Pergamon

Tetrahedron Letters 41 (2000) 3415–3418

TETRAHEDRON LETTERS

# Amberlyst-15-catalyzed intramolecular $S_N2'$ oxaspirocyclization of secondary allylic alcohols. Application to the total synthesis of spirocyclic ethers theaspirane and theaspirone

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Received 4 February 2000; revised 2 March 2000; accepted 3 March 2000

**Abstract**

A variety of substituted 1-oxaspiro[4.4]non-6-ene, 1-oxaspiro[4.5]dec-6-ene, 6-oxaspiro[4.5]dec-1-ene and 1-oxaspiro[5.5]undec-7-ene systems have been prepared by utilizing Amberlyst-15-catalyzed intramolecular $S_N2'$ oxaspirocyclizations of secondary allylic alcohols under mild reaction conditions in quantitative yields. This oxaspirocyclization was applied to the total synthesis of theaspirane and theaspirone from β-ionone in five steps.


*Keywords:* Amberlyst-15; $S_N2'$ oxaspirocyclization; secondary allylic alcohols; total synthesis; theaspirane; theaspirone.

Numerous methods are available for the syntheses of allylic oxaspirocycle systems such as **1**[1–4] (Fig. 1). In the preceding paper,[5] we reported that allylic oxaspirocycles are readily accessible by Amberlyst-15-catalyzed intramolecular $S_N2'$ oxaspirocyclization of tertiary allylic alcohols with high yields and easy work-up features. These transformations are synthetically interesting since the allylic oxaspirocyclic products obtained have a structure very similar to naturally occurring norisoprenoid spiroethers, such as theaspiranes and vetispirane, which are known aroma components in tea and vanilla, respectively.

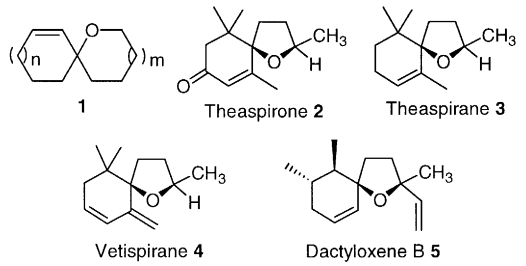


Fig. 1.

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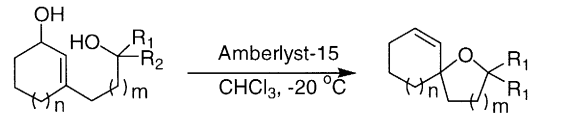
0040-4039/00/$ - see front matter 
*PII:* S0040-4039(00)00396-8

The application of Amberlyst-15-catalyzed intramolecular $S_N2'$ oxaspirocyclization of tertiary allylic alcohols to natural product synthesis has two limitations. First, 1-oxaspiro[4.4]non-6-ene and 6-oxaspiro[4.5]dec-1-ene systems can hardly be prepared by the method previously reported[5] because the tertiary allylic alcohols cannot be obtained from the corresponding 2-cyclopentenone when treated with methyllithium. Second, only a few natural products have alkyl substitution at the 7-position of 1-oxaspiro[4.5]dec-6-ene systems and at the 8-position of 1-oxaspiro[5.5]undec-7-ene systems.

In this report, we demonstrate that the route for Amberlyst-15-catalyzed intramolecular $S_N2'$ oxaspirocyclizations of secondary allylic alcohols can also be applied to the syntheses of allylic oxaspirocycles in high yields, even in cases including steric hindered tertiary nucleophile (Scheme 1). The total synthesis of theaspirane and theaspirone[6] has been achieved via oxaspirocyclization as the key step (Scheme 4).

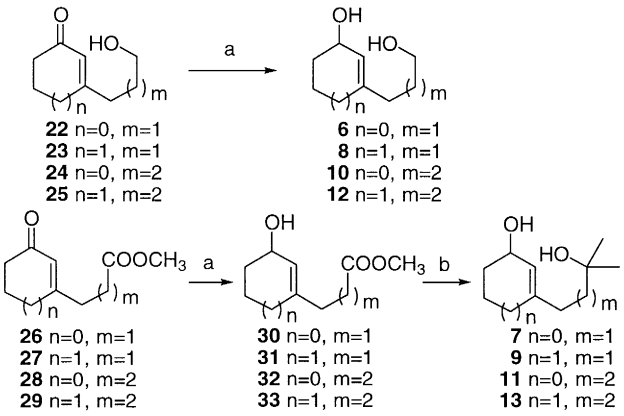



**6** n=0, m=1, $R_1$=H
**7** n=0, m=1, $R_1$=$CH_3$
**8** n=1, m=1, $R_1$=H
**9** n=1, m=1, $R_1$=$CH_3$
**10** n=0, m=2, $R_1$=H
**11** n=0, m=2, $R_1$=$CH_3$
**12** n=1, m=2, $R_1$=H
**13** n=1, m=2, $R_1$=$CH_3$

**14** n=0, m=1, $R_1$=H
**15** n=0, m=1, $R_1$=$CH_3$
**16** n=1, m=1, $R_1$=H
**17** n=1, m=1, $R_1$=$CH_3$
**18** n=0, m=2, $R_1$=H
**19** n=0, m=2, $R_1$=$CH_3$
**20** n=1, m=2, $R_1$=H
**21** n=1, m=2, $R_1$=$CH_3$

Scheme 1.

Synthesis of the requisite starting materials of secondary allylic alcohols **6**–**13** for oxaspirocyclization was accomplished as outlined in Scheme 2. Enones **22**–**25**, obtained from a reaction of the Normant Grignard reagent[7] with the vinylogous ester 3-ethoxy-2-cyclohexen-1-one and 3-ethoxy-2-cyclopenten-1-one, were oxidized to form the corresponding esters **26**–**29** (Jones reagent, acetone, 0°C, then $CH_2N_2$, diethyl ether, 0°C). The alcohols **22**–**25** and esters **26**–**29** were reduced to secondary allylic alcohols **6**, **8**, **10** and **12** and hydroxyesters **30**–**33** ($NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH)[8] in high yields, respectively. The resulting hydroxyesters **30**–**33** were converted to the corresponding tertiary alcohols **7**, **9**, **11** and **13** in quantitative yields by treatment with methyllithium in THF at –40°C. The reducing reactions and methyllithium addition reactions mentioned here gave requisite reaction products, which were used in a further reaction without any purification.




**22** n=0, m=1
**23** n=1, m=1
**24** n=0, m=2
**25** n=1, m=2

**6** n=0, m=1
**8** n=1, m=1
**10** n=0, m=2
**12** n=1, m=2

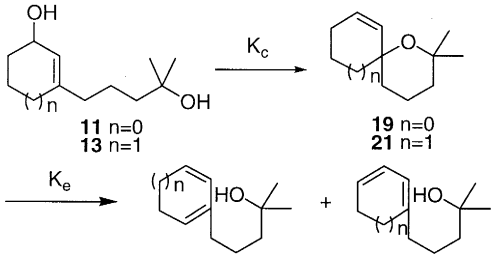
**26** n=0, m=1
**27** n=1, m=1
**28** n=0, m=2
**29** n=1, m=2

**30** n=0, m=1
**31** n=1, m=1
**32** n=0, m=2
**33** n=1, m=2

**7** n=0, m=1
**9** n=1, m=1
**11** n=0, m=2
**13** n=1, m=2

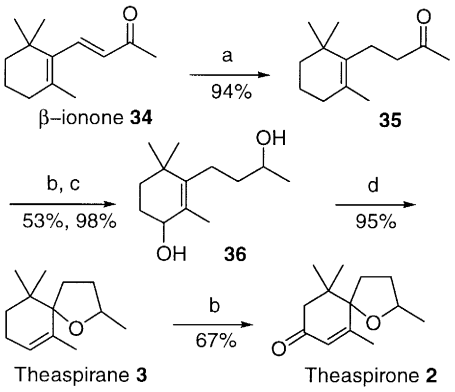
Scheme 2. (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, $CH_3OH$; (b) $CH_3Li$/diethyl ether, THF, −40°C

All the secondary allylic alcohols **6**–**13** underwent $S_N2'$ oxaspirocyclization under Amberlyst-15-catalyzed[9] conditions to produce the corresponding 1-oxaspiro[4.4]non-6-enes **14** and **15**, 1-oxaspiro[4.5]dec-6-enes **16** and **17**, 6-oxaspiro[4.5]dec-1-enes **18** and **19**, and 1-oxaspiro[5.5]undec-7-enes **20** and **21** (Scheme 1). However, the cyclization rate ($k_c$) in the secondary allylic alcohol system is much slower than that in the tertiary allylic alcohol system. On the other hand, in the case of a six-membered ring formation with steric hindered nucleophile, the elimination rate ($k_e$) is comparable to the cyclization rate ($k_c$) (Scheme 3). Therefore, the competing elimination products were accompanied with **19** and **21** even at −20°C. Except for **19** and **21**, all other oxaspirocycle products obtained by this method gave cyclization products only and in quantitative yields.




Scheme 3.

Scheme 4 details the total synthesis of theaspirane **3** and theaspirone **2**. The α,β double bond of β-ionone **34** was selectively reduced by triphenyltin hydride[10] to give **35**. The allylic methylene group within the six-membered ring was oxidized at room temperature to form a carbonyl group by using 70% *tert*-butyl hydroperoxide and catalytic amounts of chromic anhydride,[11] and a $CeCl_3$–$NaBH_4$[8] reduction of the enone and ketone provided the required diol **36**. The secondary allylic alcohol **36** underwent $S_N2'$ oxaspirocyclization under Amberlyst-15-catalyzed conditions to produce theaspirane **3**, and after allylic oxidation under previous conditions to give theaspirone **2**. Spectral data of the product were identical to those of the theaspirone reported in the literature.[3]




Scheme 4. (a) $Ph_3SnH$, benzene; (b) $CrO_3$, *t*-BuOOH, $CH_2Cl_2$; (c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, $CH_3OH$; (d) Amberlyst-15, $CHCl_3$, −20°C

## Acknowledgements

We thank the National Science Council (NSC86-2113-M-016-003) of the Republic of China and IPM-NDMC (Grant No. IPM-870503) for financial support.

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