A FACILE SYNTHESIS OF NINE- AND TEN- MEMBERED CYCLIC ETHERS UTILIZING INTRAMOLECULAR *ENDO*-MODE CYCLIZATION OF THE CONJUGATED ALLENYL KETONES

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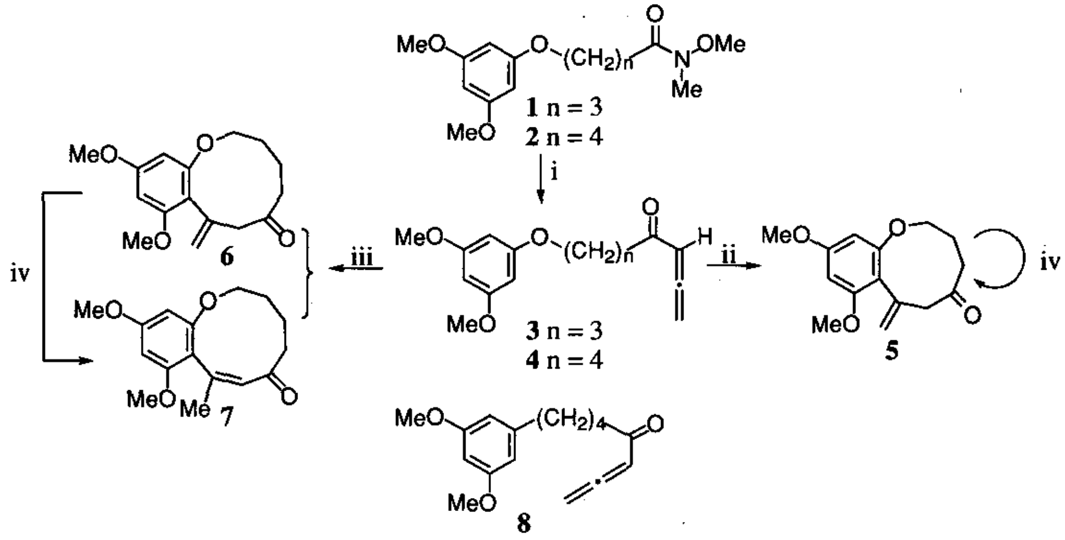
Abstract - Intramolecular *endo*-mode cyclization reactions of the conjugated allenyl ketones (**3**) and (**4**) were carried out in the presence of $BF_3 \cdot OEt_2$, $B(CF_3SO_3)_3$, and CF_3SO_3H in CH_2Cl_2 to give the corresponding nine- and ten-membered cyclic ethers (**5** - **7**) as crystalline compounds in satisfactory yields. The structure of **6** was confirmed by its X-ray crystallographic analysis.

Six- to nine-membered cyclic ethers have often appeared in marine natural products[1] such as brevetoxins[2] and ciguatoxin.[3] In general, an annulation reaction toward the medium-sized eight- to eleven-membered cyclic compounds seems to be difficult from the viewpoint of unfavorable entropy factors.[4] Recently, we have disclosed various cyclization reactions for five- to eight-membered carbocyclic compounds,[5a,b] spiro[4.5]decatriene and [5.5]undecatriene diones,[5c] and seven-membered cyclic ethers[5d] and amides[5e] on the basis of intramolecular *endo*-mode ring closure at the sp carbon atom of the conjugated allenyl ketone moiety. In the earlier studies on remarkable *endo*-mode cyclization reactions,[5] we realized that the conjugated allenyl ketone system bearing a substituted phenyl group should be suitable enough for the intramolecular cyclization being difficult in the conjugated alkenyl and alkynyl ketones. Here, we describe a facile construction method of nine- and ten-membered cyclic ethers.



Scheme 1 i, Propargylmagnesium bromide (1.5 mol eq.), THF, 0 °C, (**3** : 53%, **4** : 62%); ii, CF_3SO_3H (10 mol %), CH_2Cl_2, 0 °C (63%); iii, $B(CF_3SO_3)_3$ (2.4 mol eq.), CH_2Cl_2, -78 °C (54%); iv, NaH (1.2 mol eq.), THF, reflux (**7** : 56% with 40% recovery of **6**, 84% recovery of **5**)

Conjugated allenyl ketones (**3**) [colorless prisms, mp 39 - 40 °C (CH_2Cl_2 - hexane)] and (**4**) (pale yellow oil) were readily prepared by treatment of the corresponding *N*-methoxy-*N*-methylamides (**1**) and (**2**)[6,7] with 1.5 mol eq. of propargylmagnesium bromide (1M solution in Et_2O)[5a] in THF at 0 °C. Treatment of **3** and **4** with 1.2 mol eq. of $BF_3{\bullet}OEt_2$ in CH_2Cl_2 at -78 °C for 5 min gave the desired nine-membered cyclic ether (**5**) [colorless prisms, mp 69 - 70 °C (CH_2Cl_2 - hexane)] in 30% yield and ten-membered one (**6**) [colorless prisms, mp 92 °C (CH_2Cl_2 - hexane)] in 16% yield, respectively. Although treatment of **3** with 2.4 mol eq. of $B(CF_3SO_3)_3$ [8] at -78 °C gave the compound (**5**) in only 27% yield, the same reaction of **4** afforded a mixture of exo-methylene cyclic ether (**6**) and endo-olefinic one (**7**) in 54% total yield. The mixture could be separated on a silica gel plate (Merck Kieselgel 60 F254) with ether - hexane (2 : 1) to give each pure compound (**6**) or (**7**) [colorless prisms, mp 78 °C (CH_2Cl_2 - hexane)]. Both compounds (**3**) and (**4**) were allowed to react with a catalytic amount (10 mol %) of CF_3SO_3H in CH_2Cl_2 at 0 °C for 5 min to furnish the corresponding cyclic ether (**5**) in 63% yield and the mixture of **6** and **7** in a ratio of 1.3 : 1 and in 52% total yield. All experimental results for cyclization reactions as described above are summarized in Table 1. Interestingly, in contrast to successful cyclization of the ether (**3**), similar reactions of the methylene derivative (**8**) employing various Lewis acids and CF_3SO_3H resulted in production of a complex mixture.

The structure of exo-methylene product (**6**) was established by its X-ray crystallographic analysis[9] as shown in Figure 1. The structure of endo-olefinic product (**7**) was confirmed by identification with all spectroscopic data [HRms calcd for $C_{16}H_{20}O_4$ MW 276.1362, found *m / z* 276.1360 (M^+); ir (KBr) ν 1734 cm^{-1} (α,β-unsaturated carbonyl); ^1H nmr (400 MHz, $CDCl_3$) δ 2.13 (d, 3H, *J* = 1.5 Hz, olefinic Me), 3.75 (t, 2H, *J* = 4.9 Hz, $-OC\underline{H}_2CH_2-$), 6.05 and 6.16 (each d, each 1H, *J* = 2.5 Hz, aromatic H), 6.23 (d, 1H, *J* = 1.5 Hz, olefinic H)] of the compound (56% yield) obtained by double bond shift of the compound (**6**) under the basic conditions (NaH, THF, reflux for 3 h) as shown in Scheme 1. The structure of **5** was determined by its similar characteristic spectroscopic data [HRms calcd for $C_{15}H_{18}O_4$ MW 262.1205, found *m / z* 262.1185 (M^+); ir (KBr) ν 1704 cm^{-1} (carbonyl), 1643 cm^{-1} (exo-methylene); ^1H nmr (400 MHz, $CDCl_3$) δ 3.19 (s, 2H, allylic H), 4.11 (t, 2H, *J* = 5.4 Hz, $-OC\underline{H}_2CH_2-$), 5.35 and 5.56 (each d, each 1H, *J* = 2.0 Hz, olefinic H), 6.14 and 6.22 (each d, each 1H, *J* = 2.5 Hz, aromatic H)] to

Table 1. Intramolecular Cyclization of Conjugated Allenyl Ketones (3) and (4).

Compd	Reaction Conditions			Product	Yield[b]/%
	LA[a] or A[a]	Temp/°C	Time/min		
n = 3					
3	B	-78	5	**5**	30
"	BT	"	10	"	27
"	A	0	5	"	63
n = 4					
4	B	-78	5	**6**	16
"	BT	"	"	**6** + **7**	54[c]
"	A	0	"	"	52[d]

a) LA : Lewis acid. B = BF_3•OEt_2 (1.2 mol eq.), BT = $B(CF_3SO_3)_3$ (2.4 mol eq.), A = CF_3SO_3H (10 mol %). b) Isolation yield. c) Yield of a mixture of **6** and **7** (3.6 : 1). d) Yield of a mixture of **6** and **7** (1.3 : 1).

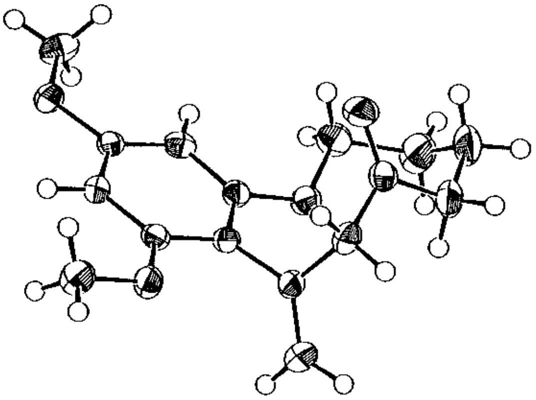


Figure 1. Perspective view of the crystallographic structure of exo - **6**.

those [HRms calcd for $C_{16}H_{20}O_4$ MW 276.1362, found m / z 276. 1353 (M^+); ir (KBr) ν 1706 cm^{-1} (carbonyl), 1646 cm^{-1} (exo-methylene); ^1H nmr (400 MHz, $CDCl_3$) δ 3.20 (s, 2H, allylic H), 3.86 (t, 2H, J = 2.4 Hz, $-OC\underline{H}_2CH_2-$), 5.08 and 5.52 (each d, each 1H, J = 2.0 Hz, olefinic H), 5.93 and 6.13 (each d, each 1H, J = 2.4 Hz, aromatic H)] of the compound (**6**). The double bond shift (exo→endo) of **5** was not recognized in the presence of NaH in THF under reflux for 4 h, instead the starting compound (**5**) was obtained in 84% recovery. This remarkable localization of the exo-methylene double bond in the nine-membered cyclic ether (**5**) under basic or acidic conditions has never been observed in other similar cyclic compounds such as seven- and eight-membered carbocyclic compounds,[5b] seven-membered cyclic ethers and amides,[5d,e] and ten-membered cyclic ether (**6**).

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7. Amides (**1**) and (**2**) were readily synthesized by starting from commercially available 3,5-dimethoxyphenol *via* the several reaction steps.
8. A solution of $B(CF_3SO_3)_3$ was prepared by treatment of $BH_3 \cdot THF$ (1M solution in THF) with 3.0 mol eq. of CF_3SO_3H in CH_2Cl_2 at 0 ℃ for 10 min.[5e]
9. The crystallographic data of **6** : $C_{16}H_{20}O_4$, FW = 276.33, trigonal, $R\bar{3}$ (#148), a = 32.093(3) Å, c = 7.204(3) Å, V = 6425(2) $Å^3$, z = 18, Dcalc = 1.285 g/cm^3, R = 0.033.

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