Communication

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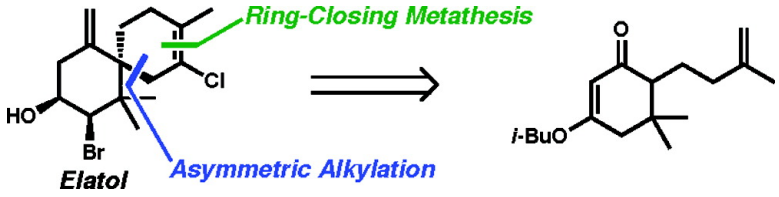
J. Am. Chem. Soc., **2008**, 130 (3), 810-811 • DOI: 10.1021/ja710294k



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Published on Web 12/29/2007

The Catalytic Asymmetric Total Synthesis of Elatol

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The chamigrene subclass of sesquiterpenes, characterized by a spiro[5.5]undecane core, is an ever-growing family of natural products (Figure 1).[1] Well over 100 members have been isolated thus far, and many of these compounds exhibit a diverse array of biological activity.[1c] In particular, elatol (**1**),[2] one of the most widely studied chamigrenes, displays antibiofouling activity,[3a,b] antibacterial activity (including human pathogenic bacteria),[3c−e] antifungal activity,[3f] and cytotoxicity against HeLa and Hep-2 human carcinoma cell lines.[3g] Despite the interesting bioactivity and compact structure of these molecules, no general strategy for their preparation has been developed, and to the best of our knowledge, no total synthesis of elatol has been reported in the 33 years since its original isolation.[4,5]

Structurally, elatol (**1**) consists of a densely functionalized A ring bearing three stereocenters, including an all-carbon quaternary stereocenter, which is vicinal to a second, nonstereogenic quaternary carbon. Within the B ring is also a fully substituted chlorinated olefin. We envisioned a strategy toward these challenging motifs based on methodological advances recently reported by our laboratories. Specifically, enantioselective decarboxylative allylation[6] could generate the all-carbon quaternary stereocenter, while ring-closing metathesis (RCM)[7] could be employed to concomitantly provide the tetrasubstituted olefin and the spirocyclic core of **1** (Scheme 1). Importantly, this approach serves as a general platform to access the chamigrene family.

We envisioned **1** to ultimately arise from sequential reductive olefin transposition and diastereoselective reduction of α-bromoketone **10**. In turn, compound **10** would be obtained from bromination of the enone resulting from 1,2-addition of a methyl anion to spirocycle **11**. Intermediate **11** itself could be the product of RCM of α,ω-diene **12**. Although generation of a fully substituted chlorinated olefin via RCM has not been previously reported,[8] we anticipated that the improved reactivity of catalyst **22**[7] (vide infra) might be sufficient for this transformation. Access to **12** would be possible via enantioselective decarboxylative allylation of an appropriately substituted vinylogous ester derivative (i.e., **13**), employing the Pd(0) complex of a phosphinooxazoline (PHOX) ligand. This would constitute a previously unexplored substrate class with this catalyst system.[9] Finally, enol carbonate **13** could be derived from commercially available dimedone (**14**).

Our synthetic efforts began with the condensation of isobutyl alcohol and dimedone (**14**) to provide known vinylogous ester **15** (Scheme 2).[10] Direct alkylation of vinylogous ester **15** with 4-iodo-2-methyl-1-butene was sluggish; however, a two-step procedure involving conjugate addition to methyl vinyl ketone (MVK) followed by Wittig methylenation afforded olefin (±)-**16** in good yield. Selective enolization of vinylogous ester (±)-**16** and trapping with chloroformate **17** allowed access to enol carbonate **13** in 73% yield. In our initial attempt, application of our standard reaction conditions[11] for Pd-catalyzed asymmetric alkylation to enol carbonate **13** provided desired alkylation adduct (+)-**12**, but in low yield.[12]

We reasoned that the poor reactivity of enol carbonate **13** in the enantioselective allylation reaction could stem from one of three possibilities: (1) slow oxidative addition to the allyl carbonate moiety, (2) slow decarboxylation to reveal the active enolate intermediate, or (3) slow alkylation of the enolate intermediate to provide the desired product **12**. In order to discern between these scenarios, we ran a set of control reactions outlined in Scheme 3. Exposure of enol carbonate **13** to conditions developed in our laboratories for enantioselective decarboxylative protonation[13] led to rapid formation of olefin **16**.[14] Furthermore, removal of the 2-chloro substituent on the allyl fragment resulted in facile decarboxylative allylation of enol carbonate **19** to yield bis(olefin) **20**. On the basis of these results, we concluded that slow alkylation, not slow oxidative addition or decarboxylation, was most likely the problematic step in this transformation.

In order to enhance the reactivity of our π-allyl Pd(II) electrophile, we attempted to increase its electrophilicity by incorporating electron-withdrawing substituents into the PHOX ligand framework.[15] Ultimately, asymmetric alkylation employing ligand **21** in benzene at 11 °C afforded the best balance between reactivity and

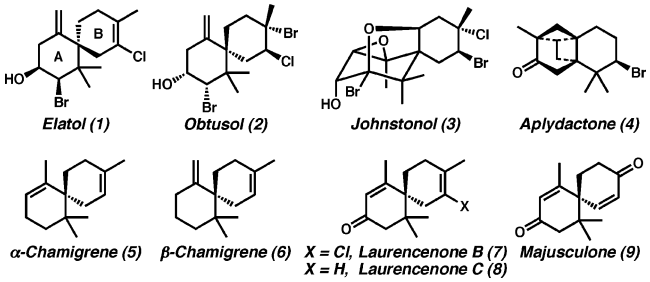
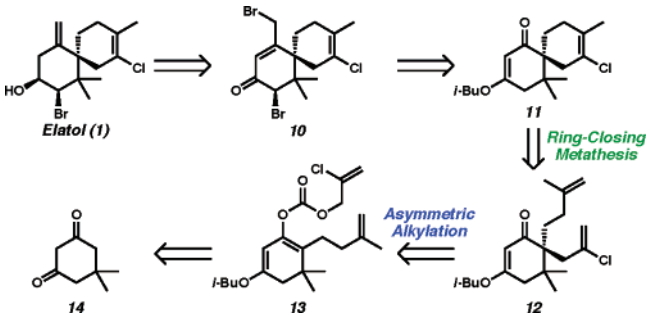
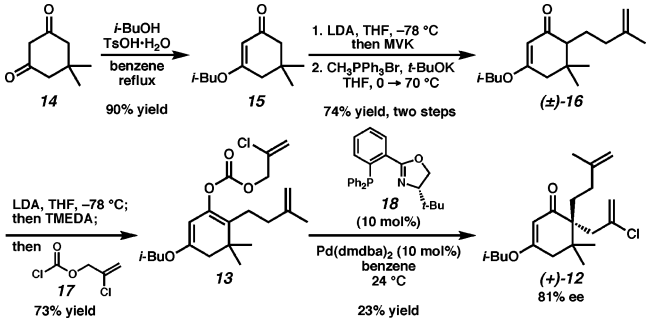


Figure 1. Examples of chamigrene natural products.

Scheme 1



Scheme 2[a]



[a] dmdba = bis(3,5-dimethoxybenzylidene)acetone.

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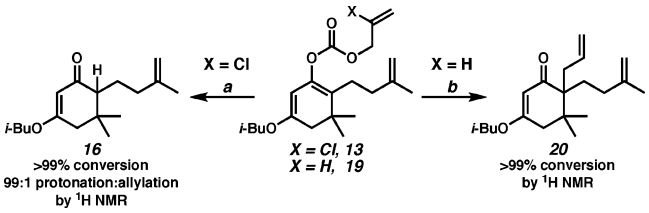
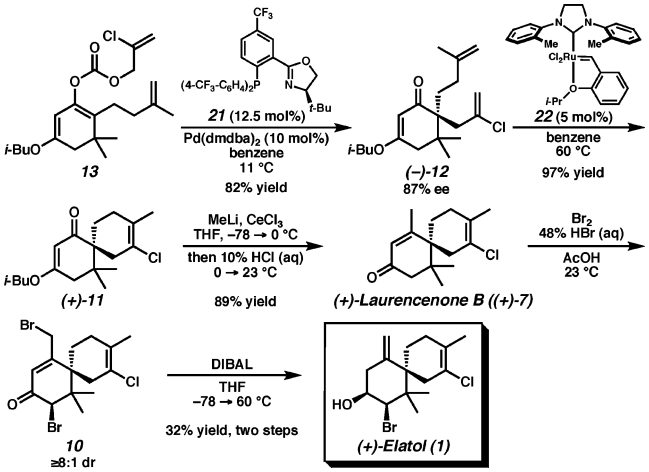
Scheme 3[a]



[a] Conditions: (a) HCO_2H, $Pd(OAc)_2$ (10 mol %), **18** (12.5 mol %), MS 4 Å, benzene, 40 °C, (b) $Pd(dmdba)_2$ (10 mol %), **18** (13 mol %), benzene, 40 °C.

Scheme 4



selectivity, providing vinylogous ester **12** in 82% yield and 87% ee (Scheme 4). Gratifyingly, when α,ω-diene **12** was subjected to our standard RCM reaction conditions with catalyst **22**, the desired fully substituted chloroalkene (+)-**11** was produced in 97% yield.[16] Addition of methyllithium in the presence of $CeCl_3$ then provided (+)-laurencenone B ((+)-**7**)[17] after acid-mediated elimination and hydrolysis.[18] Enone (+)-**7** was subsequently bis-halogenated with Br_2 to generate dibromide **10** in ≥8:1 dr.[19] Finally, the crude α-bromoketone **10** was doubly reduced with DIBAL to afford elatol (**1**) (3.9:1 syn:anti,[20] 11:1 S_N2':S_N2). Overall, enantioenriched (+)-laurencenone B ((+)-**7**) was prepared in seven steps and 34% yield from dimedone (**14**), while enantioenriched (+)-elatol (**1**) was prepared in nine steps and 11% yield.[21]

We have successfully developed a concise enantioselective route to the chamigrene natural product family, culminating in the first total syntheses of elatol (**1**) and (+)-laurencenone B ((+)-**7**), as well as the first preparation of a fully substituted chlorinated olefin via RCM. Moreover, we have demonstrated the ability of the key enantioselective alkylation reaction to access sterically encumbered enantioenriched vinylogous esters. The application of these methods to the syntheses of other chamigrene natural products and a full exploration of both vinylogous esters in enantioselective decarboxylative alkylation and vinyl chlorides in RCM are the focus of ongoing studies.

Acknowledgment. We thank the NIH-NIGMS (R01 GM080269-01, R01 GM31332-05, postdoctoral fellowships to D.E.W. and I.C.S.), Abbott, Amgen, Bristol-Myers Squibb, Merck, and Caltech for generous funding; Materia, Inc. for their kind donation of catalyst **22** used in these studies; Professors Mercedes Cueto and Karen L. Erickson for their kind donation of natural samples of elatol (**1**); Brinton Seashore-Ludlow for experimental assistance; and Professor Peter B. Dervan and David M. Chenoweth for use of their HPLC.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Use of $Pd_2(dba)_3$ in lieu of $Pd(dmdba)_2$ led to significantly less conversion.

(12) For convenience, the enantioselective allylation reaction with **13** was optimized in the opposite enantiomeric series.

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(14) A separate experiment revealed no reactivity in the absence of a Pd(0) catalyst.

(15) For preliminary results on the rate acceleration of enantioselective decarboxylative allylation of enol carbonates with electron-deficient PHOX ligands, see: Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. *Org. Lett.* **2007**, *9*, 2529−2531.

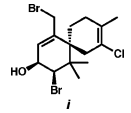
(16) $(H_2IMes)(PCy_3)(Cl)_2Ru{=}CHPh$ produced significant product for this transformation under similar reaction conditions (2.5 mol% catalyst, C_6D_6, 60 °C), but at a slower rate than catalyst **22**: 85% conversion after 24 h as measured by ^1H NMR .

(17) (a) For the isolation of laurencenone B (**7**) from the marine alga *Laurencia obtusa*, see: Kennedy, D. J.; Selby, I. A.; Thomson, R. H. *Phytochemistry* **1988**, *27*, 1761−1766. Neither the absolute configuration nor the optical rotation was specified. (b) For the preparation of (+)-laurencenone B ((+)-**7**) via the degradation of elatol (**1**), see: Brennan, M. R.; Erickson, K. L; Minott, D. A.; Pascoe, K. O. *Phytochemistry* **1987**, *26*, 1053−1057.

(18) Discrepancies between the published ^1H NMR data for the natural product (ref 17a) and that of the synthetic material exist. No ^{13}C NMR data was available for comparison. ^1H and ^{13}C NMR data for semisynthetic (+)-laurencenone B ((+)-**7**) (ref 17b) matched that of our synthetic material. See the supporting information for a detailed comparison.

(19) Purification of α-bromoketone **10** was hampered by its poor stability to silica gel and reverse phase HPLC.

(20) Determined by quenching the reaction at −78 °C in a separate run, resulting in the isolation a 3.9:1 mixture of alcohol diastereomers favoring **i**.



i

(21) Synthetic (+)-elatol ((+)-**1**) was identical in all respects to a natural sample provided by Prof. Mercedes Cueto except for the magnitude of its optical rotation: $[\alpha]^{23}_D$ +92.09° (*c* 0.22, $CHCl_3$, synthetic), $[\alpha]^{25}_D$ +109.78° (*c* 0.045, $CHCl_3$, natural). Based on 87% ee, the expected $[\alpha]_D$ value for the synthetic material would be +95.5°, which differed from the observed value by 3.6%.

JA710294K