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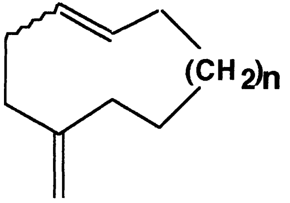
# Synthesis of Medium Ring 1,5-Dienes

Shuji USUI, Takeharu HAINO, Tatsuhiko HAYASHIBARA, Yoshimasa HIRAI,
Yoshimasa FUKAZAWA,* and Mitsuaki KODAMA†
Department of Chemistry, Hiroshima University, Higashi-Hiroshima 724
†Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Tokushima 770

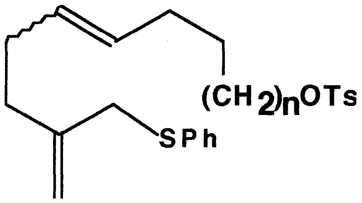
Medium ring compounds (9 to 11 membered rings) having endo (E or Z) and exo double bonds at 1,5-positions were synthesized by intramolecular cyclization of the ω-functionalyzed allylic anion stabilized by a sulfur atom. The yields of cyclization were related not only with the cyclization enthalpy (steric strain of the resultant cyclic compounds) but also with entropy factor.

Medium and macrocyclic compounds have conformational properties which are quite useful for stereochemical control. In these compounds having a π-system within the ring the π-orbitals tend to orient in the plane of the ring to minimize transannular nonbonded repulsions, and hence, intra- and intermolecular reactions can occur exclusively from one side of the π-face.1) However, stereoselectivity in medium and macrocyclic compounds has not fully been explored partly because of the difficulty in constructing these skeletons.

Though many synthetic methods have been developed, the most frequently used one is intramolecular cyclization of acyclic precursors.2-8) The yield of cyclization should be dependent on many factors such as ring size, closing positions, substituents, etc.; however, there are few systematic studies on the influence of such factors.2,3) In this paper we describe the study on the formation of medium rings (**A**, n=1,2,3) having a cis or trans endo and an exo double bond in 1,5-positions to examine the influence of the olefin geometry on the reactivity. We also attempted the evaluation of the reactivity using molecular mechanics calculations and estimation of the entropy of cyclization.

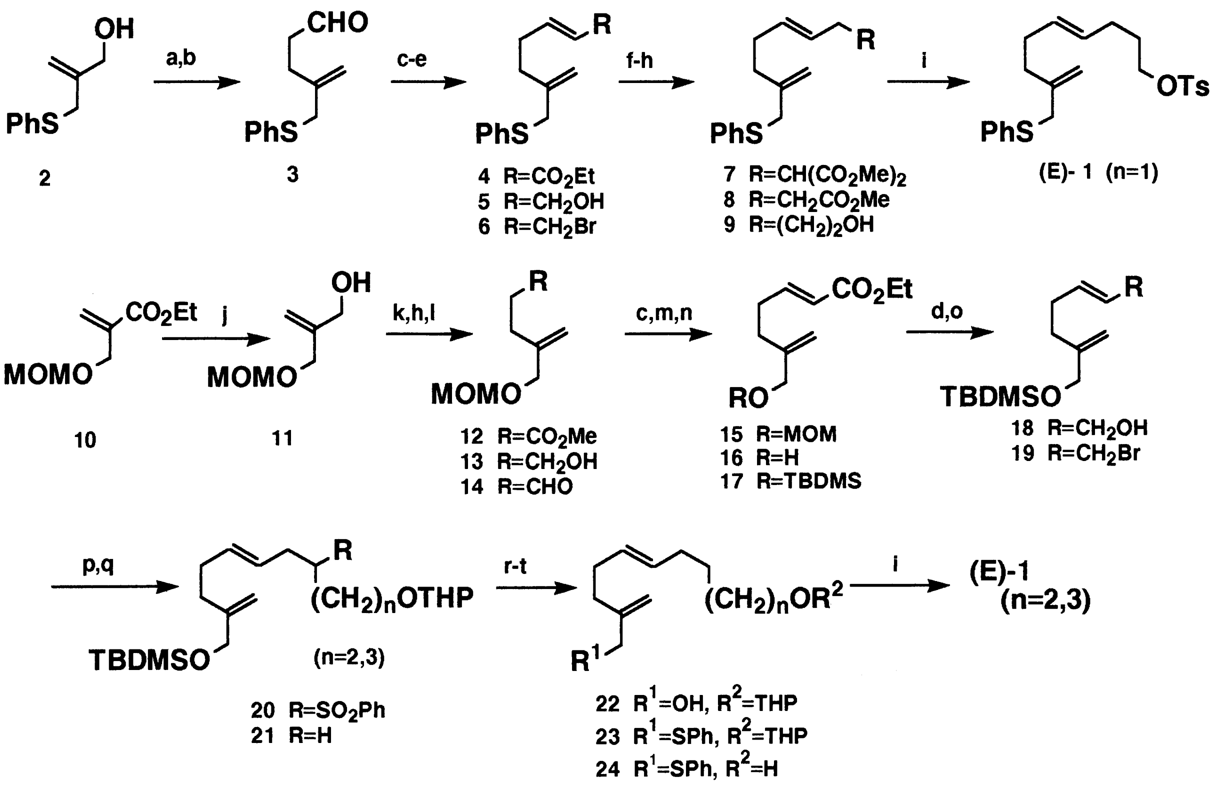


**A**



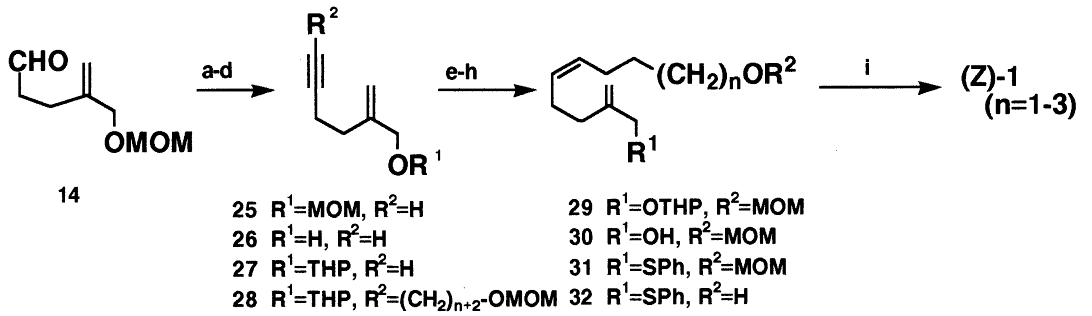
**1**

In our synthetic approach to medium rings, the intramolecular alkylation of an allylic anion stabilized by a phenylthio group was used. The preparation of the acyclic precursors **1** (n=1-3) is summarized in Scheme 1. Claisen rearrangement of the vinyl ether of **2**10) gave aldehyde **3**, which was converted into the trans unsaturated ester **4** by Horner-Emmons olefination with $(EtO)_2POCH_2CO_2Et$. Reduction of **4** followed by bromination of the resulting allylic alcohol **5** gave bromide **6**. Alkylation of dimethyl malonate anion with **6** gave **7**, which was smoothly transformed into **8**. Reduction of **8** followed by tosylation of the resulting alcohol **9** gave (E)-**1** (n=1).



(a) Ethyl vinyl ether, $Hg(OAc)_2$ (b) Δ in xylene (63%, two steps), (c) $(EtO)_2POCH_2CO_2Et$, NaH (82%)
(d) DIBAL (95%) (e) $Ph_3P$-$CBr_4$ (85%) (f) $CH_2(CO_2Me)_2$, NaH, DMF (75%) (g) NaI, HMPA (87%)
(h) $LiAlH_4$ (95%) (i) TsCl, Py (77%) (j) $AlH_3$, THF (90%) (k) $CH_3C(OMe)_3$, $PrCO_2H$ (48%)
(l) $(COCl)_2$,DMSO (84%) (m) p-TsOH, EtOH (88%) (n) TBDMSCl (85%) (o) LiBr, MsCl, $Et_3N$ (64%)
(p) $PhSO_2$-$(CH_2)_{n+1}$-OTHP, LDA (57% n=2) (q) Na-Hg, EtOH (r) n-$Bu_3NF$ (66% (two steps, n=2))
(s) $Ph_2S_2$-n$Bu_3P$ (t) HCl (51% (two steps, n=2))

**Scheme 1.**



(a) $Ph_3P$, $CBr_4$,Zn; n-BuLi (76%) (b) $BF_3OEt_2$, PhSH, $CH_2Cl_2$ (72%) (c) DHP, p-TsOH (76%)
(d) n-BuLi, I-$(CH_2)_{n+2}$-OMOM, THF-HMPA (48%,n=2) (e) $H_2$, 10% Pd-$BaSO_4$, Py (88%,n=2)
(f) PPTS, MeOH (98%,n=2) (g) $Ph_2S_2$, n-$Bu_3P$, THF (82%) (h) p-TsOH,MeOH (quant.) (i) TsCl, Py(47%, n=2)

**Scheme 2.**

The tosylates (E)-**1** (n=2 and 3) were synthesized as follows. Reduction of the ester **10**,[11] followed by carbon chain elongation of the resulting alcohol **11** afforded **12**. $LiAlH_4$ reduction of **12** gave **13**, which was oxidized to give aldehyde **14**. The aldehyde **14** was subjected to Horner-Emmons reaction to give the ester **15**. Removal of the protecting group of **15** followed by silylation gave **17**. Reduction of **17** and subsequent bromination gave **19**. Alkylation of the sulfone derivatives with **19** followed by reduction of the resulting sulfone with Na-amalgam gave **21**. After the transformation of TBDMS ether of **22** into thiophenyl group, the resulting THP ethers **23** were then converted to the tosylates (E)-**1** (n=2 and 3).

Scheme 2 shows the preparation of cis isomers (Z)-**1** (n=1-3). Treatment of the aldehyde **14** with $Ph_3P$-$CBr_4$ followed by 2 equiv. of n-BuLi gave the alkyne **25**. Conversion of the MOM ether of **25** into THP ether and subsequent alkylation of **27** with ω-iodohydrins (C3-C5) provided **28** (n=1-3). Catalytic hydrogenation of **28** over 10% Pd-$BaSO_4$ gave the cis olefin **29**. The THP protective group was removed and the alcohol **30** was transformed to sulfide **31**. Finally the MOM ether of **31** was converted into the tosylate (Z)-**1** (n=1-3).

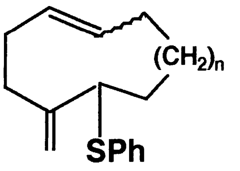
Since the effective molarity[12] of 1,ω-bifunctional group is expected in between $10^{-2}$ and $10^{-3}$M for saturated chains of 9 to 11 carbon length,[2a] we selected high dilution conditions. All the cyclization reactions were carried out under the same conditions ( 2 equiv. of LDA and 1 equiv. of DABCO in THF at a concentration of $2\times10^{-3}$M, of **1**). The results are summarized in Table 1.

Table 1. Cyclization yields and product ratios

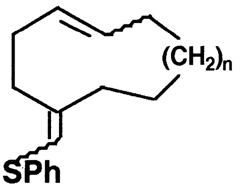
| Compounds | | Yields/% | 33/34 |
|---|---|---|---|
| (E)-1 | n=1 | 20 | 4.0 |
| | n=2 | 30 | 3.7 |
| | n=3 | 15 | 33 only |
| (Z)-1 | n=1 | 62 | 0.2 |
| | n=2 | 76 | 0.7 |
| | n=3 | 18 | 0.8 |

Table 2. Calculated and corrected strain energy(ΔSE, ΔSE')

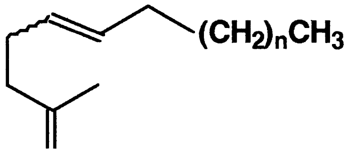
| Ring size<br>A | ΔSE<br>kcal•mol$^{-1}$ | ΔSE'(corrected)<br>kcal•mol$^{-1}$ |
|---|---|---|
| trans 9 | 16.7 | 16.7 |
| 10 | 12.9 | 15.3 |
| 11 | 10.0 | 14.8 |
| cis 9 | 8.2 | 8.2 |
| 10 | 8.7 | 11.1 |
| 11 | 8.5 | 13.3 |



**33**



**34**



**B**

The yields of the cyclization products are rather high when compared to the extremely low yields (0 - 5%) of 1,ω-bifunctional saturated chain of the corresponding lengths.[13] Introduction of the double bonds in the chain hence increased the yields significantly.[14] The yields of cis olefins are higher than those of the trans olefins. The cyclization occurred at both α- (**33**) and γ carbons of the allyl sulfide (**34**) except for (E)-**1** (n=3). In the trans olefin series, α-positions are more reactive than γ, giving high α/γ ratio of the cyclization. However, regioselectivity is completely reversed in the cis olefin series.

Since it is well known that the strain of the cyclized product is quite important and closely related to the ease of cyclization for bifunctional chain molecules,[13] the strains of the products were estimated with molecular mechanics calculations. The increment of the strain (ΔSE) can be obtained by the difference of the strain energies between the most stable conformers of the cyclic and acyclic compounds (**A** and **B**). Since both compounds are so flexible and many conformational options are possible, our special computer program for such compounds (MMRS)[15] were utilized. The ΔSE values are shown in Table 2. In the trans series the strain energies change significantly on going from 9 to 11, however, the yields are rather constant. On the other hand in the cis series the yields change significantly though the cyclic compounds have almost the same strain energies which are lower than those of the trans series.

It is thus obvious that the trend of the yields of the cyclization cannot be explained only by the strain energy in this case. Hence, the probability of encounter of the two termini of the chains should be taken into account. Elongation of the chain by one methylene unit decreases the probability which corresponds to the decrease of entropy by 4 units ( -4 e.u.).[2b]

The ΔSE ' values which are corrected by the entropic term[16] thus gave improved correlation with the yields of the formation of medium size rings (Table 2). Since there is an increasing demand for synthesis of medium and macrocyclic compounds, this type of approach might have much value to estimate the ease of cyclization. Further studies are currently in progress in our laboratory.

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16) Since the strain energy difference between the open and cyclic compounds (ΔSE) corresponds to enthalpy term, introduction of entropy term resulted in free energy type approach for the cyclization as is shown in Eq. 1, where m denotes the difference of number of ring size.

$$\Delta G = \Delta H - T\Delta S \approx \Delta SE + 4RT\cdot m = \Delta SE' \qquad (1)$$

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