Mechanism of Chiral Lewis Acid Mediated Enantiotopic Group-Selective Ring Cleavage of Cyclic Acetals Derived from *meso*-1,2-Diols

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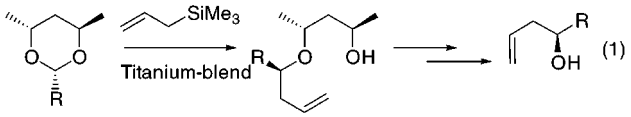
Received July 6, 1999

Diastereoselectivity and enantioselectivity of chiral oxazaborolidine-mediated ring-cleavage reactions of *meso*-2,4,5-trisubstituted 1,3-dioxolane acetals with a trimethylsilyl ketene acetal were investigated in detail and discussed in terms of a mechanism involving a contact ion pair as a product-forming intermediate. Both diastereomeric 2-phenyl derivatives *syn*- and *anti*-**11a** gave the same ring-cleavage product **13a**. However, the reaction of 2-phenylethynyl derivatives *syn*- and *anti*-**11b** proceeded almost stereospecifically, giving rise to **13b** and **14b**, respectively. In all of the reactions, isomerization of diastereomeric acetals was not observed. On the basis of these results, it was deduced that the dissociation of a Lewis acid−acetal complex is the rate-determining step, and the resulting ion pair intermediate undergoes either isomerization to a diastereomeric acetal or attack by a nucleophile depending on the structure of the acetal. The possible enantioselection at the product-forming step was ruled out. It was proposed that the observed enantioselectivity is determined by enantiodifferentiating coordination of the acetal oxygen atom by the chiral Lewis acid.

Introduction

The Lewis acid mediated cleavage of cyclic acetals has been intensively investigated in recent years and has proven to be a versatile tool in asymmetric synthesis. Titanium complex mediated reaction of chiral acetals **1**, derived from (2*R*,4*R*)-2,4-pentanediol, proceeds with a highly stereoselective introduction of a variety of carbon nucleophiles such as allyltrimethylsilane, affording a powerful method for asymmetric carbon−carbon bond formation (eq 1).[1] The ring-cleavage reaction is also



(1)

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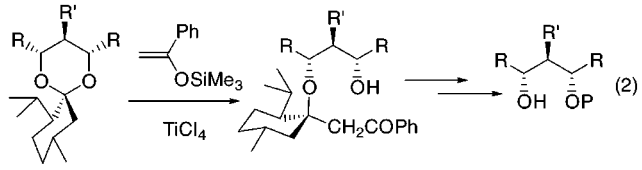
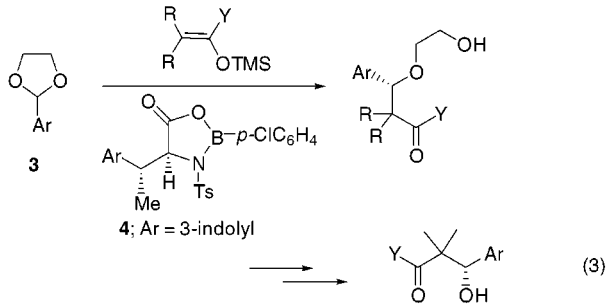
utilized in desymmetrization of prochiral diols. L-Menthone-derived spiroacetals **2** undergo exclusive equatorial C−O bond cleavage, leading to the enantiomerically pure (>95% ee) desymmetrized derivatives of the parent diols (eq 2).



(2)

2

Recent work in these laboratories revealed that the enantioselective ring cleavage of cyclic acetals can be achieved without the aid of chiral auxiliaries by using an appropriate chiral Lewis acid.[3−5] In the presence of a catalytic amount (10 mol %) of chiral oxazaborolidine **4**, the reaction of dioxolane acetals **3** with enol silyl ethers and silyl ketene acetals proceeds with high enantioselectivity (78−93% ee) to give the ring-cleavage products, which can be transformed to enantiomerically enriched secondary alcohols (eq 3).[3] A variety of *meso*-1,2-diols can



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4; Ar = 3-indolyl

(3)

be successfully desymmetrized via ring-cleavage reaction

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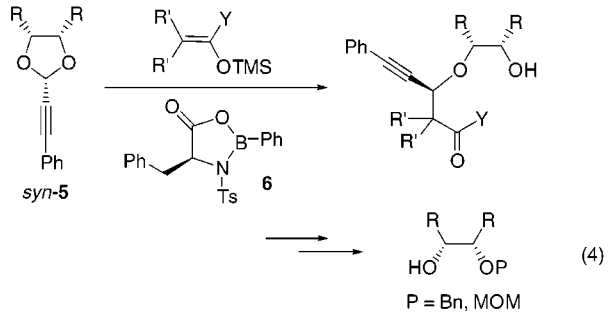
10.1021/jo991071n CCC: $18.00
Published on Web 09/14/1999

of 2-phenylethynyl acetals *syn*-**5** (eq 4).[4] The reaction



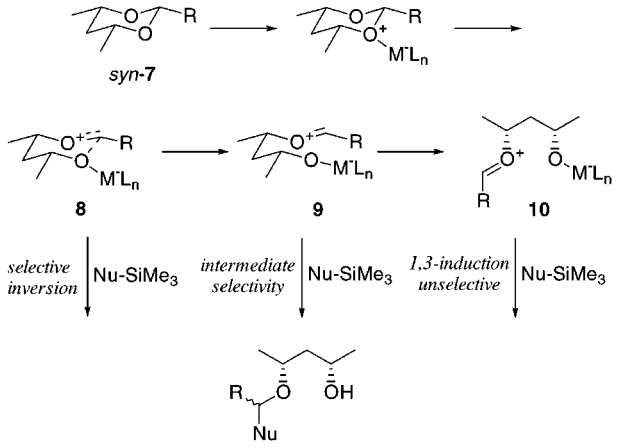
(4)

proceeds with high enantioselectivity (85−96% ee) at −78 °C by using a stoichiometric amount of chiral oxazaborolidine **6**.

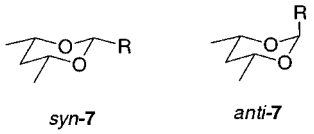
The ring cleavage of cyclic acetals possesses a unique character in the mechanism and origin of stereoselectivity. Because acetals can be regarded as difunctional compounds with two ethereal C−O groups, the cleavage reactions are classified as group-selective reactions,[6,2f] where Lewis acids play a role different from that in the more common face-selective reactions. The diastereotopic C−O bonds of spiroacetal **2** are differentiated through the ring-cleavage reaction (eq 2), whereas the discrimination of enantiotopic C−O bonds in *syn*-**5** leads to the stereoselective product formation (eq 4). Group-selective C−O bond cleavage as well as the stereochemical course (namely, inversion or retention of the acetal carbon) of the nucleophile introduction determines the stereoselectivities in eqs 1 and 3.

Recently, the mechanism of the ring-cleavage reaction has been studied extensively to clarify the origin of the high stereoselectivity observed for chiral acetals **1**.[1f,7] These studies revealed a wide mechanistic spectrum of the reaction. Heathcock et al.[7b] and Denmark et al.[1f] reported that the reaction of diastereomeric acetals *syn*- and *anti*-**7** was not stereospecific. The stereoselectivity was demonstrated to be influenced by the structure of the parent aldehyde residue (R), the nature of the Lewis acid, the solvent, and the nucleophile. The observations were incompatible with a mechanism involving direct displacement of a Lewis acid−acetal complex. Denmark et al. proposed a unified mechanistic scheme involving three types of ion pairs with different degrees of dissociation, each with a different stereochemical profile (Scheme 1).[1f] The three species are (1) a contact ion pair (**8**), (2) an external ion pair (**9**), and (3) a free oxocarbenium ion (**10**). The contact ion pair undergoes highly selective reactions in an invertive manner. The external ion pair reacts with modest selectivity due to greater access at the acetal center. The separated ion pair reacts with no selectivity due to the minimal influence of the remote stereogenic center. The degree of dissociation is enhanced

Scheme 1



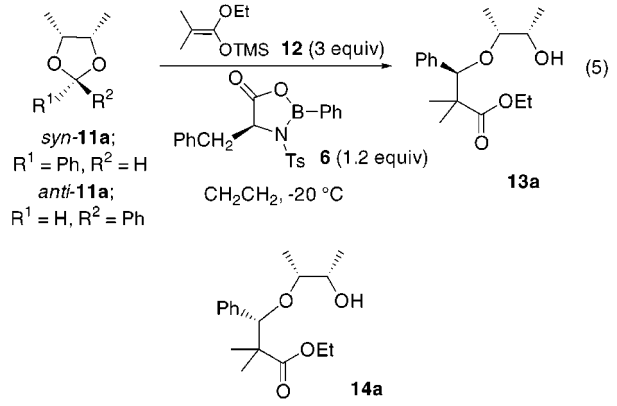
by stronger Lewis acids, by sterically demanding or cation-stabilizing substituents, by polar solvents, and by less reactive nucleophiles, and the enhanced dissociation results in low selectivities.



To extend the scope of chiral Lewis acid mediated enantioselective ring-cleavage reactions, it is essential to understand the mechanism and origin of the selectivity. For this purpose, we investigated the stereochemical aspects of the chiral oxazaborolidine-mediated ring cleavage of dioxolane acetals *syn*- and *anti*-**11a**,**b** derived from *meso*-2,3-butanediols. The study demonstrated that dissociation of a Lewis acid−acetal complex is the rate-determining step, and the resulting contact ion pair intermediate undergoes either rapid isomerization to a diastereotopic ion pair or attack by a nucleophile. The origin of enantioselectivity is discussed in terms of the above mechanistic scheme.

Results

In the course of preliminary study on the effect of an aldehyde-derived moiety in the ring cleavage of dioxolane acetals, we examined the reaction of phenyl derivatives *syn*- and *anti*-**11a**.[4a] Treatment of *syn*-**11a** with silyl ketene acetal **12** in the presence of oxazaborolidine **6** (0.3 equiv) at −20 °C for 15 h gave ring-cleavage product **13a** in 72% yield with 22% ee (eq 5). Although the enantio-



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(6) For nonenzymatic enantiotopic group-selective reactions, see: (a) Ward, R. S. *Chem. Soc. Rev.* **1990**, *19*, 1. (b) Gais, H.-J. *Methods of Organic Chemistry (Houben-Weyl)*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E21a, p 589. (c) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430 and references therein.

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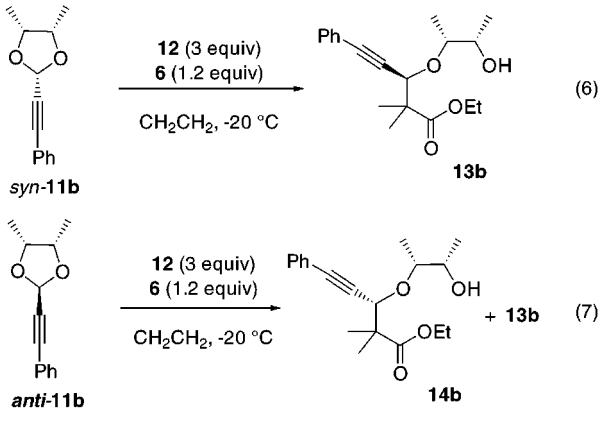
Table 1. Ring Cleavage of Acetals *syn*- and *anti*-11a,b with Oxazaborolidine 6 and Silyl Ketene Acetal 12[a]

			ring-cleavage product			recovery of acetal	
entry	acetal	time (h)	yield (%)	**13**:**14**[b]	ee (%)[c]	yield (%)	*syn*:*anti*[b]
1	*syn*-**11a**	8	94	>50:1	33		
2		0.25	82	>50:1	27	8	>50:1
3	*anti*-**11a**	8	96	>50:1	52	5	1:>50
4		1	76	>50:1	53	21	1:>50
5		0.25	53	>50:1	49	30	1:>50
6	*syn*-**11b**	4	82	>50:1	70		
7		0.25	34	>50:1	68	43	>50:1
8	*anti*-**11b**	20	59	1:16	96 (71)[d]	41	1:>50
9		4	43	1:16	96 (73)[d]	51	1:>50
10[e]		20	46	1:10	94 (65)[d]	49	1:>50
11[e,f]		20	9	1:8.4	90 (60)[d]	75	1:>50

[a] Unless otherwise noted, reactions were carried out by using **6** (1.2 equiv) and **12** (3 equiv) in CH_2Cl_2 (0.4 M) at −20 °C. [b] Determined by 500 MHz ^{1}H NMR analysis. [c] Determined by 500 MHz ^{1}H NMR analysis of the MTPA ester derivative. [d] Ee (%) of minor diastereomer **13b**. [e] A 1.2 equiv portion of **12** was used. [f] The reaction was carried out at 0.2 M.

selectivity was moderate, the reaction exhibited high diastereoselectivity. The formation of diastereomeric product **14a** was not detected. A mechanistically informative result was obtained in the reaction of diastereomeric acetal *anti*-**11a**. The acetal was considerably less reactive under similar conditions, affording exclusively the same ring-cleavage product **13a** (25% ee) in 10% yield. No isomerization was observed for the recovered acetal. The observed absence of stereospecificity suggested the intervention of ion pairs in the oxazaborolidine-mediated ring-cleavage reaction. To gain further insight into the mechanism, we examined the reactions of 2-phenyl and 2-phenylethynyl derivatives *syn*- and *anti*-**11a**,**b** with nucleophile **12** (3 equiv) by using a stoichiometric amount (1.2 equiv) of **6** at −20 °C (eqs 5−7, Table 1).



The reaction of *syn*-**11a** for 8 h afforded **13a** of 33% ee exclusively in 94% yield (entry 1). When the reaction was stopped after 0.25 h, the starting acetal was recovered in 8% yield without isomerization to *anti*-**11a** (entry 2). Under these stoichiometric conditions, the reaction of *anti*-**11a** also afforded **13a** exclusively (entries 3−5). The anti acetal was less reactive but exhibited uniformly higher ee (ca. 50%) than the syn isomer. Isomerization of the recovered acetals was not observed even in the higher conversion. In the absence of nucleophile **12**, both *syn*-**11a** and *anti*-**11a** underwent rapid isomerization leading to an equilibrating mixture (*syn*-**11a**:*anti*-**11a** = ca. 3:1) (Table 2, entries 1−4). Starting either from *syn*-**11a** or from *anti*-**11a**, the equilibration was reached within 1 h even with 0.3 equiv of **6**.

Table 2. Isomerization of Acetals *syn*- and *anti*-11a,b with Oxazaborolidine 6[a]

entry	acetal	**6** (equiv)	time (h)	*syn*:*anti*[b]
1	*syn*-**11a**	0.3	1	3.0:1
2		1.2	8	3.0:1
3	*anti*-**11a**	0.3	1	3.2:1
4		1.2	8	3.2:1
5	*syn*-**11b**	1.2	8	1:1.4
6[c]		1.2	72	1:1.6
7	*anti*-**11b**	0.3	8	1:2.2
8		1.2	8	1:1.5

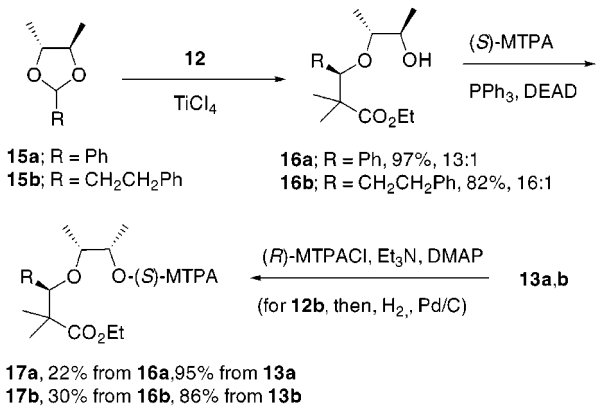
[a] All reactions were carried out in CH_2Cl_2 (0.4 M) at −20 °C. Unless otherwise noted, the starting acetal was recovered in >95% yield. [b] Determined by 500 MHz ^{1}H NMR analysis. [c] The acetal was recovered in 60% yield.

A similar set of experiments was carried out for phenylethynyl derivatives *syn*- and *anti*-**11b** at −20 °C (eqs 6 and 7). The reaction of *syn*-**11b** also proceeded with high diastereoselectivity to give diastereomer **13b** as the sole product (Table 1, entries 6 and 7). In comparison with the phenyl derivative, enantioselectivity was higher (ca. 70% ee)[8] while the reaction was slower (entry 2 vs 7). Again, no isomerization was observed for the recovered acetal. In sharp contrast to the phenyl derivative, *anti*-**11b** afforded another diastereomer **14b** together with a minor formation of **13b** (**14b**:**13b** = 16:1) (entries 8 and 9). Interestingly, the enantioselectivity of major isomer **14b** was high (96% ee) while that of minor isomer **13b** was moderate (71% ee). When the reaction was carried out with a reduced amount (1.2 equiv) of nucleophile **12**, the diastereoselectivity was lowered to 10:1 (entry 10). Further lowering (8.4:1) was observed under dilute conditions using twice as much solvent (entry 11). Even under the standard conditions, the ring-cleavage reaction of *anti*-**11b** was slow and did not attain completion after 20 h (entry 8).[9] Isomerization of the recovered acetal was not observed at all. Control experiments showed that, in the absence of the nucleophile, *syn*- and *anti*-**11b** underwent isomerization to give an equilibrating mixture (*syn*-**11b**:*anti*-**11b** = ca. 2:3) in 8 h (Table 2, entries 5−8). Judging from the incomplete equilibration in the experiment using 0.3 equiv of **6** (entry 7), the rate of isomerization for *syn*- and *anti*-**11b** is slower than that for the phenyl derivatives.

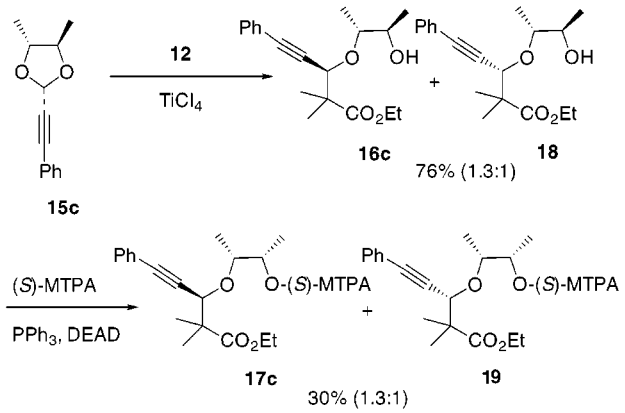
The absolute structures of ring-cleavage products **13a**,**b** were determined by correlation to (*S*)-MTPA esters **17a**,**b** (Scheme 2). $TiCl_4$-mediated ring cleavage of chiral acetal (4*R*,5*R*)-**15a**,**b** stereoselectively gave ring-cleavage products **16a**,**b**.[1a−c] Esterification of **16a**,**b** with (*S*)-MTPA under the Mitsunobu conditions afforded esters **17a**,**b** with stereochemical inversion.[10] Ester **17a** thus prepared was identical in all respects with the major diastereomer formed by the reaction of *syn*- and *anti*-**11a** with (*R*)-MTPACl. Ester **17b** was identical with the major isomer obtained by hydrogenation of the (*S*)-MTPA ester of **13b**. Ring cleavage of 2-phenylethynyl derivative (4*R*,5*R*)-**15c** mediated by $TiCl_4$ proceeded nonselectively to give a 1.3:1 mixture of diastereomeric products **16c** and **18** in 76% yield. (Scheme 3). Esterification of the mixture with (*S*)-MTPA under the Mitsunobu conditions afforded a 1.3:1 mixture of **17c** and **19**. Esters **17c** and **19** thus obtained

(8) The reaction at −78 °C gave higher ee of 96%.[4a]
(9) No ring cleavage was observed for *anti*-**13b** at −78 °C.
(10) Mitsunobu, O. *Synthesis* **1981**, 1.

Scheme 2



Scheme 3



were identical to the major (*S*)-MTPA esters derived from **13b** and **14b**, respectively.

Discussion

Facile isomerization between *syn*-**11a,b** and *anti*-**11a,b** observed in the absence of nucleophile **12** implies the involvement of intermediates with the dissociated acetal carbon−oxygen bond in the oxazaborolidine-mediated enantioselective ring cleavage of dioxolane acetals. Judging from the high diastereoselectivity observed, external ion pairs and free oxocarbenium ions are less likely for the intermediates. We propose a mechanism involving contact ion pairs as the product-forming intermediates (Scheme 4).

Phenyl derivative *syn*-**11a** gave ring-cleavage product **13a** (and *ent*-**13a**) with complete diastereoselectivity. According to Scheme 4, major enantiomer **13a** is produced through a pathway involving initial formation of the complex *syn*-**20a** in which the *pro*-*R* oxygen atom is coordinated to oxazaborolidine **6** (designated as BL^*_3), followed by dissociation to contact ion pair *syn*-**21a** and subsequent attack of the nucleophile in an invertive manner. Similarly, minor enantiomer *ent*-**13a** is formed via complex *syn*-**20′a**, in which the *pro*-*S* oxygen atom is coordinated, and via ion pair *syn*-**21′a**. Diastereomeric dioxolane *anti*-**11a** also gave **13a** (and *ent*-**13a**) exclusively. The formation of **13a** indicates the isomerization of the initially formed ion pair *anti*-**21a** to *syn*-**21a**. Isomerization between the ion pair intermediates has been discussed previously for six-membered cyclic acetals.[1f,7b−d] The absence of diastereomeric ring-cleavage product **14a** indicates that the isomerization of *anti*-**21a** proceeds much faster than its capture by the nucleophile ($k_2 \gg k_5$[**12**]). In these reactions, *syn*-**11a** was not detected in the recovered acetal. This strongly suggests that the ion pair *syn*-**21a** thus formed is exclusively captured by the nucleophile to give **13a** before it undergoes ring closure to complex *syn*-**20a** (k_4[**12**] $\gg k_{-1}$). Ring cleavage of *syn*-**11a** proceeds also through ion pair *syn*-**21a**. Therefore, it is deduced that the dissociation of complexes *syn*-**20a** to form contact ion pairs *syn*-**21a** is the rate-determining step of the reaction of *syn*-**11a**.[11]

The results obtained for phenylethynyl derivatives *syn*- and *anti*-**11b** can also be discussed according to the proposed pathway (Scheme 4). In contrast to the phenyl derivatives, they underwent ring cleavage almost stereospecifically: the syn isomer gave ring-cleavage product **13b** exclusively, whereas the anti isomer afforded isomeric product **14b** with high stereoselectivity (16:1). The observation can be rationalized if we assume that the isomerization of ion pair *anti*-**21b** to ion pair *syn*-**21b** is slower than its reaction with the nucleophile ($k_2 < k_5$[**12**]). Isomerization between *syn*- and *anti*-**11b** was observed in the absence of nucleophile **12**, but it was slower than that of the phenyl derivatives. The rate of isomerization might be dependent on the difference in relative energy between *anti*-**21** and *syn*-**21**. In comparison with the phenyl group, a sterically less demanding phenylethynyl group may reduce the energy difference leading to the slower isomerization of *anti*-**21b**.[12] According to the pathway, the difference between k_2 and k_5[**12**] will be decreased by carrying out the reaction at lower concentration of **12**, resulting in the increase of the formation of minor product **13b**. Indeed, a 10:1 mixture of **14b** and **13b** was obtained in the reaction using 1.2 equiv of **12** (Table 1, entry 10). The diastereoselectivity was further lowered (8.4:1) when the above reaction was carried out by using twice as much solvent (entry 11).

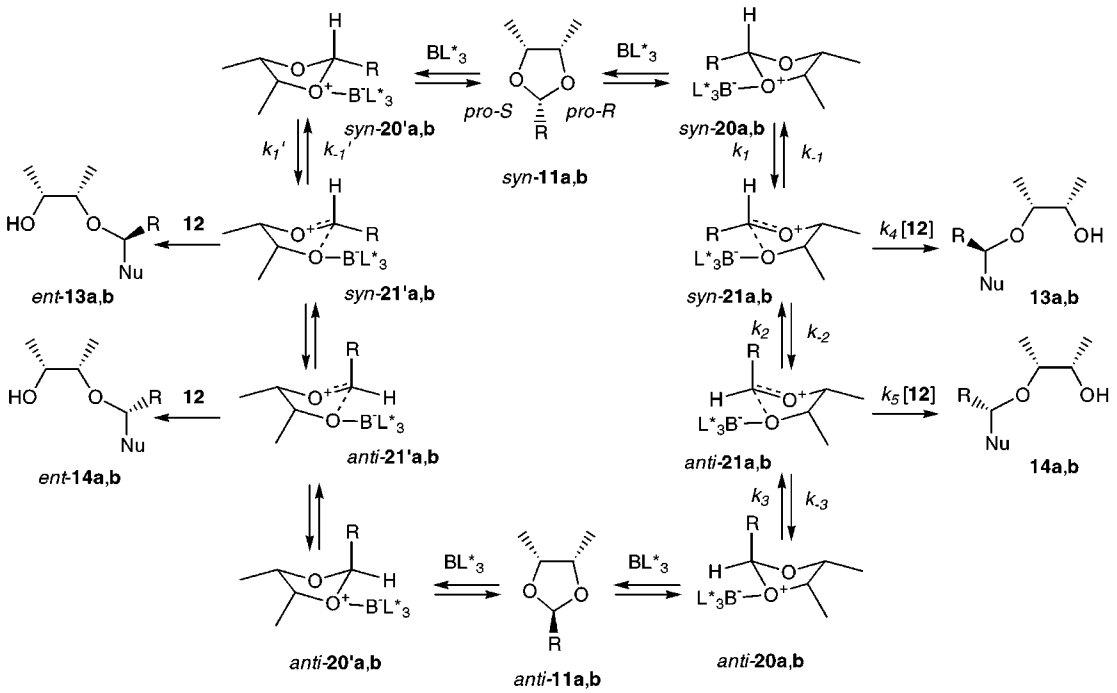
No isomerization of recovered *anti*-**11b** was observed in its reaction even under the conditions where the isomerization of the initially produced ion pair *anti*-**21b** competes with its capture by the nucleophile. Judging from the observation, the ring-closure of ion pair *syn*-**21b** to give *syn*-**11b** is again slow in comparison with its capture by the nucleophile to give a minor diastereomer **13b**. Therefore, dissociation of Lewis acid−acetal complex *syn*-**20** to form contact ion pair *syn*-**21** is deduced to be the common rate-determining step for *syn*-**11a** and *anti*-**11b**. For the reactions of *anti*-**11a**,**b**, we can assume similar rate-determining dissociation of complex *anti*-**20** because it is less probable that *anti*-**20** undergoes ring-closure much faster than isomeric *syn*-**20**. The absence of significant rate depression in the reaction of *anti*-**11b** with a reduced amount of the nucleophile (entry 10) provides support for the assumption.

Ion pairs *syn*- and *anti*-**21** are also involved in the isomerization of *syn*- and *anti*-**11a**,**b** in the absence of nucleophile **12**. Rate-determining dissociation to the ion pairs requires equal rates for ring-cleavage and isomerization reactions. Isomerization of *anti*- and *anti*-**11a**,**b**, however, proceeded faster than the corresponding ring-cleavage reaction. The apparent discrepancy might be derived from the catalytic nature of isomerization that ensures constant concentration of oxazaborolidine **6**

(11) In the above discussion, the reaction pathway leading to **13a** (i.e., the right half of Scheme 4) was considered. A similar discussion can be made for the left half of the scheme leading to *ent*-**13a**.

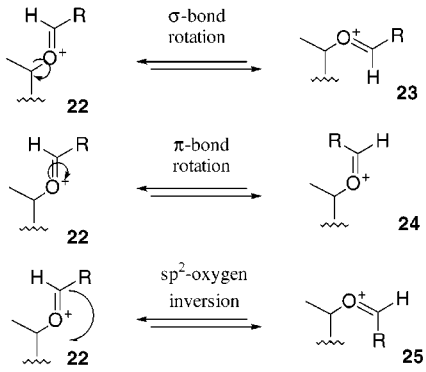
(12) Alternatively, relative slow isomerization might be due to the lower degree of dissociation for these ion pairs in comparison to that for the phenyl derivatives.

Scheme 4[a]

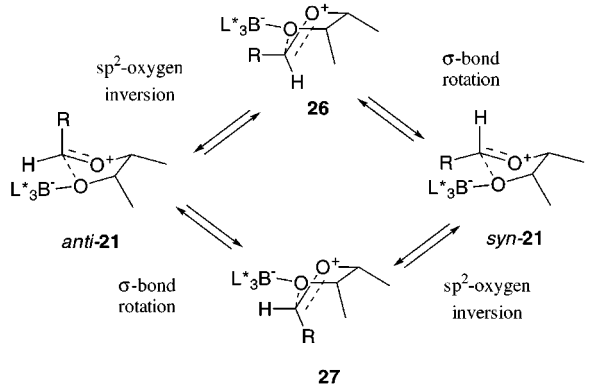


[a] **a**: R = Ph; **b**: R = PhC≡C; BL*$_3$ = **6**; Nu = Me_2CCO_2Et.

Scheme 5



Scheme 6



throughout the reaction. On the other hand, the concentration of **6** decreases during the ring-cleavage reaction because the regeneration of the oxazaborolidine is slow.[13]

Three possible modes have been proposed for the isomerization of oxocarbenium ion intermediates (Scheme 5).[7d] Through a C−O σ-bond rotation, carbenium ion **22** is converted to **23** without changing the anti orientation of the R group. On the other hand, carbenium ions **24** and **25** with the *syn*-R group are formed through a C=O π-bond rotation and through an sp^2-oxygen inversion, respectively.[14] Of these, π-bond rotation is less likely for isomerization of contact ion pairs such as *syn*- and *anti*-**21** because the neighboring O−BL*$_3$ moiety would hinder the rotation. Pathways for the isomerization may, therefore, involve a σ-bond rotation and an sp^2-oxygen inversion (Scheme 6). The oxygen inversion of ion pair *anti*-**21** would afford conformer **26**, which then undergoes a σ-bond rotation to give *syn*-**21**. An alternative pathway involving an initial σ-bond rotation is less likely because intermediate **27** is sterically less favorable than **26**.

According to the proposed reaction mechanism (Scheme 4) in which formation of contact ion pair intermediates is the rate-determining step, the enantioselectivity of the reaction is determined by the relative rates of dissociation for diastereomeric acetal−Lewis acid complexes, k_1[*syn*-**20**]/$k_{1'}$[*syn*-**20′**] (or k_3[*anti*-**20**]/$k_{3''}$[*anti*-**20′**]). On the basis of a reasonable assumption that the structure of ion pairs is similar to that of Lewis acid−acetal complexes, it is probable that rate constants k_1 and $k_{1'}$, as well as k_3 and $k_{3'}$, are not much different. Accordingly, selective coordination of the *pro-R* oxygen atom by the chiral Lewis acid **6** to form complex *syn*-**20** over *syn*-**20′** (and *anti*-**20** over *anti*-**20′**) should be a predominant factor in the observed enantioselectivity.[15] In this respect, the structural elucidation of the diastereomeric Lewis acid−acetal complexes is important to understand the origin of

(13) Formation of a small amount of the TMS ether derivatives of **13a**,**b** and **14b** was always observed in the crude mixture of the ring-cleavage reaction before treatment with aqueous AcOH/THF (see Experimental Section).

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enantioselectivity in more detail. Low-temperature (−20 °C) ^{1}H NMR analysis of the dioxolane acetals in the presence of Lewis acid **6**, however, did not show appreciable changes in the chemical shifts of the two components, suggesting that the equilibrium constant for complex formation is small. Phenylethynyl derivatives *syn*- and *anti*-**11b** showed enantioselectivity higher than that of the corresponding phenyl derivatives. Anti acetals *anti*-**11a**,**b** exhibited better enantioselection than the syn diastereomers. Such trends may afford some indirect information on the structure of the Lewis acid−acetal complexes.

Conclusion

It has been shown that stereoselectivity in the ring cleavage of dioxolane acetals mediated by oxazaborolidine **6** can be understood in terms of a mechanism involving a contact ion pair as a product-forming intermediate. Stereochemical outcomes obtained in a series of reactions for diastereomeric 2-phenyl and -phenylethynyl derivatives led us to infer that the dissociation of a Lewis acid−acetal complex is the rate-determining step and the resulting ion pair intermediate undergoes either isomerization to a diastereomer or attack by a nucleophile, depending on the structure. Elucidation of the rate-determining step allowed us to ruled out the possible enantioselection at the product-forming step of the attack of a nucleophile. The observed enantioselectivity is most likely rationalized by enantiodifferentiating coordination of the acetal oxygen atom by chiral Lewis acid **6**.

Experimental Section

General. Unless otherwise noted, ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 and 125 MHz, respectively. All commercially available reagents were used without further purification. Dichloromethane was distilled from CaH_2. Organic extracts were dried over Na_2SO_4. Flash chromatography was conducted on silica gel (Wakogel C-300). *N*-Tosyl-L-phenylalanine[16,17] and silyl ketene acetal **12**[18] were prepared according to the literature procedures.

***rel*-(2*S*,3*S*,4*R*)-4,5-Dimethyl-2-phenyl-1,3-dioxolane (*syn*-11a) and *rel*-(2*R*,3*S*,4*R*)-4,5-Dimethyl-2-phenyl-1,3-dioxolane (*anti*-11a).** To a solution of benzaldehyde (1.52 g, 15 mmol) and *meso*-2,3-butanediol (1.50 g, 16.5 mmol) in benzene (8 mL) was added a *p*-toluenesulfonic acid monohydrate (29 mg, 0.15 mmol). The resulting solution was heated under reflux with a Dean−Stark trap for 3 h. The mixture was poured into aqueous $NaHCO_3$ and extracted twice with ether. The combined organic layers were dried and concentrated in vacuo. Purification of the residue by flash chromatography (5% Et_2O in hexane) gave, in the order of elution, *anti*-**11a** (0.61 g, 23%) and *syn*-**11b** (1.00 g, 37%). The structural determination was made on the basis of NOESY spectral measurements; a NOE was observed for *syn*-**11a** between the protons attached at the C-2 and C-4. Data for *syn*-**11a**: ^{1}H NMR δ 1.30 (6H, m), 4.36 (2H, m), 5.80 (1H, s), 7.35−7.45 (3H, m), 7.48 (2H, m); ^{13}C NMR δ 15.52, 75.09, 102.80, 126.76, 128.32, 129.14, 137.89; IR (liquid film) 1090 cm^{-1}. Data for *anti*-**11a**: ^{1}H NMR δ 1.27 (6H, m), 4.39 (2H, m), 6.14 (1H, s), 7.25−7.45 (3H, m), 7.49 (2H, m); ^{13}C NMR δ 14.44, 74.55, 101.52, 126.03, 128.30, 128.68, 139.93; IR (liquid film) 1095 cm^{-1}.

***rel*-(2*S*,3*S*,4*R*)-4,5-Dimethyl-2-phenylethynyl-1,3-dioxolane (*syn*-11b) and *rel*-(2*R*,3*S*,4*R*)-4,5-Dimethyl-2-Phenylethynyl-1,3-dioxane (*anti*-11b).** To a solution of 3,3-diethoxy-1-phenylpropyne (1.28 g, 10 mmol) and *meso*-2,3-butanediol (1.08 g, 12 mmol) in toluene (10 mL) was added *p*-toluenesulfonic acid monohydrate (19 mg, 0.10 mmol). The resulting solution was heated at 100 °C for 14 h. The mixture was poured into aqueous $NaHCO_3$ and extracted twice with ether. The combined organic layers were dried and concentrated in vacuo. Purification of the residue by flash chromatography (5% Et_2O in hexane) gave, in the order of elution, *anti*-**11b** (0.99 g, 49%) and *syn*-**11b** (0.58 g, 29%). The structural determination was made on the basis of NOESY spectral measurements; a NOE was observed for *syn*-**11b** between the protons attached at the C-2 and C-4. Data for *syn*-**11b**: ^{1}H NMR δ 1.25 (6H, m), 4.22 (2H, m), 5.73 (1H, s), 7.30−7.40 (3H, m), 7.52 (2H, m); ^{13}C NMR δ 15.10, 75.29, 84.84, 85.45, 92.24, 121.72, 128.20, 128.90, 131.98; IR (liquid film) 2240, 1105 cm^{-1}. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.05; H, 7.02. *Data for anti*-**11b**: ^{1}H NMR δ 1.22 (6H, m), 4.47 (2H, m), 6.01 (1H, s), 7.30−7.40 (3H, m), 7.48 (2H, m); ^{13}C NMR δ 14.56, 74.03, 84.62, 85.67, 91.83, 121.80, 128.21, 128.75, 131.85; IR (liquid film) 2220, 1090 cm^{-1}. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 76.93; H, 6.96.

General Procedure for Oxazaborolidine-Mediated Ring-Cleavage Reaction (Table 1). To a solution of *N*-tosyl-L-phenylalanine[16,17] (192 mg, 0.60 mmol) in CH_2Cl_2 (5 mL) at room temperature under argon was added dichlorophenylborane (0.78 mL, 0.60 mmol). After being stirred for 30 min, the mixture was concentrated in vacuo, and the residue was dissolved in CH_2Cl_2 (0.6 mL). The resulting 1 M solution of oxazaborolidine **6** (0.48 mL, 0.48 mmol) was added to a solution of acetal **11** (0.4 mmol) and silyl ketene acetal **12** (126 mg, 0.12 mmol) in CH_2Cl_2 (0.52 mL) at −20 °C. After being stirred for the time indicated in Table 1 at −20 °C, the mixture was quenched by the addition of aqueous $NaHCO_3$ and filtered. The filtrate was extracted twice with ether. The organic layers were dried and concentrated in vacuo. The residue was treated with aqueous AcOH (70%, 2 mL) and THF (2 mL) at room temperature for 3 h. The mixture was diluted with water, extracted twice with ether, and washed with aqueous $NaHCO_3$. The organic layers were dried and concentrated in vacuo. The crude products were purified by flash column chromatography (5−25% Et_2O in hexane). The ratios of **13**:**14** were determined by ^{1}H NMR analyses. The enantioselectivity was determined by ^{1}H NMR analyses of the MTPA ester derivatives.

Ethyl (3*R*,1′*R*,2′*S*)-3-(2′-Hydroxy-1′-methylpropyloxy)-2,2-dimethyl-3-phenylpropanoate (13a): ^{1}H NMR δ 1.03 (3H, s), 1.05 (6H, d, J = 6.4 Hz), 1.16 (3H, s), 1.31 (3H, t, J = 7.1 Hz), 1.67 (1H, br), 3.30 (1H, dq, J = 3.1 and 6.3 Hz), 3.80 (1H, dq, J = 3.1 and 6.4 Hz), 4.13 (1H, qd, J = 7.1 and 10.7 Hz), 4.21 (1H, qd, J = 7.1 and 10.7 Hz), 4.79 (1H, s), 7.30−7.40 (5H, m); ^{13}C NMR δ 11.67, 14.19, 17.43, 18.71, 22.71, 47.92, 60.59, 69.93, 75.56, 82.55, 127.85, 127.92, 128.54, 137.64, 176.57; IR (liquid film) 3450 (br), 1720 cm^{-1}. Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.22; H, 8.95. Data for (*S*)-MTPA ester derivative (**17a**): ^{1}H NMR δ 0.99 (3H, s), 1.13 (3H, d, J = 6.0 Hz), 1.14 (3H, s), 1.15 (3H, d, J = 6.9 Hz), 1.26 (3H, t, J = 7.1 Hz), 3.37 (1H, m), 3.58 (3H, br s), 4.06−4.18 (2H, m), 4.81 (1H, s), 5.18 (1H, dq, J = 3.1 and 6.6 Hz), 7.30−7.60 (10H, m) [a minor diastereomer resonated at δ 0.98 (3H, s), 1.05 (3H, d, J = 6.3 Hz), 1.13 (3H, s), 1.26 (3H, t, J = 7.1 Hz), 1.29 (3H, d, J = 6.3 Hz), 3.58 (3H, br s), 4.78 (1H, s) and 5.12 (1H, dq, J = 4.0 and 6.4 Hz)].

Ethyl (3*R*,1′*R*,2′*S*)-3-(2′-Hydroxy-1′-methylpropyloxy]-2,2-dimethyl-5-phenyl-4-pentynoate (13b): ^{1}H NMR δ 1.11 (3H, d, J = 6.3 Hz), 1.15 (3H, d, J = 6.5 Hz), 1.27 (3H, t, J = 7.1 Hz), 1.34 (3H, s), 1.36 (3H, s), 2.20 (1H, br), 3.81 (1H, dq, J = 3.4 and 6.3 Hz), 3.95 (1H, dq, J = 3.3 and 6.4 Hz), 4.12−4.25 (2H, m), 4.70 (1H, s), 7.31−7.36 (3H, m), 7.47 (2H, m); ^{13}C NMR δ 13.16, 14.19, 17.47, 19.24, 22.60, 47.69, 60.71, 69.75, 73.40, 77.37, 85.88, 87.05, 122.37, 128.30, 128.52, 131.72, 175.5; IR (liquid film) 3450 (br), 2220, 1725 cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.40; H, 8.19. Data for (*S*)-MTPA ester of **13b**: ^{1}H NMR δ 1.18 (3H, d, J = 6.3 Hz), 1.27 (3H, t, J = 7.1 Hz), 1.29 (3H, d, J = 6.8 Hz), 1.32 (3H, s), 1.39 (3H, s), 3.55 (3H, br s), 3.95 (1H, dq, J = 4.0

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and 6.3 Hz), 4.10−4.22 (2H, m), 4.73 (1H, s), 5.29 (1H, dq, J = 3.8 and 6.4 Hz), 7.30−7.44 (8H, m), 7.59 (2H, m) [a minor diastereomer resonated at δ 1.08 (3H, d, J = 6.2 Hz), 4.68 (1H, s) and 5.16 (1H, m)].

Ethyl (3*S*,1′*R*,2′*S*)-3-(2′-Hydroxy-1′-methylpropyloxy]-2,2-dimethyl-5-phenyl-4-pentynoate (14b): ^{1}H NMR δ 1.12 (3H, d, J = 6.4 Hz), 1.19 (3H, d, J = 6.4 Hz), 1.31 (3H, s), 1.31 (3H, t, J = 7.1 Hz), 1.39 (3H, s), 2.67 (1H, br d, J = ca. 5.5 Hz), 3.82 (1H, dq, J = 2.7 and 6.4 Hz), 3.94 (1H, m), 4.15−4.27 (2H, m), 4.81 (1H, s), 7.30−7.36 (3H, m), 7.47 (2H, m); ^{13}C NMR δ 14.09, 15.01, 16.97, 18.45, 23.44, 47.53, 61.12, 68.06, 74.10, 78.17, 86.08, 86.65, 122.56, 128.30, 128.46, 131.68, 177.77; IR (liquid film) 3480 (br), 2220, 1725 cm^{-1}. Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.65; H, 8.14. Data for (*S*)-MTPA ester of **14b**: ^{1}H NMR δ 1.24 (3H, t, J = 6.9 Hz), 1.24 (3H, d, J = 6.5 Hz), 1.29 (3H, s), 1.29 (3H, d, J = 6.5 Hz), 1.32 (3H, s), 3.59 (3H, br s), 3.92 (1H, dq, J = 2.8 and 6.5 Hz), 4.04−4.19 (2H, m), 4.74 (1H, s), 5.27 (1H, dq, J = 2.7 and 6.5 Hz), 7.30−7.44 (8H, m), 7.59 (2H, m). Data for (*R*)-MTPA ester of **14b**: ^{1}H NMR δ 1.20 (3H, d, J = 6.4 Hz), 1.24 (3H, s), 1.27 (3H, t, J = 6.9 Hz), 1.29 (3H, s), 1.33 (3H, d, J = 6.5 Hz), 3.60 (3H, br s), 3.88 (1H, dq, J = 3.5 and 6.5 Hz), 4.07−4.24 (2H, m), 4.58 (1H, s), 5.19 (1H, dq, J = 3.6 and 6.5 Hz), 7.30−7.44 (8H, m), 7.59 (2H, m).

Isomerization Experiments of Dioxolane Acetals *syn*- and *anti*-11a,b (Table 2). The reactions were carried out according to a procedure similar to that described in the general procedure for the ring-cleavage reaction except that silyl ketene acetal **12** was not employed. After extractive workup the crude mixture was passed through a short flash chromatography and analyzed by ^{1}H NMR.

(4*R*,5*R*)-4,5-Dimethyl-2-phenyl-1,3-dioxolane (15a). The acetal was prepared by the reaction of (2*R*,3*R*)-2,3-butanediol and benzaldehyde dimethyl acetal in 95% yield by a procedure similar to that for **11a**. Data for **15a**: ^{1}H NMR δ 1.36 (3H, d, J = 5.7 Hz), 1.42 (3H, d, J = 5.6 Hz), 3.80−3.89 (2H, m), 5.98 (1H, s), 7.35−7.45 (3H, m), 7.52 (2H, m); ^{13}C NMR δ 16.86, 78.59, 80.31, 102.60, 126.43, 128.29, 129.05, 138.65; IR (liquid film) 1090 cm^{-1}.

(4*R*,5*R*)-4,5-Dimethyl-2-phenylethyl-1,3-dioxolane (15b). The acetal was prepared by the reaction of (2*R*,3*R*)-2,3-butanediol and 3-phenylpropanal in 81% yield by a procedure similar to that for **11a**. Data for **15b**: ^{1}H NMR δ 1.29 (3H, d, J = 5.6 Hz), 1.34 (3H, d, J = 5.7 Hz), 2.00 (2H, m), 2.79 (2H, m), 3.64−3.70 (2H, m), 5.13 (1H, t, J = 4.6 Hz), 7.20−7.35 (5H, m); ^{13}C NMR δ 16.95, 17.28, 29.93, 36.2178.21, 79.79, 102.50, 125.77, 128.32, 128.36, 141.72; IR (liquid film) 1110 cm^{-1}.

(4*R*,5*R*)-4,5-Dimethyl-2-phenylethynyl-1,3-dioxolane (15c). The acetal was prepared by the reaction of (2*R*,3*R*)-2,3-butanediol and 3,3-diethoxy-1-phenylpropyne in 97% yield by a procedure similar to that for **11b**. Data for **15c**: ^{1}H NMR δ 1.34 (3H, d, J = 6.2 Hz), 1.40 (3H, d, J = 6.1 Hz), 3.68 (1H, qd, J = 6.1 and 7.6 Hz), 3.94 (1H, qd, J = 6.2 and 7.6 Hz), 5.91 (1H, s), 7.30−7.40 (3H, m), 7.49 (2H, m); ^{13}C NMR δ 16.42, 17.14, 78.48, 79.67, 85.04, 85.61, 92.29, 121.65, 128.20, 128.83, 131.86; IR (liquid film) 2200, 1090 cm^{-1}.

Ethyl (3*R*,1′*R*,2′*R*)-3-(2′-Hydroxy-1′-methylpropoxy)-2,2-dimethyl-3-phenyl-propanoate (16a). To a solution of **15a** (112 mg, 0.623 mmol) and **12** (410 mg, 2.2 mmol) in CH_2Cl_2 (10 mL) was added $TiCl_4$ (0.1 mL, 0.9 mmol) at −78 °C. After the mixture was stirred for 0.5 h, methanol (0.5 mL) was added. The mixture was poured into 1 N HCl and extracted twice with CH_2Cl_2. The organic layers were dried and concentrated in vacuo. Purification of the residue by flash column chromatography (10−25% Et_2O in hexane) gave 166 mg (90% yield) of a 13:1 mixture of **16a** and its C-3 epimer: ^{1}H NMR (300 MHz) δ 1.00 (3H, s), 1.03 (3H, d, J = 6.1 Hz), 1.07 (3H, d, J = 6.3 Hz), 1.14 (3H, s), 1.26 (3H, t, J = 7.1 Hz), 2.50 (1H, br s), 3.12 (1H, quint, J = 6.1 Hz), 3.52−3.58 (1H, m), 4.09 (1H, qd, J = 7.1 and 10.8 Hz), 4.18 (1H, qd, J = 7.1 and 10.8 Hz), 4.78 (1H, s), 7.25−7.35 (5H, m) [a minor diastereomer resonated at δ 0.81 (3H, d, J = 6.3 Hz), 0.95 (3H, s), 1.04 (3H, d, J = 6.4 Hz), 1.30 (3H, t, J = 7.1 Hz), 4.84 (1H, s)]; ^{13}C NMR (75.6 MHz) δ 14.14, 14.20, 18.77 (2C), 22.76, 47.82, 60.54, 71.26, 75.55, 81.91, 127.82, 127.95, 128.75, 136.93, 176.45; IR (liquid film) 3450 (br), 1720 cm^{-1}. Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.60; H, 9.00.

Ethyl (3*R*,1′*R*,2′*R*)-3-(2′-Hydroxy-1′-methylpropoxy)-2,2-dimethyl-5-phenylpentanoate (16b). The ring-cleavage reaction of **15b** according to a procedure similar to that described above gave a 16:1 mixture of **16b** and its C-3 epimer in 82% yield. Data for **16b**: ^{1}H NMR (300 MHz) δ 1.01 (3H, d, J = 6.1 Hz), 1.13 (3H, s), 1.14 (3H, d, J = 5.2 Hz), 1.20 (3H, s), 1.25 (3H, t, J = 7.1 Hz), 1.73−1.91 (2H, m), 2.64 (1H, ddd, J = 6.3, 10.0 and 13.5 Hz), 2.70 (1H, br d, J = 2.6 Hz), 2.81 (1H, ddd, J = 7.0, 10.0 and 13.5 Hz), 3.32 (1H, dq, J = 6.1 and 6.8 Hz), 3.52 (1H, m), 3.73 (1H, t, J = 4.8 Hz), 4.03−4.19 (2H, m), 7.15−7.21 (3H, m), 7.26−7.31 (2H, m) [a minor diastereomer resonated at δ 1.22 (3H, s), 1.26 (3H, t, J = 7.1 Hz)]; ^{13}C NMR (75.6 MHz) δ 14.10, 15.14, 18.53, 20.43, 21.84, 34.17, 34.29, 47.50, 60.41, 71.13, 77.80, 79.03, 125.95, 128.26, 128.41, 141.81, 176.75; IR (liquid film) 3450 (br), 1720 cm^{-1}. Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.77; H, 9.38. Found: C, 71.07; H, 9.63d.

Ethyl (3*R*,1′*R*,2′*R*)-3-(2′-Hydroxy-1′-methylpropoxy)-2,2-dimethyl-5-phenyl-4-pentynoate (16c) and Ethyl (3*S*,1′*R*,2′*R*)-3-(2′-Hydroxy-1′-methylpropoxy)-2,2-dimethyl-5-phenyl-4-pentynoate (18). The ring-cleavage reaction of **15c** according to a procedure similar to that described above gave a 1.3:1 mixture of **16c** and **18** in 76% yield. Data for **16c** and **18**: ^{1}H NMR δ 1.10 (3H of major isomer, d, J = 6.5 Hz), 1.11 (3H of minor isomer, d, J = 6.5 Hz), 1.16 (3H of minor isomer, d, J = 6.5 Hz), 1.24 (3H of major isomer, d, J = 6.5 Hz), 1.25−1.32 (9H, m), 1.34 (3H of major isomer, s), 1.37 (3H of minor isomer, s), 3.48−3.61 (2H, m), 4.12−4.30 (2H, m), 4.71 (1H of major isomer, s), 4.80 (1H of minor isomer, s), 7.30−7.41 (3H, m), 7.48 (2H, m).

(*S*)-MTPA Ester 17a. To a solution of **16a** (26 mg, 0.088 mmol), triphenylphosphine (26 mg, 0.1 mmol), and (*S*)-MTPA (23 mg, 0.1 mmol) in THF (1 mL) at room temperature was added a solution of diethyl azodicarboxylate (17 mg, 0.1 mmol) in THF (0.5 mL). After the mixture was stirred for 4 h, THF was removed in vacuo. The residue was treated with ether and then filtered. The filtrate was concentrated in vacuo. Purification of the residue by flash column chromatography gave 10 mg (22% yield) of **17a**, which was identical with the major isomer of the (*S*)-MTPA ester of **13a** by ^{1}H NMR analysis.

(*S*)-MTPA Ester 17b. The ester was prepared from **16b** in 30% yield by a procedure similar to that described above. Data for **17b**: ^{1}H NMR (300 MHz) δ 1.08 (3H, d, J = 6.4 Hz), 1.11 (3H, s), 1.19 (3H, s), 1.21 (3H, d, J = 6.5 Hz), 1.24 (3H, t, J = 7.1 Hz), 1.70−1.78 (2H, m), 2.45−2.75 (2H, m), 3.53−3.58 (4H, m), 3.74 (1H, t, J = 4.9 Hz), 4.06−4.14 (2H, m), 5.20 (1H, dq, J = 3.1 and 6.5 Hz), 7.08−7.38 (8H, m), 7.56−7.59 (2H, m).

Hydrogenation of (*S*)-MTPA Ester of 13b. To a solution of (*S*)-MTPA ester of **13b** (70% ee) (20.3 mg, 0.064 mmol) in THF (0.5 mL) was added Pd/C (10%) (10 mg).[19] The mixture was treated under hydrogen atmosphere for 1 h at room temperature and then filtered. The filtrate was concentrated in vacuo. Purification of the residue by silica gel flash column chromatography gave 14.7 mg (72% yield) of a 3.5:1 mixture of diastereomeric (*S*)-MTPA esters. The major diastereomer was identical to **17b** by ^{1}H NMR analysis.

(*S*)-MTPA Esters 17c and 19. The Mitsunobu esterification of a 1.3:1 mixture of **16c** and **18** with (*S*)-MTPA according to a procedure similar to that described for the preparation of **17a** gave a 1.3:1 mixture of **17c** and **19** in 30% combined yield. The major and minor products were identical with the (*S*)-MTPA esters of **13b** and **14b**, respectively.

Acknowledgment. This work was supported by the Grant-in-Aid for Scientific Research on Priority Area no.08245101 from the Ministry of Education, Science, Sports and Culture of the Japanese Government.

JO991071N

(19) Epimerization at the propargylic position (C-3) took place when ethanol was used as a solvent.