shown), and characterized further by FABMS (clusters starting at 2285.3 and 1052.3) and ESMS (average mass 2285.6 ± 0.6). In the same way, Pmc-alkylated dynorphin was isolated (~90% pure by HPLC), and characterized by ESMS (average mass 2371.4 ± 0.4).

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Registry No. [Ala^8]-dynorphin A, 143037-37-0.

Lewis Acid Promoted Stereoselective Carbon–Carbon Bond Formation of 3-Formyl-Δ^2-isoxazolines

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4,5-Disubstituted 3-formyl-Δ^2-isoxazolines undergo the aldol, allylation, and carbonyl ene reactions in the presence of appropriate Lewis acid to give the adducts with an effective 1,3-asymmetric induction. The stereoselectivity of the reaction mainly depends on the nature of the Lewis acid and the relative configuration of the ring. It is remarkable that both diastereomers can be readily prepared stereoselectively. For example, $TiCl_4$ promotes the 1,3-syn-selective aldol reaction over 93/7 of selectivity, while the 1,3-anti adducts are prepared by the reaction catalyzed by $BF_3{\cdot}OEt_2$. This difference in stereoselectivity is to be attributed to the preferable conformation of isoxazoline–Lewis acid complex intermediates, which depends on the nature of Lewis acid. Without the 4-substituent of isoxazolines the selectivity is not observed. The 5-substituent is too far from the formyl carbon to influence the face differentiation of the formyl group. Subsequent treatment of the adducts with $LiAlH_4$ affords 2-amino 1,4-diol derivatives. The protective group of the hydroxyl group on the C(3) side chain is crucial for the stereoselectivity of the reduction. An almost complete diastereoselectivity of the relative configuration at four contiguous stereogenic centers is readily achieved by the reduction of the adducts protected by *O*-methoxymethyl (O-MOM). Consequently, the present strategy provides a facile method for the preparation of the compounds containing a sequence of several stereocenters.

Introduction

Δ^2-Isoxazolines (4,5-dihydroisoxazoles) have been found to be useful intermediates in organic synthesis as a result of the development of their chemistry for the past decade.[1] We can summarize their synthetic utilities as follows: easy preparation, diversity of their conversion, and characteristic ring structure. Firstly, they are readily prepared via an inter- or an intramolecular 1,3-dipolar cycloaddition of nitrile oxides.[1a,h] It is also an important feature that the relative configuration of the ring substituents can be readily controlled by choosing the geometries of starting olefins, since the 1,3-dipolar cycloaddition of nitrile oxides generally takes place in a highly stereoselective manner. Alternatively, introduction of a 4-substituent of the ring is readily achieved via Jäger alkylation in a highly C(4)/C(5) trans selective way.[2] Secondly, they can be converted into various important synthetic units such as β-hydroxy ketones[3] or γ-amino alcohols[4] without the loss of stereochemistry of the ring substituents.[1b-d,f] This feature characterizes the isoxazoline synthesis as an alternative stereoselective aldol method.[1f] Additionally, Jäger et al. extensively studied the stereoselective conversion of the ring into γ-amino alcohols, and with this strategy they accomplished total synthesis of amino sugar derivatives.[5,6] Finally, the isoxazoline ring has a characteristic structure in a relatively rigid five-membered ring, containing two heteroatoms which serve as Lewis bases. The last feature is supposed to be useful in developing methods for controlling the stereochemistry of the carbon adjacent to the ring. So far there have been several reports concerning this issue,[7] whereas very scarcely has there been reported

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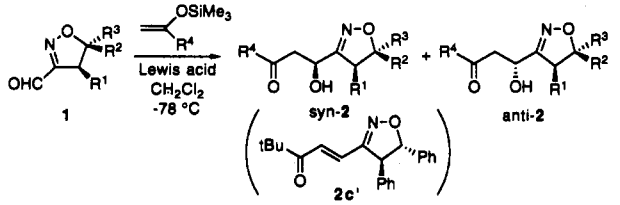
Table I. Lewis Acid Catalyzed Aldol Reaction of 1

run	1	R^1	R^2	R^3	R^4	R^5	Lewis acid (equiv)	time (h)	2; yield[a] (%)	syn/anti[b]
1	1a	$-(CH_2)_3-$		H	Ph	H	$TiCl_4$ (0.1)	1	2a; 89	96/4
2	1a	$-(CH_2)_3-$		H	Ph	H	$SnCl_4$ (1.0)	1	2a; 48	96/4
3	1a	$-(CH_2)_3-$		H	Ph	H	$ZnBr_2$ (1.0)	2	2a; 93	63/37
4	1a	$-(CH_2)_3-$		H	Ph	H	$AlCl_3$ (1.0)	2	2a; 57	11/89
5	1a	$-(CH_2)_3-$		H	Ph	H	$BF_3{\cdot}OEt_2$ (1.0)	4	2a; 90	4/96
6	1a	$-(CH_2)_3-$		H	Ph	H	Li[c] (1.0)	4	2a; 54	16/84
7	1b	Ph	H	Ph	Ph	H	$TiCl_4$ (0.1)	1	2b; 76	96/4
8	1b	Ph	H	Ph	Ph	H	$BF_3{\cdot}OEt_2$ (1.0)	1	2b; 89	39/61
9	1b	Ph	H	Ph	t-Bu	H	$TiCl_4$ (1.3)	48	2c; 70[d]	96/4[e]
10	1c	Me	H	Me	Ph	H	$TiCl_4$ (0.1)	6	2d; 93	93/7
11	1c	Me	H	Me	Ph	H	$BF_3{\cdot}OEt_2$ (1.0)	8	2d; 54	27/73
12	1d	Me	iPr	H		$-(CH_2)_4-$	$TiCl_4$ (1.0)	1	2e; 70	97/3
13	1d	Me	iPr	H		$-(CH_2)_4-$	$BF_3{\cdot}OEt_2$ (1.0)	2	2e; 89	4/96
14	1e	H	Ph	H	Ph	H	$TiCl_4$ (0.1)	2	2f; 96	53/47[f]
15	1e	H	Ph	H	Ph	H	$BF_3{\cdot}OEt_2$ (1.0)	2	2f; 88	24/76[f]

[a] Isolated yield. [b] Determined by HPLC analyses unless noted otherwise. [c] The reaction was carried out by the use of the lithium enolate of acetophenone, which was generated from acetophenone and LDA at −78 °C in THF. [d] Dehydrated product 2c′ was isolated in 17% yield. [e] Determined by 250-MHz ^1H NMR. [f] Stereochemistry of 2f was not specified.

Scheme I



an effective stereocontrolling method for introducing a secondary hydroxyl group into adjacent carbon to C(3) (C(3α) position) of isoxazoline.[8] We anticipated that the combination of Lewis acid and 3-formyl-Δ^2-isoxazoline would provide a useful method for stereoselective carbon–carbon bond formation.[7h,i,l] In this paper, we report that the Lewis acid catalyzed aldol, allylation, and carbonyl ene reactions of 3-formyl-Δ^2-isoxazolines take place along with effective 1,3-asymmetric inductions, and thereby both diastereomers, 1,3-syn and 1,3-anti, are prepared stereoselectively. We also show here that the reductive ring cleavage of the adducts provides a useful method to prepare 2-amino 1,4-diol derivatives. By use of an appropriate protective group of the hydroxyl group on C(3α) of isoxazoline, an almost complete control of the relative configuration at the four contiguous stereogenic centers is readily achieved.

Results and Discussion

Lewis Acid Catalyzed Reaction of 3-Formyl-Δ^2-isoxazolines 1. We prepared the 3-formyl-Δ^2-isoxazolines 1 via the route of the cycloaddition of α,α-dimethoxyacetonitrile oxide to olefins and subsequent hydrolysis. Treatment of 2,2-dimethoxy-1-nitroethane[9] with phenylisocyanate in the presence of olefins[10] gave 3-(dimethoxymethyl)-Δ^2-isoxazolines in moderate to good yields. This acetal, although dimethyl acetals are generally hydrolyzed easily, was too unreactive under the conventional conditions to furnish corresponding aldehyde.[11,12] We have found that potassium hydrogen sulfate supported on silica gel[13] acts as an effective catalyst for the hydrolysis of the acetal moiety and gives 3-formyl-Δ^2-isoxazolines 1 in good yields.

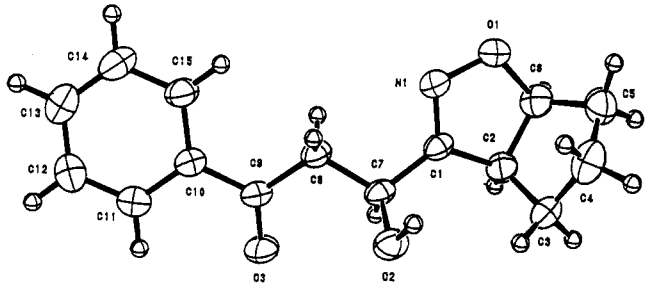


Figure 1. The structure of *syn*-2a.

The exposure of 1 to Lewis acid in the presence of silyl enol ether furnished corresponding 3-(α-hydroxyalkyl)-Δ^2-isoxazoline 2 (Scheme I). The results are summarized in Table I. Treatment of 1a with α-[(trimethylsilyl)oxy]styrene in the presence of $TiCl_4$ afforded aldol adduct 2a in 89% yield (run 1). The reaction proceeded smoothly at −78 °C and was completed within 1 h. Interestingly, a catalytic amount of $TiCl_4$ (0.1 equiv) was sufficient for the reaction. ^1H NMR analysis showed that the obtained 2a consisted of an almost single isomer. The precise diastereomer ratio was found to be 96/4 by means of HPLC analysis. The stereochemistry of 2a was identified by X-ray crystallographic analysis (Figure 1), and the relative configuration between the C(4) and C(3α) was unequivocally revealed to be the 1,3-syn configuration. Thus, $TiCl_4$-catalyzed aldol reaction of 1a takes place syn se-

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Table II. Lewis Acid Catalyzed Allylation Reaction of 1

run	1	R^1	R^2	R^3	M	Lewis acid (equiv)	time (h)	3; yield[a] (%)	syn/anti[b]
1	1a	$-(CH_2)_3-$		H	Me_3Si	$TiCl_4$ (1.0)	2	3a; 94	96/4
2	1a	$-(CH_2)_3-$		H	Me_3Si	$SnCl_4$ (1.0)	3	3a; 93	97/3
3	1a	$-(CH_2)_3-$		H	Me_3Si	$AlCl_3$ (1.0)	15	3a; 65	91/9
4	1a	$-(CH_2)_3-$		H	Me_3Si	$BF_3{\cdot}OEt_2$ (2.0)	3	3a; 24	20/80
5	1a	$-(CH_2)_3-$		H	Bu_3Sn	$BF_3{\cdot}OEt_2$ (2.0)	3	3a; 73	13/87
6	1b	Ph	H	Ph	Me_3Si	$TiCl_4$ (1.0)	2	3b; 70	81/19
7	1b	Ph	H	Ph	Bu_3Sn	$BF_3{\cdot}OEt_2$ (2.0)	4	3b; 64	48/52
8	1e	H	Ph	H	Me_3Si	$TiCl_4$ (1.0)	2	3c; 99	52/48[c]
9	1e	H	Ph	H	Bu_3Sn	$BF_3{\cdot}OEt_2$ (2.0)	4	3c; 82	51/49[c]

[a] Isolated yield. [b] Determined by HPLC analyses (cosmosil PYE-5). [c] Stereochemistry of 3c was not specified.

Table III. Lewis Acid Catalyzed Ene Reaction of 1

run	1	R^1	R^2	R^3	Lewis acid (equiv)	temp (°C)	time (h)	4; yield[a] (%)	syn/anti[b]
1	1a	$-(CH_2)_3-$		H	$SnCl_4$ (1.0)	−78	1	4a; 70	99/1
2	1a	$-(CH_2)_3-$		H	$TiCl_2(OiPr)_2$ (2.0)	rt	20	4a; 74	95/5
3	1a	$-(CH_2)_3-$		H	$TiCl_4$ (1.0)	−78	24	4a; trace	–
4	1a	$-(CH_2)_3-$		H	$BF_3{\cdot}OEt_2$ (1.0)	−78	36	4a; trace	–
5	1a	$-(CH_2)_3-$		H	Et_2AlCl (1.5)	−78	3	4a; 59	1/99
6	1b	Ph	H	Ph	$TiCl_2(OiPr)_2$ (2.0)	rt	2	4b; 72	82/18
7	1b	Ph	H	Ph	$SnCl_4$ (1.0)	−78	6	4b; 59	96/4
8	1b	Ph	H	Ph	Et_2AlCl (1.5)	−78	4	4b; 0	–
9	1e	H	Ph	H	$TiCl_2(OiPr)_2$ (2.0)	rt	14	4c; 56	54/46[c]
10	1e	H	Ph	H	Et_2AlCl (1.5)	−78	4	4c; 26	47/53[c]

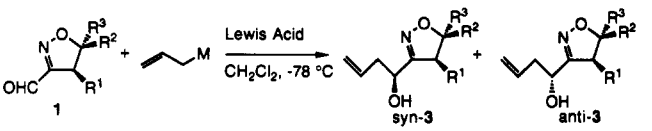
[a] Isolated yield. [b] Determined by HPLC analyses (cosmosil PYE-5). [c] Stereochemistry of 4c was not specified.

lectively. Other kinds of Lewis acid such as $SnCl_4$, $ZnCl_2$, $AlCl_3$, and $BF_3{\cdot}OEt_2$ also acted as an effective catalyst to give **2a** in moderate to good yields (runs 2–5). With high selectivity we prepared *syn*-**2a** under the $SnCl_4$-catalyzed conditions, although the yield of **2a** was moderate (run 2). The reaction promoted by $ZnCl_2$ resulted in the formation of a mixture of two diastereomers of **2a** (run 3). The *anti*-**2a** was formed as a major isomer by $AlCl_3$ catalyst in a moderate yield (run 4). BF_3-catalyzed reaction gave the best result for the preparation of *anti*-**2a** (syn/anti = 4/96) (run 5). Although the aldol adduct **2a** was also prepared by the reaction of the 1 and the lithium enolate of acetophenone in 54% yield, the anti selectivity (16/84) was slightly lower than in the case of BF_3-catalyzed condition (run 6). Hence, syn- and anti-selective aldol reaction to **1a** are accomplished by using $TiCl_4$ and $BF_3{\cdot}OEt_2$, respectively.

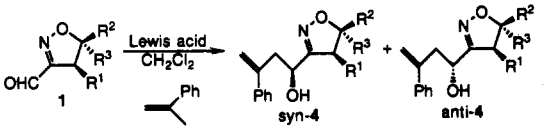
We examined the generality of the stereoselectivity of the aldol reaction. $TiCl_4$-catalyzed aldol reaction always proceeds syn selectively when the 4-substituent is present (run 7, 9, 10, 12). The relative configuration of C(4)/C(5) rarely affects the syn selectivity. Nucleophilic addition of pinacole enolate to **1b** takes 48 h at −78 °C to give *syn*-**2c** along with the dehydration product, α,β-unsaturated-2-isoxazoline **2c'** (run 9). This is due to the low nucleophilicity of the enolate. BF_3-catalyzed reaction of 4,5-cis-disubstituted 1 afforded *anti*-**2** in good stereoselectivity (runs 5 and 13), whereas in the reaction of 4,5-trans-disubstituted 1, the anti-selectivity fell to a moderate level (runs 8 and 11). The relative configuration of C(4)/C(5) affects the anti selectivity. **1e**, namely C(4) unsubstituted, suffers the nonselective aldol reaction and gives a mixture of *syn*-**2f** and *anti*-**2f** (runs 14 and 15). Hence, the 4-substituent is needed to obtain sufficient syn and anti selectivity.

We next tried nucleophilic addition of allyl group to 1 (Scheme II). The results are summarized in Table II. The allylation of **1a** by allyltrimethylsilane smoothly proceeded in the presence of $TiCl_4$ and gave **3a** in 94% yield (run 1). $SnCl_4$, serving as another effective catalyst, afforded **3** in 93% yield (run 2). These adducts **3a** virtually contain the same single isomer whose diastereomeric ratios are determined to be 96/4 and 97/3, respectively, by

Scheme II



Scheme III



HPLC analyses. The relative configuration of **3a** was proved to be the syn configuration after the conversion of **3a**, which is discussed in a later section. Surprisingly, *syn*-**3a** was formed preferentially under the $AlCl_3$-catalyzed conditions, although $AlCl_3$-catalyzed aldol reaction proceeded anti selectively (run 3 and Table I, run 4). The possibility being that this result might offer an interesting suggestion to the reaction pathway, we, nevertheless, did not pursue this issue any more because the anti selectivity of other Lewis acids was superior to that of $AlCl_3$. *anti*-**3a** was prepared by the combination of BF_3 and allylsilane, but the yield of **3a** was far from satisfactory (run 4). The use of allyltributylstannane in place of allylsilane improved both the yield and the anti selectivity (run 5). $TiCl_4$–allylsilane and $BF_3{\cdot}OEt_2$–allylstannane afford the syn and anti adducts, respectively, and this result we applied to other compounds **1**. As was expected, the reaction of $TiCl_4$–allylsilane afforded *syn*-**3** selectively with the existence of the 4-substituent (runs 1 and 6). The relative configuration of C(4) and C(5) did not affect the stereoselectivity. However, the treatment of **1b** with allylstannane in the presence of $BF_3{\cdot}OEt_2$ gave a mixture of *syn*- and *anti*-**3b** (run 7). Thus, the cis configuration between the 4- and the 5-substituents is needed for high anti selectivity. The allylation proceeded nonselectively without the 4-substituent (run 8 and 9). These results are very similar to those observed in the aldol reaction.

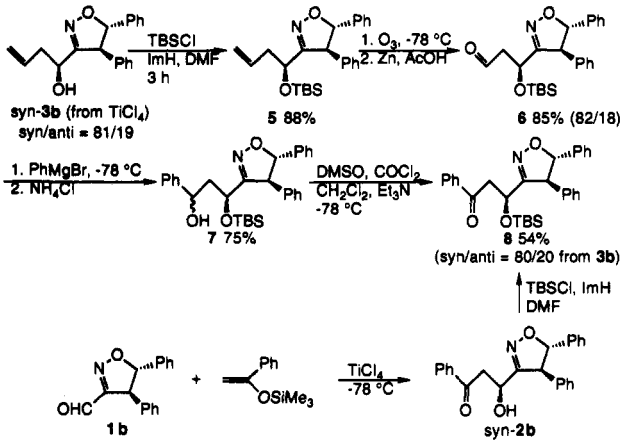
This method was also applied to the carbonyl ene reaction of 1 induced by Lewis acid (Scheme III).[14] Table

Table IV. t_R Values and Chemical Shifts (δ) of *syn*- and *anti*-2, -3, and -4

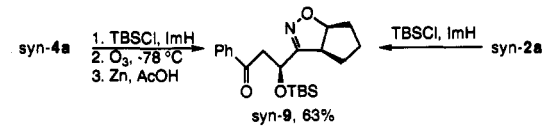
compd	t_R (min) A (syn)	t_R (min) B (anti)	δ (ppm) for H4 A (syn)	δ (ppm) for H4 B (anti)	column[a]	mobile phase[b] (%)	flow rate (mL/min)
2a	9.52	10.62	3.71	3.92	ODS-80	55	0.8
2b	6.87	7.27	4.46	4.62	ODS-80	80	0.8
2c	nd[c]	nd[c]	4.39	4.56			
2d	11.43	12.33	2.97	3.15	ODS-80	50	0.8
2e	14.16, 15.89[d]	14.78[e]	3.03[f]	3.26[f]	ODS-80	50	0.8
3a	10.71	10.12	3.64	3.73	PYE-5	50	0.8
3b	11.05	10.52	4.28	4.43	PYE-5	70	1.0
4a	9.62	8.08	3.57	3.72	PYE-5	70	1.0
4b	13.65	11.56	4.28	4.34	PYE-5	80	1.0

[a] Reversed-phase HPLC column: see Experimental Section. [b] Volume % of MeOH in MeOH–H_2O. [c] Not determined. [d] Two diastereomers of *syn*-**2e** were separated. [e] Two diastereomers of *anti*-**2e** were not separated. [f] H4 resonances of two diastereomers appeared at the same chemical shift.

Scheme IV



Scheme V



III shows the results Relatively weak Lewis acid such as $SnCl_4$ gave **4** in good yields (run 1 and 7). $TiCl_2(OiPr)_2$ also afforded **4** in moderate to good yield only when the excess amount of $TiCl_2(OiPr)_2$ was used at room temperature, because its Lewis acidity is weak (runs 2, 6, and 9). Since the Lewis acidity of $TiCl_4$ and $BF_3{\cdot}OEt_2$ is apparently too strong to furnish **4** (runs 3 and 4), an appropriate Lewis acidity is needed to obtain **4** in high yields. The syn selectivity is usually higher under $SnCl_4$ conditions than under that of $TiCl_2(OiPr)_2$ conditions (runs 1, 7 vs runs 2, 6). We tried several Lewis acids to prepare anti-ene adducts selectively, and Et_2AlCl acted as an appropriate Lewis acid, giving *anti*-**4a** in 59% yield (run 5). Although the yield of **4a** was moderate, the anti selectivity was satisfactory. However, we hardly obtained **4b** from **1b** by Et_2AlCl. Of course, without the 4-substituent, the syn and anti selectivity are not observed in the reaction of isoxazoline **1e**.

The configuration of **3** was determined by its conversion to **8**, as is shown in Scheme IV. Compound **3b**, prepared under the $TiCl_4$ conditions (**3b-A** (*syn*-**3a**)/**3b-B** (*anti*-**3b**) = 81/19, Table II, run 6), was converted into isoxazoline 3ω-aldehyde **6** by the protection of the hydroxyl group[15] and the subsequent ozonolysis. Compound **6** consisted of two diastereomers whose ratio was 82/18. Treatment of **6** with phenylmagnesium bromide gave alcohol **7** as an about 1:1 diastereomeric mixture. Swern oxidation of **7** led to O-protected aldol **8**, which, processed here, contained two diastereomers, **8A** (major) and **8B** (minor), with the ratio of **8A**/**8B** = 80/20. Since the ratio of **3b-A**/**3b-B** is very similar to that of **8A**/**8B**, **8A** must have been converted from **3b-A** and **8B** from **3b-B**. The NMR spectra of **8A** and **8B** are identical with those of *syn*-**8** and *anti*-**8**, prepared separately from *syn*-**2b** and *anti*-**2b**, respectively. Hence, we conclude that the configuration of **3b-A** is *syn*-**3b** and that of **3b-B**, *anti*-**3b**. The configuration of ene adducts **4** was also determined in a similar manner (Scheme V).

The configuration of the other adducts **2**, **3**, and **4** were determined by the separate comparison of spectral data and HPLC results, which are summarized in Table IV. The major series of isomers prepared under $TiCl_4$ or $SnCl_4$ conditions we call **2A**, **3A**, and **4A**, and the minor, on the other hand, we call **2B**, **3B**, and **4B**. The HPLC analyses of these compounds were performed, using an ODS-80T column, usual silica C_{18} packed column, for **2**, or alternatively on a PYE-5 column, 2-(1-pyrenyl)ethylated silica gel packed column,[16] for **3** and **4**. With ODS-80T, each compound of the individual pair of the diastereomers, **3** and **4**, was almost too close to each other, in regards their retention time, to separate. **2A** is smaller than **2B** in t_R values, and **3A** and **4A** are larger than **3B** and **4B**. The signals of H4 in **2A**, **3A**, and **4A** always appear at higher field than those in **2B**, **3B**, and **4B**. These results suggest that **2A**, **3A**, and **4A** have the same configuration between C(3α) and C(4); the same holds with **2B**, **3B**, and **4B**. Thus, we conclude that the main adducts prepared under $TiCl_4$ or $SnCl_4$ conditions, **2A**, **3A**, and **4A**, have the 1,3-syn configuration and the rest of the isomers have the 1,3-anti configuration.

The three carbon–carbon bond forming reactions of **1** are stereoselectively promoted by appropriate Lewis acids: $TiCl_4$ and $SnCl_4$, which afford the syn adducts, and $BF_3{\cdot}OEt_2$ and Et_2AlCl which, on the other hand, afford the anti adduct. The syn selectivity depends solely on the existence of C(4) substituent of isoxazoline, while good anti selectivity requires a 4,5-cis relationship between their substituents. The reaction of C(4)-unsubstituted **1e** occurs nonselectively in the presence of any kind of Lewis acid. This difference in stereoselectivity can be attributed to the preferable conformation of isoxazoline–Lewis acid complex intermediates, which depends on the nature of Lewis acid.[17] The isoxazoline ring has the nitrogen which serves

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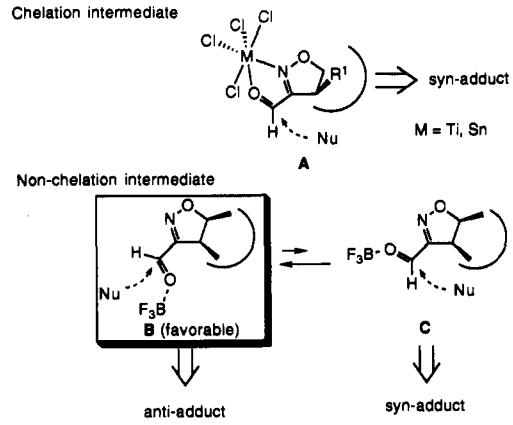
Table V. Conversion of 3 into Amino Diol Derivative 11–14

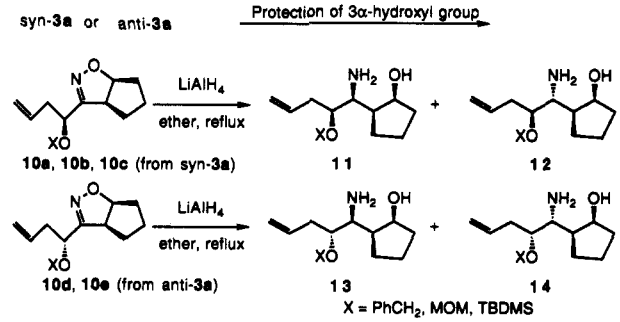
run	3a	X	10; yield[a] (%)	amino diol	yield[a] (%)	11/12[b]	13/14[b]
1	*syn*-3a	$PhCH_2$	10a; 94	11a + 12a	57	83/17	
2	*syn*-3a	MOM	10b; 87	11b + 12b	65	92/8	
3	*syn*-3a	TBDMS	10c; 93	11c + 12c	0[c]		
4	*anti*-3a	$PhCH_2$	10d; 94	13a + 14a	67		76/24
5	*anti*-3a	MOM	10e; 87	13b + 14b	79		93/7

[a] Isolated yield. [b] Determined by HPLC analyses (Tosoh TSK-80). [c] Starting material 10c was recovered.

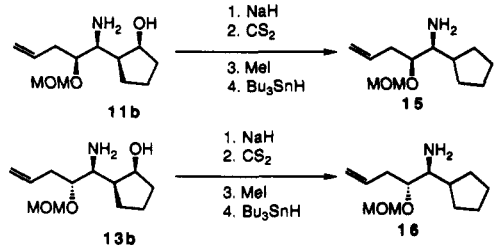
Scheme VI



Scheme VII



Scheme VIII



as a weak Lewis base. Both the oxygen in the formyl group and the nitrogen in the isoxazoline in 1 can coordinate to $TiCl_4$, which has at least two coordination sites, and thus chelating intermediate **A** shown in Scheme VI is formed. This fused intermediate **A** ought to have a planar structure because of the N=C—C=O conjugate system. Besides, the Δ^2-isoxazoline ring is of an almost planar structure, which X-ray analysis of *syn*-**2a** (Figure 1) illustrates, showing that the torsion angles of O1–N1–C1–C2 and O1–C6–C2–C1 are 1.1° and 4.3°, respectively. The ring substituent R^1 of **A** is fixed firmly due to its ring structure so that it offers an effective bias for the differentiation of the formyl face. Consequently, the nucleophiles attack from the opposite side of the 4-substituent, R^1, giving the syn adduct stereoselectively.

On the other hand, the Lewis acid with a single coordination site such as BF_3 cannot form the chelating structure like **A**. We consider two conformers, **B** and **C**, in Scheme VI as reaction intermediates. In order to estimate their relative stability, the AM1 calculations were applied to conformers **B** and **C**.[18,19] As expected, the s-trans conformer **B** is more stable than the s-cis conformer **C** by 2.2 kcal/mol.[20] Our calculation supports that the conformer **B** is more stable than the conformer **C**. The nucleophilic attack on the formyl group should mainly occur to conformer **B** from the opposite site of the ring substituents and gives anti isomer selectively. In both cases, the 5-substituent is too far from the formyl carbon to influence the face selectivity of the formyl face.

Stereoselective Reductive Ring Cleavage of the Adducts 3a. Although the stereochemical course of the reductive ring cleavage of C(4)- and/or C(5)-substituted isoxazolines was extensively studied by Jäger and his coworkers,[4] only a few have studied the stereochemical course of reductive ring cleavage of the isoxazolines bearing the asymmetric center on C(3α).[21] We became interested in the stereochemical course of the reduction of the present adducts **3**, which have three asymmetric centers in the C(4), C(5), and the C(3α). If the stereoselective reduction occurs, the present method provides a useful preparation of amino diol derivatives which contain four contiguous asymmetric centers. We tried the reduction of **3** after the hydroxyl group was protected. Jäger and his co-workers showed that the protecting group of the hydroxyl group affects the stereochemical course of the reduction.[22] We chose the methoxymethyl, benzyl, and *tert*-butyldimethylsilyl groups for the protective group. During the protection of **3a** and subsequent flash column chromatography, we purified **10** as single diastereomers. We used $LiAlH_4$ to reduce **10** in ether (Scheme VII). The results are summarized in Table V. The reductive cleavage of the ring proceeded smoothly with the compounds **10a, 10b, 10d,** and **10e**, giving amino diol derivatives **11–14** in 57–79% yields. Interestingly, **10c** was inert to $LiAlH_4$ even in refluxing THF. Compounds **10a** and **10d** protected by the benzyl group gave a mixture of a pair of diastereomers of the amino diol derivative. For example, the reduction of *syn*-**10a** resulted in a mixture of **11a** and **12a**. The ratio of **11a/12a** is found to be 83/17 after HPLC analysis. In contrast, compounds **10b** and **10e** protected by the methoxymethyl group gave **11** and **13** as an almost single stereoisomer; we observed the ratios of **11b/12b** and **13b/14b** as 92/8 and 93/7, respectively. This result suggests that the relative size of the protective groups is important for accomplishing a selective reduction.

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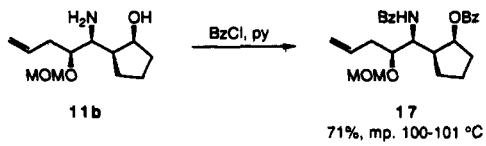
Scheme IX



11b 17
71%, mp. 100-101 °C

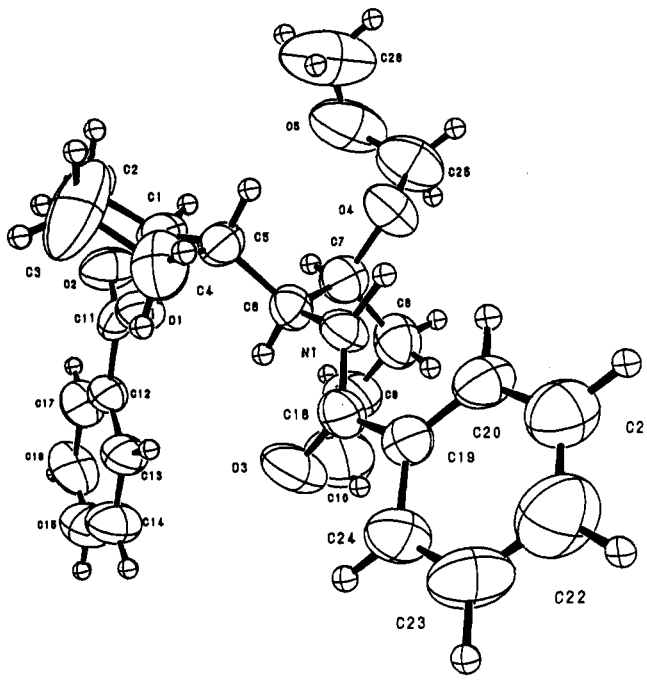


Figure 2. The structure of 17.

The configuration of 11–14 was confirmed in this way (Scheme VIII). The compounds **11b** and **13b** were converted into β-amino alcohol derivatives **15** and **16** after the hydroxy group in the cyclopentane ring was removed by converting it into a xanthate group which was then treated with tributyltin hydride.[23] This conversion reduced the number of asymmetric centers of **11** and **13** from four to two, and thereby simplified their configuration.

As compounds **15** and **16** exhibited different NMR spectra, we concluded that compounds **15** and **16** are not identical. Thus, the relative configuration of the β-amino ether component in **15** and **16** must be different. In order to confirm the configuration of **11b**, X-ray crystallographic analysis of the compound **17**, derived from **11b**, was carried out (Scheme IX). We show the ORTEP chart of **17** in Figure 2. As the present benzoylation never changes the configuration of **11b**, we conclude that the configuration of **11b** is as it is shown in Scheme IX. The configuration of the β-amino alcohol component in **17** is syn, so is that in **15**. This reveals that the configuration of the component in **16** must be anti. With the stereochemical relationship among the other stereogenic centers having already been made clear, we conclude that the configuration of **13b** is shown in Scheme VI. Compounds **11** and **13** each contain four contiguous asymmetric centers; hence, there exist eight possible racemic diastereomers. Our present strategy provides, out of the eight, a highly stereoselective preparation of two isomers, **11** and **13**.

Our results reveal that the stereochemical course of the reduction is mainly governed by the substituent on the isoxazoline ring, rather than by the configuration of the asymmetric carbon in the side chain, the C(3α) position.

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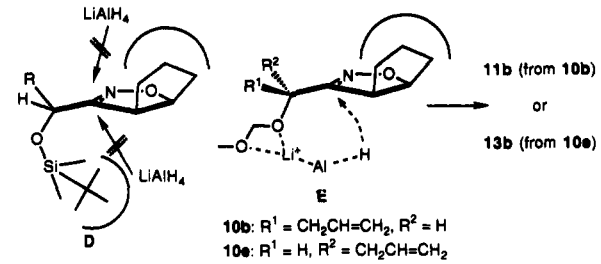
Scheme X



10b: $R^1 = CH_2CH{=}CH_2$, $R^2 = H$
10e: $R^1 = H$, $R^2 = CH_2CH{=}CH_2$

We assume the reaction process is as follows: firstly, the hydride of $LiAlH_4$ attacks the imino group (C=N) of isoxazoline from the opposite side of the ring substituent, and then the N–O bond is cleaved. This is quite reasonable because the ring substituent is fixed firmly due to the five-membered ring structure of the isoxazoline, while the conformation of the C(3) side chain is more flexible than the ring substituents due to their open-chain structure. The choice of the protective group also affects not only the stereoselectivity but also the reactivity toward reduction. For example, the reduction of **10b** and **10e** which are protected by the methoxymethyl group provides **11** or **13** in a highly selective way, while **10c** protected by the *tert*-butyldimethylsilyl group is inert under the same reaction conditions. **10a** and **10d** protected by the benzyl group smoothly react with $LiAlH_4$ to give an amino diol derivative in good yields but with low selectivity. The order of the steric size of these three protective groups is as follows: *tert*-butyldimethylsilyl > benzyl ≈ methoxymethyl. These results suggest that the favorable conformation of the C(3) side chain is fixed according to the size of the protective groups. The relatively large *tert*-butyldimethylsilyl group most probably exists in that conformation in which it is oriented to the opposite side of the ring substituent, so that it can avoid the steric interference between itself and the ring substituent (Scheme X, **D**). Since both sides of the imino face are always shielded, one by the ring substituent, and the other by the large *tert*-butyldimethylsilyl group, the reducing reagent cannot attack the imino group. On the other hand, with the methoxymethyl group, a relatively small group containing two oxygens which is likely to chelate the lithium cation,[22] the steric size of the MOM–Li^+ chelation should not be as small. We can thereby assume that the fused cyclopentane ring gives enough steric bias against it. Hence, the conformation drawn in Scheme X, **E**, should be a favorable conformation to minimize the steric interaction between the fused cyclopentane ring and the Li–MOM chelation. $LiAlH_4$ approaches the imino group from the lithium-chelating site of the conformer **E**, giving amino diol derivatives **11b** or **13b** selectively.

Conclusion

The present method, Lewis acid promoted nucleophilic addition–reductive ring cleavage, offers a facile method for stereoselective preparation amino diols involving contiguous multiasymmetric centers. In the addition process, the choice of appropriate Lewis acid offers both of the possible diastereomers proceeding from **1**, syn and anti selectively. In the reduction process, we not only demonstrate a facile preparation of amino diols, but must note again that two diastereomers out of the eight possible isomers are available in more than 92/8 diastereomeric selectivity. Since 3-formyl-Δ^2-isoxazolines are readily prepared in short steps from commercially available reagents, the present strategy provides a useful method for constructing complex organic molecules. Further

mechanistic and theoretical studies on this issue is now under way in our laboratory.

Experimental Section

^{1}H NMR spectra were measured by a Hitachi R-250H NMR spectrometer at 250 MHz or a JEOL GX-270 NMR spectrometer at 270 MHz. ^{13}C NMR were recorded on the Hitachi spectrometer. $CDCl_3$ was used as solvent with tetramethylsilane as an internal standard. Mass spectra were recorded on Hitachi M-80B mass spectrometer at 70 eV (EI). Elemental analyses were performed by Advanced Instrumentation Center for Chemical Analysis, Ehime University. High-performance liquid chromatography (HPLC) analyses were carried out on ODS-80T (silica C_{18} packed column, 4.6-mm i.d. × 15 cm, purchased from Tosoh Co. Ltd.) or Cosmosil 5-PYE (2-(1-pyrenyl)ethylated silica packed column,[16] 4.6-mm i.d. × 15 cm, purchased from Nacalai tesque Co. Ltd. Kyoto, Japan) with a Tosoh CCPE pump and a UV 8000 UV detector or an RI 8000 RI detector. CH_2Cl_2 was dried over calcium hydride and distilled before use. THF and diethyl ether were dried over benzophenone ketyl and distilled before use. 2,2-Dimethoxy-1-nitroethane,[9] silica gel supported potassium hydrogen sulfate,[13] silyl enol ethers,[24] and allyltributylstannane[25] were prepared by the previously reported method. Allyltrimethylsilane and *tert*-butyldimethylchlorosilane were purchased from Shin'etsu Chemical Co. Ltd. A hexane solution of diethyl aluminum chloride was purchased from Kanto Kagaku Co. Ltd.

Preparation of 3-Formyl-Δ^2-isoxazolines 1a: General Procedure. To a refluxing solution of 2,2-dimethoxy-1-nitroethane (12.19 g, 90.3 mmol) and triethylamine (1 drop, ca. 50 mg) in benzene–cyclopentane (1:1 v/v, 50 mL) was added phenylisocyanate (24 g, 202 mmol) in benzene (100 mL) dropwise during 24 h by using a syringe pump. The reaction mixture became a heterogeneous solution and a white precipitate was formed. After 24 h, the precipitates were filtered off and the filtrate was washed with dilute HCl. The solvent was evaporated, and the residue was distilled under reduced pressure to give isoxazoline 3-acetal in 77% yield (12.88 g, bp 75–78 °C/1 mmHg): ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.08 (d, d, J = 4.9, 9.2 Hz, 1 H), 4.98 (s, 1 H), 3.71 (t, J = 8.0 Hz, 1 H), 3.44 (s, 3 H), 3.40 (s, 3 H), 2.05–2.22 (m, 2 H), 1.37–1.84 (m, 4 H). Treatment of this acetal (10.18 g, 55 mmol) with silica gel supported potassium hydrogen sulfate[12] (50 g) in wet CCl_4 (200 mL) at refluxing temperature for 4 h gave crude **1a**. Distillation under reduced pressure gave pure **1a** in 70% yield (5.36 g, 64–66 °C/1 mmHg): ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.89 (s, 1 H), 5.31 (d, d, 1 H, J = 5.5, 9.1 Hz), 3.83 (t, 1 H, J = 9.2 Hz), 2.19 (d, d, 1 H, J = 6.1, 13.5 Hz), 1.96 (d, d, 1 H, J = 6.7, 12.2 Hz), 1.65–1.86 (m, 3 H), 1.29–1.42 (m, 1 H). Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52. Found: C, 60.76; H, 6.68. The other compounds **1** were also prepared in a similar manner.

Lewis Acid Catalyzed Aldol Reaction of 1: Preparation of *syn*-2a. General Procedure. To a solution of **1a** (142 mg, 1.02 mmol) in CH_2Cl_2 (5 mL) under nitrogen atmosphere was added $TiCl_4$ (0.01 mL, 0.09 mmol) at −78 °C. α-[(Trimethylsilyl)oxy]styrene (294 mg, 1.53 mmol) was added to the mixture, and the resulting solution was stirred at −78 °C until **1a** disappeared on TLC analysis. The reaction mixture was poured into 1 M HCl (50 mL) and extracted with CH_2Cl_2 (50 mL × 3). The organic layers were combined, washed with brine, and dried over anhydrous Na_2SO_4. The crude adduct, which was obtained after filtration and evaporation, was subjected to flash column chromatography (silica gel/hexane–ethyl acetate (3:1) v/v) to give syn-enriched **2a** in 89% yield (235 mg) as white crystals (mp 100–102 °C). The syn/anti ratio was found to be 96/4 by HPLC analysis. ^{1}H NMR data of **2a–2d** are summarized in Table VI: ^{13}C NMR ($CDCl_3$) δ 203.1, 133.3, 128.8, 128.3, 87.7, 65.2, 53.6, 43.4, 35.4, 31.4, 23.6. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 68.48; H, 6.61; N, 5.30. Found: C, 69.36; H, 6.69; N, 5.30.

The following aldol adducts **2** were prepared in a similar manner.

anti-**2a**: 90% yield (from BF_3-catalyzed conditions); syn/anti = 4/96; mp 102–104 °C. Anal. Calcd for $C_{15}H_{17}NO_3$: C, 68.48; H, 6.61; N, 5.40. Found: C, 69.37; H, 6.68; N, 5.39.

syn-**2b**: 76% yield; syn/anti = 96/4; mp 118–119 °C. Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.46; H, 6.18; N, 3.96.

anti-**2b**: 89% yield; syn/anti = 39/61. Diastereomerically pure *anti*-**2b** was obtained by flash choromatography (hexane–ethyl acetate (10:1) v/v), mp 104–105 °C. Anal. Calcd for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.69; H, 5.87; N, 3.62.

syn-**2c**: 70% yield; syn/anti = 96/4; mp 70–71 °C. Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 74.95; H, 7.14; N, 3.51. Dehydrated adduct **2c'** was also obtained as colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.21–7.44 (m, 11 H), 6.45 (d, J = 15.9 Hz, 1 H), 5.55 (d, J = 7.3 Hz, 1 H), 4.45 (d, J = 7.3 Hz, 1 H), 0.92 (s, 9 H).

syn-**2d**: 93% yield; syn/anti = 93/7; liquid. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.80; H, 6.83; N, 5.67.

anti-**2d**: 54% yield; syn/anti = 27/73. Diastereomerically pure *anti*-**2d** was obtained by flash choromatography (hexane–ethyl acetate (10:1) v/v): liquid; MS m/z (M^+) calcd for $C_{14}H_{17}NO_3$ 247.1208, found 247.1193.

syn-**2e**: 70% yield; syn/anti = 97/3; mp 98–100 °C; obtained as a mixture of two syn isomers in a ratio of 85/15; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.98–5.01 (m, 1 H for major isomer), 4.67 (t, J = 5.8 Hz, 1 H for minor isomer), 3.85 (d, d, J = 7.6, 9.6 Hz, 1 H for major isomer), 3.71 (d, J = 5.0 Hz, 1 H for minor isomer), 3.03 (quint, J = 6.9 Hz, 1 H), 2.76–2.92 (m, 1 H), 2.29–2.48 (m, 2 H), 1.58–2.25 (m, 8 H), 1.09 (d, J = 7.3 Hz, 6 H), 0.95 (d, J = 6.7 Hz, 3 H). Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.01; H, 8.93; N, 5.85.

anti-**2e**: 89% yield; syn/anti = 4/96; oil; obtained as a mixture of two anti isomers in a ratio of 55/45; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.96 (d, d, J = 2.4, 4.9 Hz, 1 H for minor isomer), 4.39 (d, d, J = 4.6, 8.2 Hz, 1 H for major isomer), 3.87 (d, d, J = 7.9, 11.6 Hz, 1 H for major isomer), 3.83 (d, d, J = 4.5, 6.1 Hz, 1 H for minor isomer), 3.26 (quint, J = 7.8 Hz, 1 H), 2.90–3.13 (m, 1 H), 2.30–2.50 (m, 2 H), 1.60–2.25 (m, 8 H), 1.09 (d, J = 6.7 Hz, 6 H for minor isomer), 1.08 (d, J = 7.3 Hz, 6 H for major isomer), 0.96 (d, J = 6.7 Hz, 3 H for major isomer), 0.95 (d, J = 6.7 Hz, 3 H for minor isomer). Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.26; H, 9.15; N, 5.57.

2f: 96% yield (under $TiCl_4$ conditions); oil; obtained as a mixture of a pair of diastereomers (**2f-X** and **2f-Y**, **2f-X** has larger R_f value on TLC). The ratio of **2f-X**/**2f-Y** is 53/47 by $TiCl_4$ and 24/76 by BF_3·OEt_2. **2f-X** and **2f-Y** were separated by flash column chromatography (hexane–ethyl acetate (10:1) v/v). **2f-X**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.99 (d, J = 7.3 Hz, 2 H), 7.61 (t, J = 7.3 Hz, 1 H), 7.49 (t, J = 7.9 Hz, 2 H), 7.35 (s, 5 H), 5.62 (d, d, J = 8.5, 11.0 Hz, 1 H), 5.09 (d, d, J = 5.5, 11.6 Hz, 1 H), 3.8–4.0 (br, 1 H), 3.81 (d, d, J = 5.5, 11.6 Hz, 1 H), 3.53–3.59 (m, 1 H), 3.53 (d, d, J = 11.0, 17.0 Hz, 1 H), 3.25 (d, d, J = 8.7, 17.5 Hz, 1 H). **2f-Y**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.99 (d, J = 7.3 Hz, 2 H), 7.61 (t, J = 7.3 Hz, 1 H), 7.49 (t, J = 7.9 Hz, 2 H), 7.35 (s, 5 H), 5.62 (d, d, J = 8.5, 11.0 Hz, 1 H), 5.07 (d, d, J = 6.1, 11.0 Hz, 1 H), 3.8–4.0 (br, 1 H), 3.68 (d, d, J = 11.0, 17.4 Hz, 1 H), 3.53–3.59 (m, 2 H), 3.08 (d, d, J = 8.6, 17.4 Hz, 1 H). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.41; H, 5.82; N, 4.53.

Lewis Acid Catalyzed Allylation Reaction of 1 (Method A): Preparation of *syn*-3a. To a solution of **1a** (150 mg, 1.08 mmol) and allyltrimethylsilane (172 mg, 1.51 mmol) in CH_2Cl_2 (5 mL) was added $TiCl_4$ (165 mL, 1.5 mmol) at −78 °C. The reaction mixture was stirred at the same temperature for 4 h. After the disappearance of **1a** on TLC analysis, the reaction mixture was poured into 50 mL of dilute HCl and extracted with CH_2Cl_2 (3 × 50 mL). The organic layer was combined and dried over Na_2SO_4. The crude adduct, which was obtained after evaporation, was subjected to flash column chromatography (hexane–ethyl acetate (3:1) v/v) to give **3a** in 98% yield (192 mg) as a colorless oil: *syn*-**3a**/*anti*-**3a** = 94/6 (Cosmosil 5-PYE column); ^{1}H NMR data of *syn*-**3a** and *syn*-**3b** are summarized in Table VI. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.74. Found: C, 66.33; H, 8.17; N, 7.64.

Lewis Acid Catalyzed Allylation Reaction of 1 (Method B): Preparation of *anti*-3a. To a solution of **1a** (200 mg, 1.44 mmol) and BF_3·OEt_2 (0.41 g, 2.89 mmol) in CH_2Cl_2 (10 mL) at

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Table VI. ^{1}H NMR Spectral Data of 2a–2d, 3a, 3b, 4a, 4b, 5, 6, *syn*-8, *anti*-8, *syn*-9, and 10[a]

compd	H5	H4	H3α	H3β		others
syn-2a	5.10 (d, J = 8.8 Hz) (d, J = 4.6 Hz)	3.71 (t, J = 8.5 Hz)	5.05 (t, J = 5.8 Hz)	3.52 (d, J = 6.1 Hz, 2 H)		7.98 (d, J = 7.3 Hz, 2 H), 7.67 (t, J = 7.3 Hz, 1 H), 7.48 (t, J = 7.3 Hz, 2 H), 3.0–3.4 (br, 1 H), 2.07–2.26 (m, 2 H), 1.49–1.78 (m, 4 H)
anti-2a	5.07 (d, J = 8.6 Hz) (d, J = 4.9 Hz)	3.92 (t, J = 8.6 Hz)	4.98 (d, J = 7.3 Hz) (d, J = 4.3 Hz)	3.60 (d, J = 18.3 Hz) (d, J = 4.3 Hz)	3.51 (d, J = 18.3 Hz) (d, J = 7.6 Hz)	7.97 (d, J = 7.9 Hz, 2 H), 7.58 (t, J = 7.3 Hz, 1 H), 7.46 (t, J = 7.3 Hz, 2 H), 3.3–3.6 (br, 1 H), 2.03–20.8 (m, 2 H), 1.40–1.80 (m, 4 H)
syn-2b	5.53 (d, J = 5.5 Hz)	4.46 (d, J = 5.5 Hz) (d, J = 1.8 Hz)	5.10 (d, J = 7.9 Hz) (d, J = 3.1 Hz)	3.17 (d, J = 17.7 Hz) (d, J = 3.1 Hz)	3.00 (d, J = 17.7 Hz) (d, J = 8.5 Hz) (d, J = 1.8 Hz)	7.74 (d, J = 7.3 Hz, 2 H), 7.54 (t, J = 7.3 Hz, 1 H), 7.24–7.42 (m, 12 H), 3.32–3.47 (br, 1 H)
anti-2b	5.51 (d, J = 6.1 Hz)	4.62 (d, J = 6.1 Hz)	4.75 (t, J = 5.5 Hz)	3.60 (d, J = 6.1 Hz, 2 H)		7.94 (d, J = 7.3 Hz, 2 H), 7.56 (t, J = 7.3 Hz, 1 H), 7.25–7.46 (m, 12 H), 3.45–3.70 (br, 1 H)
syn-2c	5.53 (d, J = 5.5 Hz)	4.39 (d, J = 5.5 Hz)	4.89 (t, J = 3.7 Hz) (d, J = 8.6 Hz)	2.66 (d, J = 18.3 Hz) (d, J = 3.7 Hz)	2.48 (d, J = 18.3 Hz) (d, J = 8.6 Hz)	7.25–7.45 (m, 10 H), 3.15–3.22 (m, 1 H), 1.00 (s, 9 H)
syn-2d	4.28 (quint, J = 6.7 Hz)	2.97 (quint, J = 7.3 Hz)	5.09 (d, J = 6.7 Hz) (d, J = 4.6 Hz)	3.54 (d, J = 17.7 Hz) (d, J = 6.7 Hz)	3.48 (d, J = 17.7 Hz) (d, J = 2.4 Hz)	7.98 (d, J = 7.9, 2 H), 7.62 (t, J = 7.9 Hz, 1 H), 7.48 (t, J = 7.9 Hz, 2 H), 1.55–1.7 (br, 1 H), 1.36 (d, J = 6.7 Hz, 3 H), 1.34 (d, J = 7.3 Hz, 3 H)
anti-2d	4.27 (quint, J = 6.7 Hz)	3.15 (quint, J = 7.0 Hz)	5.03 (d, J = 6.4 Hz) (d, J = 4.3 Hz)	3.62 (d, J = 18.3 Hz) (d, J = 4.3 Hz)	3.56 (d, J = 17.7 Hz) (d, J = 6.5 Hz)	7.99 (d, J = 7.0 Hz, 2 H), 7.60 (t, J = 7.3 Hz, 1 H), 7.49 (d, J = 7.3 Hz, 2 H), 3.5–4.0 (br, 1 H), 1.35 (d, J = 6.4 Hz, 3H) 1.29 (d, J = 7.0 Hz, 3 H)
syn-3a	5.10 (d, J = 9.1 Hz) (d, J = 5.5 Hz)	3.64 (t, J = 8.0 Hz)	4.51 (t, J = 4.9 Hz)	2.40–2.64 (m, 2 H)		5.86 (t, d, d, J = 6.7, 10.3, 17.1 Hz, 1 H), 5.19 (d, J = 17.1 Hz, 1 H), 5.18 (d, J = 9.2 Hz, 1 H), 2.7–2.9 (br, 1 H), 1.91–2.18 (m, 2 H), 1.43–1.80 (m, 4 H)
anti-3a	5.07 (d, J = 8.6 Hz) (d, J = 4.9 Hz)	3.73 (t, J = 8.5 Hz)	4.51 (d, J = 6.7 Hz) (d, J = 5.5 Hz)	2.48–2.65 (m, 2 H)		5.86 (t, d, d, J = 6.7, 10.4, 14.0 Hz, 1 H), 5.23 (d, J = 16.5 Hz, 1 H), 5.20 (d, J = 10.4 Hz, 1 H), 2.05–2.18 (m, 2 H), 1.26–2.80 M, 4 H)
syn-3b	5.52 (d, J = 6.1 Hz)	4.28 (d, J = 6.7 Hz)	4.42 (t, J = 4.9 Hz)	2.35 (d, J = 13.9 Hz) (t, J = 6.1 Hz) (d, J = 1.2 Hz)	2.17 (d, J = 14.6 Hz) (t, J = 7.3 Hz)	7.24–7.44 (m, 10 H), 5.72 (t, d, d, J = 6.7, 9.8, 17.1 Hz, 1 H), 5.12 (d, J = 9.8 Hz, 1 H), 5.02 (d, d, J = 1.2, 18.9 Hz, 1 H), 2.49–2.52 (br, 1 H)
anti-3b[b]	5.50 (d, J = 6.1 Hz)	4.43 (d, J = 6.1 Hz)	4.33 (d, J = 7.5 Hz) (d, J = 5.0 Hz)	2.42–2.64 (m, 2 H)		7.25–7.43 (m, 10 H), 5.78 (t, d, d, J = 7.0, 9.2, 16.2 Hz, 1 H), 5.12 (d, J = 11.0 Hz, 1 H), 5.11 (d, d, J = 1.5, 17.0 Hz, 1 H), 1.6 (br, 1 H)
syn-4a	4.98 (d, J = 8.9 Hz) (d, J = 4.5 Hz)	3.57 (t, J = 8.24 Hz)	4.49 (m)	3.09 (d, J = 14.3 Hz) (d, J = 4.5 Hz)	2.87 (d, J = 14.0 Hz) (d, J = 8.5 Hz)	7.26–7.44 (m, 5 H), 5.45 (s, 1 H), 5.26 (s, 1 H), 2.38–2.42 (br, 1 H), 2.06 (d, d, J = 4.5, 13.1 Hz, 1. H), 1.80–1.90 (m, 1 H), 1.61–1.71 (m, 2 H), 1.39–1.51 (m, 2 H)
anti-4a	5.02 (d, J = 9.5 Hz) (d, J = 5.2 Hz)	3.72 (t, J = 8.2 Hz)	4.50 (d, J = 9.8 Hz) (t, J = 3.7 Hz)	3.18 (d, J = 14.0 Hz) (d, J = 4.3 Hz)	2.86 (d, J = 14.3 Hz) (d, J = 9.5 Hz)	7.30–7.45 (m, 5 H), 5.47 (s, 1 H), 5.24 (s, 1 H), 1.97–2.11 (m, 2 H), 1.61–1.71 (m, 4 H), 1.40–1.51 (m, 1 H)
syn-4b	5.50 (d, J = 7.3 Hz)	4.28 (d, J = 7.3 Hz)	4.44 (t, J = 4.6 Hz)	2.84 (d, J = 14.1 Hz) (d, J = 4.3 Hz)	2.50 (d, J = 14.0 Hz) (d, J = 9.2 Hz)	7.14–7.43 (m, 15 H), 5.33 (s, 1 H), 5.03 (s, 1 H), 2.29 (d, J = 4.9 Hz, 1 H)
syn-5	5.50 (d, J = 4.9 Hz)	4.30 (d, J = 4.9 Hz)	4.54 (t, J = 7.0 Hz)	1.85 (t, J = 7.0 Hz, 2 H)		7.29–7.40 (m, 10 H), 5.48–5.62 (m, 1 H), 4.91 (d, d, J = 1.2, 10.4 Hz, 1 H), 4.77 (d, d, J = 1.2, 17.1 Hz, 1 H), 0.78 (s, 9 H), –0.03 (s, 3 H), –0.13 (s, 3 H)
syn-6	5.58 (d, J = 4.9 Hz)	4.33 (d, J = 4.9 Hz)	5.18 (t, J = 6.7 Hz)	2.18 (d, J = 6.7 Hz, 2 H) (d, J = 1.8 Hz)		9.48 (t, J = 1.8 Hz, 1 H), 7.29–7.41 (m, 10 H), 0.74 (s, 9 H), –0.14 (s, 6 H)
syn-8	5.60 (d, J = 5.5 Hz)	4.41 (d, J = 5.5 Hz)	5.34 (d, J = 8.9 Hz) (d, J = 4.0 Hz)	2.78 (d, J = 15.9 Hz) (d, J = 8.5 Hz)	2.54 (d, J = 16.5 Hz) (d, J = 4.3 Hz)	7.34–7.58 (m, 15 H), 0.66 (s, 9 H), –0.10 (s, 3 H), –0.13 (s, 3 H)
anti-8	5.37 (d, J = 6.7 Hz)	4.42 (d, J = 6.7 Hz)	5.06 (t, J = 6.4 Hz)	3.76 (d, J = 17.1 Hz) (d, J = 7.3 Hz)	3.26 (d, J = 17.1 Hz) (d, J = 5.5 Hz)	7.90 (d, J = 7.3 Hz, 2 H), 7.25–7.51 (m, 13 H), 0.68 (s, 9 H), –0.19 (s, 3 H), –0.27 (s, 3 H)
syn-9	5.28 (d, J = 7.9 Hz) (d, J = 4.3 Hz)	3.67 (t, J = 8.5 Hz)	5.06 (d, J = 8.6 Hz) (d, J = 4.3 Hz)	3.45 (d, J = 15.3 Hz) (d, J = 8.2 Hz)	3.23 (d, J = 15.3 Hz) (d, J = 4.6 Hz)	7.88 (d, J = 7.3 Hz, 2 H), 7.50 (t, J = 7.3 Hz, 1 H), 7.39 (t, J = 7.9 Hz, 2 H), 1.96–2.09 (m 2 H), 1.45–1.73 (m, 4 H) 0.73 (s, 9 H), –0.09 (s, 6 H)

Table VI (Continued)

compd	H5	H4	H3α	H3β		others
10a	5.05 (d, J = 9.2 Hz) (d, J = 4.3 Hz)	3.60 (t, J = 8.9 Hz) (d, J = 2.4 Hz)	4.34 (d, J = 7.9 Hz) (d, J = 6.1 Hz)	2.63 (d, J = 14.6 Hz) (t, J = 7.3 Hz)	2.48 (d, J = 14.0 Hz) (t, J = 6.7 Hz)	7.32–7.34 (m, 5 H), 5.82 (t, d, d, J = 6.7, 9.8, 17.1 Hz, 1 H), 5.14 (d, d J = 1.2, 17.1 Hz, 1 H), 5.11 (d, d, J = 1.2, 9.8 Hz, 1 H), 4.57 (d, J = 11.6 Hz, 1 H), 4.44 (d, J = 12.2 Hz, 1 H), 1.93–2.15 (m, 2 H), 1.49–1.79 (m, 4 H)
10b	5.07 (d, J = 8.6 Hz) (d, J = 4.9 Hz)	3.61 (t, J = 7.9 Hz)	4.51 (t, J = 7.0 Hz)	2.48 (q, J = 6.7 Hz, 2 H)		5.78 (t, d, d, J = 6.7, 9.8, 17.1 Hz, 1 H), 5.17 (d, J = 17.1 Hz, 1 H), 5.13 (d, J = 9.8 Hz, 1 H), 4.68 (d, J = 6.7 Hz, 1 H), 4.62 (d, J = 6.7 Hz, 1 H), 3.32 (s, 3 H), 1.88–2.06 (m, 2 H), 1.36–1.70 (m, 4 H)
10d	5.02–5.12 (m)	3.66 (t, J = 8.6 Hz)	4.33 (t, J = 7.0 Hz)	2.66 (d, J = 14.7 Hz) (t, J = 7.0 Hz)	2.47 (d, J = 14.7 Hz) (t, J = 7.0 Hz)	7.32–7.39 (m, 5 H), 5.78 (t, d, d, J = 6.1, 9.8, 17.1 Hz, 1 H), 5.15 (d, J = 17.1 Hz, 1 H), 5.10 (d, J = 9.8 Hz, 1 H), 4.56 (d, J = 11.6 Hz, 1 H), 4.31 (d, J = 11.6 Hz, 1 H), 2.09–2.20 (m, 2 H), 1.44–1.79 (m, 4 H)
10e	5.06 (d, J = 8.5 Hz) (d, J = 5.5 Hz)	3.66 (t, J = 8.9 Hz)	4.51 (t, J = 7.0 Hz)	2.59 (d, J = 14.7 Hz) (t, J = 7.3 Hz)	2.52 (d, J = 14.6 Hz) (t, J = 6.7 Hz)	5.81 (t, d, d, J = 6.7, 10.3, 17.1 Hz, 1 H), 5.17 (d, d, J = 1.2, 17.1 Hz, 1 H), 5.11 (d, J = 10.4 Hz, 1 H), 4.68 (d, J = 6.7 Hz, 1 H), 4.56 (d, J = 6.7 Hz, 1 H), 3.39 (s, 3 H), 2.06–2.13 (m, 2 H), 1.34–1.77 (m, 4 H)

[a] NMR spectra were measured by Hitachi R-250H at 250 MHz unless noted otherwise. [b] Measured by JEOL GX-270 at 270 MHz.

−78 °C was added allyltributyltin (0.95 g, 2.87 mmol), and the reaction mixture was stirred for 3 h at −78 °C and for 1 h at ambient temperature. The resulting solution was treated by the same workup as in the preparation of *syn*-**3a** to give *anti*-**3a** in 73% yield (190 mg) as colorless oil: syn/anti = 13/87 (HPLC); ^{1}H NMR data of *anti*-**3a** and *anti*-**3b** are summarized in Table VI. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.74. Found: C, 66.47; H, 8.04; N, 7.83.

The following allylation adducts **3** were prepared in a similar manner.

syn-**3b**: prepared by method A; 70% yield; syn/anti = 81/19; colorless oil. Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.92; H, 6.50; N, 4.81.

anti-**3b**: prepared by method B; 64% yield; syn/anti = 48/52. Diastereomerically pure *anti*-**3b** was obtained by flash chromatography (hexane–ethyl acetate (10:1) v/v): colorless oil; MS m/z (M^+) calcd for $C_{19}H_{19}NO_2$ 292.1415, found 293.1418.

3c: two diastereomers (**3c-X** and **3c-Y**, **3c-X** has larger R_f value on TLC) were obtained. They were separated by flash column chromatography (hexane–ethyl acetate (10:1) v/v). Their configuration was not determined. **3c-X**: oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28–7.42 (m, 5 H), 5.85 (t, d, d, J = 6.7, 10.4, 17.1 Hz, 1 H), 5.61 (d, d, J = 8.5, 11.0 Hz, 1 H), 5.20 (d, d, J = 1.2, 15.9 Hz, 1 H), 5.19 (d, J = 11.6 Hz, 1 H), 4.58–4.70 (m, 1 H), 3.43 (d, d, J = 11.0, 16.5 Hz, 1 H), 3.05 (d, d, J = 8.2, 17.4 Hz, 1 H), 2.48–2.57 (m, 2 H), 3.30–2.38 (br, 1 H). **3c-Y**: oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.31–7.40 (m, 5 H), 5.83 (t, d, d, J = 7.3, 9.8, 17.7 Hz, 1 H), 5.61 (d, d, J = 8.5, 11.0 Hz, 1 H), 5.18 (d, J = 11.6 Hz, 1 H), 5.17 (d, d, J = 1.2, 15.9 Hz, 1 H), 4.65 (t, J = 6.4 Hz, 1 H), 3.50 (d, d, J = 10.7, 17.4 Hz, 1 H), 2.98 (d, d, J = 8.2, 17.4 Hz, 1 H), 2.50 (d, t, J = 1.2, 6.7 Hz, 2 H), 2.0–2.4 (br, 1 H); MS m/z (M^+) calcd for $C_{13}H_{15}NO_2$ 217.1103, found 217.1112. Anal. Calcd for $C_{13}H_{15}NO_2$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.93; H, 6.48; N, 6.40.

Lewis Acid Catalyzed Carbonyl Ene Reaction of 1: Preparation of *syn*-4a. To a solution of **1a** (134 mg, 0.96 mmol) and α-methylstyrene (231 mg, 1.95 mmol) in CH_2Cl_2 (10 mL) was added $SnCl_4$ (0.15 mL, 1.27 mmol) at −78 °C. The reaction mixture was stirred for 2 h until the starting **1a** disappeared on TLC analysis. The resulting solution was treated by the same workup procedure as in the preparation of **3a** to give *syn*-**4a** in 70% yield (174 mg) as a colorless oil: *syn*-**4a**/*anti*-**4a** = 99/1 (cosmosil 5-PYE); ^{1}H NMR data of **4a** and **4b** are summarized in Table VI; MS m/z (M^+) calcd for $C_{16}H_{19}NO_2$ 257.1416, found 257.1402. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.71; H, 7.26; N, 5.15.

The following ene adducts **4** were prepared in a similar manner.

anti-**4a**: 59% yield; syn/anti = 1/99; oil. Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.21; H, 7.28; N, 5.86.

syn-**4b**: 59% (under $SnCl_4$ conditions); syn/anti = 96/4; oil. Anal. Calcd for $C_{25}H_{23}NO_2$: C, 81.27; H, 6.27; N, 3.79. Found: C, 81.03; H, 6.15; N, 3.87.

4c: two diastereomers (**4c-X** and **4c-Y**, **4c-X** has larger R_f value on TLC) were obtained. They were separated by flash column chromatography (hexane–ethyl acetate (10:1) v/v). Their configuration was not determined. **4c-X**: oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.23–7.44 (m, 10 H), 5.52 (t, J = 9.8 Hz, 1 H), 5.45 (s, 1 H), 5.23 (s, 1 H), 4.62 (d, d, J = 4.9, 8.5 Hz, 1 H), 3.40 (d, d, J = 10.6, 17.4 Hz, 1 H), 3.08 (d, d, J = 4.9, 14.0 Hz, 1 H), 3.03 (d, d, J = 8.6, 17.1 Hz, 1 H), 2.88 (d, d, J = 8.6, 17.1 Hz, 1 H), 2.1–2.3 (br, 1 H). **4c-Y**: oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.22–7.43 (m, 10 H), 5.53 (d, d, J = 8.6, 11.0 Hz, 1 H), 5.42 (s, 1 H), 5.19 (s, 1 H), 4.64 (d, d, J = 5.5, 7.9 Hz, 1 H), 3.46 (d, d, J = 11.0, 17.1 Hz, 1 H), 2.92–3.56 (m, 2 H), 2.86 (d, d, J = 8.6, 14.0 Hz, 1 H), 2.2–2.35 (br, 1 H). Anal. Calcd for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.75; H, 6.51; N, 4.94.

Conversion of *syn*-2b to *syn*-8. A solution of *syn*-**2b** (827 mg, 2.23 mmol), TBDMSCl (1006 mg, 6.68 mmol), and imidazole (909 mg, 13.4 mmol) in DMF (20 mL) was stirred at 60 °C for 36 h. After disappearance of *syn*-**2b**, the reaction mixture was diluted with hexane (150 mL), and the resulting solution was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Crude **8** was purified by flash column chromatography (hexane–ethyl acetate (10:1) v/v) to give **8** in 72% yield (775 mg); white crystals; mp 76–77 °C; ^{1}H NMR data of *syn*-**8**, *anti*-**8**, and *syn*-**9** are summarized in Table VI; ^{13}C NMR ($CDCl_3$) δ 133.1, 129.5, 128.8, 128.7, 128.2, 125.2, 90.6, 65.9, 62.9, 45.6, 25.7, −4.9. Anal. Calcd for $C_{30}H_{35}NO_3Si$: C, 74.19; H, 7.26; N, 2.88. Found: C, 74.53; H, 7.38; N, 2.98.

Silyl ethers *anti*-**8** and *syn*-**9** were also prepared in a similar way.

anti-**8**: 55% yield; oil; ^{13}C NMR ($CDCl_3$) δ 133.2, 129.5, 129.4, 129.0, 128.9, 128.7, 128.4, 128.1, 125.8, 91.9, 64.2, 63.0, 44.0, 25.8, −4.5.

syn-**9**: mp 71–72 °C. Anal. Calcd for $C_{21}H_{31}NO_3Si$: C, 67.52; H, 8.36; N, 3.70. Found: C, 67.50; H, 8.39; N, 3.63.

Conversion of *syn*-3b into 8: Preparation of 5. A mixture of *syn*-**3b** (801 mg, 2.73 mmol), TBDMSCl (758 mg, 5.03 mmol), and imidazole (858 mg, 12.6 mmol) in DMF (10 mL) was stirred

at 80 °C for 3 h. After a similar workup as in the preparation of 8, compound 5 was obtained: 978 mg (88%); colorless oil; ^{1}H NMR data are summarized in Table VI.

Ozonolysis of 5. Ozone, generated by an ozone generator, was passed through an ethanol solution of 5 (945 mg, 2.32 mmol) at −78 °C for about 3 h until 5 disappeared. The reaction solution was warmed to 0 °C, and then Zn dust (2.12 g) and AcOH–H_2O (10 mL, 1:1 v/v) were added to it and it was stirred for 1 h. After filtration, the filtrate was concentrated in vacuo. The residue was subjected to flash column chromatography (hexane–ethyl acetate (10:1) v/v) to give aldehyde 6 in 85% yield (811 mg): colorless oil; syn/anti = 82/18 (250 MHz NMR); ^{1}H NMR data are summarized in Table VI.

Grignard Reaction of 6. To a solution of 6 (195 mg, 0.48 mmol) in THF was added phenylmagnesium bromide, generated from phenyl bromide (192 mg, 1.22 mmol) and magnesium (25 mg, 1.04 mmol) in THF (5 mL), at −78 °C under nitrogen atmosphere. The reaction mixture was stirred for 1 h at the same temperature and then for 4 h at room temperature. The reaction was quenched by NH_4Cl_{aq}, and the water layer was extracted with ethyl acetate (50 mL × 3). The combined organic layer was dried and concentrated. The crude adduct was subjected to flash column chromatography (hexane–ethyl acetate (10:1 then 3:1) v/v) to give 7 in 75% yield (173 mg), colorless oil. The obtained 7 consisted of a pair of diastereomers whose ratio was 55/45: ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.97–7.38 (m, 15 H), 5.63 (d, J = 4.3 Hz, 1 H for major isomer), 5.59 (d, J = 5.5 Hz, 1 H for minor isomer), 4.92 (t, J = 7.3 Hz, 1 H for major isomer), 4.74 (d, d, J = 4.8 Hz, 7.0 Hz, 1 H for minor isomer), 4.54–4.67 (m, 1 H), 4.41 (d, J = 4.9 Hz, 1 H for major isomer), 4.25 (d, J = 4.9 Hz, 1 H for minor isomer), 1.8–2.2 (br, 1 H), 1.38–1.75 (m, 2 H), 0.83 (s, 9 H for minor isomer), 0.80 (s, 9 H for major isomer), 0.019 (s, 3 H for major isomer), −0.02 (s, 3 H for minor isomer), −0.08 (s, 3 H for minor isomer), −0.10 (s, 3 H for major isomer).

Oxidation of 7. To a solution of oxalyl chloride (100 mL, 1.0 mmol) was slowly added freshly distilled DMSO (0.15 mL, 2.1 mmol) at −78 °C. After 20 min, 7 (90 mg, 0.18 mmol) was added to the solution and the solution was stirred for 1 h at the same temperature. After the addition of triethylamine (0.55 mL), the solution was stirred at room temperature for 1 h. It was poured into water (50 mL), and the aqueous layer was extracted with EtOAc (3 × 50 mL). The organic layers were combined, dried, and concentrated in vacuo to give crude 8. The product was purified by flash column chromatography (hexane–ethyl acetate (20:1) v/v) to give 8 in 54% yield (48 mg). This 8 contained two diastereomers, whose ratio was clearly determined to be 80/20 by an integration ratio of 250-MHz ^{1}H NMR (signals at δ 3.76 and 3.26 for minor isomer vs 2.78 and 2.54 for major isomer). ^{13}C and ^{1}H NMR spectra of the major isomer, 8A, were identical with that of *syn*-8 prepared by silylation of *syn*-1b, and the ^{1}H NMR spectrum of the minor isomer, 8B, was identical with that of *anti*-8.

Conversion of *syn*-4a into 9. A mixture of *syn*-4a (819 mg, 3.19 mmol), TBDMSCl (1.21 g, 8.03 mmol), and imidazole (1.11 g, 16.3 mmol) in DMF (10 mL) was stirred at 55 °C for 10 h. After the same workup as in the preparation of 8, the silyl ether of *syn*-4a was obtained as colorless oil: 1.06 g (90%); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.28–7.46 (m, 5 H), 5.43 (s, 1 H), 5.18 (s, 1 H), 5.01 (d, d, J = 4.6, 9.5 Hz, 1 H), 4.68 (d, d, J = 4.3, 8.5 Hz, 1 H), 3.69 (d, t, J = 2.4, 8.6 Hz, 1 H), 2.94 (d, d, J = 4.0, 14.6 Hz, 1 H), 2.83 (d, d, J = 8.2, 14.6 Hz, 1 H), 2.01–2.07 (m, 2 H), 1.64–1.75 (m, 4 H), 0.85 (s, 9 H), −0.07 (s, 3 H), −0.13 (s, 3 H). Ozonolysis of this ether was performed in a similar procedure as in the preparation of 6 to give 9 in 70% yield. The NMR spectrum of 9 was identical with that of the authentic sample.

Protection of the Hydroxy Group of *syn*-3a. General Procedure. To a suspension of NaH (60%, 272 mg, 6.8 mmol) in THF (20 mL) was added *syn*-3a (620 mg, 3.4 mmol) slowly over 30 min at 0 °C. The reaction mixture was stirred for 2 h at room temperature until the evolution of hydrogen ceased. Methoxymethyl chloride (550 mg, 6.8 mmol) was added to the mixture, and the resulting solution was stirred at the refluxing temperature for 12 h. The reaction mixture was poured into water (50 mL), and THF was evaporated in vacuo. The residue was extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and dried. After evaporation of ethyl acetate in vacuo, crude product was subjected into flash column chromatography (hexane–ethyl acetate (3:1) v/v) to give **10b** in 87% yield (667 mg), colorless oil. ^{1}H NMR data of 10 are summarized in Table 6. The other compounds 10 were prepared in a similar way, colorless oil. These compounds were purified to be single diastereomers before the $LiAlH_4$ reduction (flash column chromatography, hexane–ethyl acetate (10:1) v/v).

Preparation of Amino Diol Derivatives 11a. General Procedure. To a suspension of $LiAlH_4$ (680 mg, 18 mmol) in ether (100 mL) was added **10a** (2.436 g, 9.0 mmol) in ether (10 mL) over 30 min at 0 °C. Then the reaction mixture was refluxed for 5 h. Water (5 mL) and 20% $NaOH_{aq}$ (5 mL) were added to the solution at 0 °C. White precipitates were filtered off, dried in vacuo, and then washed with ethyl acetate. The aqueous layer of the filtrate was extracted with EtOAc (3 × 50 mL), and the organic layers were combined and dried. After the evaporation of the solvent in vacuo, the residue was subjected to flash column chromatography (hexane–ethyl acetate (3:1) v/v then ethyl acetate) to give a mixture of **11a** and **12a** in 57% yield (430 mg). The ratio of **11a**/**12a** was 83/17: colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$) for **11a** δ 7.30–7.39 (m, 5 H), 5.87 (t, d, d, J = 7.3, 9.8, 16.8 Hz, 1 H), 5.14 (d, J = 18.9 Hz, 1 H), 5.12 (d, J = 9.2 Hz, 1 H), 4.67 (d, J = 11.0 Hz, 1 H), 4.44 (d, J = 11.6 Hz, 1 H), 4.27 (m, 1 H), 3.23–3.33 (m, 2 H), 2.18–2.61 (m, 5 H), 1.41–1.93 (m, 7 H). For **12a**: δ 7.30–7.39 (m, 5 H), 5.87 (t, d, d, J = 7.3, 9.8, 16.8 Hz, 1 H), 5.14 (d, J = 18.9 Hz, 1 H), 5.12 (d, J = 9.2 Hz, 1 H), 4.63 (d, J = 9.8 Hz, 1 H), 4.49 (d, J = 11.0 Hz, 1 H), 4.19 (m, 1 H), 3.23–3.33 (m, 2 H), 2.18–2.61 (m, 5 H), 1.41–1.93 (m, 7 H). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.80; H, 9.62; N, 4.86.

The following amino diol derivatives were prepared in a similar way.

11b: 65% yield; **11b**/**12b** = 92/8; colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.84 (t, d, d, J = 7.0, 9.8, 17.1 Hz, 1 H), 5.12 (d, d, J = 1.2, 17.1 Hz, 1 H), 5.10 (d, J = 11.0 Hz, 1 H), 4.73 (d, J = 6.7 Hz, 1 H), 4.65 (d, J = 6.7 Hz, 1 H), 4.30 (m, 1 H), 3.39 (s, 3 H), 3.34–3.48 (m, 1 H), 3.18 (d, d, J = 3.1, 6.1 Hz, 1 H), 2.6–3.0 (br, 2 H), 2.44 (t, d, J = 6.7, 14.7 Hz, 1 H), 2.29 (t, d, J = 6.7, 14.7 Hz, 1 H), 1.76–1.95 (m, 2 H), 1.51–1.71 (m, 6 H). Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.48; H, 9.97; N, 5.93.

13a: 67% yield; **13a**/**14a** = 76/24; colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$) for **13a** δ 7.29–7.34 (m, 5 H), 5.88 (t, d, d, J = 6.7, 10.4, 17.1 Hz, 1 H), 5.15 (d, J = 17.1 Hz, 1 H), 5.10 (d, J = 9.8 Hz, 1 H), 4.70 (d, J = 11.0 Hz, 1 H), 4.42 (d, J = 11.0 Hz, 1 H), 4.17 (m, 1 H), 3.38 (m, 2 H), 2.45–2.49 (m, 2 H), 2.10–2.30 (m, 3 H), 1.53–1.87 (m, 7 H). For **14a**: δ 7.29–7.34 (m, 5 H), 5.88 (t, d, d, J = 6.7, 10.4, 17.1 Hz, 1 H), 5.15 (d, J = 17.1 Hz, 1 H), 5.10 (d, J = 9.8 Hz, 1 H), 4.68 (d, J = 11.6 Hz, 1 H), 4.44 (d, J = 11.6 Hz, 1 H), 4.27 (m, 1 H), 3.37 (m, 2 H), 2.45–2.49 (m, 2 H), 2.10–2.30 (m, 3 H), 1.53–1.87 (m, 7 H). Anal. Calcd for $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 73.85; H, 8.91; N, 5.30.

13b: 79%; **13b**/**14b** = 93/7; colorless oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.87 (t, d, d, J = 6.7, 10.4, 17.1 Hz, 1 H), 4.70 (d, d, J = 1.2, 7.3 Hz, 1 H), 4.65 (d, d, J = 2.4, 7.3 Hz, 1 H), 4.28 (m, 1 H), 3.46 (t, d, J = 5.8, 11.3 Hz, 1 H), 3.39 (s, 3 H), 3.29 (d, d, J = 3.1, 5.5 Hz, 1 H), 2.5–2.9 (br, 2 H), 2.38 (t, J = 6.1 Hz, 2 H), 1.83–1.96 (m, 2 H), 1.57–1.69 (m, 6 H). Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 61.85; H, 10.11; N, 5.82.

Dehydroxylation of Amino Diol Monoethers 11b and 13b. To a suspension of NaH (60%, 250 mg, 6.2 mmol) in THF (50 mL) was added **13b** (850 mg, 3.1 mmol) at 0 °C, and the resulting solution was stirred for 2 h at room temperature until hydrogen evolution ceased. CS_2 which was freshly distilled from P_2O_5 (0.74 mL, 12.4 mmol) was added, and the resulting solution was refluxed for 2 h. Methyl iodide (440 mg, 3.1 mmol) was added to the solution at −78 °C, and the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was poured into water (20 mL), and the solvent was evaporated in vacuo until the total volume became about 10 mL. The residue was extracted with EtOAc (6 × 50 mL). The combined organic layer was dried and evaporated. The crude product was purified by flash column chromatography (hexane–ethyl acetate (3:1)) to give the corresponding xanthate (637 mg). This xanthate was dissolved into a solution of Bu_3SnH (1164 mg, 4.0 mmol) and AIBN (10 mg) in benzene (10 mL), and the solution was refluxed for 12 h. Benzene

was removed in vacuo, and the residue was subjected into flash column chromatography (hexane then hexane–ethyl acetate (3:1)) to give β-amino alcohol **16** in 64% yield (515 mg) as a colorless oil. Compound **15** was also prepared in the same procedure in 30%.

15: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.77–5.93 (m, 1 H), 5.16 (d, J = 11.0 Hz, 1 H), 5.15 (d, J = 16.5 Hz, 1 H), 4.72 (s, 3 H), 3.61 (d, d, J = 4.3, 9.8 Hz, 1 H), 3.50 (s, 3 H), 3.37–3.44 (m, 1 H), 2.52–2.60 (m, 1 H), 2.17–1.24 (m, 2 H), 1.61–2.03 (m, 9 H).

16: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.71–5.88 (m, 1 H), 5.20 (d, d, J = 1.2, 17.1 Hz, 1 H), 5.18 (d, J = 8.5 Hz, 1 H), 4.77 (t, J = 3.7 Hz, 1 H), 4.64 (d, J = 7.4 Hz, 1 H), 4.59 (d, J = 7.4 Hz, 1 H), 3.74 (t, J = 4.8 Hz, 1 H), 3.63 (d, d, J = 6.1, 11.6 Hz, 1 H), 3.48 (s, 3 H), 2.32–2.39 (m, 2 H), 2.11–2.17 (m, 1 H), 1.55–2.00 (m, 9 H).

Dibenzoylation of 11b. The amino diol monoether **11b** (193 mg, 0.84 mmol) and benzoyl chloride (316 mg, 2.25 mmol) were dissolved in pyridine (5 mL), and the reaction mixture was stirred for 2 days at room temperature. The solution was poured into aqueous $NaHCO_3$ (30 mL), and the resulting solution was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layer was washed with 1 M HCl and brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent in vacuo, the residue was purified by flash column chromatography (hexane–ethyl acetate (3:1) v/v) to give **17** in 71% yield (260 mg) as white crystals: mp 100–101 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.10 (d, J = 7.3 Hz, 2 H), 7.83 (d, J = 7.9 Hz, 2 H), 7.44–7.60 (m, 6 H), 6.51 (d, J = 10.4 Hz, 1 H), 5.47–5.56 (m, 2 H), 4.93 (d, J = 17.1 Hz, 1 H), 4.77 (d, J = 6.7 Hz, 1 H), 4.68 (d, J = 6.7 Hz, 1 H), 4.64 (d, d, J = 2.4, 10.4 Hz, 1 H), 4.62–4.72 (m, 1 H), 3.77 (d, d, J = 4.6, 8.9 Hz, 1 H), 3.43 (s, 3 H), 2.25–2.41 (m, 2 H), 1.85–2.20 (m, 6 H), 1.58–1.70 (m, 1 H). Anal. Calcd for $C_{26}H_{31}NO_5$: C, 71.37; H, 7.14; N, 3.20. Found: C, 71.52; H, 7.42; N, 3.03.

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Supplementary Material Available: X-ray crystallographic data for compounds *syn*-**2a** and **17** (20 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

The Dodecahedryl Radical. Reactivity Analysis by Conjugate Addition to π-Electron-Deficient Acceptors and Structural Investigation by Electron Spin Resonance Spectroscopy

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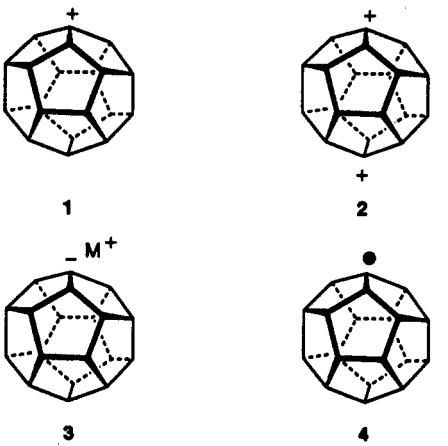
The bromo and phenylseleno derivatives of dodecahedrane have been identified as suitable precursors to the dodecahedryl radical (**4**). This reactive intermediate exhibits only modest reactivity, lending itself to capture by the most powerful radical traps, which include acrylonitrile, 2-cyclopentenone, and allyltri-*n*-butylstannane. ESR studies performed on the same two starting materials have provided additional striking evidence that **4** and its closest model, the 1-adamantyl radical, differ widely in their properties. Reaction conditions that result in smooth generation of the adamantyl species did not lead to ESR spectra that can be related to **4**.

The exquisite I_h symmetry of dodecahedrane stems from a highly rigid spherical structure[2] in which each methine carbon experiences minimal deformation from ideal tetrahedral character. The out-of-plane bending angle (θ) for any of the 20 sp^3-hybridized corners is approximately 21°. Ionization to generate monocation **1** is accompanied by considerable deformation of the cationic center toward planarity, which cannot be fully realized because of structural constraints. Counterbalancing bond-angle distortions materialize at the flanking centers to reduce θ to about 11°.[3] Notwithstanding the energetic costs of these substantive geometric changes, **1** can be readily generated,[3,4] the electrophilic chemistry of dodecahedrane serving as a notably useful means for achieving functionalization of the hydrocarbon.[5] Remarkably, the dodecahedryl cage is also quite tolerant of conversion to the 1,16-dication (**2**), despite the onset of added structural deformation, intense Coulombic repulsion, and adverse through-space interactions.[3,4]

The dodecahedryl anion has proven somewhat more elusive.[6] A reduced capability for the formation of **3** was indicated by the half-wave potential for reduction of the bromide, which at −2.16 V (vs SCE) is considerably more



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