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A Total Synthesis of (±)-*trans*-Kumausyne

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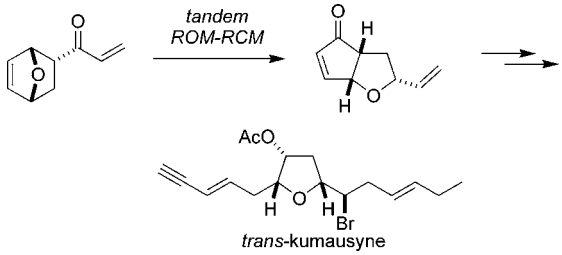
ABSTRACT



A short total synthesis of (±)-*trans*-kumausyne is reported. Key steps include a tandem ring-opening–ring-closing metathesis and the effective introduction of the pentenyl side chain by allylation–cross metathesis.

Red algae of the genus *Laurencia*, growing in the coastal waters around Japan, have proven to be prolific producers of halogenated secondary metabolites. Representative examples of these metabolites include the kumausynes,[1a] kumausallene,[1b] and laurefucin[2] (Figure 1). These compounds

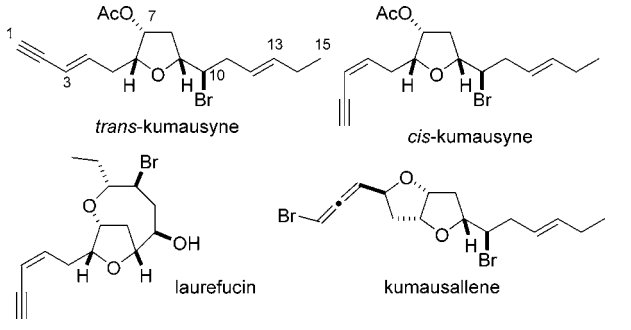


Figure 1. *trans*-Kumausyne and related metabolites from *Laurencia* sp.

have attracted substantial interest from the synthesis community, and efforts to date have resulted in completed syntheses of *trans*-kumausyne[3] and kumausallene[4] by several groups, as well as a number of reports describing subunit and formal syntheses.[5]

As part of our program to explore the strategic potential of tandem ring-opening−ring-closing (ROM−RCM) and ring-opening−ring-closing−cross metathesis (ROM−RCM−CM) of simple ring systems, we describe in this Letter a total synthesis of (±)-*trans*-kumausyne employing this strategy.[6]

(1) (a) Suzuki, T.; Koizumi, K.; Suzuki, M.; Kurosawa, E. *Chem. Lett.* **1983**, 1643. (b) Suzuki, T.; Koizumi, K.; Suzuki, M.; Kurosawa, E. *Chem. Lett.* **1983**, 1639.

(2) (a) Fukuzawa, A.; Kurosawa, E.; Irie, T. *Tetrahedron Lett.* **1972**, *13*, 3. (b) Furusaki, A.; Kurosawa, E.; Fukuzawa, A.; Irie, T. *Tetrahedron Lett.* **1973**, *14*, 4579.

(3) Total syntheses: (a) Brown, M. J.; Harrison, T.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5378. (b) Osumi, K.; Sugimura, H. *Tetrahedron Lett.* **1995**, *36*, 5789. (c) Boukouvalas, J.; Fortier, G.; Radu, I.-I. *J. Org. Chem.* **1998**, *63*, 916. (d) Lee, E.; Yoo, S.-K.; Cho, Y.-S.; Cheon, H.-S.; Chong, Y. H. *Tetrahedron Lett.* **1997**, *38*, 7757.

(4) Total syntheses: (a) Grese, T. A. Hutchinson, K. D.; Overman, L. E. *J. Org. Chem.* **1993**, *58*, 2468. (b) Evans, P. A.; Murthy, V. S.; Roseman, J. D.; Rheingold, A. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 3175.

(5) (a) Fernandez De La Pradilla, R.; Viso, A. *Rec. Res. Dev. Org. Bioorg. Chem.* **2001**, *4*, 123. (b) Gadikota, R. R.; Callam, C. S.; Lowary, T. L. *J. Org. Chem.* **2001**, *66*, 9046. (c) Garcia, C.; Martin, T.; Martin, V. S. *J. Org. Chem.* **2001**, *66*, 1420. (d) Mereyala, H. B.; Gadikota, R. *Tetrahedron: Asymmetry* **2000**, *11*, 743. (e) Fernandez de la Pradilla, R.; Montero, C.; Priego, J.; Martinez-Cruz, L. A. *J. Org. Chem.* **1998**, *63*, 9612. (f) Andrey, O.; Glanzmann, C.; Landais, Y.; Parra-Rapado, L. *Tetrahedron* **1997**, *53*, 2835. (g) Lee, E.; Yoo, S.-K.; Choo, H.; Song, H. Y *Tetrahedron Lett.* **1998**, *39*, 317.

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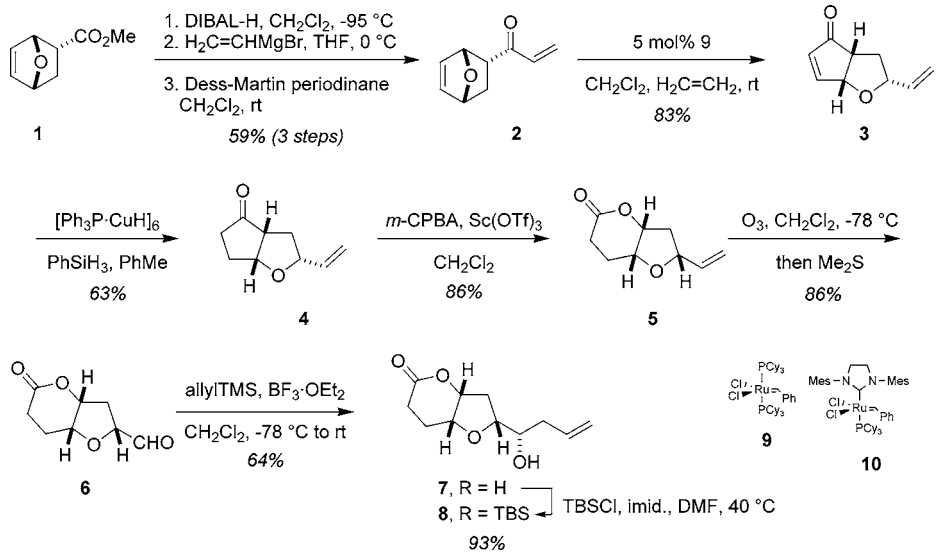
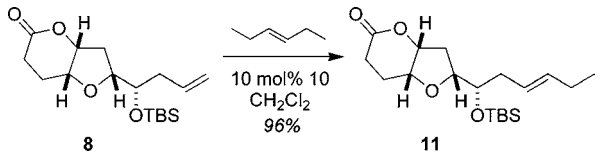
Scheme 1



Our synthesis begins with known ester **1**, which is readily available by Diels−Alder reaction of furan and methyl acrylate (Scheme 1).[7] Reduction to the aldehyde with diisobutylaluminum hydride, followed by addition of vinylmagnesium bromide and subsequent oxidation of the crude mixture of allylic alcohols with Dess−Martin periodinane, provided enone **2** in 59% yield over the three steps. Subjecting this material to 5 mol % Grubbs catalyst **9** in CH_2Cl_2 under an atmosphere of ethylene resulted in smooth tandem ROM−RCM to give furan **3** in 83% yield.[8,9] Enone reduction with Stryker's reagent and $PhSiH_3$ following Lipshutz's protocol[10] afforded ketone **4** in 63% yield and set the stage for the introduction of the third oxygen substituent on the tetrahydrofuran ring by Baeyer−Villiger oxidation. When ketone **4** was subjected to *m*-CPBA in the presence of scandium triflate,[11] Baeyer−Villiger oxidation occurred smoothly to give bicyclic lactone **5** in 71% yield.[12] Ozonolysis of the olefin proceeded in 86% yield to give sensitive aldehyde **6**, which was immediately reacted with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ to give homoallylic alcohol **7** in 64% yield after chromatography. Subsequent protection of the alcohol with TBSCl and imidazole in DMF at 40 °C provided **8** in 93% yield.

The remaining carbons of the pentenyl side chain were conveniently installed by a cross metathesis (Scheme 2). To this end, a CH_2Cl_2 solution of **8** was exposed to 20 equiv of *trans*-3-hexene in the presence of 10 mol % carbene **10** to give the desired alkene **11** in 96% yield.[13]

Scheme 2



The synthesis was completed as shown in Scheme 3. Lactone opening with lithiotrimethylsilylacetylene (**11**→**12**) and subsequent acetylation of the secondary alcohol provided

(6) (a) Minger, T. L.; Phillips, A. J. *Tetrahedron Lett.* **2002**, *43*, 5357. (b) Pfeiffer, M. W. B.; Phillips, A. J. *J. Am. Chem. Soc.* **2005**, 127, 5334.

(7) (a) Kotsuki, H.; Asao, K.; Ohnishi, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 3339. (b) For a catalytic asymmetric synthesis, see: Evans, D. A.; Barnes, D. M.; Johnson, J. S.; Lectka, T.; von Matt, P.; Miller, S. J.; Murry, J. A.; Norcross, R. D.; Shaughnessy, E. A.; Campos, K. R. *J. Am. Chem. Soc.* **1999**, *121*, 7582.

(8) For other examples of tandem ROM−RCM in a target-oriented setting, see: (a) Blechert, S.; Stapper, C. *Eur. J. Org.* Chem. **2002**, *16*, 2855. (b) Stapper, C.; Blechert, S. *J. Org. Chem.* **2002**, *67*, 6456. (c) Stragies, R.; Blechert, S. *J. Am. Chem. Soc.* **2000**, *122*, 9584. (d) Wrobleski, A.; Sahasrabudhe, K.; Aube, J. *J. Am. Chem. Soc.* **2002**, *124*, 9974.

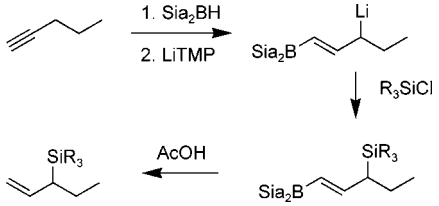
(9) This sequence could also be carried out without purification of sensitive enone **2**. The overall yield for the sequence from **1**→**3** by this permutation was 49%.

(10) (a) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291. (b) Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron Lett.* **1998**, *39*, 4627.

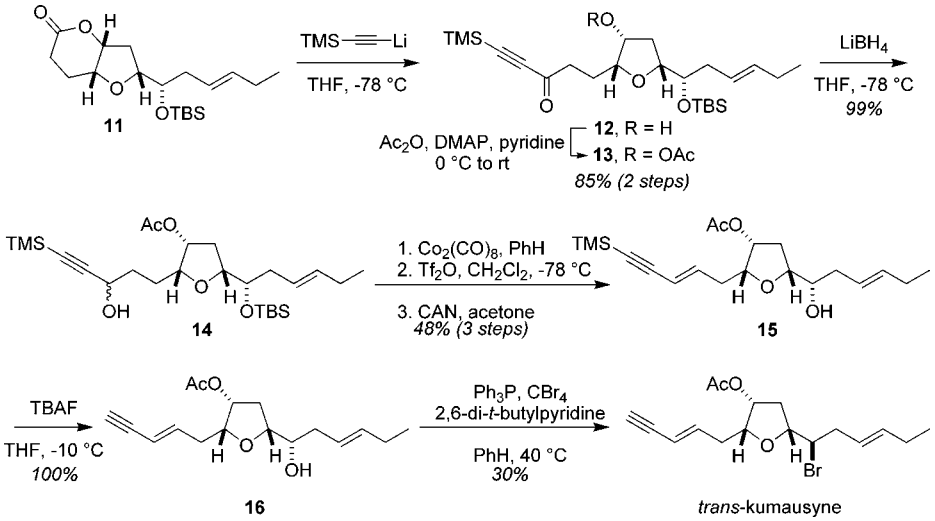
(11) Kotsuki, H.; Arimura, K.; Araki, T.; Shinohara, T. *Synlett* **1999**, 462.

(12) Efforts to perform the Baeyer−Villiger oxidation at later points in the sequence were unsuccessful due to competitive olefin epoxidation. Epoxidation with MCPBA alone produced mixtures of products derived from epoxidation and Baeyer−Villiger oxidation.

(13) In all other syntheses of kumausyne and kumausallene, the pentenyl side chain was installed by a variation on Overman's original solution (see ref 3a), which consists of Sakurai allylation of a related aldehyde with 3-trimethylsilyl-1-pentene or 3-triethylsilyl-1-pentene. Although these reagents are prepared in a straightforward manner by the scheme shown below, they are low-boiling and difficult to handle. The protocol described here has the advantage of employing commercially available materials and should, in principle, be quite general provided that the alkene required for the subsequent cross-metathesis is readily available.



Scheme 3



alkynyl ketone **13** in 85% yield over the two steps. Although reduction of the ketone was readily achieved with $LiBH_4$ to give **14**, elimination of the propargylic alcohol proved to be remarkably difficult. After a number of common procedures failed, we resorted to elimination via the Nicholas reaction.[14] Treatment of **14** with $Co_2(CO)_8$, followed by triflic anhydride-mediated elimination, and decomplexation with ceric ammonium nitrate provided enyne **15** in 48% overall yield for the three steps. Desilylation with TBAF in THF gave alcohol **16** in quantitative yield and set the stage for the conversion of the secondary alcohol to a bromide. Following Overman's procedure,[3a] alcohol **16** was treated with freshly purified Ph_3P and CBr_4 in the presence of 2,6-di-*tert*-butylpyridine in benzene at 40 °C. After workup, (±)-*trans*-kumausyne was obtained by preparative TLC in 30% yield. The synthetic material had spectral properties fully consistent with those reported in the literature and with ^1H and ^{13}C NMR spectra that were provided by Professor Larry Overman.

(14) (a) Nicholas, K. M.; Pettit, R. *J. Organomet. Chem.* **1972**, *44*, C21. (b) For a closely related example, see: Overman, L. E.; Berger, D.; Renhowe, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 9305.

In conclusion, we have described a concise 19-step synthesis of (±)-*trans*-kumausyne. Noteworthy features of the synthesis include a tandem ROM−RCM reaction that converts a structure readily available by Diels−Alder reaction into an advanced intermediate for the synthesis of kumausyne, a highly selective Baeyer−Villiger reaction, and the use of cross metathesis for the elaboration of a homoallylic alcohol into the pentenyl side-chain.

Acknowledgment. We thank Professor Larry Overman for a copy of spectra for *trans*-kumausyne. This work was supported by the National Cancer Institute (NCI CA110246). Spectra were obtained using NMR facilities purchased partly with funds from an NSF Shared Instrumentation Grant (CHE-0131003).

Supporting Information Available: Experimental procedures, characterization data, and copies of spectra for compounds **2→8**, **11→16**, and *trans*-kumausyne. This material is available free of charge via the Internet at http://pubs.acs.org.

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