JOC Article

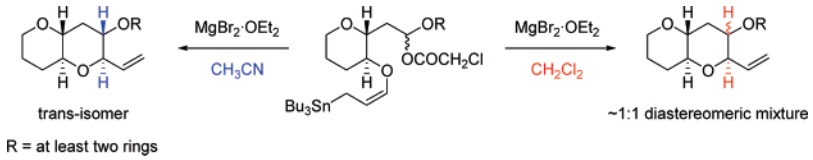
Solvent-Controlled Stereoselective Formation of a Cyclic Ether in the Lewis Acid-Mediated Allylation of an α-Chloroacetoxy Acyclic Ether. Very High Stereoselectivity in CH_3CN vs Low Stereoselectivity in CH_2Cl_2

Ilya D. Gridnev,[†] Shigetoshi Kikuchi,[†] Abeda S. Touchy,[†] Isao Kadota,[‡] and Yoshinori Yamamoto*,[†]

Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan, and Department of Chemistry, Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushima-naka, Okayama 700-8530, Japan

yoshi@mail.tains.tohoku.ac.jp

Received July 5, 2007



The $MgBr_2$·OEt_2-mediated intramolecular allylation of a 4:1 diastereoisomeric mixture of the α-chloroacetoxyl ether **1a** bearing the A-G/JK ring system of brevetoxin B *in CH_2Cl_2* gave a 1:1 diastereoisomeric mixture of the trans- and cis-cyclization products **4a** and **5a** having the A-G/I-K ring system, while that *in CH_3CN* afforded the trans-isomer **4a** nearly as the single product. To help clarify a reason for this marked solvent effect in the cyclization of the brevetoxin B precursor, DFT computations for the starting materials, intermediates, transition states, and products were carried out. The cyclization would proceed through a carbocation intermediate **3a** having sp^2 flat structure (S_N1 type mechanism) *in CH_2Cl_2*, in which the activation energies leading to both diastereoisomers are approximately identical, while *in CH_3CN* alkylnitrilium salts **6a** would be formed through the coordination of CH_3CN to the carbocation leading to an sp^3-type intermediate in which sever steric hindrance takes place in the transition state leading to the undesired diastereoisomer. The scope of this novel solvent-controlled stereoselectivity was tested for simple compounds. In small model compounds the marked solvent dependence was absent, but the model bearing two consecutive cyclic ether rings **1b** exhibited a remarkable solvent effect similar to that observed in the brevetoxin B system.

Introduction

We recently reported a convergent total synthesis of brevetoxin B.[1] The key steps for this synthesis were (i) the Lewis acid-mediated intramolecular allylation of the α-chloroacetoxy ether bearing the A-G/JK ring system of brevetoxin B, leading to the A-G/I-K ring system, and (ii) subsequent ring closing metathesis leading to the A-K ring system (Scheme 1).[2]

The $MgBr_2$·OEt_2-mediated allylation in CH_3CN gave the desired stereoisomer (trans-cyclization product) in 82% yield with >95% diastereoselectivity, while the allylation in CH_2Cl_2 gave a 1:1 diastereoisomeric mixture of the A-G/I-K ring system in 78% yield.[3] The cyclization in other solvents, such as ether, toluene, and nitromethane, also showed no stereoselectivity as observed in CH_2Cl_2. Accordingly, subsequent investigations including computational studies (vide post) were carried out in CH_3CN and CH_2Cl_2. At that time, it was not clear why the use of acetonitrile as a solvent gave nearly 100% stereoselectivity and why the use of dichloromethane produced nonstereoselectivity. Without further consideration on the origin of the stereoselectivity, we proceeded to the final goal, the total synthesis of brevetoxin B. Now, we wish to report a reason why the high stereoselectivity was obtained in acetonitrile and why not in dichloromethane.

[†] Tohoku University.
[‡] Okayama University.

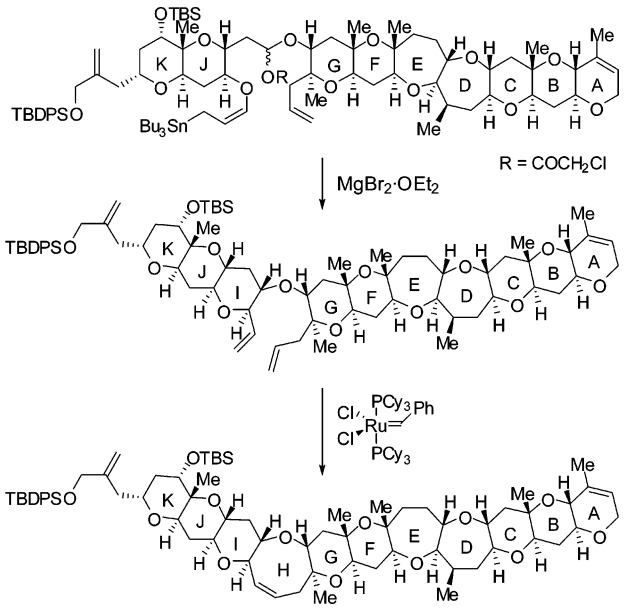
(1) Kadota, I.; Takamura, H.; Nishii, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9246.

(2) Kadota, I.; Yamamoto, Y. *Acc. Chem. Res.* **2005**, *38*, 423−432.

(3) The use of other Lewis acids such as BF_3·OEt_2 gave poor results.

10.1021/jo7013752 CCC: $37.00
Published on Web 10/06/2007

SCHEME 1



Results and Discussion

(1) Experimental Results in CH_2Cl_2 and CH_3CN. A sequence of the reactions which most probably take place in the Lewis acid-mediated cyclization of the allyltin acetal **1a,** leading to the formation of the I ring **4a**, is shown in Scheme 2.

The coordination of an oxygen of the α-chloroacetoxy group to $MgBr_2$ (**2a**),[4] followed by removal of α-chloroacetoxy magnesiate, would produce the carbocation intermediate **3a**. The intramolecular allylation of **3a** must give either the trans-isomer **4a** or the cis-isomer **5a**, or a mixture of both isomers. The trans-product **4a** was required for the construction of the target molecule, and a 4:1 mixture of diastereomers **1a** was available; the absolute stereochemistry of the diastereomers **1a** was not determined. Upon treatment of **1a** with $MgBr_2$·OEt_2 in dichloromethane at 0 °C, only a 1:1 mixture of the trans- and cis-cyclization products **4a** and **5a** was obtained in 78% yield. On the other hand, by changing the solvent from dichloromethane to acetonitrile the trans-isomer **4a** was obtained in 82% yield with greater than 95% diastereoselectivity (Scheme 2);[1] the allylation in acetonitrile was carried out at 40 °C, and the cis-isomer **5a** was detected only as a weak spot on TLC, but not in ^{1}H NMR spectra of a crude reaction mixture.

Since a 4:1 diastereoisomeric starting material **1a** was used for the cyclization and a 1:1 diastereoisomeric mixture of the products **4a** and **5a** was obtained in CH_2Cl_2, it is reasonable to conclude that the cyclization proceeds through an S_N1-type mechanism via the carbocation **3a** in CH_2Cl_2. If the cyclization proceeds through an S_N2-type mechanism, a 1:4 diastereomeric mixture of the products should be obtained. Why was **4a** obtained almost exclusively in a high yield in CH_3CN? Did the cyclization proceed in an S_N2 fashion in CH_3CN? If so, a 1:4 diastereoisomeric mixture of the products should be obtained in CH_3CN.

(2) DFT Computations. To help clarify a reason for the high stereoselectivity in the allylation reaction carried out in acetonitrile, we performed DFT calculations[5] of the starting compounds, reaction products, cationic intermediates, and transition states, as well as alkylnitrilium salts that are likely to be formed in the presence of a large excess of acetonitrile (see the Supporting Information).[6,7] The most important computational results are schematically presented in Figure 1.

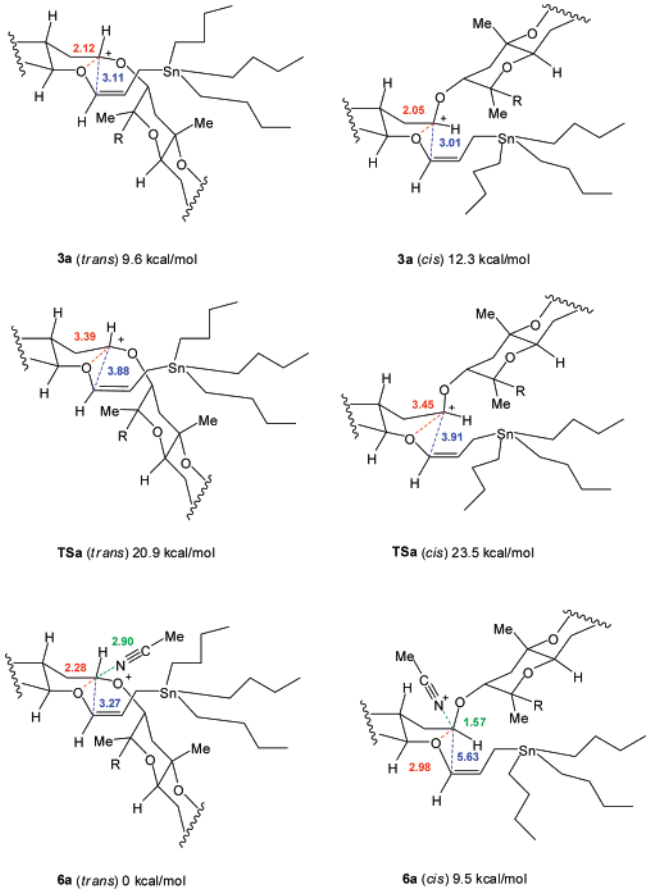


FIGURE 1. Schematic representation of the computational results for the cyclizations of **3a**. The numbers indicate the corresponding bond lengths (in Å) for the intermediates of **3a** cyclization. The relative energies for **3a** as well as those for **TSa** were computed by adding the energy of a free acetonitrile molecule.

Since the reaction from **1a** to **4a** and **5a** in CH_2Cl_2 proceeded most probably through an S_N1-type reaction, we carried out the computation on the transformation from the carbocation intermediate **3a** to the C−C bond-forming products. The activation barriers for trans- and cis-cyclizations leading to **4a** and **5a** are practically equal (11.3 and 11.2 kcal/mol, respectively): **TSa** (trans) − **3a** (trans) = 20.9 − 9.6, and **TSa** (cis) − **3a** (cis) = 23.5 − 12.3. Therefore, in the case of **3a**, which is generated from **1a** in CH_2Cl_2, the lack of stereoselectivity is observed.

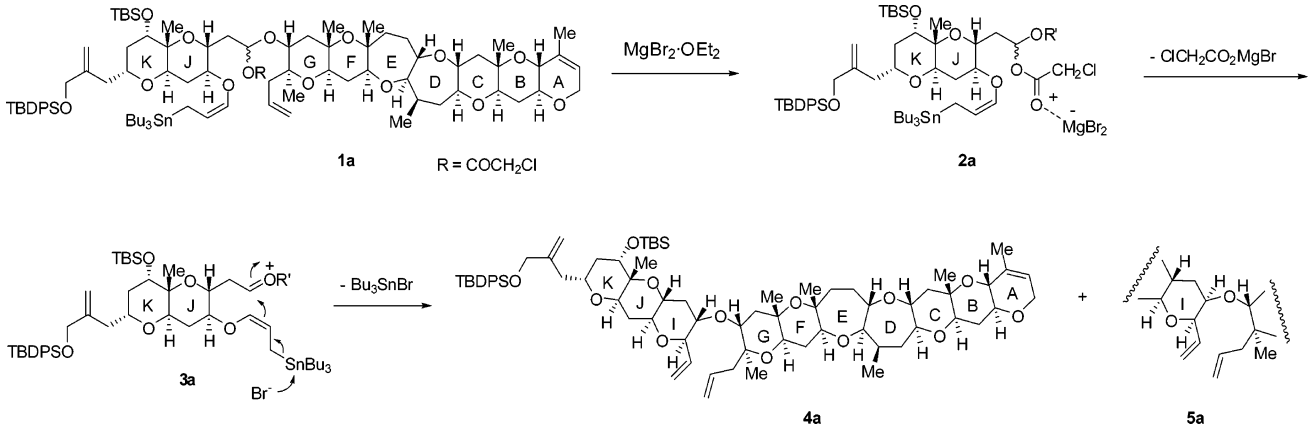
(4) Yamamoto, Y. *J. Org. Chem.*, published online June 19, 2007, http://dx.doi.org/10.1021/jo070579k.

(5) Computations were performed on the B3LYP/SDD level of theory with the Gaussian 03 software package (see the Supporting Information for the reference and computational details).

(6) For reviews see: (a) Ulrich, H. *The Chemistry of Imidoyl Chlorides*; Plenum: New York, 1968. (b) Gridnev I. D.; Gridneva N. A. *Russ. Chem. Rev.* **1995**, *64*, 1091.

(7) (a) Meerwein, H.; Laasch, P.; Mersch, R.; Spille, J. *Chem. Ber.* **1956**, *89*, 209. (b) Kabuss, S. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 675. (c) Ta-Shma, R.; Rappoport, Z. *J. Am. Chem. Soc.* **1976**, *98*, 1877. (d) Ta-Shma, R.; Rappoport, Z. *J. Am. Chem. Soc.* **1976**, *98*, 8460. (e) Ta-Shma, R.; Rappoport, Z. *J. Am. Chem. Soc.* **1977**, *99*, 8460. (f) Ruane, P. H.; McClelland, R. A.; Hegarty, A. F.; Steenken, S. *J. Chem. Soc., Perkin Trans. 2* **1999**, 43. (g) Ruane, P. H.; Ahmed, A. R.; McClelland, R. A. *J. Chem. Soc., Perkin Trans. 2* **2002**, 312.

SCHEME 2



Concerning the product stability, either **4a** or its complex with tributyltin cation **4a**·$[SnBu_3]^+$ is slightly more stable than **5a** or **5a**·$[SnBu_3]^+$ (for 1.3 or 2.5 kcal/mol, respectively), and therefore the stability difference between the products is very small (see the Supporting Information).

The geometries of both cationic precursors **3a** (trans) and **3a** (cis) are quite close to the structures of the corresponding transition states **TSa** (trans) and **TSa** (cis) (Figure 1). In either **3a** (trans) or **3a** (cis) two molecular units are kept together by the attractive interaction between the carbocationic center and the neighboring oxygen atom that is well reflected in quite short C−O interatomic distances (Figure 1): 2.12 and 2.05 Å, respectively. In the corresponding transition states **TSa** (trans) and **TSa** (cis) the C−O interatomic distances are increased (3.39 and 3.45 Å, respectively) demonstrating that the attractive interaction must be overcome before the cyclization can occur. The transition state **TSa** (trans) is 2.6 kcal/mol lower in energy than **TSa** (cis) due to the adjacent location of the bulky tributyltin group and huge $C_{32}H_{51}O_8$ substituent in **TSa** (cis). It is clear that the hindrance between these groups in **TSa** (cis) would increase dramatically with the deviation of the carbocationic center from planarity caused by participation of the nucleophilic solvent. On the other hand, in **TSa** (trans) such participation can be tolerated, since in this structure the bulky substituents are brought apart.

In acetonitrile, the alkylnitrilium salt **6a** would be formed.[6,7] The optimized structures of two enantiomeric alkylnitrilium salts **6a** (trans) and **6a** (cis) are shown in Figure 1. In the case of the precursor of the trans-cyclization product, the global conformational minimum **6a** (trans) was located (Figure 1). Both intramolecular stabilization by the oxygen atom and intermolecular stabilization via nitrile coordination contribute to the stability of this conformation. On the other hand, intramolecular stabilization cannot be achieved in **6a** (cis) due to the strong hindrance between the huge $C_{32}H_{51}O_8$ substituent and bulky tributyltin group (Figure 1, and see Figure 2 shown later), and therefore the allylation in CH_3CN cannot proceed through **6a** (cis) but proceed through **6a** (trans). The difference between **6a** (trans) and **6a** (cis) was 9.5 kcal/mol; theoretically, this corresponds to a >99:1 ratio of the trans:cis product, which roughly speaking matches the observed ratio (>95:5).

Thus, we conclude that the cyclization of **1a** in acetonitrile proceeds through the nitrilium salt intermediate **6a** (trans); an S_N2-type reaction takes place for **6a** (trans) and the allylation occurs from the side opposite to CH_3CN coordination, giving nearly 100% trans-stereoselectivity. In other words, the sp^2 flat structures (**3a**) are able to accommodate the strong steric hindrance between Bu_3Sn and the huge ladder A-G ring framework; however, the sp^3 structures (*trans*-**6a** and *cis*-**6a**) are no more tolerable to the steric repulsion, leading to the very significant energy difference between *trans*-**6a** and *cis*-**6a**.

(3) Scope and Limitation of the Solvent-Controlled Stereoselectivity. Being able to rationalize the stereoselective cyclization of **1a** in acetonitrile, we next considered the following possibility. Can we obtain a single product from a mixture of diastereoisomeric starting materials having more simple structures, that is to say, can we extend the scope of the solvent-controlled stereoselectivity to more simple and general systems? In order to obtain high diastereoselectivity, we cannot rely on the *ordinary* S_N2 mechanism, because in this case each diastereomer is a precursor of either cis- or trans-cyclization product, and the diastereoisomeric ratio of the starting materials reflects directly the ratio of the products. We can produce a carbocation, pushing the reaction to the S_N1 mechanism, but as observed above in the flat sp^2-reaction center even large substituents can accommodate themselves in either conformation, which results in a nonstereoselective reaction.

Nevertheless, if we introduce acetonitrile as a solvent, which is capable of forming sp^3-intermediates, the energy difference between the direct precursors of trans- and cis-products becomes large enough to ensure the stereoselective trans-cyclization, because the leaving group must be left behind, pushing the $C_{32}H_{51}O_8$ substituent exactly in the direction of the tributyltin group in **6a** (cis) as well as in a corresponding transition state (Figure 1).

It is clear that the ability to play this trick must be strongly dependent on the size of R′ (the A-G ring system in **1a**, and see Table 1). Thus, we prepared the model compounds **1b**−**e** which had much smaller R′ groups, compared to **1a**. The α-acetoxy ether derivatives **1b**−**e** were treated with $MgBr_2$·OEt_2 under the identical reaction conditions as above. In the cyclizations of the small model compounds **1d**−**e** the effects of changing solvent from CH_2Cl_2 to CH_3CN on the stereoselectivity were minute.[6] However, interestingly, in all the cases the diastereoselectivities in CH_3CN were slightly higher than those in CH_2Cl_2, perhaps because of the participation of the nitrilium intermediates to some extent. In the case of **1c**, in which two isopropyl groups were substituted at the carbon α to the ether oxygen, the *trans*-**4c**/*cis*-**5c** ratio increased a bit in both CH_2Cl_2 and CH_3CN. Interestingly, in the case of **1b**, in which the R′ was modeled by two fuzed six-membered rings, the solvent effect of the same order as in **1a** was observed (Table

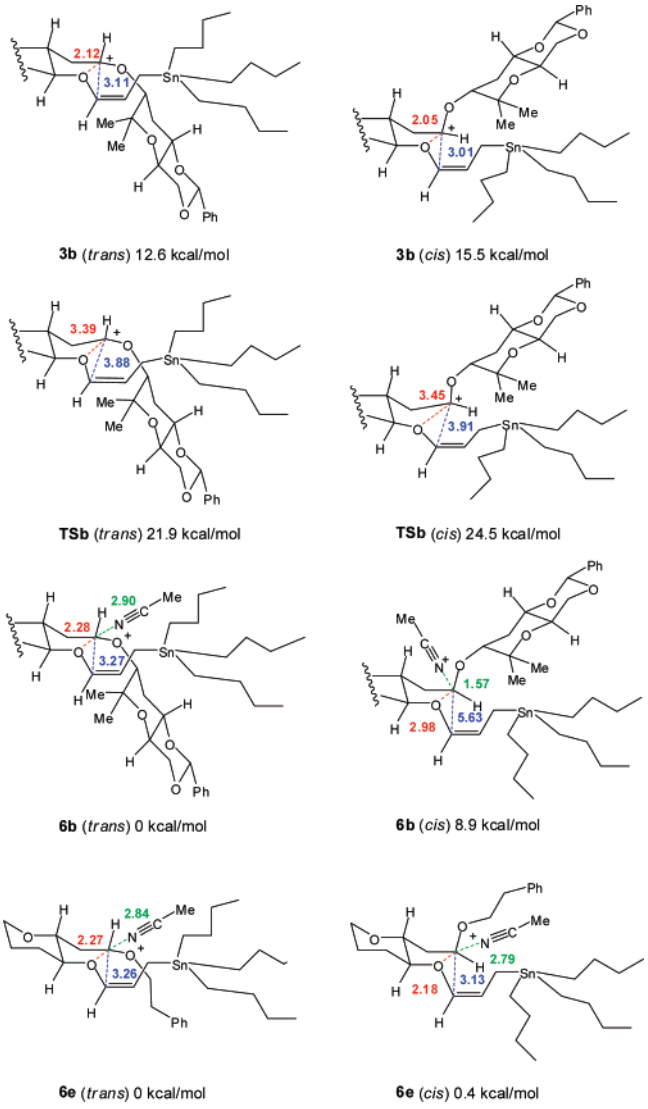


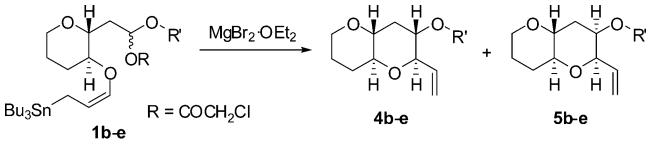
FIGURE 2. Schematic representation of the computational results for the cyclizations of **3b**. The numbers indicate the corresponding bond lengths (in Å) for the intermediates of **3b** cyclization. The relative energies for **3b** as well as those for **TSb** were computed by adding the energy of a free acetonitrile molecule.

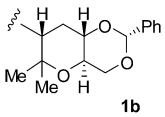
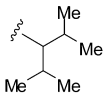
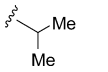
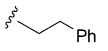
1). These results strongly indicate that the steric bulkiness at the α-position of the carbon attached to the ether oxygen is not so influential to the solvent-controlled stereoselectivity, but the second ring in the R′ group exerts a very strong effect on the stereoselectivity.

To re-confirm the mechanism on the solvent-controlled stereoselectivity mentioned in the case of **3a**, we carried out computations for **3b** (the carbocation generated from **1b**), **TSb** (the transition states leading to *trans*-**4b** and *cis*-**4b**), and **6b** and **6e** (the corresponding nitrilium salts) (Figure 2).

Again, there is not so much difference between the activation barriers for the trans- and cis-cyclizations from the carbocation intermediates **3b**: **TSb** (trans) − **3b** (trans) = 9.3 kcal/mol, and **TSb** (cis) − **3b** (cis) = 9.0 kcal/mol. On the other hand, there is a significant difference in energies between the nitrilium salts **6b** (trans) and **6b** (cis), as observed in the case of **6a**; the energy difference of 8.9 kcal/mol correspondes approximately

TABLE 1. Cyclization of Compounds 1b−e[a]



R'	yield[b] (ratio, **4**:**5**)[c]	
	in CH_2Cl_2	in CH_3CN
 **1b**	75% (62:38)	88% (>95:5)[d]
 **1c**	87% (67:33)	74% (83:17)
 **1d**	80% (41:59)	24% (73:27)
 **1e**	82% (53:47)	78% (77:23)

[a] Reactions were carried out with 4 equiv of $MgBr_2$·OEt_2 at 0 °C. [b] Isolated yield. [c] The ratio was detemined by ^{1}H NMR analysis of a crude reaction mixture. [d] The cis-isomer **5b** was detected only as a weak spot on TLC, but not in the ^{1}H NMR of a crude reaction mixture.

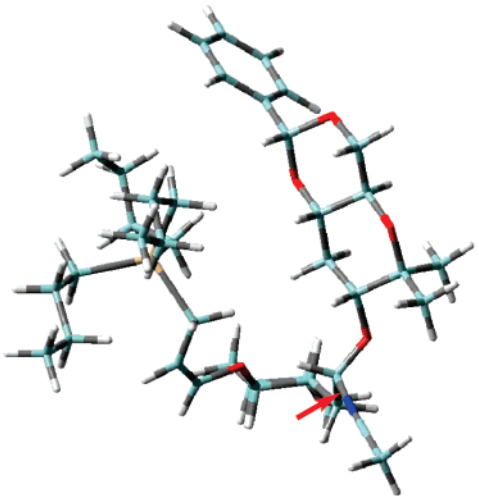


FIGURE 3. Optimized geometry (B3LYP/SDD) of the alkylnitrilium salt **6b** (cis). Further counterclockwise rotation around the bond marked by the arrow approaching the transition state for S_N2 cis-cyclization is completely blocked by the hindrance between R′ and Bu_3Sn. Furthermore, it is the second ether ring of the substituent R′ that makes this hindrance untolerable, whereas the substitution at the α-position of the R′ would not increase the hindrance. Color code: red (oxygen), blue (nitrogen), and yellow (Sn).

to the isomer ratio of >99:1. In Figure 3, the optimized geometry of the alkylnitrilium salt **6b** is shown. It is clearly shown that the second ring of the substituent R′ makes the steric hindrance untolerable, and the substituent at the position α to the carbon attached to the ether oxygen does not increase the hindrance. The results on the computation for **6e**(trans) and **6e**(cis) are interesting, since the energy difference is only 0.4 kcal/mol (Figure 2); this indicates that, even if nitrilium salts participate in the reaction, the solvent-controlled stereoselectivity is not observed when a small substituent is at the R′ position.[8]

TABLE 2. Cyclization of 1e in Various Solvents[a]

entry	solvent	ratio (**8a**:**8b**)	yield, %
1	CH_2Cl_2	53:47	82
2	CH_3CN	77:23	78
3	CH_2Cl_2/CH_3CN (1:1)	76:24	74
4	CH_3NO_2	52:48	67
5	toluene	53:47	64
6	ether	56:44	70
7	THF		0

[a] Reactions were carried out with 4 equiv of $MgBr_2 \cdot OEt_2$. [b] Isolated yield. [c] The ratio was detemined by ^1H NMR analysis of a crude reaction mixture.

A more detailed solvent effect in the reaction of **1e**, which gave a mixture of **4e** and **5e**, was investigated, and the results are summarized in Table 2. Nearly a 1:1 mixture of the diastereoisomers **4e** and **5e** was obtained in the ordinary solevents (entries 1 and 4−6), and this result is very similar to the observation in the case of the I ring formation of brevetoxin B, as mentioned in the introductory section. However, slightly increased diastereoisomeric ratios were obtained in CH_3CN and CH_3CN/CH_2Cl_2 (1:1) even in the case of the small substituent $PhCH_2CH_2$. In THF, no reaction took place perhaps because of strong coordination of the solvent to the Lewis acid.

(8) We were able to reproduce this result computationally. Thus, the optimized geometry of alkylnitrilium salt **6e** (cis) is close to that of **6e** (trans) (the bond-forming distances are 3.13 and 3.26 Å, respectively), and is only 0.4 kcal/mol higher in energy.

Conclusion

We have found a new way of controlling the stereoselectivity of nucleophilic substitution via double switch of the reaction mechanism. This approach allows stereoselective reactions to be carried out with non-isomerically pure starting compounds. Although only relatively large molecules are eligible for this trick, the sufficient bulkiness can be effectively discovered computationally.

Acknowledgment. This work was financially supported by the Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental details, characterization data, NMR charts of new compounds, full Gaussian reference, computational details, Cartesian coordinates, and energies of all optimized structures and transition states. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7013752