HETEROCYCLES, Vol. 74, 2007, pp. 185 - 189. © The Japan Institute of Heterocyclic Chemistry
Received, 29th August, 2007, Accepted, 28th September, 2007, Published online, 28th September, 2007. COM-07-S(W)46

SYNTHESIS OF (±)-LAUTHISAN†

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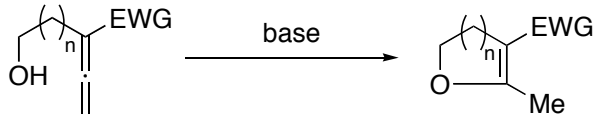
Abstract – A new total synthesis of (±)-lauthisan was accomplished based on the endo-mode ring-closing reaction of 1-(5-hydroxyhept-1-yl)-3-pentyl-1-phenylsulfonylallene.

As a part of our programs[1] 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 C_1-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 (±)-lauthisan[3] as a preliminary examination for total syntheses of marine natural products, laurencin and laurefucin.



1 n = 1~4 **2**

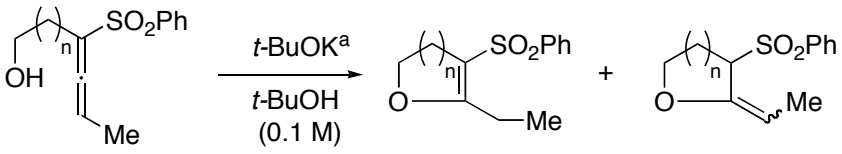
EWG = S(O)Ph, SO_2Ph, $POPh_2$, $PO(OEt)_2$, CO_2Bn

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 conditions[2] 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).



3 *endo*-**5** *exo*-**5**

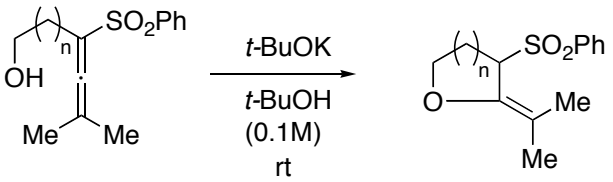
Entry	Substrate	n	Products and Yield (%)	*endo* : *exo*
1	**3a**	1	**5a** (87)	73 : 27 (*Z*)[b]
2	**3b**	2	**5b** (89)	19 : 81 (*E*)[b]
3	**3c**	3	**5c** (84)	0 : 100 (*E*)
4	**3d**	4	**5d** (84)	0 : 100 (*E*)

[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 phenylsulfonylallenes, leading to the formation of five- to eight-membered oxacycles, proceeds irrespective of the substitution pattern at the allenic terminus.



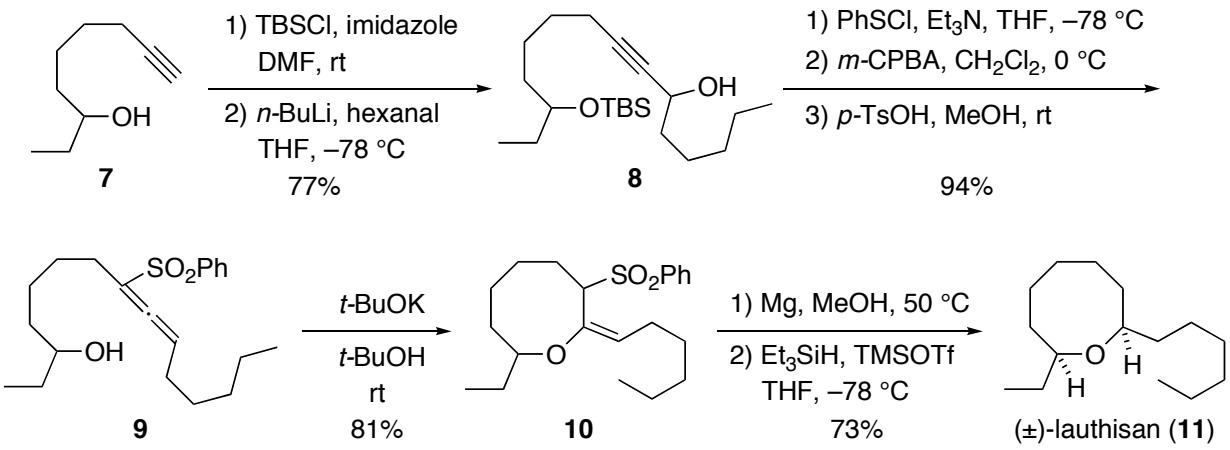
4 *exo*-**6**

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 (±)-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 °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 °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 °C[9] to afford (±)-lauthisan (**11**)[10, 11] in 73% yield (Scheme 2).



Scheme 2. Synthesis of (±)-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 (±)-lauthisan (**11**) from the known non-1-yn-7-ol (**7**).

ACKNOWLEDGEMENTS

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan, for which we are grateful.

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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 ^{1}H 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]