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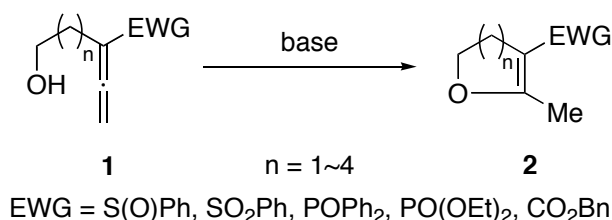
SYNTHESIS OF (±)-LAUTHISAN[†]

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Abstract – A new total synthesis of (±)-lauthisan was accomplished based on the endo-mode ring-closing reaction of 1-(5-hydroxyhept-1-yl)-3-pentyl-1-phenylsulfonyllallene.

As a part of our programs¹ on the development of the efficient methods for the preparation of various kinds of ring-closed products, we reported a novel method for the synthesis of five- to medium-sized oxacycles **2** based on the endo-mode ring-closing reaction of 1,1-disubstituted allenes **1**, which possess both an electron-withdrawing group and the ω-hydroxyalkyl appendage at C₁-position of the allenyl moiety (Scheme 1).² This paper deals with several experiments regarding the scope of the endo-mode ring-closing reaction using tri- and tetrasubstituted allenes and its application to synthesis of (±)-lauthisan³ as a preliminary examination for total syntheses of marine natural products, laurencin and laurefucin.

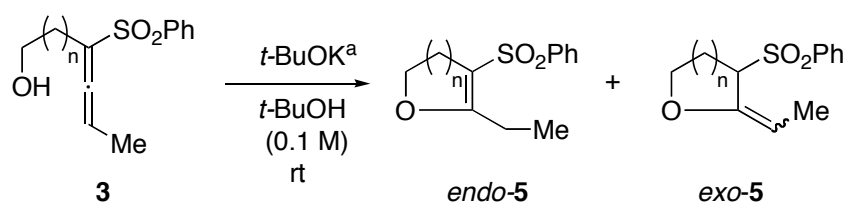


Scheme 1. Endo-mode ring-closing reaction of allenyl alcohols

The tri- and tetrasubstituted allenes **3** and **4** for the ring-closing reaction were prepared by the similar procedure described for the preparation of **1**.² The ring-closing reaction of **3** was carried out according to the previously optimized conditions² for the ring-closing reaction of 1,1-disubstituted allenes **1**. Thus, compound **3a** was exposed to *t*-BuOK (1.5 equiv) in *t*-BuOH at room temperature for less than 5 min to

[†] This paper is dedicated to Professor Dr. Ekkehard Winterfeldt on the occasion of his 75th birthday.

produce the *endo*-double bond derivative, *endo-5a*, along with the *exo*-double bond isomer, *exo-(Z)-5a* (87%: *endo-5a* : *exo-(Z)-5a* = 73 : 27) (Table 1, Entry 1).⁴ Similar treatment of the one carbon homologated **3b** predominantly furnished the *exo*-double bond derivative, *exo-(E)-5b*, along with *endo-5b* (89%: *endo-5b* : *exo-(E)-5b* = 19 : 81) (Entry 2). The exclusive formation of the *exo*-double bond derivatives, *exo-(E)-5c* and *exo-(E)-5d*, were recorded when **3c** and **3d** were submitted to the ring-closing conditions (Entries 3,4).



Entry	Substrate	n	Products and Yield (%)	<i>endo</i> : <i>exo</i>
1	3a	1	5a (87)	73 : 27 (<i>Z</i>) ^b
2	3b	2	5b (89)	19 : 81 (<i>E</i>) ^b
3	3c	3	5c (84)	0 : 100 (<i>E</i>)
4	3d	4	5d (84)	0 : 100 (<i>E</i>)

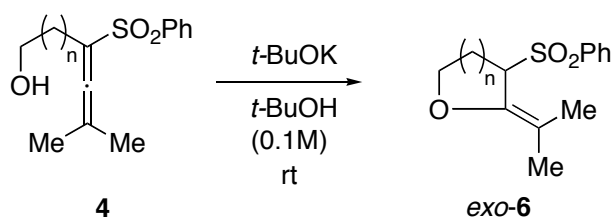
^a The starting **3** was completely consumed within 5 min.

^b The ratio was determined on the basis of isolated amounts of each isomer.

Table 1. Ring-closing reaction of 1,1,3-trisubstituted allenes

Independent exposure of *endo-5a* and *exo-5a* to the ring-closing conditions for a longer reaction time (1 h) provided an equilibrium mixture of *endo-5a* and *exo-5a* in a ratio of 90 to 10. The six-membered *endo-5b* was found to be stable under the ring-closing conditions, while *exo-(E)-5b* was completely isomerized to *endo-5b* within 5 h. These experiments revealed that *endo-5a,b* must be thermodynamically controlled products. It should be mentioned that both seven- and eight-membered products *exo-5c,d* were inactive toward base-catalyzed isomerization.

We next investigated the *endo*-mode ring-closing reaction of tetrasubstituted allenes **4**. Exposure of **4** to the standard basic conditions consistently gave the *exo*-double bond isomers, *exo-6*, in high yields and the corresponding *endo*-double bond derivatives could not be detected in the reaction mixture (Table 2). The *exo-6* was shown to be stable under the basic conditions and no isomerization to the corresponding *endo*-derivatives could be observed. Thus, it can be concluded that the *endo*-mode ring-closing reaction of phenylsulfonallenes, leading to the formation of five- to eight-membered oxacycles, proceeds irrespective of the substitution pattern at the allenic terminus.

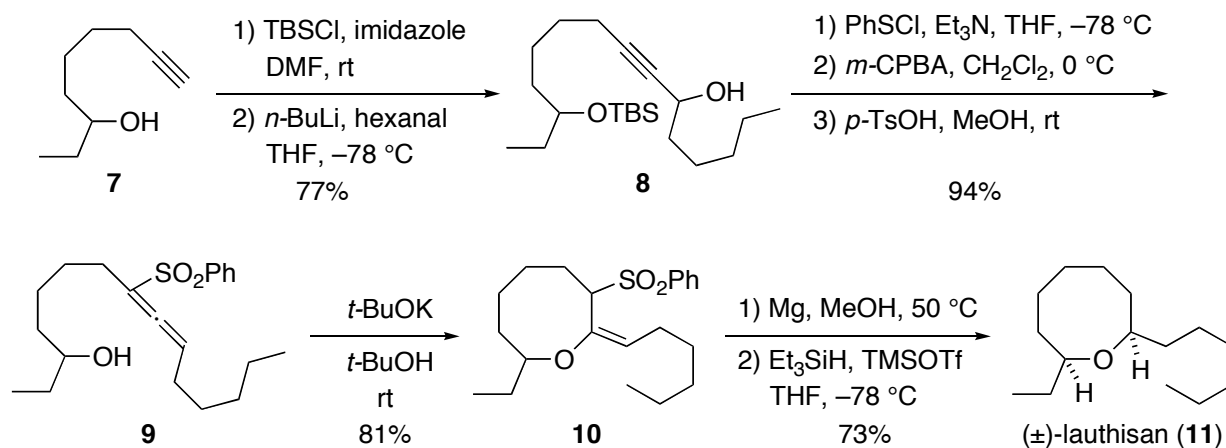


Entry	Substrate	n	Time ^a (min)	Product and Yield (%)
1	4a	1	> 5	6a (91)
2	4b	2	10	6b (90)
3	4c	3	20	6c (94)
4	4d	4	180	6d (84)

^a The reaction mixture was quenched when the complete consumption of **4** was detected by TLC.

Table 2. Ring-closing reaction of tetrasubstituted allenes

Synthesis of (\pm)-lauthisan (**11**) by taking advantage of the endo-mode ring-closing reaction of 1,1,3-trisubstituted allene was the next subject in this paper. Thus, protection of the secondary hydroxyl moiety of the known non-1-yn-7-ol (**7**)⁵ with the TBS was followed by treatment with *n*-BuLi in THF at $-78\text{ }^{\circ}\text{C}$ and the resulting acetylide was quenched by hexanal to give the propargyl alcohol **8**⁶ in 77% yield. Compound **8** was then converted into the trisubstituted allene **9**⁶ in 94% yield. Exposure of **9** to the standard ring-closing conditions (*t*-BuOK in *t*-BuOH at room temperature for 40 min) furnished (*E*)-8-ethyl-2-hexylidene-3-(phenylsulfonyl)oxocane (**10**)⁷ in 81% yield. The final stage of this synthesis was the removal of a phenylsulfonyl group as well as reduction of enol ether moiety. Treatment of **10** with Mg in MeOH at $50\text{ }^{\circ}\text{C}$ ⁸ effected dephenylsulfonylation to produce the corresponding eight-membered oxacycle, which was subsequently exposed to Et_3SiH in THF in the presence of TMSOTf at $-78\text{ }^{\circ}\text{C}$ ⁹ to afford (\pm)-lauthisan (**11**)^{10,11} in 73% yield (Scheme 2).



Scheme 2. Synthesis of (\pm)-lauthisan

In conclusion, we have described here that (i) tri- and tetrasubstituted allenes were suitable substrates in the endo-mode ring-closing reaction and (ii) successful application of our method to completion of the total synthesis of (\pm)-lauthisan (**11**) from the known non-1-yn-7-ol (**7**).

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4. The stereochemistry of *exo*-**5** was determined by NMR spectral consideration.
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6. Compounds **8** and **9** must be a mixture of two diastereoisomers judging from the reaction conditions used. However, their ^1H and ^{13}C NMR spectra appeared as if they were a single isomer.
7. Compound **10** was obtained as a single isomer. The (*E*)-stereochemistry was tentatively determined by comparison with the related compounds, although the relative stereochemistry of two chiral

centers was not determined yet.

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10. The structure of synthetic lauthisan was confirmed by comparison with spectral data in the literatures.
11. The stereoselective reduction of **10** might be rationalized in terms of the attack of the hydride species from the sterically less hindered face (α -face) on the basis of the literature precedent.^{3k}