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Formal Total Syntheses of (+)-Prelaureatin and (+)-Laurallene by Diastereoselective Brook Rearrangement-Mediated [3 + 4] Annulation

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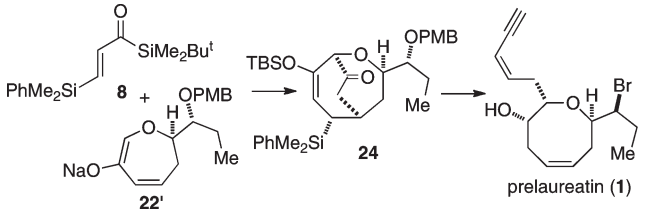

The formal syntheses of (+)-prelaureatin (**1**) and (+)-laurallene (**2**), halogenated eight-membered-ring ethers, are described. The key step of our strategy relies on diastereoselective construction of a trans-α,α′-disubstituted oxocene structure through a Brook rearrangement-mediated [3 + 4] annulation with acryloylsilane **9** and 6-oxa-2-cycloheptenone derivative **22′**.

Prelaureatin (**1**)[1] (Figure 1) is a biogenetic precursor[2] of several members of the laurenan structural subclass such as laurallene (**2**),[3] which is one of two basic structural types of halogenated eight-membered-ring ethers isolated from red algae of the genus *Laurencia*.[4] Although much attention has been focused on the synthesis of **1** and **2** due to their unique structural features, few syntheses have been reported,[5,6] probably because of the difficulty in establishing a trans-α,α′-disubstituted oxocene structure originating from its kinetic and thermodynamic instability compared to the cis-isomer.[7] That is in contrast to extensive studies on the synthesis of another subclass, the lauthisan-type represented by laurencin (**3**),[8] that involves a cis-α,α′-disubstituted pattern at the ether oxygen.

The first total syntheses of **1** and **2** were reported by Crimmins and co-workers, who used an asymmetric glycolate aldol addition (**4** → **5**) and ring-closing metathesis (**6** → **7**) for construction of the trans-α,α′-disubstitution pattern and the oxocene core, respectively (Scheme 1).[5a]

We have recently reported the synthesis of Crimmins's intermediate **7**, in which diastereoselective Brook rearrangement-mediated [3 + 4] annulation was used for construction of the eight-membered ether system.[9] Here, we report another formal total synthesis of prelaureatin (**1**) and laurallene (**2**) via advanced Crimmins's intermediate **8** using a similar but more efficient strategy.

Scheme 2 provides an outline of the previously reported synthesis of **7**. Although this synthesis features the stereoselective construction of trans-α,α′-substitution by taking advantage of the stereospecificity of the [3 + 4] annulation that we have developed, that presents some drawbacks. The major one is that **7** is a relatively early intermediate in Crimmins's synthesis and that this synthesis requires many more steps than his approach. One of the causes for the lengthy pathway in our synthesis is the reduction−oxidation sequence of the formyl group in **12**, which was derived from [3 + 4] annulation (**9** + **10** → **11**) followed by oxidative cleavage of the two-carbon tether. These steps were required to avoid an epimerization at the 2-position in **16**, which would be expected if the enone system was introduced prior to cleavage of the tether (**11** → **12**).

In an attempt to overcome this problem, we examined an alternative synthetic route that would allow more efficient synthesis of an advanced intermediate **8**. The plan is based on the use of oxacycloheptenone enolate **17** bearing the substitution pattern required for **8** as a four-carbon unit in the [3 + 4] annulation and based on the introduction of the enone system at an earlier stage in the synthesis (Scheme 3). Toward the latter end, the enone carbonyl group in **18** (Y = OH) should be chemo- and stereoselectively reduced and protected prior to cleavage of the two-carbon tether to convert to **19** (Y = OH). The formyl group resulting from the cleavage can be used for a shift of the double bond, after which the group can be removed.

(1) Fukuzawa, A.; Takasugi, Y.; Murai, A. *Tetrahedron Lett*. **1991**, *32*, 5597–5598.

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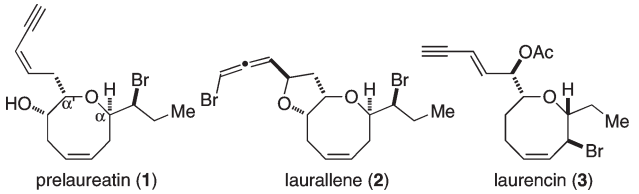
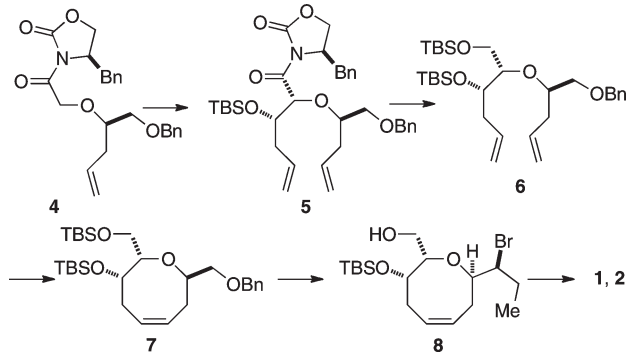
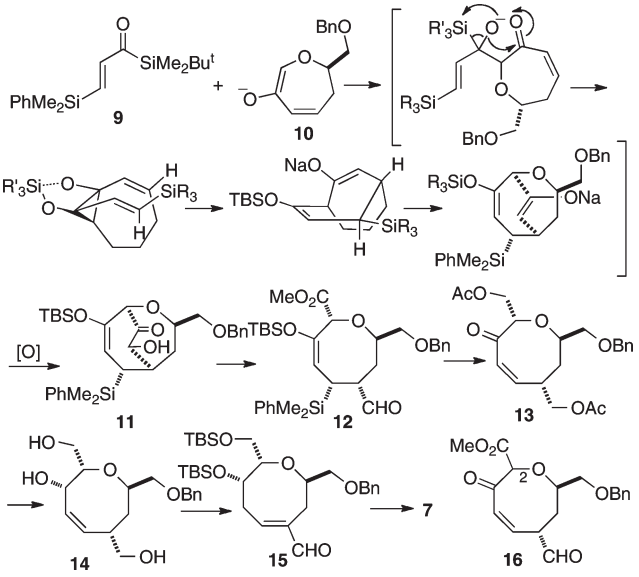


FIGURE 1. Structures of prelaureatin (**1**), laurallene (**2**), and laurencin (**3**).

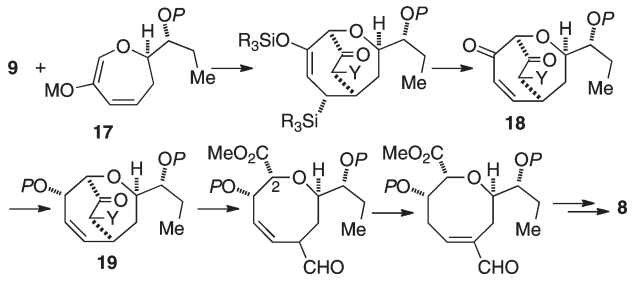
SCHEME 1. Crimmins's Synthesis of Prelaureatin (1) and Laurallene (2)



SCHEME 2. Our Previous Formal Synthesis of 1 and 2



SCHEME 3. Synthetic Plan for 8



To test the feasibility of this approach, we first attempted selective reduction of model substrates **20** and **21**,[9] but in both cases mixtures of diol derivatives and the starting materials were formed (Figure 2).

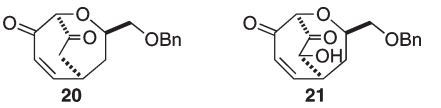
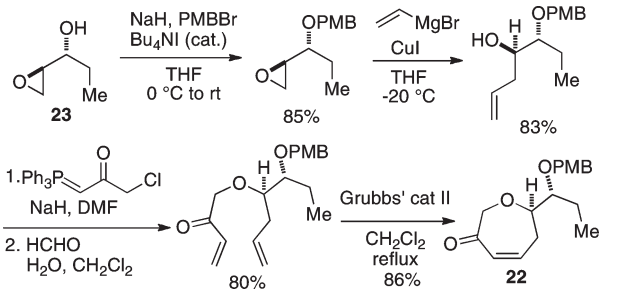


FIGURE 2. Structures **20** and **21**.

SCHEME 4. Synthesis of 22



In light of this result, we set out to slightly modify our strategy so that two carbonyl groups in **18** can be distinguished. Attempted [3 + 4] annulation[10,11] with **9** and sodium enolate of **22**, prepared from known epoxy alcohol **23**[12] as shown in Scheme 4,[13] followed by hydroxylation by Davis' reagent[14] in a one-pot operation proved less rewarding in terms of yield in this case. We therefore focused on α-hydroxylation of **18** (Y = H) via oxidation of the corresponding silyl enol ether, which would also enable us to distinguish the two carbonyl groups in **18** (Y = H).

[3+4] annulation of **9** and sodium enolate **22′** proceeded in a highly diastereoselective manner to afford exclusively **24** in 80% yield (Scheme 5).[15] The observed excellent selectivity could be explained in terms of the approach of the acryloylsilane from the same side as the C-7 substituent in **22′** that is sterically less hindered because of pseudoequatorial disposition of the substituent on the seven-membered ring. Furthermore, ab initio calculations[16] of the ground state of **22′** suggested that the PMB group efficiently blocks the face through a chelation involving the methoxy group and the sodium atom (Figure 3). Treatment of **24** with NBS followed by TBAF afforded enone **25** in 69% yield, which was converted to silyl enol ether **26** in 95% yield by exposure to

(10) Sawada, Y.; Sasaki, M.; Takeda, K. *Org. Lett.* **2004**, *6*, 2277–2279.
(11) For the construction of eight-membered carbocycles, see: (a) Takeda, K.; Sawada, Y.; Sumi, K. *Org. Lett.* **2002**, *4*, 1031–1033. For the original Brook rearrangement-mediated [3+4] annulation protocol for seven-membered carbocycles, see: (b) Takeda, K.; Takeda, M.; Nakajima, A.; Yoshii, E. *J. Am. Chem. Soc.* **1995**, *117*, 6400–6401. (c) Takeda, K.; Nakajima, A.; Yoshii, E. *Synlett* **1996**, 753–754. (d) Takeda, K.; Nakajima, A.; Takeda, M.; Okamoto, Y.; Sato, T.; Yoshii, E.; Koizumi, T.; Shiro, M. *J. Am. Chem. Soc.* **1998**, *120*, 4947–4959. (e) Takeda, K.; Nakajima, A.; Takeda, M.; Yoshii, E.; Zhang, J.; Boeckman, R. K., Jr. *Org. Synth.* **1999**, *76*, 199–213. (f) Takeda, K.; Ohtani, Y. *Org. Lett.* **1999**, *1*, 677–679. (g) Takeda, K.; Nakane, D.; Takeda, M. *Org. Lett.* **2000**, *2*, 1903–1905. (h) Nakai, Y., Kawahata, M., Yamaguchi, K., Takeda, K. *J. Org. Chem.* **2007**, *70*, 1379−1387.
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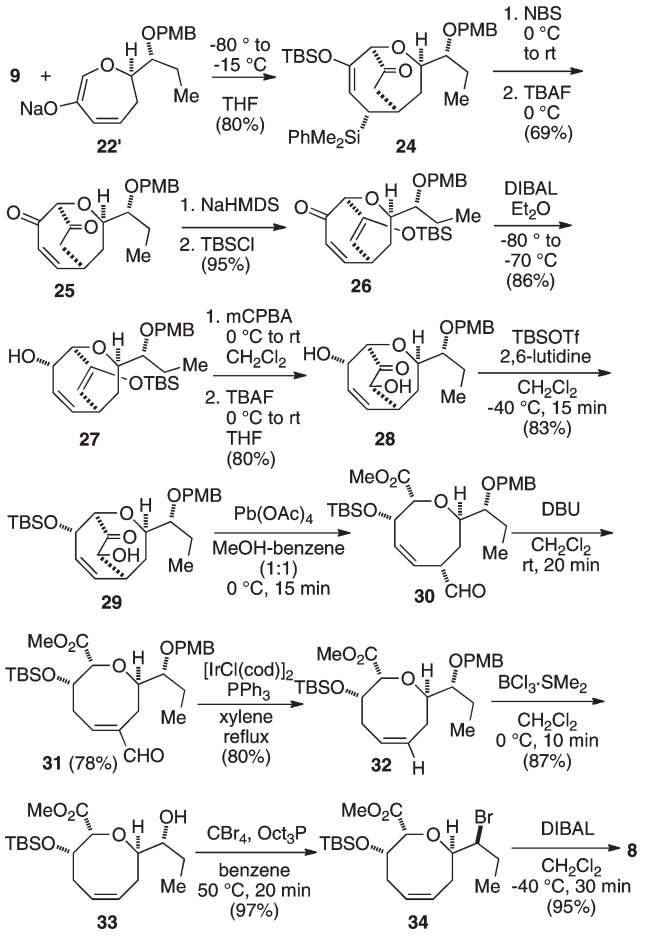
(15) The stereostructure of **24** was assigned by spectral comparison with structurally related compounds[9] and confirmed by conversion into **8**.
(16) Calculations were performed with the Spartan'06 program. Spartan'06 (Ver. 1.0.1 for Mac); Wavefunction, Inc: Irvine, CA.

SCHEME 5. Synthesis of 8



NaHMDS and TBSCl. The ketone in **26** could be stereoselectively reduced by DIBAL to give **27**. Treatment of **27** with mCPBA followed by TBAF produced diol **28**, which was converted to **29** by selective protection.

Oxidative cleavage of the two-carbon tether in **29** was conducted by $Pb(OAc)_4$ to give **30**, whose double bond was shifted by exposure to DBU to afford **31** in 78% overall yield. Decarbonylation of **31** by refluxing in toluene with Wilkinson's catalyst was unsuccessful, resulting in decomposition of the starting material. With Tsuji's catalyst $[IrCl(cod)]_2$ and PPh_3[17] under modified conditions, however, **32** was obtained in 80% yield. Transformation of **32** to Crimmins's intermediate **8** was accomplished by a three-step sequence involving removal of the PMB group, bromination of the resulting alcohol, and DIBAL reduction of ester to alcohol. The spectral data of **8** were consistent with the literature data. Since compound **8** has been transformed into prelaureatin (**1**) and laurallene (**2**) by seven and six steps, respectively, by Crimmins et al., formal total syntheses of them were thus achieved.[18]

(17) Iwai, T.; Fujihara, T.; Tsuji, Y. *Chem. Commun.* **2008**, 6251–6215.

(18) The overall yields of the present, our previous, and Crimmins's syntheses from **23** and (*R*)-1-(benzyloxy)pent-4-en-2-ol to **8** are 7.3% (18 steps), 3.2% (22 steps), and 21.3% (13 steps), respectively.

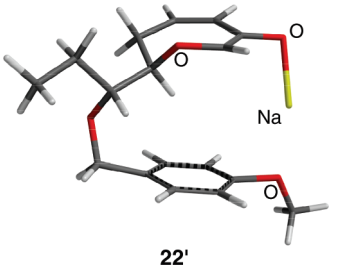


FIGURE 3. Structure of **22′** at RI-MP2/6-31+G*.

In summary, we have demonstrated the usefulness of our Brook rearrangement-mediated [3 + 4] annulation, which allows the one-pot construction of highly functionalized eight-membered oxygen heterocycles.

Experimental Section

(1*R*,3*R*,5*R*,6*S*)-8-(*tert*-Butyldimethylsilyloxy)-6-(dimethyl(phenyl)silyl)-3-((*R*)-1-(4-methoxybenzyloxy)propyl)-2-oxabicyclo[3.3.2]-dec-7-en-9-one (24). To a cooled (−80 °C) solution of NaHMDS (1.66 M in THF, 1.37 mL, 2.27 mmol) in THF (30 mL) was added a solution of **9** (692 mg, 2.27 mmol) in THF (8 mL) over 8 min and then the solution was stirred at the same temperature for 15 min. To this solution was added a solution of **22** (600 mg, 2.27 mmol) in THF (8 mL) over 5 min and the mixture was allowed to warm to −15 °C over 30 min. The reaction mixture was poured into 10% aqueous NH_4Cl solution (30 mL) and extracted with Et_2O (3 × 20 mL). Combined organic phases were washed with saturated brine (30 mL), dried, and concentrated. The residual oil was subjected to column chromatography (silica gel, 50 g, elution with hexane/AcOEt = 4:1) to give **24** (982 mg, 80%) as a pale yellow oil: R_f 0.39 (hexane/AcOEt = 5:1), $[\alpha]^{25}_D$ 107.2 (*c* 1.00, $CHCl_3$); IR (film) 1707, 1252 cm^{-1}; ^1H NMR (C_6D_6) δ 0.19 and 0.19 (each 3H, s), 0.27 (6H, s), 0.98 (9H, s), 1.03 (3H, t, J = 7.3 Hz), 1.50−1.58 (1H, m), 1.69 (1H, dd, J = 12.8, 12.8 Hz), 1.73−1.78 (1H, m), 1.92−1.97 (1H, m), 2.04−2.06 (1H, br m), 2.16−2.18 (1H, br m), 2.25 (1H, dd, J = 19.5, 4.1 Hz), 2.63 (1H, dd, J = 19.5, 3.4 Hz), 3.35 (3H, s), 3.38−3.42 (1H, m), 3.79−3.83 (1H, m), 4.46 (1H, d, J = 11.5 Hz), 4.51 (1H, d, J = 11.5 Hz), 5.02 (1H, s), 5.24 (1H, dd, J = 4.6, 1.4 Hz), 6.85 (2H, d, J = 8.5 Hz), 7.24−7.25 (m), 7.29 (2H, d, J = 8.5 Hz), 7.42−7.44 (m); ^{13}C NMR (C_6D_6) δ −4.4, −4.2, −3.8, −3.5, 10.9 18.1 23.2, 25.8, 26.9, 36.3, 36.8, 43.5, 54.7, 72.8, 74.3, 83.0, 89.3, 111.3, 114.0, 128.3, 129.4, 129.6, 131.8, 134.0, 137.5, 147.6, 159.7, 203.0; HRMS calcd for $C_{34}H_{50}O_5Si_2$ 594.3197, found 594.3186. This reaction can be performed on a multigram scale.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.