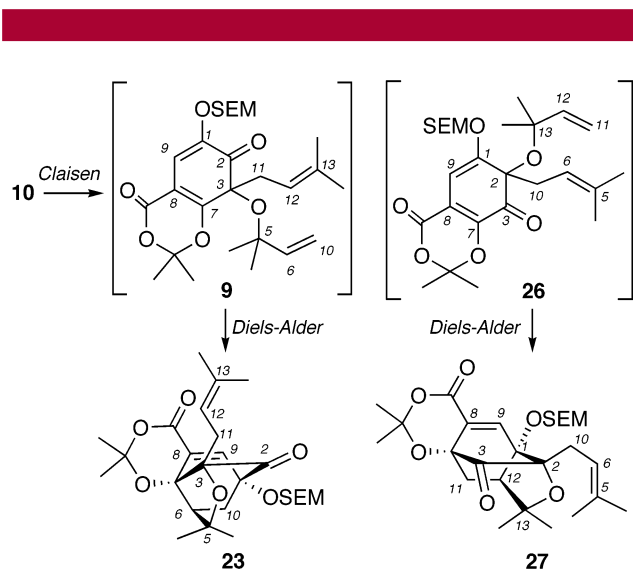


Figure 3. Possible isomers anticipated from the tandem Claisen/Diels–Alder reaction of compound **10**.

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

(20) Tisdale, E. J.; Chowdhury, C.; Vong, B. G.; Li, H.; Theodorakis, E. A. *Org. Lett.* **2002**, *4*, 909–912. McClure, K. F.; Danishefsky, S. J.; Schulte, G. K. *J. Org. Chem.* **1994**, *59*, 355–360.

(21) Although both acidic and basic conditions are known to open dioxanones, only basic hydrolysis was found to bring about the desired change in **23**. For related references, see: Harada, T.; Yoshida, T.; Kagamihara, Y.; Oku, A.; *J. Chem. Soc., Chem. Commun.* **1993**, 1367–1370. Marriot, J. H.; Barber, A. M. M.; Hardcastle, I. R.; Rowlands, M. G.; Grimshaw, R. M.; Neidle, S.; Jarman, M. *J. Chem. Soc., Perkin Trans. I* **2000**, 4265–4278.

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>.

OL034276Y

(22) Reported fluoride-based deprotection methods for SEM ethers were completely ineffective. For selected references on this protecting group, see: Lipshutz, B. H.; Pegram, J. J. *Tetrahedron Lett.* **1980**, *21*, 3343–3346. Kan, T.; Hashimoto, M.; Yanagiya, M.; Shirahama, H. *Tetrahedron Lett.* **1988**, *29*, 5417–5418.

(23) Tricyclic alkene cannot participate as a dienophile during the Diels–Alder reaction due to its decreased reactivity.

(24) There exists support for a dipolar transition state in the Claisen rearrangement. For selected references on this issue, see: Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Peck, D. R.; Curran, D. P. *J. Am. Chem. Soc.* **1987**, *109*, 1160–1170. Wilcox, C. S.; Babston, R. E. *J. Am. Chem. Soc.* **1986**, *108*, 6636–6642. Gajewski, J. J.; Jurayi, J.; Kimbrough, D. R.; Gande, M. E.; Ganem, B.; Carpenter, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 1170–1186. Wipf, P.; Rodriguez, S. *Adv. Synth. Catal.* **2002**, *344*, 434–440.

(25) For a recent application of the aromatic Claisen rearrangement in natural products synthesis, see: Pettus, T. R.; Inoue, M.; Chen, X.-T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2000**, *122*, 6160–6168. Pettus, T. R.; Chen, X.-T.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 12684–12685.