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Diastereoselective Brook Rearrangement-Mediated [3 + 4] Annulation: Application to a Formal Synthesis of (+)-Laurallene

Michiko Sasaki,[†] Azusa Hashimoto,[†] Koudai Tanaka,[†] Masatoshi Kawahata,[‡] Kentaro Yamaguchi,[‡] and Kei Takeda[†,*]

Department of Synthetic Organic Chemistry, Graduate School of Medical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-Ku, Hiroshima 734-8553, Japan, and Tokushima Bunri University, Shido, Sanuki, Kagawa 769-2193, Japan

takedak@hiroshima-u.ac.jp

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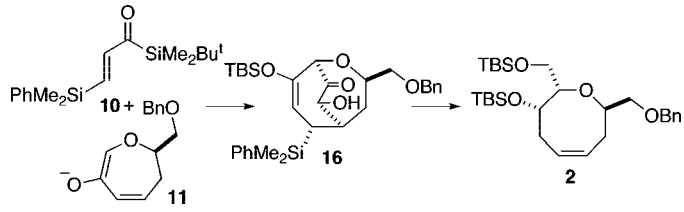
ABSTRACT



The formal synthesis of (+)-laurallene, a halogenated eight-membered ring ether, was accomplished. The synthesis involves construction of a trans α,α′-disubstituted oxocene structure 16 through a Brook rearrangement-mediated [3 + 4] annulation using acryloylsilane 10 and 6-oxa-2-cycloheptenone 9 and its conversion into 2, which has been transformed into (+)-laurallene by Crimmins and co-workers.

Laurallene (**1**) belongs to a laurenane structural subclass that is one of two basic structural types of halogenated eight-membered ring ethers isolated from red algae of the genus *Laurencia*.[1] Although much interest has been shown in the synthesis of **1** due to its unique structural feature, few syntheses have been reported,[2] probably because of the difficulty in establishing a trans α,α′-disubstituted oxocene structure.[1–3] That is in contrast to the extensive studies on the synthesis of another subclass, the lauthisan type, that involves a cis α,α′-disubstituted pattern at the ether oxygen.[4] The first total synthesis of **1** was reported by Crimmins and co-workers, who used ring-closing metathesis to close the eight-membered ring, allowing construction of the oxocene core.

As part of our ongoing program on the development of new synthetic reactions featuring a tandem carbon−carbon bond formation, we have recently reported a Brook rearrangement-mediated [3 + 4] annulation methodology for the construction of eight-membered oxacycles.[5–7] In this paper, we report a

[†] Hiroshima University
[‡] Tokushima Bunri University

(1) Fukuzawa, A.; Kurosawa, E. *Tetrahedron Lett.* **1979**, 2797–2800.
(2) (a) Crimmins, M. T.; Elie, A. T. *J. Am. Chem. Soc.* **2000**, *122*, 5473–5476. (b) Saitoh, T.; Suzuki, T.; Sugimoto, M.; Hagiwara, H.; Hoshi, T. *Tetrahedron Lett.* **2003**, *44*, 3175–3178.
(3) (a) Fujiwara, K. *J. Synth. Org. Chem. Jpn.* **2007**, *65*, 502–510. (b) Fujiwara, K.; Souma, S.; Mishima, H.; Murai, A. *Synlett* **2002**, 1493–1495. (c) Kim, H.; Lee, H.; Lee, D.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2007**, *129*, 2269–2274. (d) Sugimoto, M.; Suzuki, T.; Hagiwara, H.; Hoshi, T. *Tetrahedron Lett.* **2007**, *48*, 1109–1112.
(4) (a) Fujiwara, K. In *Topics in Heterocyclic Chemistry*; Kiyota, H., Ed.; Springer: Berlin, 2006; Vol. 5, pp, 97−148. (b) Fujiwara, K.; Yoshimoto, S.; Takizawa, A.; Souma, S.; Mishima, H.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2005**, *46*, 6819–6822. (c) Baek, S.; Jo, H.; Kim, H.; Kim, H.; Kim, S.; Kim, D. *Org. Lett.* **2005**, *7*, 75–77. (d) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653–5660. (e) Krüger, J.; Hoffmann, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7499–7504. (f) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483–7498. (g) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958–5966. (h) Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345–4348.
(5) Sawada, Y.; Sasaki, M.; Takeda, K. *Org. Lett.* **2004**, *6*, 2277–2279.

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formal synthesis of (+)-laurallene carried out to show the synthetic utility of the methodology. The target molecule is the Crimmins' intermediate (**2**), which has been converted by Crimmins and co-workers[2a] into laurallene (**1**) and prelaureatin,[8] the biogenetic precursor of several members of the laurenan structural subclass including **1** (Figure 1).

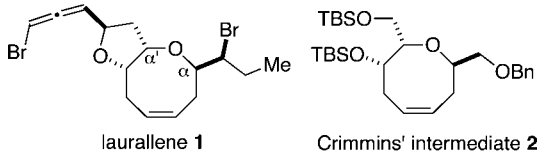
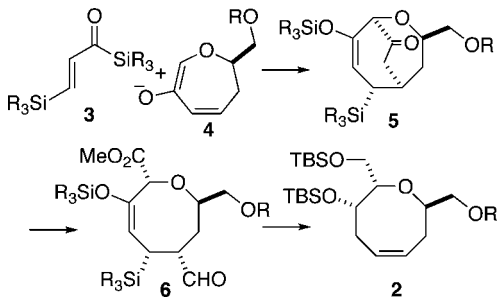


Figure 1. Laurallene **1** and Crimmins' intermediate **2**.

Our synthetic plan involves conversion of **5**, which is a [3 + 4] annulation product from acryloylsilane **3** and 6-oxa-2-cycloheptenone enolate **4** and has a latent trans α,α′-functionality, into **2** via functional group manipulation (Scheme 1). Crucial

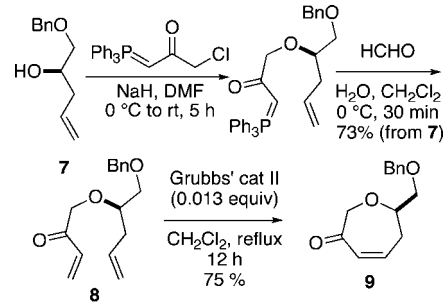
Scheme 1. Synthetic Plan for Crimmins' Intermediate **2**



to the successful implementation of this strategy is the facial selectivity in the [3 + 4] annulation, which controls the relative stereochemistry of the α,α′-substituents.

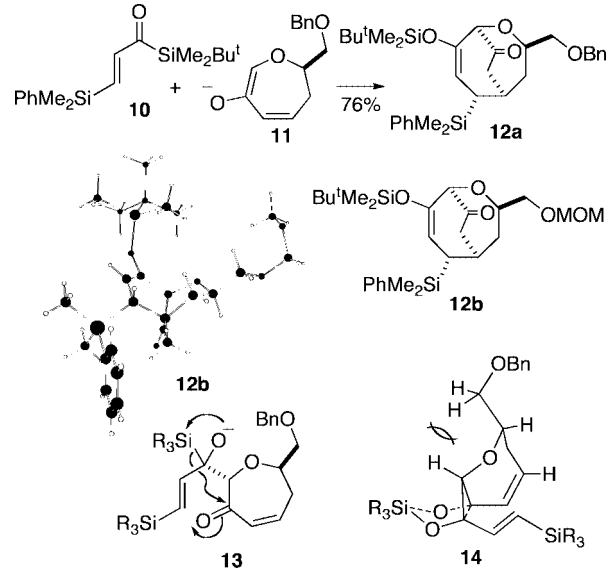
The requisite 6-oxa-2-cycloheptenone **9** for the annulation was prepared starting from (*S*)-glycidol derivative **7**[9] via ring-closing metathesis of **8** (Scheme 2).[10]

Scheme 2. Synthesis of **9**



When acryloylsilane **10**[7c] was added to a solution of lithium enolate **11**, generated from **9** by LDA at −80 °C, and then the solution was warmed to room temperature, the annulation product **12a** was obtained in 76% yield as a single isomer (Scheme 3).

Scheme 3. [3 + 4] Annulation of **10** and **11**



The use of sodium enolate generated by NaHMDS also worked well. The relative stereochemistry was determined on the basis of X-ray analysis of the MOM-protected derivative **12b**. This indicates that the addition of enolate **11** to acryloylsilane **10** occurred selectively at the same side as the benzyloxymethyl group. The exclusive formation of the product resulting from attack from the more hindered side can be explained by invoking that there exists a rapid equilibrium[7c,g] between a 1,2-adduct and the starting materials at −80 °C in reactions of acryloylsilanes with ketone enolates.[11] Thus, the transition state from the major 1,2-adduct **13** to a divinylcyclopropanediolate intermediate **14** leading to *epi*-**12a** should be higher energy than that for the minor 1,2-adduct, which was generated via attack from the more hindered side. This may be due to the fact that the

(6) For the construction of eight-membered carbocycles, see: Takeda, K.; Sawada, Y.; Sumi, K. *Org. Lett.* **2002**, *4*, 1031–1033.

(7) For the original Brook rearrangement-mediated [3 + 4] annulation protocol for seven-membered carbocycles, see: (a) Takeda, K.; Takeda, M.; Nakajima, A.; Yoshii, E. *J. Am. Chem. Soc.* **1995**, *117*, 6400–6401. (b) Takeda, K.; Nakajima, A.; Yoshii, E. *Synlett* **1996**, 753–754. (c) Takeda, K.; Nakajima, A.; Takeda, M.; Okamoto, Y.; Sato, T.; Yoshii, E.; Koizumi, T.; Shiro, M. *J. Am. Chem. Soc.* **1998**, *120*, 4947–4959. (d) Takeda, K.; Nakajima, A.; Takeda, M.; Yoshii, E.; Zhang, J.; Boeckman, R. K., Jr. *Org. Synth.* **1999**, *76*, 199–213. (e) Takeda, K.; Ohtani, Y. *Org. Lett.* **1999**, *1*, 677–679. (f) Takeda, K.; Nakane, D.; TakedaM., *Org. Lett.* **2000**, *2*, 1903–1905. (g) Nakai, Y.; Kawahata, M.; Yamaguchi, K.; Takeda, K. *J. Org. Chem.* **2007**, *70*, 1379–1387.

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

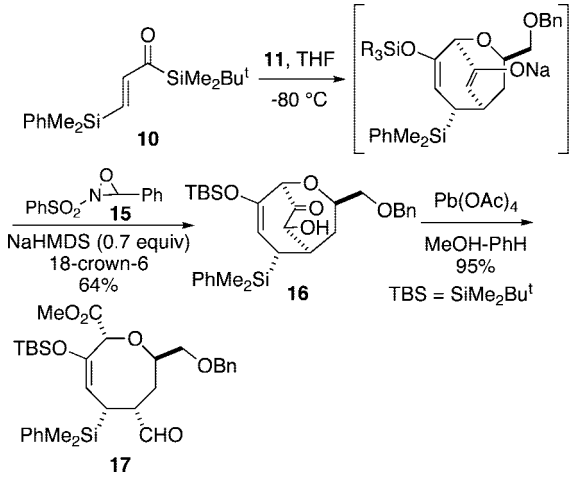
(9) (a) Gravestock, M. B.; Knight, D. W.; Lovell, J. S.; Thornton, S. R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1661–1663. (b) Takano, S.; Sekiguchi, Y.; Sato, N.; Ogasawara, K. *Synthesis* **1987**, 139–141.

(10) Cossy, J.; Taillier, C.; Bellosta, V. *Tetrahedron Lett.* **2002**, *43*, 7263–7266.

transition state is product-like in which unfavorable steric interactions between the benzyloxymethyl group and the hydrogen atom on the cyclopropane ring as shown in **14** can develop upon the formation of the cyclopropane ring. Our previous studies[7c] also indicate that the existence of an equilibrium between a 1,2-adduct and divinylcyclopropanediolate via a retro-aldol/retro-Brook sequence is unlikely.

Having obtained the bicyclo[3.3.2]decene skeleton with the desired stereoselectivity, we next examined the annulation and subsequent oxidation of the resultant enolate to an α-hydroxyketone in a one-pot operation. When Davis' oxaziridine **15**[12] was added to a THF solution of sodium enolate[13] of **12a** with an extra amount of NaHMDS and 18-crown-6, α-hydroxy ketone **16** was obtained in 64% yield, which was a better yield than that obtained by the procedure with isolation of **12a** (Scheme 4). Oxidative cleavage of the

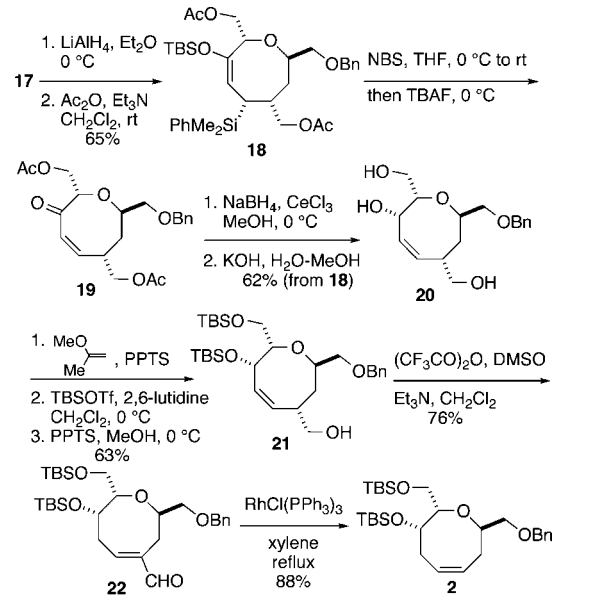
Scheme 4. Synthesis of **17** via One-Pot [3 + 4] Annulation/Oxidation



two-atom internal tether was achieved with $Pb(OAc)_4$ in MeOH-benzene to give **17** in 95% yield.

The remaining steps necessary for the conversion of **17** into Crimmins' intermediate (**2**) are shown in Scheme 5. The α-silyl enol silyl ether in **17** was transformed into enone **19** by a three-step sequence involving conversion into the diacetate **18** by reduction of the aldehyde and ester moieties followed by acetylation and reaction with NBS followed by *n*-Bu_4NF (TBAF).[7c] Stereoselective reduction of the ketone in **19** was achieved by $NaBH_4$ to give an alcohol as a single diastereomer,[14] which was converted into triol **20** (62%

Scheme 5. Transformation of **17** to Crimmins' Intermediate



overall yield from **18**) by methanolysis. The migration of a double bond from the C4−C5 position to the C5−C6 position and selective removal of the hydroxymethyl group at C6 could be achieved by a five-step sequence. Thus, treatment of **20** with 2-methoxypropene in the presence of pyridinium *p*-toluenesulfonate (PPTS) followed by reaction with TBSOTf and 2,6-lutidine and then methanolysis of the resulting 1-methoxyethyl group afforded the selectively protected alcohol **21** in 63% overall yield. Swern oxidation of **21** using trifluoroacetic anhydride[15] and then removal of the resulting aldehyde using the Wilkinson catalyst gave Crimmins' intermediate (**2**) in 67% overall yield. Comparison of the spectroscopic data and the specific optical rotation of our sample of **2** with those kindly provided by Professor Crimmins showed them to be identical.

In summary, we have accomplished a formal synthesis of (+)-laurallene using Brook rearrangement-mediated [3 + 4] annulation, demonstrating the synthetic utility of the methodology.

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Supporting Information Available: Full experimental details and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) An alternative explanation for the observed diastereoselectivity is that the approach of the acylsilane to the enolate occurrs from the same side as the benzylozymethyl substituent due to its psuedo equatorial disposition on the seven membered ring, as suggested by a reviewer.

(12) (a) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A.; Pribish, J.; Vedejs, E. *Org. Synth.* **1987**, *66*, 203–210. (b) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241–3243.

(13) In this case, the use of lithium enolate resulted in a sluggish reaction in the stage of the oxidation even with the addition of an extra amount of NaHMDS and the crown ether.

(14) The relative stereochemistry of the resulting alcohol was determined to be that shown after conversion into **2**.

(15) The use of oxalyl chloride gave much lower yield.