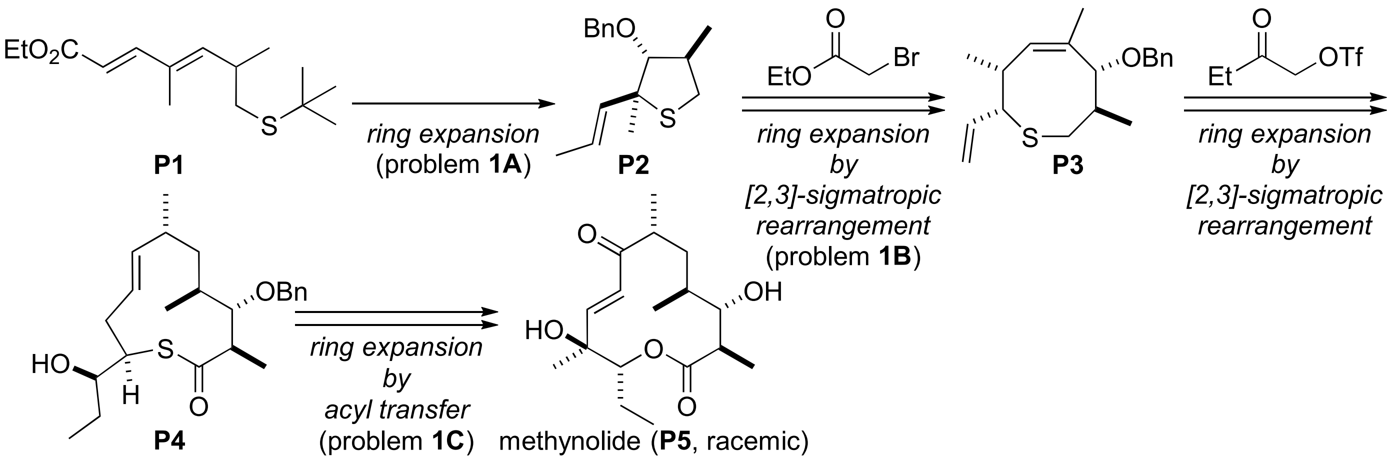
Problem Session (6) -Answer-

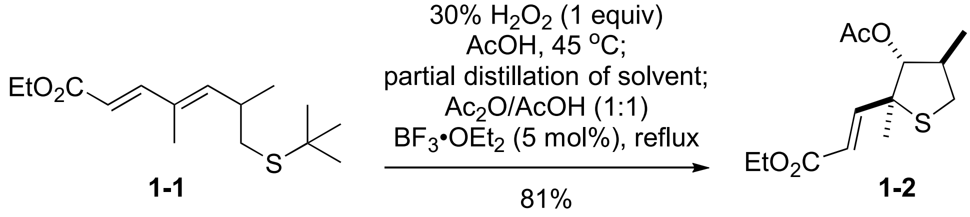
2024.9.21. Yuto Hikone

Topic: Strategies for sulfur-mediated ring system construction.

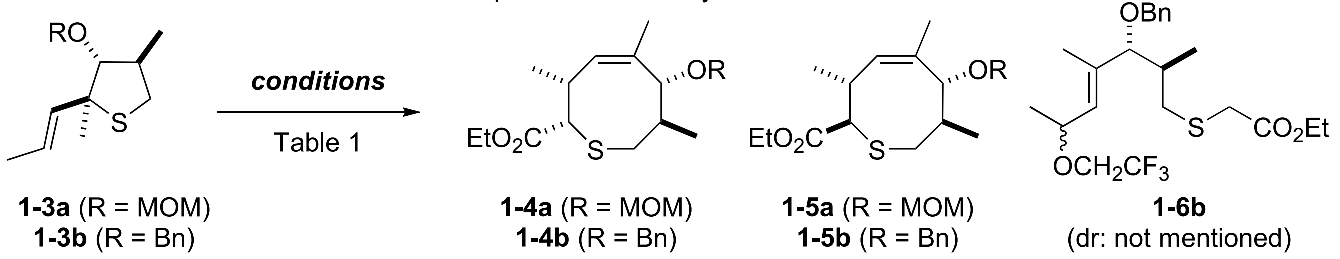
Problem 1: Construction of large ring system by multiple sulfur-based ring expansions



1 **A**. Please provide reaction mechanism.



B. Please deduce the reason for the improvement of the yield.



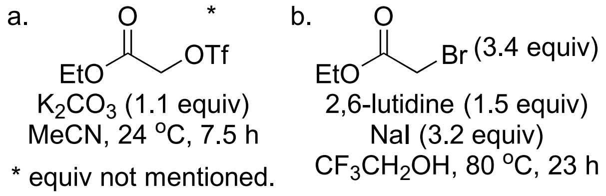
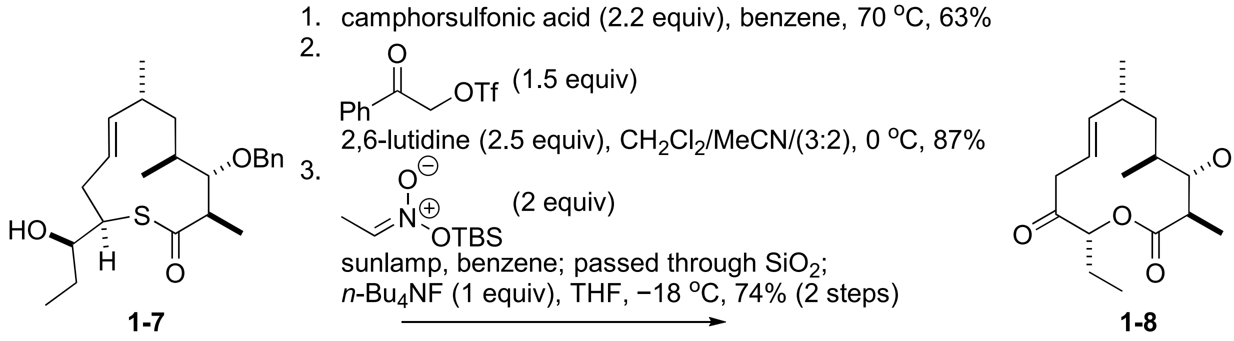


Table 1

entry	*conditions*	**products**
1 (**1-3a**)	a	**1-4a**: 36%
2 (**1-3b**)	b	**1-4b**:**1-5b**: 67% (7:1) **1-6b**: 7%

C. Please provide each reaction mechanism.

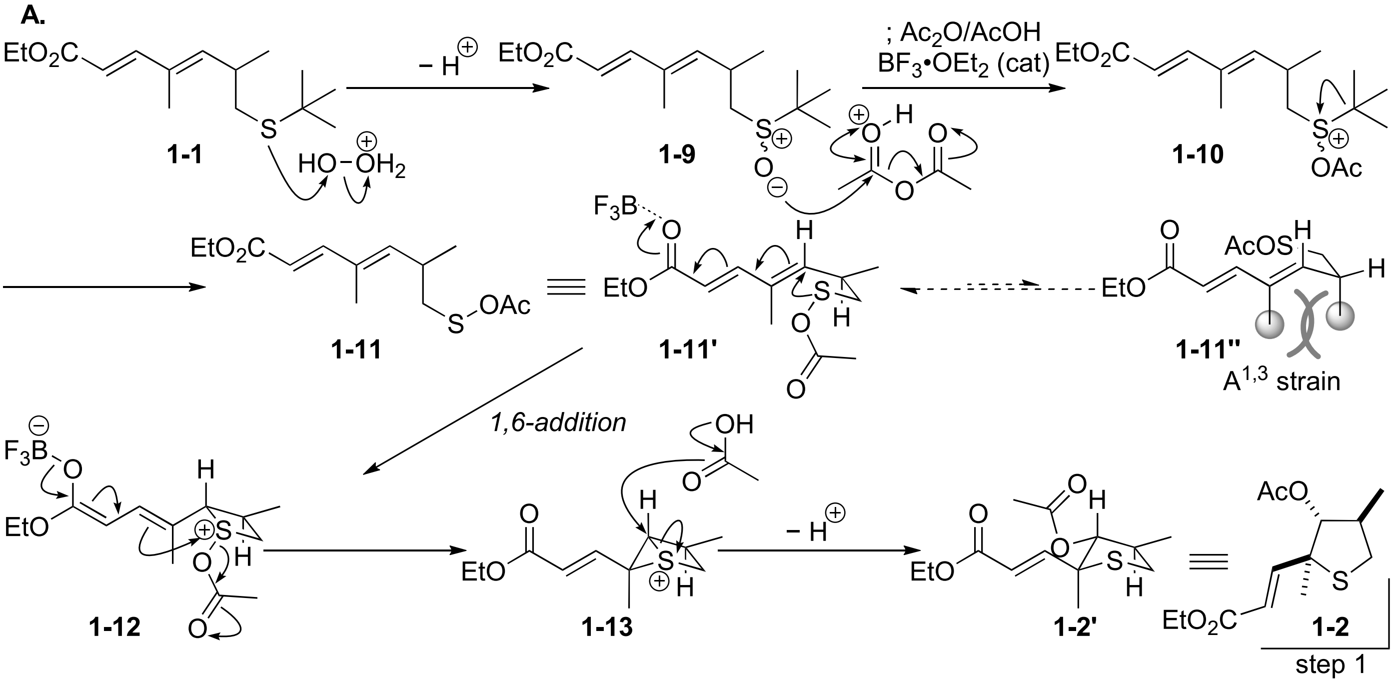


A and **B**: Vedejs, E.; Buchanan, R. A.; Conrad, P. C.; Meier, G. P.; Mullins, M. J.; Schaffhausen, J. G.; Schwartz, C. E. *J. Am. Chem. Soc.* **1989**, *111*, 8421.

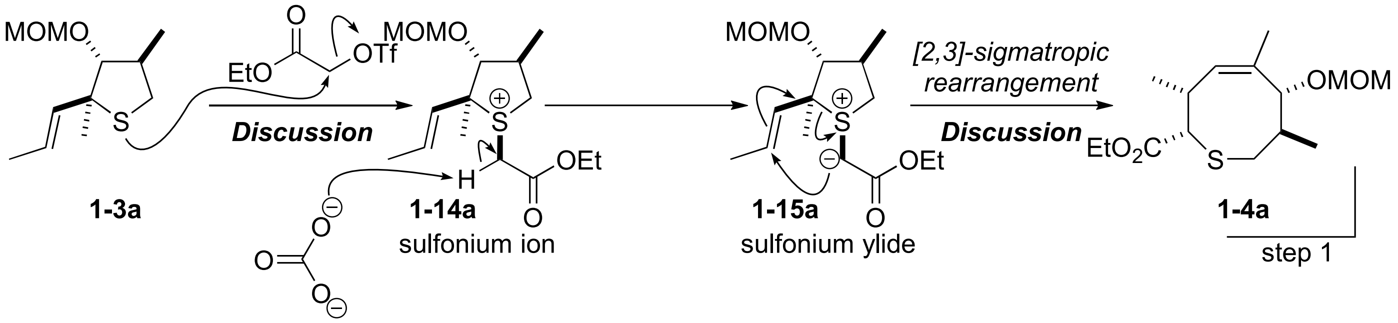
C: Vedejs, E.; Buchanan, R. A.; Watanabe, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8430.

Answer

A.

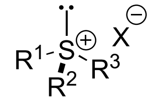


B. ***conditions a*** (**1-3a**, EtO_2CCH_2OTf, K_2CO_3, MeCN, 24 ^oC, 7.5 h)

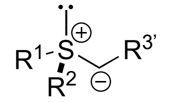


Discussion **: diastereoselectivity at sulfur and its relationship with [2,3]-singmatropic rearrangement**

1-1. Sulfonium salts and sulfonium ylides



1-16A
sulfonium salt

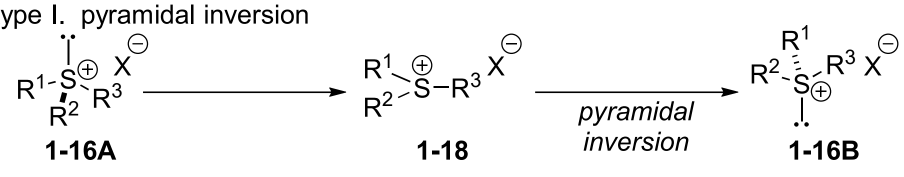


1-17A
sulfonium ylide

Sulfonium salts and sulfonium ylides have a pyramidal structure and exhibit optical activity.

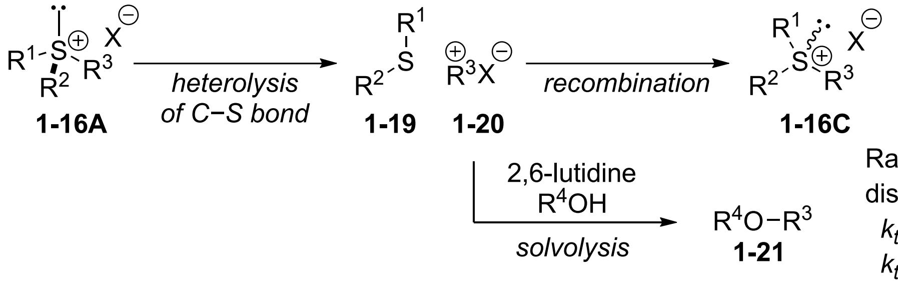
1-2. Racemization at sulfur center
possible mechanism:
type I. pyramidal inversion
type II. heterolysis/recombination

type I. pyramidal inversion



k_a : rate of loss of optical activity

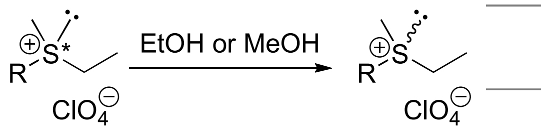
type II. heterolysis/recombination



k_t : rate of solvolysis

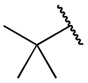
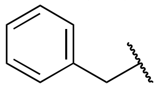
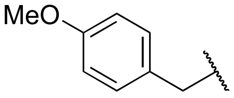
Racemization mechanism was distinguished by comparing k_t with k_a.
$k_t << k_a$: type I
$k_t \sim k_a$: type II

i. Acyclic sulfonium salt



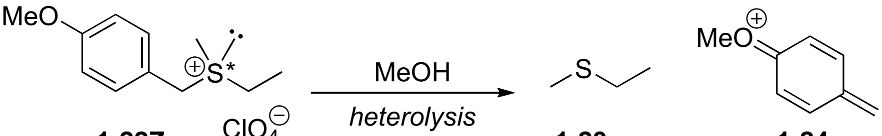
1-22X/Y/Z → **1-22X/Y/Z** (optically less active)

Table 2

R	loss of optical activity $(10^5 \times k_a\,[\mathrm{s}^{-1}])$	solvolysis $(10^5 \times k_t\,[\mathrm{s}^{-1}])$	type
 **1-22X**	47.1 (50 °C)	4.51 (50 °C)	I[ref 1]
 **1-22Y**	- (25 °C) 0.65 (50 °C)	- (25 °C) >0.0203 (50 °C)[a]	I[ref 2]
 **1-22Z**	0.659 (25 °C) 30.8 (50 °C)	0.394 (25 °C) 20.3 (50 °C)	II[ref 2]

$t_{1/2} = \ln 2/k$ (cf. $t_{1/2} \sim 19$ h when $k = 1\times10^{-5}\,[\mathrm{s}^{-1}]$)

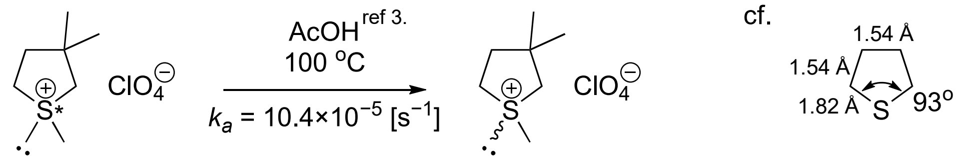
[a] deduced number.
Manuscript saids that **1-20Z** undergoes solvolysis over three powers of ten faster than **1-22Y** in methanol at 50 °C.



1-22Z → **1-23** + **1-24** stabilized cation

Highly stabilized cationic species **1-24** generates from **1-22Z**, leading to the fast loss of optical activity and solvolysis of **1-22Z**.

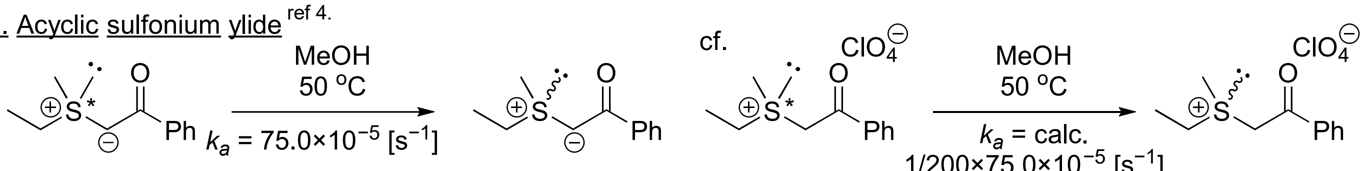
ii. Cyclic sulfonium salt



1-25 → **1-25** (optically less active)

High temperature was required to racemize cyclic sulfonium ion.

iii. Acyclic sulfonium ylide[ref 4.]

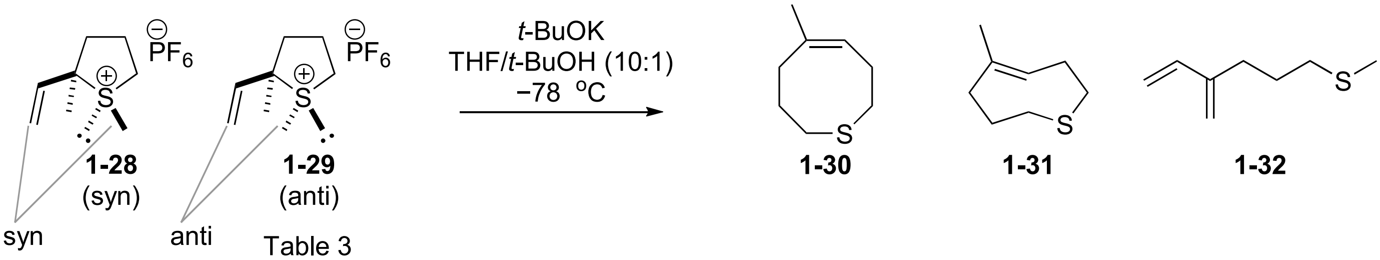


1-26 → **1-26** (optically less active)

cf. **1-27** → **1-27** (optically less active)

Sulfonium ylide racemizes ca. 200 times faster than its sulfonium salt counterpart.

1-3. [2,3]-sigmatropic rearrangement: stereochemistry at sulfur



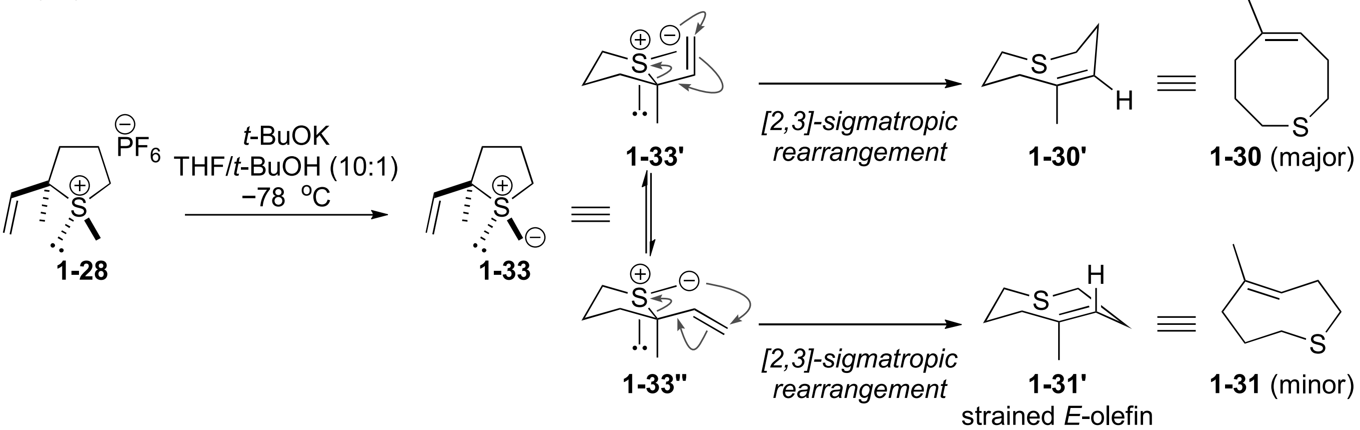
1-28 (syn) **1-29** (anti) → **1-30** **1-31** **1-32**

Table 3

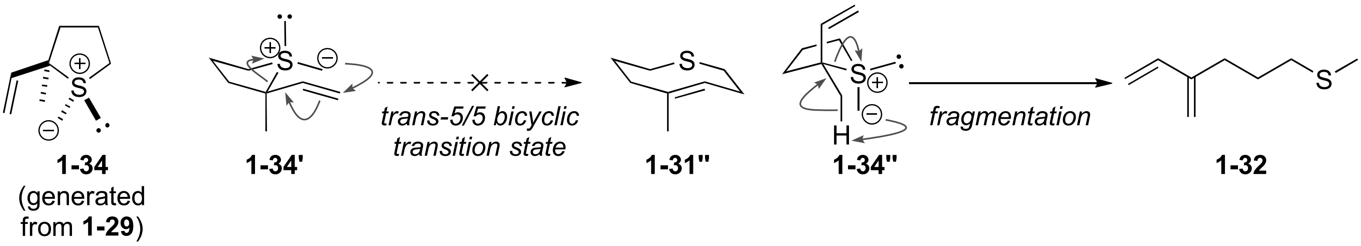
entry	starting material **1-28** : **1-29**	*product ratio* **1-30** : **1-31** : **1-32**	*recovery SM ratio* **1-28** : **1-29**
1	7 : 3 2.88 g (10.0 mmol)	10 : 0.6 : 1 900 mg	0 : 1 800 mg
2	0 : 1 (recovery of entry 1)	0 : 0 : 1	-

Rational for the product distributions in table 3 (page 3)

i. syn ylide

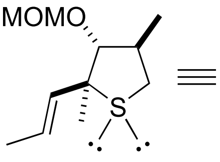


ii. anti ylide

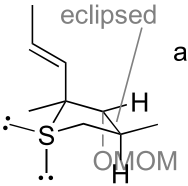
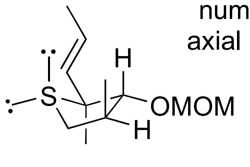
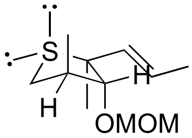
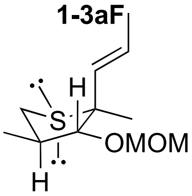
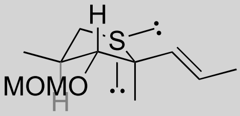
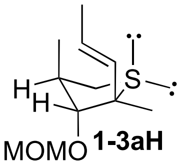
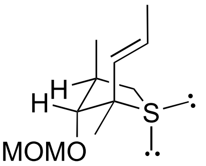
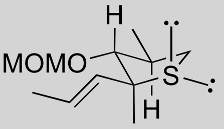
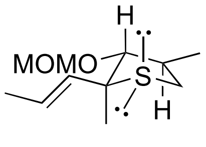
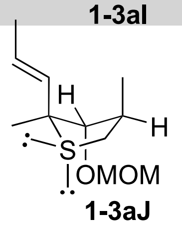


1-4. Real system

1-4-1. Conformation analysis



1-3a

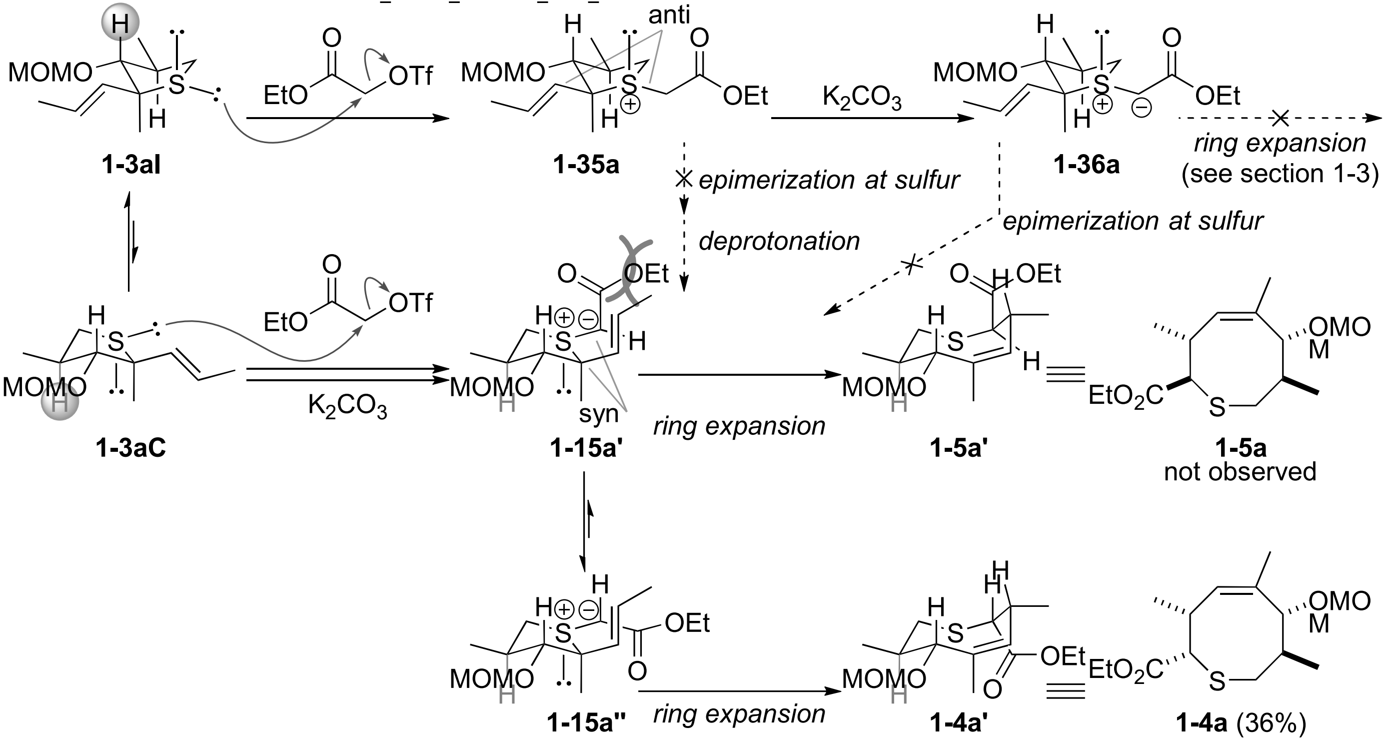
	number of axial groups[a]	eclipsed bond		number of axial groups	eclipsed bond
 **1-3aA**	2	C−C	 **1-3aF**	1	C−C
 **1-3aB**	3	C−C	 **1-3aG**	1	C−C
 **1-3aC**	1	C—S	 **1-3aH**	3	C—S
 **1-3aD**	3	C—S	 **1-3aI**	1	C—S
 **1-3aE**	1	C−C	 **1-3aJ**	3	C−C

[a] except for H and lone pair

- minimizing the number of axial groups to avoid 1,3-diaxial interaction
- allocating S atom at one of the eclipsed positions of the 5-membered ring to release torsional energy (length: C-S bond > C-C bond, steric hinderance: lone pair<H<R (≠ H)[ref 5.])

1-3aC and **1-3aI** would have lower energy than the other confomers.

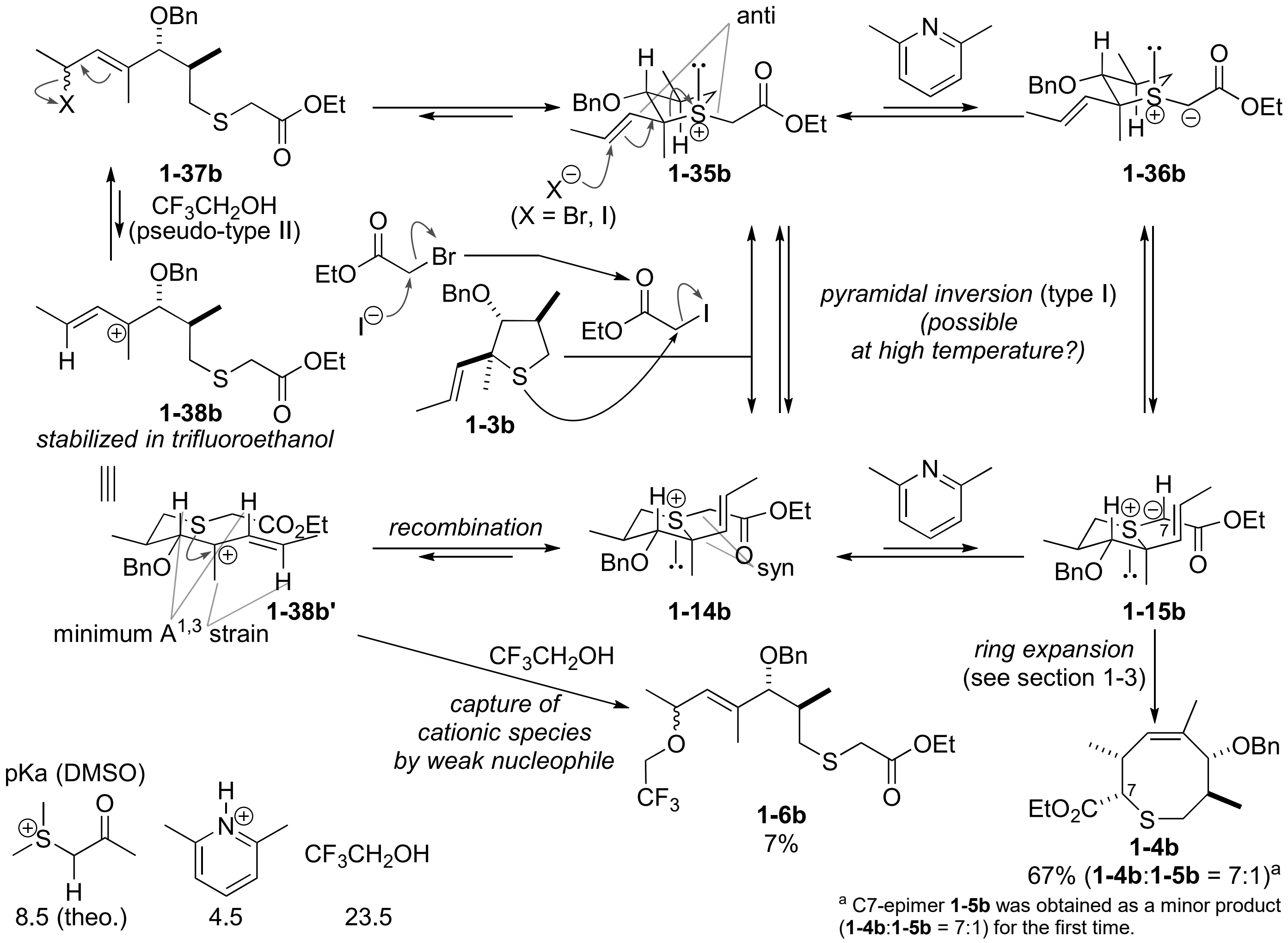
1-4-2. ***conditions a*** (**1-3a**, EtO_2CCH_2OTf, K_2CO_3, MeCN, 24 ºC, 7.5 h)



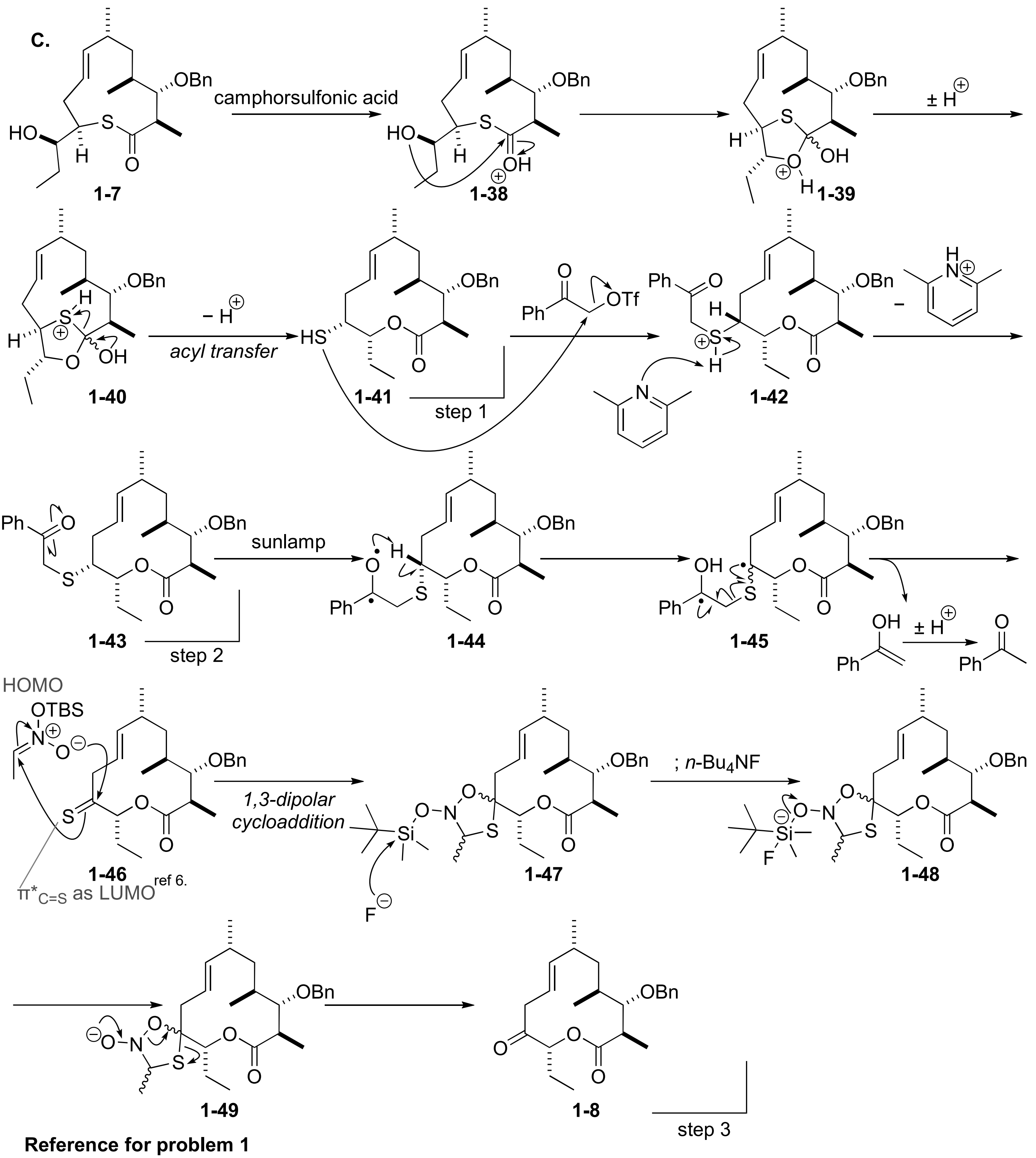
Authors said that poor diastereoselective alkylation at sulfur led to the low yield of **1-4a**(36%). If so, the low yield reflects the biased equilibrium between **1-3aC** and **1-3al** where **1-3aC** is less favored.
If epimerization of sulfonium ion **1-35a** or sulfonium ylide **1-36a** had occurred, these products would have been transformed into **1-15a''**, contributing to the additional generation of **1-4a**.

conditions b (**1-3b**, EtO_2CCH_2Br, 2,6-lutidine, NaI, CF_3CH_2OH, 80 ºC, 23 h)

Problem: How to improve the yield of ring-expanded product?
Approach: epimerization of sulfur center

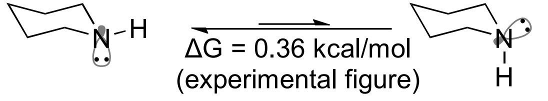


[a] C7-epimer **1-5b** was obtained as a minor product (**1-4b**:**1-5b** = 7:1) for the first time.



Reference for problem 1

ref 1. Darwish, D.; Tourigny, G. *J. Am. Chem. Soc.* **1966**, *88*, 4303.
ref 2. Darwish, D.; Hui, S. H.; Tomilson, R. *J. Am. Chem. Soc.* **1968**, *90*, 5631.
ref 3. Garbesi, A.; Corsi, N.; Fava, A. *Helv. Chim. Acta.* **1970**, *53*, 1499.
ref 4. Cere, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A. *J. Org. Chem.* 1979, *44*, 4128.
ref 5. a) Anet, F. A. L.; Yavari, I. Nitrogen inversion in piperidine. *J. Am. Chem. Soc.* **1977**, *99*, 2794.
b) Clauss, A. D.; Nelsen, S. F.; Ayoub, M.; Moore, J. W.; Landis, C. R.; Weinhold, F. *Chem. Educ. Res. Pract.* **2014**, *15*, 417.

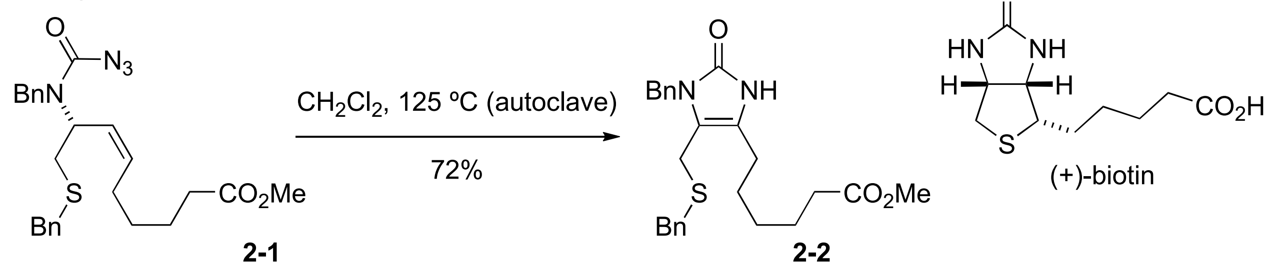


ref 6. Natural bond orbital (NBO) analysis revealed that smaller $(2p_{\pi})_C/(3p_{\pi})_S$ interaction resulted in the waeker antibonding character in $\pi^*_{C=S}$, thus lower LUMO level than the corresponding carbonyl.
Wu, Y.; Wright, A. I. *Phys. Chem. Chem. Phys.* **2022**, *25*, 1342.

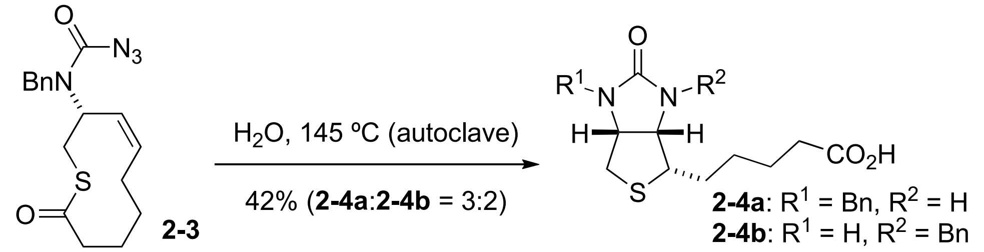
Problem 2: Construction of small ring system from large ring system

2 Please provide each reaction mechanism.

A



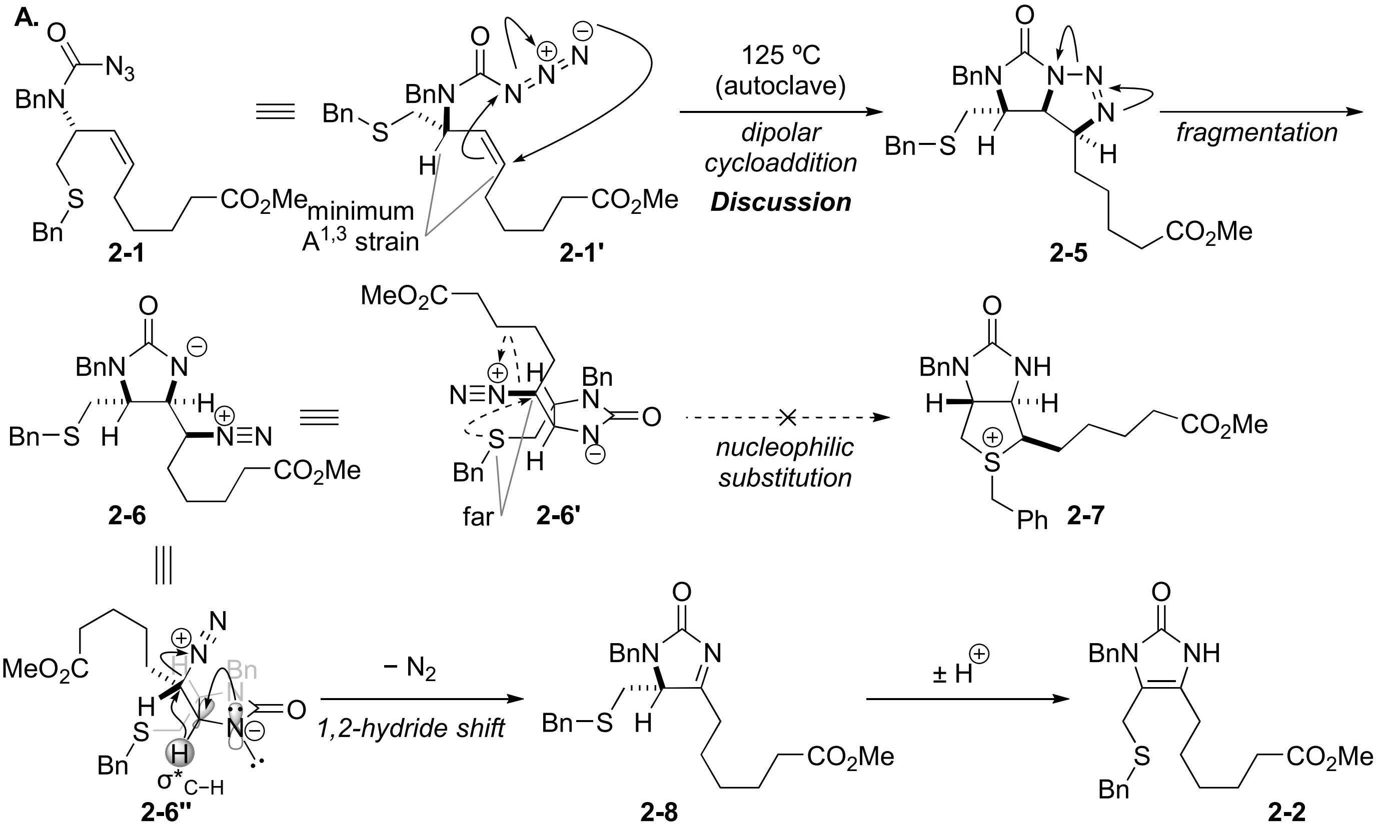
B



Deroose, F. D.; De Clercq, P. J. *J. Org. Chem.* **1995**, *60*, 321.

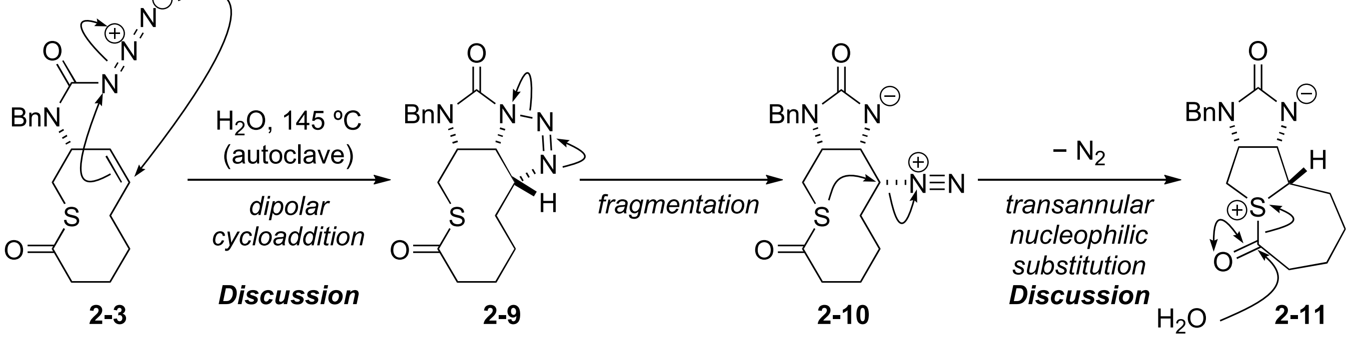
Answer

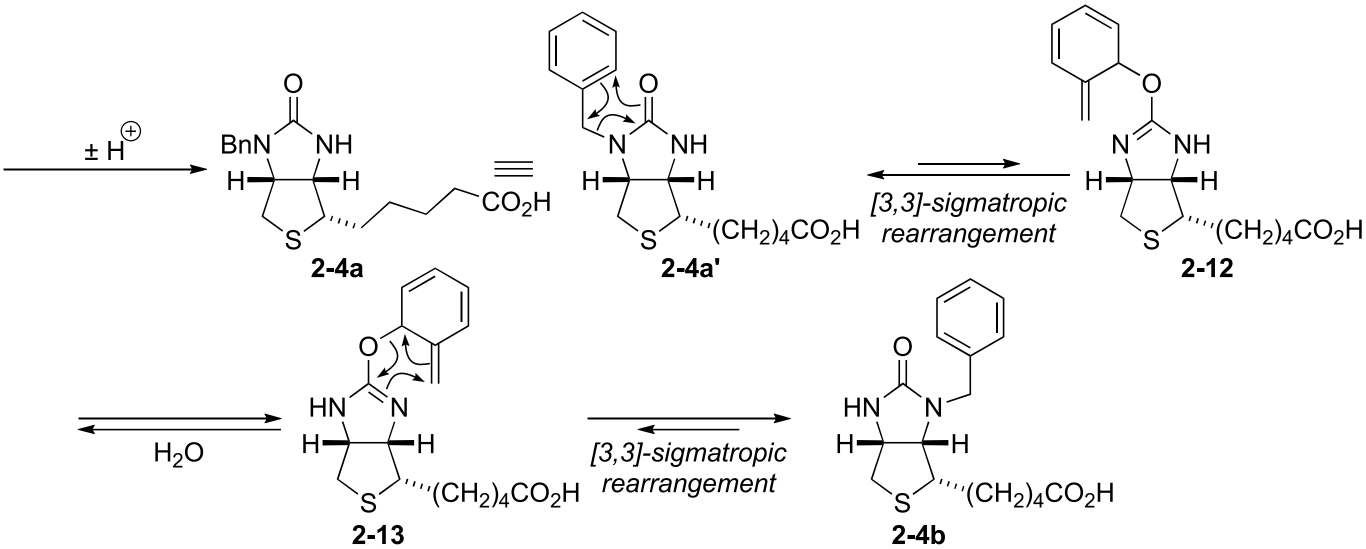
A.



Conformation of **2-1** was determined so as to minimize A^{1,3} strain of its alkene. This led to the undesired facial selectivity of 1,3-dipolar cycloaddition, making difficult to construct *cis*-fused tetrahydrothiophene ring system. To alter the facial selectivity of alkene, macrothiolactone strategy was devised by the authors (part B).

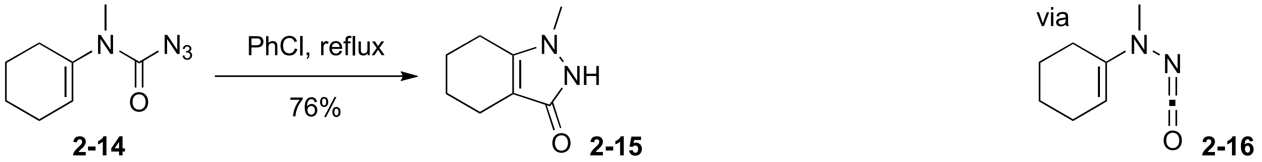
B.



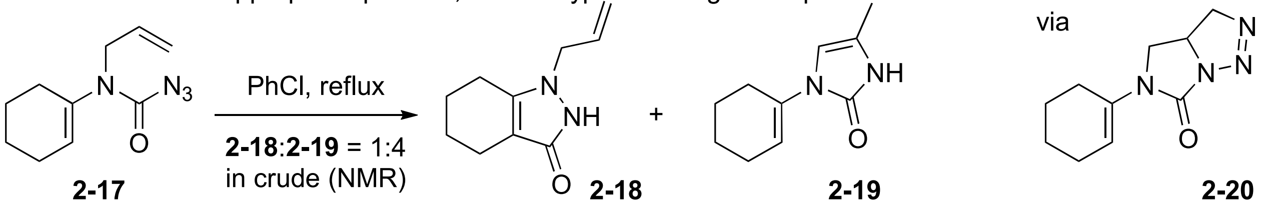


Discussion

1. Reactivity of carbamoylazide[ref 1.]



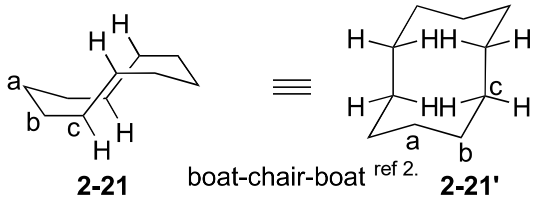
Without alkene at appropriate position, Curtius-type rearrangement proceeded.



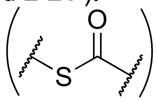
Dipolar cycloaddition was faster than Curtius-type rearrangement.

2. Rationla for the selective transannular cyclization

2-1. Conformation of 2-10 based on cyclodecane system

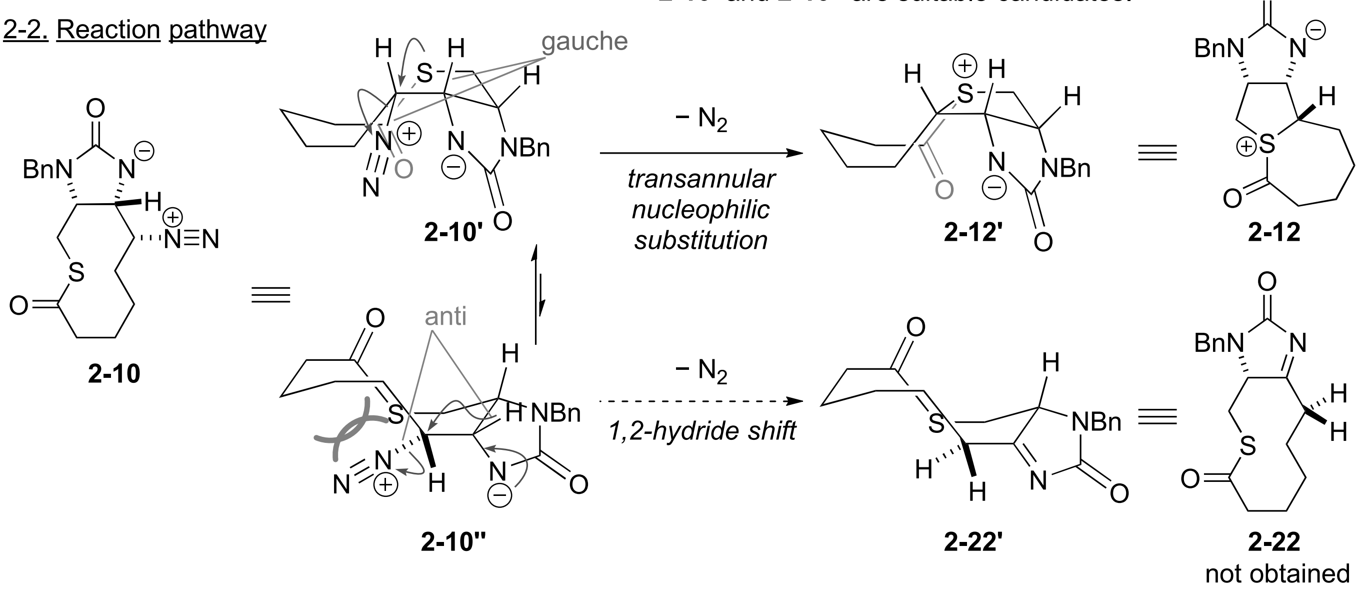


Allocating sp^2-rich structure at position c is favored to minimize the transannular interaction in the cyclodecane framework **2-21** (and **2-21'**).

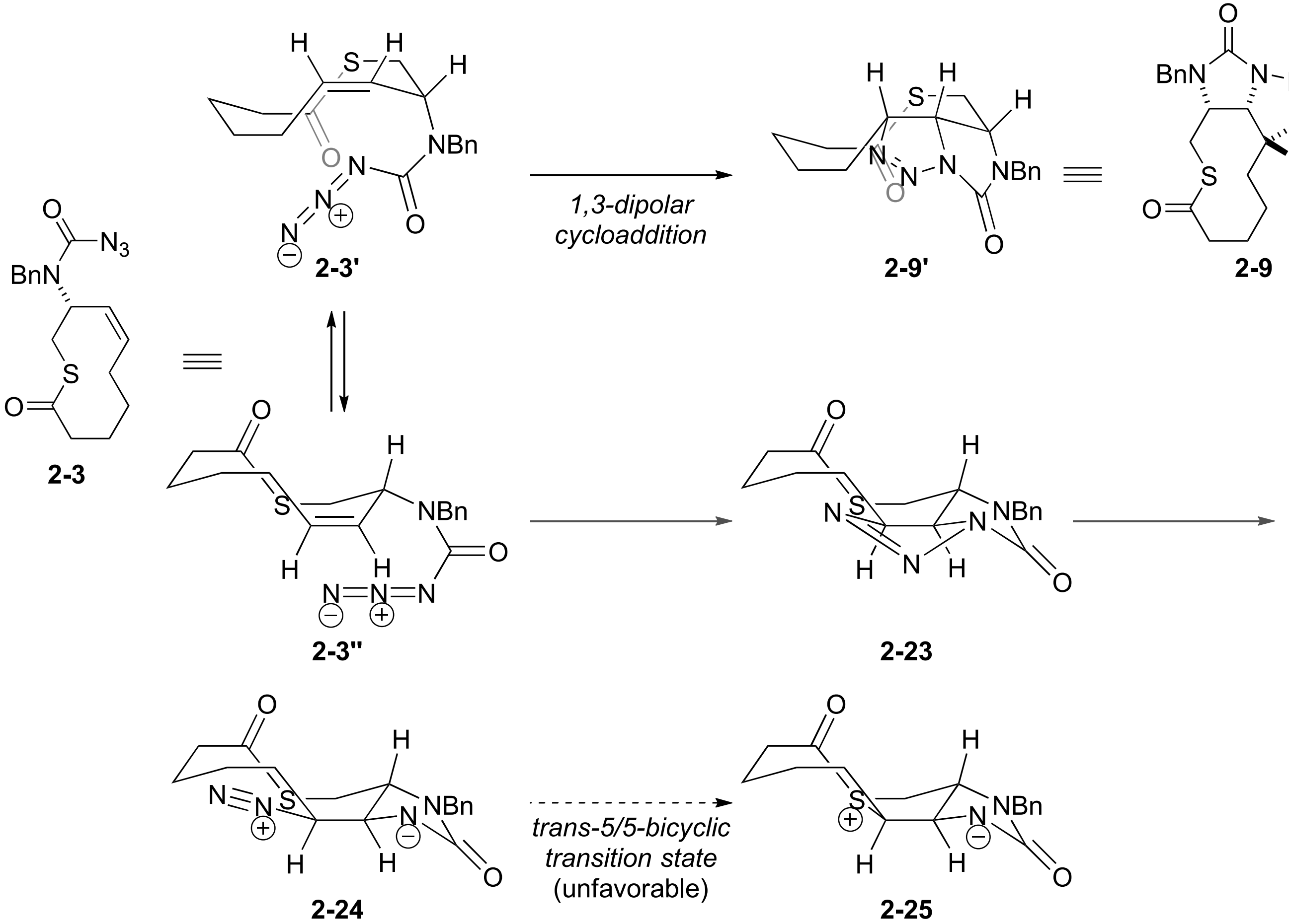
-> Thioester moiety  occupies position c.

-> **2-10'** and **2-10''** are suitable candidates.

2-2. Reaction pathway



2-3. Stereoselectivity of 1,3-dipolar cycloaddition



Reference for problem 2

1. John P. Chupp. *Journal of Heterocyclic Chemistry* **1971**, *8*, 557.
2. BCB is the solid-state conformation of cyclodecane and the major conformation in NMR at low temperature. Pawar, D. M.; Smith, S. V.; Mark, H. L.; Odom, R. M.; Noe, E. A. *J. Am. Chem. Soc.* **1998**, *120*, 10715.