Asymmetric Cycloaddition of *N*-Metalated Azomethine Ylides with the Optically Active α,β-Unsaturated Esters Derived from α-Amino Acids

Shuji KANEMASA,* Hidetoshi YAMAMOTO,† Eiji WADA, Tosio SAKURAI,†† and Kunio URUSHIDO††
Institute of Advanced Material Study, Kyushu University, Kasugakoen, Kasuga 816
†Department of Molecular Science and Technology, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University, Kasugakoen, Kasuga 816
††Faculty of Education, Shinshu University, Nishinagano, Nagano 380
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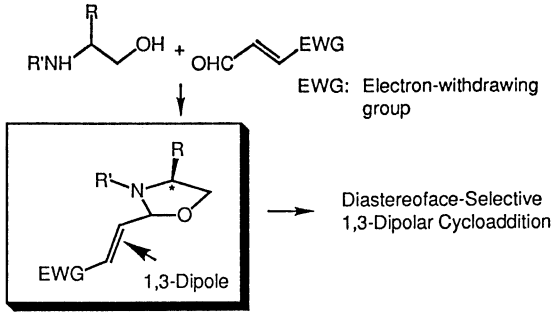
α,β-Unsaturated esters bearing a chiral oxazolidine or perhydropyrrolo[1,2-*c*]imidazole auxiliary at the β-position have been prepared and applied to the cycloadditions with *N*-metalated azomethine ylides derived from α-(benzylideneamino) esters. These reactions are found to proceed with an exclusively high diastereofacial selectivity to give 2,4-pyrrolidinedicarboxylates with four consecutive chiral centers after the removal of chiral auxiliary. Detailed stereochemistry in the transition state is discussed.

No example is known so far, to the best of our knowledge, for the stereocontrol of 1,3-dipolar cycloaddition by the aid of Lewis acid catalyst.[1] This makes a striking contrast with the case of Diels-Alder reaction which similarly proceeds through a frontier orbital-controlled transition state involving six pai electrons. The high diastereo- and enantioselectivities have been established in many asymmetric versions[2] of Lewis acid-catalyzed Diels-Alder reactions.[3]

Accordingly, most of the hitherto reported examples for asymmetric 1,3-dipolar cycloadditions have been performed without Lewis acid catalyst by using chiral dipoles or dipolarophiles.[4] As a result, the level of diastereoselectivity achieved is rather low, depending upon the proper choice or combination of 1,3-dipoles and dipolarophiles.

The pioneering work of asymmetric 1,3-dipolar cycloaddition using azomethine ylide 1,3-dipoles was reported by Padwa's group, while the diastereoselectivity was disappointingly low.[5] Later, a high diastereoselectivity (100% de for exo cycloadduct; 68% de for endo one, exo:endo=60:40) was observed in the reaction of 1-methylpyridinio-3-oxide with a chiral vinyl sulfoxide;[6a] two examples of asymmetric induction were added to the intramolecular cycloadditions of azomethine ylides.[6b,c] These are all known for the asymmetric cycloadditions of azomethine ylide.

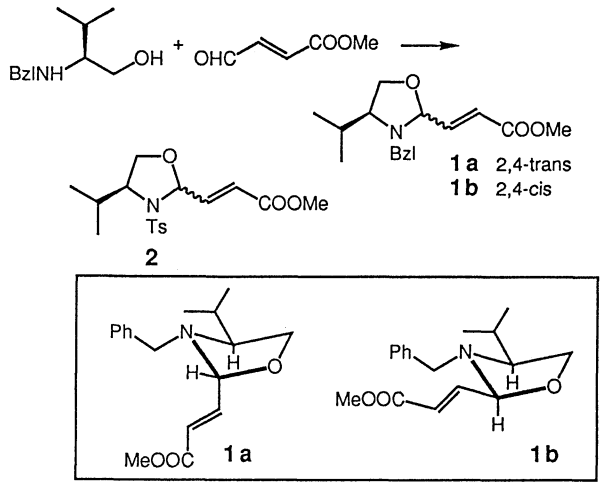


We have recently discovered that *N*-metalated azomethine ylides derived from α-(alkylideneamino) esters undergo highly stereoselective cycloadditions with α,β-unsaturated carbonyl compounds.[7] Since these ylides are highly reactive enough to react with a crotonate at −78 °C, the asymmetric cycloaddition utilizing these ylides is promissing. In the present article, the detail of our work along this line is described.[8]

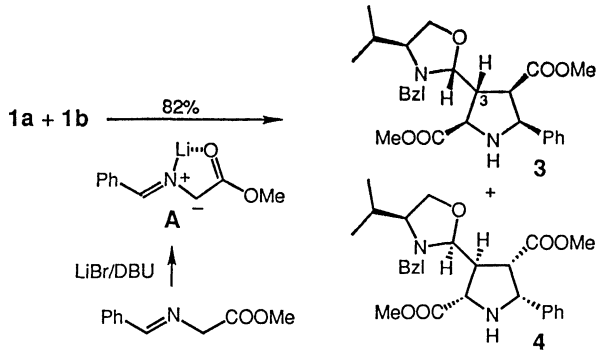
We planned to examine chiral auxiliaries of the oxazolidine types shown above because they have some synthetic advantages such as: 1) α,β-Unsaturated carbonyl compounds bearing a chiral 2-oxazolidinyl unit at β-position are accessible from readily available chiral β-amino alcohols and the corresponding α,β-unsaturated aldehydes. 2) One side of the olefin moiety would be effectively blocked by the adjacent *N*-substituent R′ so that only the other side may be open to the attack by a 1,3-dipole. 3) A variety of substituent R can be introduced on the asymmetric carbon from optically pure 2-amino alcohols which are available by the reduction of natural α-amino acids or esters.

Results and Discussion

2-Oxazolidinyl Chiral Auxiliary. The reaction of (*S*)-*N*-benzylvalinol with methyl (*E*)-4-oxo-2-butenoate in diethyl ether produced a mixture of two 2-epimers of methyl (*E*)-3-[(4*S*)-3-benzyl-4-isopropyloxazolidin-2-yl]propenoate (**1a** and **1b**); the isomer ratio changed depending upon the reaction conditions: The same reaction in the presence of anhydrous magnesium sulfate as dehydrating reagent, at 0 °C or at room temperature each for 1 h, gave a 40:60 (^{1}H NMR, 80%) or 37:63 (90%) mixture of **1a** and **1b**, respectively (Scheme 1). After the lapse of long reaction time (r.t., 12 h), the isomer ratio reversed into 60:40 (95%). Attempted separation and purification by chromatography of the 40:60 mixture on



Scheme 1.



Scheme 2.

silica gel by using dichloromethane caused serious weight loss, and the ratio of 87 : 13 resulted. After all, the condensation was carried out in the presence of silica gel (Merck, Silica gel 60) at room temperature for 24 h to produce an 86 : 14 mixture of **1a** and **1b** (90%). These facts indicate that **1a** and **1b** are the thermodynamic and kinetic products, respectively.

Although their stereostructures could not be determined on the basis of spectral data such as ^{1}H and ^{13}C NMR spectra, **1b** was assigned as cis isomer, and accordingly **1a** trans, on the ground of X-ray-assigned stereostructure of the minor cycloadduct **4** derived from **1b**. This will be discussed later. No significant NOE enhancement between H-2 and H-4 of **1a** was observed, supporting the 2,4-trans stereochemistry of the oxazolidine ring.

In the condensation of β-amino alcohols or thiols with aldehydes, oxa(or thia)zolidines as condensation products are generally mixtures of 2,4-cis and 2,4-trans isomers, the former being the major products.[9] In some cases, exclusively cis-selective condensations have been observed.[10] Such cis-isomer preference has been well documented in saturated five-membered ring systems: 1,3-cis-Isomers are generally more stable than the corresponding 1,3-trans isomers, since two bulky substituents at 1- and 3-positions of cis-isomers can occupy quasi-equatorial positions in envelope conformation.[11] However, the rare example of higher thermodynamic stability for 2,4-trans isomers has been recently reported in the case of 2-vinyloxazolidines bearing a conjugated carbonyl moiety.[12] The preferred formation of our 2,4-trans olefin **1a** would be on the same basis.

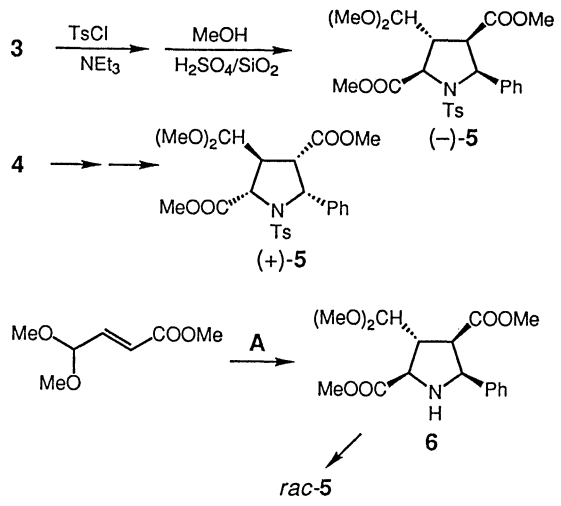
The liability of α,β-unsaturated ester **1** to hydrolysis would depend upon the basicity of ring nitrogen. Accordingly, a tosyl substituent was introduced on the nitrogen with an expectation of lowering its basicity. However, the olefin **2** was still labile, undergoing serious decomposition during purification by silica-gel column chromatography.

Separation and purification of either **1a** or **1b** were unsuccessful because of their susceptibility toward hydrolysis during chromatographic operation. However, we expected that use of the mixture in cycloadditions would give us some important informations on the efficiency of the 2-oxazolidinyl chiral auxiliary in diastereofacial selectivity. Comparison of the diastereofacial selectivities in the cases of 2,4-trans **1a** and 2,4-cis **1b** isomers is also attracting.

Thus, the 86 : 14 mixture of **1a** and **1b** was treated with *N*-lithiated azomethine ylide **A**, derived from methyl *N*-benzylideneglycinate by the action with lithium bromide and diazabicyclo[5.4.0]undec-7-ene (DBU), at −78 °C for 3.5 h in tetrahydrofuran (THF) to give a 75 : 25 mixture (^{1}H NMR) of two diastereomeric cycloadducts **3** and **4** in 82% of combined yield (Scheme 2).

We have already reported the absolutely high stereoselectivity in cycloadditions of *N*-lithiated azomethine ylides with (*E*)-α,β-unsaturated esters.[7] Accordingly, it was anticipated that four diastereomeric cycloadducts would be produced from the mixture of α,β-unsaturated esters **1a** and **1b**; the isomer ratio depends upon the selection of the olefin faces of **1a** and **1b**. The formation of only two diastereomers **3** and **4**, out of four possible diastereomers, would indicate that cycloadditions of *N*-lithiated azomethine ylide **A** with α,β-unsaturated esters **1a** and **1b** were both absolutely diastereoselective. These cycloadducts **3** and **4** were separated from each other by high performance liquid chromatography (HPLC, Merck Lobar) using dichloromethane–diethyl ether as an eluent.

Removal of the oxazolidine chiral controller from **3** and **4** was performed by a sequence of *N*-tosylation and acetal exchange reaction (Scheme 3). Thus, **3** or **4** was allowed to react with *p*-toluenesulfonyl chloride and triethylamine in dichloromethane at room temperature for 24 h to give the corresponding *N*-tosylpyrrolidine. Acetal exchange reaction of the resulting *N*-tosylpyrrolidine was carried out successfully when heated under reflux in methanol for 24 h in the presence of conc sulfuric acid (methanol/sulfuric acid=10 : 1 v/v) and silica gel. Both sulfuric acid and silica gel were essential for this acetal exchange reac-



Scheme 3.

tion and lack of either of them resulted in quantitative recovery of the starting *N*-tosylpyrrolidine. The role of silica gel can not be fully explained so far, while some examples for the catalysis of silica gel are known in dehydration of alcohols or hydrolysis of acetals.[13]

The cycloadduct pyrrolidines (−)-**5** (obtained in 80% yield based on **3**) and (+)-**5** (87% yield based on **4**) showed $[\alpha]_D^{20}=-40.36°$ (*c* 0.99, $CHCl_3$) and +39.84° (*c* 1.00, $CHCl_3$) of optical rotations, respectively, indicating that (−)-**5** and (+)-**5** are enantiomers to each other.

The structures of both (−)-**5** and (+)-**5** were confirmed by comparison of spectral data with those of the authentic sample of *rac*-**5**. Compound *rac*-**5** was easily prepared by the *N*-tosylation of pyrrolidine **6** which had been stereoselectively synthesized by the 1,3-dipolar cycloaddition of azomethine ylide **A** with methyl (*E*)-4,4-dimethoxybutenoate (Scheme 3).

Stereostructure Assignment of Cycloadducts. Absolute configuration of the minor cycloadduct **4** was determined by the X-ray analysis. The stereostructure of **4** in crystalline state is illustrated in Fig. 1 by means of a ball and stick molecular model, in which the oxazolidine chiral controller has a 2,4-cis relationship and absolute configuration of the newly formed pyrrolidine ring is 2*S*,3*S*,4*S*,5*R*. The H-2 (δ=4.01) and H-3 (3.09) of **4** are located spatially close to the oxygen and nitrogen of chiral oxazolidine ring, respectively, being magnetically deshielded by their anisotropy in ^1H NMR spectrum (Compare with those of the reference compound **7**).[7] A similar low field shift induced by the anisotropy of an acetal moiety was observed in the case of *rac*-**5** (H-2: 3.90; H-3: 3.12; H-4: 3.37). A small vicinal coupling constant (J=2.6 Hz) between H-3/H-2′ is also consistent with their synclinal relationship in crystalline state.

On the other hand, the major cycloadduct **3** showed a larger $J_{3\text{-}2'}$ (6.6 Hz) and the deshielding pattern was quite different from that of **4**. Both H-2 (δ=3.89) and H-4 (3.44), not H-3 (2.67), are deshielded in this case.

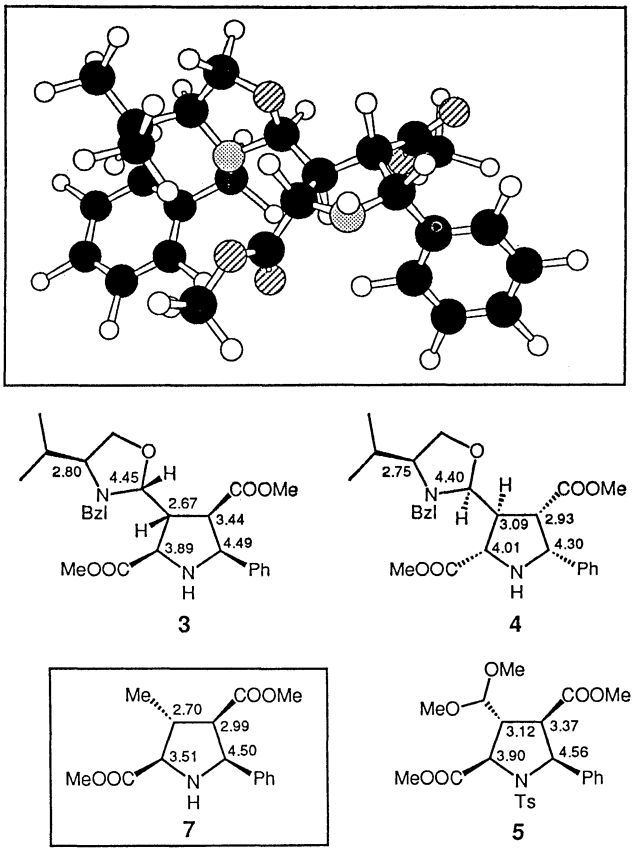


Fig. 1. The stereostructure of **4** determined by X-ray crystal analysis and ^1H NMR spectra of **3**—**5** and **7**.

Based on these results, the 2,4-trans configuration and the synperiplanar conformation between H-3/H-2′ of **4** were confirmed.

As described above, when the cycloaddition was carried out with the 86/14 olefin mixture of 2,4-trans/2,4-cis isomers **1a,b**, the diastereomer ratio of the resulting cycloadducts was 75/25. Based on the observation that this 86 : 14 ratio did not change under the conditions of cycloaddition (treatment of the mixture with lithium bromide and DBU in THF or with LiBr/DBU complex[14] in $CDCl_3$, both at room temperature), it can be concluded that no isomerization between α,β-unsaturated esters **1a** and **1b** has taken place during the cycloaddition.

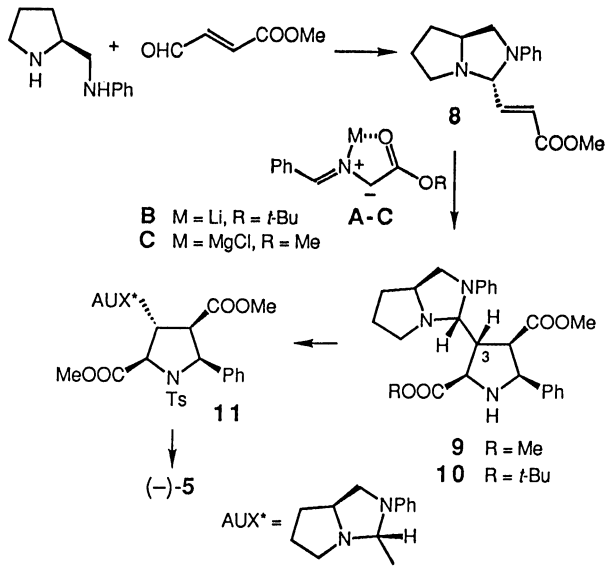
The X-ray analysis showed the minor cycloadduct **4** to be the product derived from the 2,4-cis olefin **1b**. Accordingly, the major cycloadduct **3** must have been produced from the major isomer **1a**, 2,4-trans isomer. In other words, the cycloaddition of these α,β-unsaturated esters **1a,b** with the *N*-lithiated azomethine ylide was absolutely diastereoselective in both cases. The transition state for each case will be discussed later.

Perhydropyrrolo[1,2-*c*]imidazol-3-yl Chiral Auxiliary. The ready availability of α,β-unsaturated esters **1a,b** and their high diastereofacial selectivity, unveiled in the cycloaddition with *N*-lithiated azomethine ylide

A, are attracting. However, one critical disadvantage was the difficulty of separation and purification of **1a** and **1b** due to their liability to hydrolysis. Accordingly, a higher 1,3-asymmetric induction was needed on the construction of five-membered chiral auxiliary.

Methyl (*E*)-3-[(3*R*,7a*S*)-2-phenylperhydropyrrolo-[1,2-*c*]imidazol-3-yl]propenoate (**8**) was selected as a chiral dipolarophile of the above mentioned type since its stereoselective synthesis from (*S*)-2-(anilinomethyl)pyrrolidine and methyl (*E*)-4-oxo-2-butenoate is already known.[15] Though this α,β-unsaturated ester **8** has been successfully used in the asymmetric Michael reactions with Grignard reagents by the same authors,[15] its use in cycloadditions is unknown.

The reaction of **8** with *N*-lithiated azomethine ylide **A** smoothly took place at −78 °C for 5 h in THF to give cycloadduct **9** in 82% yield (Scheme 4 and Table 1, Entry 1). To our delight, **9** was a single diastereomer (^{1}H NMR), indicating the occurrence of exclusively diastereoface-selective cycloaddition between **A** and **8**.



Scheme 4.

This exclusively diastereoface-selective formation of **9** was not affected when the reaction was performed at room temperature (**9**: 79% yield, Entry 3) or even at a higher temperature (40 °C, 63% yield, Entry 4) as shown in Table 1. However, the same reaction carried out either at 60 °C by using LiBr/NEt$_3$ (Entry 5) or at −78 °C by using lithium diisopropylamide (LDA, Entry 6) led to the formation of complex mixture. Use of *N*-lithiated azomethine ylide **B** bearing a *t*-butyl ester moiety resulted in the quantitative formation of cycloadduct **10** either at −78 °C or at room temperature (Entries 10 and 11). *N*-Magnesioazomethine ylide **C**, generated from methyl *N*-benzylideneglycinate and *t*-butylmagnesium chloride at −78 °C, slowly reacted with **8** at the same temperature to give 30% yield of **9** as a single diastereomer (Scheme 4).

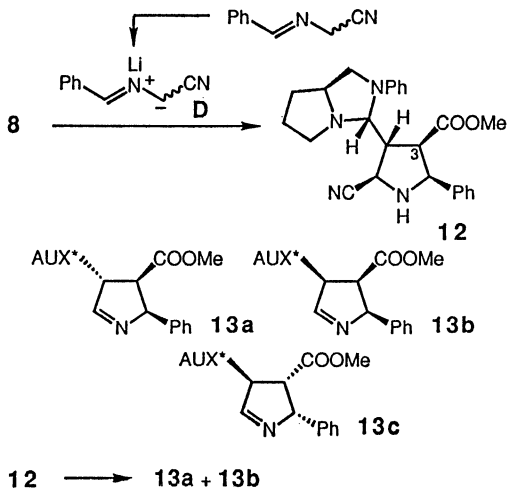
Comparison of ^{1}H NMR spectrum of **10** with that of **9** indicates that these products have the identical stereochemistry (See Experimental). The ^{1}H NMR spectral assignment of **9** was based on the H/H COSY and NOE spectra. It is clear that **9** occupies a conformation in which 4-COOMe (δ=2.90) is doubly shielded by two phenyl moieties, 5-Ph and *N*-Ph. The absolute configuration of **9** was spectroscopically assigned as shown in Scheme 4, especially on the basis of its NOE spectra where a strong NOE was observed between H-4 and H-7a′. Their close location was confirmed in the molecular model inspection. In the end, the absolute structure of cycloadduct **9** was determined by its conversion into (−)-**5** via *N*-tosyl derivative **11**.

When *N*-lithiated azomethine ylide **D** of the cyano-stabilized type was allowed to react with α,β-unsaturated ester **8**, the diastereoselective cycloadduct

Table 1. Asymmetric 1,3-Dipolar Cycloaddition Reaction of *N*-Metalated Azomethine Ylides **A**—**D** with Chiral Olefin **8**[a]

Entry	Base (equivalent)	Imine (equivalent)	Ylide type	Reaction conditions Temp/°C	Time/h	Product	Yield[b] %	Isomer ratio[c]
1	LiBr/DBU (1.6/1.3)	PhCH=NCH$_2$COOMe (1.1)	**A**	−78	2.2	**9**	82	Single
2	LiBr/DBU (1.6/1.3)	PhCH=NCH$_2$COOMe (1.1)	**A**	−78	5	**9**	100	Single
3	LiBr/NEt$_3$ (1.5/1.2)	PhCH=NCH$_2$COOMe (1.0)	**A**	R.t.	24	**9**	79	Single
4	LiBr/NEt$_3$ (1.5/1.2)	PhCH=NCH$_2$COOMe (1.0)	**A**	40	30	**9**	63	Single
5	LiBr/NEt$_3$ (1.5/1.2)	PhCH=NCH$_2$COOMe (1.0)	**A**	60	30	[d]	—	
6	LDA (1.2)	PhCH=NCH$_2$COOMe (1.0)	**A**	−78	24	[d]	—	
7	*t*-BuMgCl (1.1)	PhCH=NCH$_2$COOMe (1.0)	**B**	−78	42	**9**	30	Single
8	LiBr/DBU (1.6/1.3)	PhCH=NCH$_2$COOBu-*t* (1.1)	**C**	−78	5	**10**	100	Single
9	LiBr/NEt$_3$ (1.5/1.2)	PhCH=NCH$_2$COOBu-*t* (1.0)	**C**	R.t.	24	**10**	96	Single
10	LDA (1.2)	PhCH=NCH$_2$CN (1.2)	**D**	−78	1	**12**+**13a** +**13b**+**13c**	100	13:76:4:7 (93:7)[e]
11	LDA (1.2)	PhCH=NCH$_2$CN (1.0)	**D**	−78	5	**13a**+**13b** +**13c**	96	74:8:18 (82:18)[e]

a) All reactions were carried out in THF with one equivalent amount of olefin **8**. b) Yield of isolated products. c) Determined by ^{1}H NMR spectrum. d) Complex mixture of many products. e) The calculated diastereofacial selectivity is given in parenthesis.



Scheme 5.

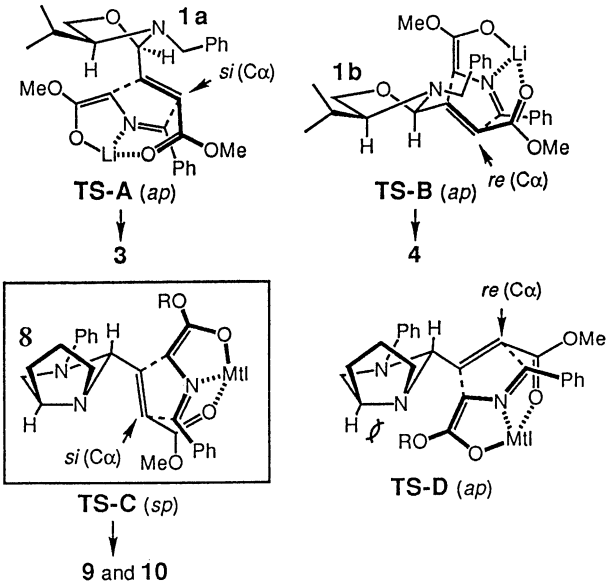


Fig. 2. Proposed transition states for the asymmetric 1,3-dipolar cycloadditions of chiral olefins **1** and **8** with *N*-metalated azomethine ylides.

12 was accompanied by some stereoisomers of 1-pyrrolines **13**, the products produced by the elimination of hydrogen cyanide from the initial cycloadducts (Scheme 5). Only **12** was separated in a pure form the mixture since it crystallized out on treatment with ethanol.

The HCN elimination from **12** actually took place under the conditions of cycloaddition (with LDA at −78 °C in THF)[16] to give an inseparable mixture of **13a,b**. The structural assignment of **13a,b** was based on ^{1}H and ^{13}C NMR spectra of the mixture as well as the reported example of ready epimerization at the 3-position of 1-pyrrolines through an imine/enamine tautomerism.[16,17] The major isomer **13a** was tentatively assigned as 3,4-trans isomer, and therefore the minor one 3,4-cis isomer.

The stereostructure of **12** was determined as shown in Scheme 5 on the basis of ^{1}H NMR spectra (H/H COSY and NOE spectra) where 3-COOMe (δ=2.78) is doubly deshielded by both 2-Ph and N-Ph, the $J_{4\text{-}3'}$ is small (3.7 Hz), and strong NOEs are observed between H-3/H-7a′ and H-5/H-5′. The origin of 1-pyrroline **13a**, and hence **13b**, is either **12** or its 5-epimer, but it would not be so important to solve it. It is noteworthy that the formation of **12** and **13a,b** has resulted from the same diastereofacial attack of ylide **D**. The formation of **13c** was only based on ^{1}H NMR spectrum of the crude reaction mixture.

As shown in Table 1, the diastereofacial selectivity in the cycloaddition reaction of ylide **D** with α,β-unsaturated ester **8** was not so high (93 : 7, Entry 10). Although the geometry of the ylidic carbon of ylide **D** is currently ambiguous, sterically less bulky substituents (H and CN) on this carbon, compared with ylides **A–C**, would be a main reason for the low selectivity. Use of excess amount of LDA lowered the selectivity (Entry 11).

Transition State. Based on the assigned absolute configuration of cycloadducts **3** and **4**, produced from the chiral α,β-unsaturated esters **1a** and **1b** bearing an oxazolidine chiral auxiliary, the approach of *N*-lithiated azomethine ylide **A** onto **1a,b** was figured out (Fig. 2). It is clear that ylide **A** reacted with **1a** at the *si*(Cα)-face producing **3**, and the attack of ylide **A** to the olefin face must have occurred from the side opposite to the extruding *N*-benzyl moiety. As a result, the C(2)-C(β) antiperiplanar conformer of **1a** has exclusively participated in the cycloaddition with **A** (**TS-A**). Similarly, the exclusive ylide attack at the *re*(Cα)-face of C(2)-C(β) antiperiplanar conformer of **1b** produced cycloadduct **4** (**TS-B**). These results are not surprising because antiperiplanar conformation in the related cases is thermodynamically more stable than synperiplanar one.[18]

On the other hand, the cycloadduct **9** (and also **10**) was not the diastereomer expected to form from the transition state **TS-D** in which the thermodynamically more favored C(3)-C(β) antiperiplanar conformer of **8** is involved. The attack of ylides **A–C** to the olefin face of **8** should occur so selectively from the side opposite to the extruding *N*-Ph moiety that the formation of **9** and **10** must have arisen from the exclusive participation of thermodynamically less favored synperiplanar conformer (**TS-C**). Some critical steric repulsion exists in **TS-D** between the ester moiety of ylide and the bridgehead methine moiety of α,β-unsaturated ester **8**; this may be responsible for the absolute inhibition of **TS-D**. The low diasteroselectivity in the cycloaddition with cyano-stabilized azomethine ylide **D** would have reflected by the relative increase of steric stabilization of **TS-D**.

In conclusion, chiral α,β-unsaturated esters bearing an oxazolidine or a perhydropyrrolo[1,2-*c*]-imidazole chiral auxiliary at the β-position undergo

exclusively diastereoface-selective cycloadditions with *N*-metalated azomethine ylides. Since the oxazolidine chiral auxiliary can not be prepared as a single stereoisomer and its purification is quite difficult due to its ready hydrolysis, the perhydropyrrolo[1,2-*c*]imidazole controller may be more conveniently utilized. The α,β-unsaturated esters **1** and **8** would be successfully applied to the cycloadditons with other 1,3-dipoles as they are the types activated by an electron-deficient ester substituent.

Experimental

General. Melting points were recorded on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were taken with JASCO IRA-1 or A-702 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a Hitachi R-40 (^{1}H NMR: 90 MHz) or a JEOL GSX-270 (270 MHz for ^{1}H NMR and 67.94 MHz for ^{13}C NMR) instrument. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Mass spectra and high-resolution mass spectra (HRMS) were taken with a JEOL-01SG-2 spectrometer where the ionization energy of 70 eV was employed unless otherwise stated. Elemental analyses were performed on a Hitachi 026 CHN analyzer. Optical rotations were measured on a Horiba SEPA-200 polarimeter. For preparative column chromatography, Wakogel C-200, C-300 (Wako), and Silica gel 60 (Merck) were employed. Flash chromatography was carried out on an Eyela EF-10 apparatus using a column (20×180 mm) packed with Silica gel 60 (Merck, size: 0.04—0.063 mm).

Materials. Methyl (*E*)-4-oxo-2-butenoate was prepared by the selenium dioxide-oxidation of methyl crotonate according to the reported procedure.[18] Its condensation with (*S*)-2-(anilinomethyl)pyrrolidine gave olefin **8** as a single diastereomer.[15]

Methyl (*E*)-3-[4(*S*)-3-Benzyl-4-isopropyloxazolidin-2-yl]-propenoate (1a+1b). (*S*)-*N*-Benzylvalinol was first prepared as follows: A mixture of benzaldehyde (2.97 ml, 29.2 mmol) and ethyl (*S*)-valinate (4.25 g, 29.3 mmol) in chloroform (80 ml) was stirred at room temperature for 2 h. The mixture was dried over magnesium sulfate and evaporated in vacuo to give ethyl (*S*)-*N*-benzylvalinate (7 g) which was used for the following procedure without further purification. To a solution of this *N*-benzylvalinate in dry THF (40 ml) was added, slowly at 0 °C under nitrogen, a suspension of lithium aluminum hydride (2.2 g, 58.5 mmol) in THF (50 ml). The mixture was heated under reflux for 2 h and the stirring was continued for 36 h at room temperature. After ice-cold water (50 ml) was added carefully, the mixture was extracted with diethyl ether (150 ml×4). The combined extracts were dried over magnesium sulfate and evaporated in vacuo. The residue (6.8 g) was distilled under a reduced pressure to give a colorless liquid of (*S*)-*N*-benzylvalinol (5.2 g, 92% based on ethyl valinate): bp 110 °C/40 Pa (bulb-to-bulb). To a solution of (*S*)-*N*-benzylvalinol (0.19 g, 0.98 mmol) in diethyl ether (2.5 ml) were added methyl (*E*)-4-oxo-2-butenoate (0.11 g, 0.98 mmol) and silica gel (Merck Kieselgel 60, 50 mg). After the mixture was stirred at room temperature for 24 h, the silica gel was filtered off and washed with ethyl acetate (50 ml). The combined filtrate and washings were evaporated in vacuo to give an 86 : 14 (^{1}H NMR) mixture of **1a** and **1b** as a colorless liquid (0.26 g, 90%). Since these compounds **1a+1b** were too labile to be purified by column chromatography, no analytical sample was available. **1a+1b**: Colorless liquid; IR (neat) 3435, 2980, 1725, 1432, 1265, 1170, and 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) **1a**: δ=0.83, 0.96 (each 3H, d, J=6.6 Hz, *i*-Pr), 1.61 (1H, octet, J=6.6 Hz, *i*-Pr), 2.78 (1H, dt, $J_{4\text{-}5}$=7.1, 6.6, and $J_{4\text{-}CH}$=6.6 Hz, H-4), 3.67 (1H, dd, J_{gem}=8.4 and $J_{5\text{-}4}$=6.6 Hz, one of H-5), 3.69 (3H, s, COOMe), 3.77, 3.86 (each 1H, d, J_{gem}=13.4 Hz, $PhCH_2$), 3.99 (1H, dd, J_{gem}=8.4 and $J_{5\text{-}4}$=7.1 Hz, the other of H-5), 4.79 (1H, d, $J_{2\text{-}CH}$=5.1 and 1.1 Hz, H-2), 5.86 (1H, dd, J_{trans}=15.8 and $J_{CH\text{-}2}$=1.1 Hz, =CH), 6.62 (1H, dd, J_{trans}=15.8 and $J_{CH\text{-}2}$=5.1 Hz, =CH), and 7.2—7.4 (5H, m, Ph). **1b**: δ=0.87, 0.94 (each 3H, d, J=6.6 Hz, *i*-Pr), 1.82 (1H, m, *i*-Pr), 2.91 (1H, dt, $J_{4\text{-}5}$=7.6, 7.3, and $J_{4\text{-}CH}$=6.6 Hz, H-4), 3.72 (3H, s, COOMe), 4.98 (1H, dd, $J_{2\text{-}CH}$=4.8 and 1.7 Hz, H-2), 6.03 (1H, d, J_{trans}=15.8 Hz, =CH), and 6.85 (1H, dd, J_{trans}=15.8 and $J_{CH\text{-}2}$=4.8 Hz, =CH). Other signals are overlapping with those of **1a**. ^{13}C NMR ($CDCl_3$) **1a**: δ=18.11, 20.17, 31.71 (each *i*-Pr), 51.53 (COOMe), 59.83 ($PhCH_2$), 68.12, 70.41 (C-4 and C-5), 94.87 (C-2), 122.11, 127.32, 128.30, 129.00, 138.94 (Ph and =CH), 146.66 (=CH), and 166.62 (COOMe). **1b**: δ=18.63, 20.36, 28.52 (each *i*-Pr), 52.11 (COOMe), 92.34 (C-2). Other signals are ovelapping with those of **1a**.

Cycloaddition of 1a+1b Leading to 3 and 4. To a solution of lithium bromide (0.782 g, 9 mmol) in dry THF (5 ml) were added, at −78 °C under nitrogen, methyl *N*-benzylideneglycinate (1.063 g, 6 mmol in THF (10 ml)), DBU (1.096 g, 7.2 mmol in THF (5 ml)), and an 86 : 14 mixture of **1a** and **1b** (1.447 g, 5 mmol in THF (5 ml)) in this order. After stirred at the same temperature for 3.5 h, the mixture was quenched with saturated aqueous ammonium chloride (30 ml) and extracted with diethyl ether (50 ml×3). The combined extracts were dried over magnesium sulfate and evaporated in vacuo to give a pale yellow oil which was chromatographed on silica gel by using hexane-ethyl acetate (2 : 1 v/v) to give a 75 : 25 (^{1}H NMR) mixture of **3** and **4** (1.918 g, 82%). The both diastereomers were separated from each other by HPLC (Merck Lobar, art 10401) with dichloromethane-diethyl ether (9 : 1 v/v).

3: Colorless liquid; IR (neat) 3340, 2950, 1730, and 1430 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.86, 0.91 (each 3H, d, J=6.6 Hz, *i*-Pr), 1.72 (1H, octet, J=6.6 Hz, *i*-Pr), 2.67 (1H, ddd, $J_{3\text{-}2}$=7.7, $J_{3\text{-}4}$=4.0, and $J_{3\text{-}2'}$=2.6 Hz, H-3), 2.80 (1H, m, H-4′), 3.12 (3H, s, 4-COOMe), 3.44 (1H, dd, $J_{4\text{-}5}$=7.7 and $J_{4\text{-}3}$=4.0 Hz, H-4), 3.68 (1H, d, J_{gem}=13.6 Hz, one of $PhCH_2$), 3.78 (3H, s, 2-COOMe), 3.79 (1H, d, J_{gem}=13.6 Hz, the other of $PhCH_2$), 3.8—3.9 (3H, m, H-2 and H-5′), 4.45 (1H, d, $J_{2'\text{-}3}$=2.6 Hz, H-2′), 4.49 (1H, d, $J_{5\text{-}4}$=7.7 Hz, H-5), and 7.2—7.3 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=16.76, 19.80, 30.08 (each *i*-Pr), 50.75, 50.90 (C-3 and C-4), 51.01, 52.11 (each COOMe), 56.67 ($PhCH_2$), 62.11 (C-2), 65.73 (C-5), 66.97, 68.61 (C-4′ and C-5′), 96.38 (C-2′), 126.68, 127.24, 127.28, 128.02, 128.16, 129.23, 138.15, 138.58 (each Ph), 173.07, and 173.49 (each COOMe); MS *m/z* (rel intensity, %) 467 (M^+ +1, 23), 466 (M^+, 74), 423 (15), 245 (17), 205 (15), and 204 (base peak). HRMS Found: *m/z* 466.2465. Calcd for $C_{27}H_{34}N_2O_5$: M, 466.2466.

4: Colorless prisms (ethanol); mp 138—140 °C; $[\alpha]_D^{22}$= −28.2° (*c* 1.21, $CHCl_3$); IR (KBr) 3370, 2935, 1720, 1424, and 1210 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=0.82, 0.88 (each 3H, d, J=6.6 Hz, *i*-Pr), 1.56 (1H, octet, J=6.6 Hz, *i*-Pr), 2.75 (1H, dt,

$J_{4'-5'}$=7.9 and $J_{4'-5'}$=$J_{4'-CH}$=6.6 Hz, H-4'), 2.93 (1H, dd, J_{4-5} =7.3 and J_{4-3}=3.7 Hz, H-4), 3.09 (1H, ddd, $J_{3-2'}$=6.6, J_{3-2} =5.5, and J_{3-4}=3.7 Hz, H-3), 3.19 (3H, s, 4-COOMe), 3.71 (1H, d, J_{gem}=12.8 Hz, one of $PhCH_2$), 3.75 (1H, J_{gem}=8.4 and $J_{5'-4'}$=6.6 Hz, one of H-5'), 3.83 (3H, s, 2-COOMe), 3.86 (1H, d, J_{gem}=12.8 Hz, the other of $PhCH_2$), 3.97 (1H, dd, J_{gem}=8.4 and $J_{5'-4'}$=7.9 Hz, the other of H-5'), 4.01 (1H, d, J_{2-3}=5.5 Hz, H-2), 4.30 (1H, d, J_{5-4}=7.3 Hz, H-5), 4.40 (1H, d, $J_{2'-3}$=6.6 Hz, H-2'), and 7.2—7.4 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=17.97, 20.17, 31.91 (each *i*-Pr), 49.91, 51.20 (C-3 and C-4), 52.34, 52.50 (each COOMe), 59.19 ($PhCH_2$), 61.60 (C-2), 65.11 (C-5), 67.69, 69.80 (C-4' and C-5'), 96.44 (C-2'), 126.62, 127.38, 127.50, 128.04, 128.39, 130.00, 138.43, 138.48 (each Ph), 173.21, and 173.76 (each COOMe); MS *m/z* (rel intensity, %) 467 (M^+ +1, 24), 466 (M^+, 74), 245 (36), 205 (12), 204 (82), 162 (10), and 91 (base peak). Found: C, 69.70; H, 7.47; N, 5.71%. Calcd for $C_{27}H_{34}N_2O_5$: C, 69.51; H, 7.34; N, 6.00%.

X-Ray Structure Analysis of 4. The single crystal was grown from the ethanol solution. The X-ray diffraction data were collected with a Rigaku AFC-5 four circle diffractometer with graphite-monochromatized Mo K_α radiation (λ=0.71703). The structure analysis was performed with a TEXSAN (Molecular Structure Corporation) system.

The space group is $P2_12_12_1$, a=10.986 (5), b=26.57 (2), c=8.713 (3) Å, V=2543 (2) Å^3, Z=4. The structure was solved by the direct method MITHRIL,[19] and refined by the full-matrix least squares. The final R-factor was 0.052 for the 1423 observed reflections.[20]

Removal of the Chiral Auxiliary from 3 Leading to (−)-5. To a solution of the major cycloadduct **3** (0.418 g, 0.896 mmol) in chloroform (10 ml) were added at 0 °C *p*-toluenesulfonyl chloride (0.188 g, 0.985 mmol) and triethylamine (0.14 ml, 0.985 mmol). After the mixture was stirred at room temperature for 24 h, the solvent was evaporated in vacuo. The residue was triturated with diethyl ether (30 ml), the precipitate was removed off by filtration and washed with another portion of diethyl ether (100 ml). The combined filtrate and washing were evaporated in vacuo to give colorless solid of the *N*-tosyl derivative of **3** (0.574 g). This solid was dissolved in methanol (20 ml) containing silica gel (Merck Kieselgel 60, 1 g) and concentrated sulfuric acid (2 ml). After heated under reflux for 24 h, the mixture was neutralized with saturated aqueous sodium hydrogencarbonate, and extracted with dichloromethane (60 ml×3). The combined extracts were dried over magnesium sulfate and evaporated in vacuo to give (−)-**5** (0.188 g, 80% based on **3**) after trituration with ethanol: $[\alpha]_D^{20}$=−40.36° (*c* 0.99, $CHCl_3$). The filtrate was evaporated in vacuo and the residue was chromatographed on silica gel by using ethyl acetate to give (*S*)-*N*-benzylvalinol (0.049 g, 53%).

A similar procedure was applied to the minor cycloadduct **4** to give (+)-**5** (77%): $[\alpha]_D^{20}$=39.84° (*c* 1.00, $CHCl_3$).

Preparation of Authentic Sample of *rac*-5. Dimethyl *t*-3-dimethoxymethyl-*c*-5-phenyl-*r*-2,*c*-4-pyrrolidinedicarboxylate (**6**): Methyl (*E*)-4,4-dimethoxy-2-butenoate (0.801 g, 5 mmol) was added to a solution of methyl *N*-benzylideneglycinate (0.886 g, 5 mmol), lithium bromide (0.651 g, 7.5 mmol), and triethylamine (0.84 ml, 6 mmol) in THF (10 ml). The mixture was stirred at room temperature for 24 h, poured into aqueous ammonium chloride, and extracted with diethyl ether (40 ml×3). The combined extracts were dried over magnesium sulfate and evaporated in vacuo to give **6** (1.16 g, 69%) which was purified by column chromatography on silica gel by using diethyl ether: Pale yellow liquid; IR (neat) 3325, 2952, 1736, 1432, and 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.80 (1H, br, NH), 3.12 (1H, dt, J_{3-2}=7.0 and J_{3-CH}=J_{3-4}=4.8 Hz, H-3), 3.17 (3H, s, 4-COOMe), 3.37 (1H, dd, J_{4-5}=7.7 and J_{4-3}=4.8 Hz, H-4), 3.41, 3.45 (each 3H, s, OMe), 3.83 (3H, s, 2-COOMe), 3.90 (1H, d, J_{2-3}=7.0 Hz, H-2), 4.46 (1H, d, J_{CH-3}=4.8 Hz, 3-CH), 4.56 (1H, d, J_{5-4}=7.7 Hz, H-5), and 7.2—7.3 (5H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=50.50, 51.22, 51.26, 52.37 (C-3, C-4, and 2×COOMe), 55.02, 55.61 (each MeO), 61.77 (C-2), 65.64 (C-5), 105.47 (3-CH), 126.71, 127.50, 128.12, 138.48 (each Ph), 173.28, and 173.34 (each COOMe); MS *m/z* (rel intensity, %) 337 (M^+, 1), 319 (11), 306 (33), 305 (90), 290 (47), 278 (31), 274 (11), 262 (30), 246 (25), 214 (12), 178 (27), 177 (63), 117 (18), 89 (12), and 75 (base peak). Found: C, 60.52; H, 6.68; N, 3.97%. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15%.

To a solution of **6** (0.318 g, 0.943 mmol) in chloroform (5 ml) were added *p*-toluenesulfonyl chloride (0.216 g, 1.131 mmol) and triethylamine (0.16 ml, 1.131 mmol). The mixture was stirred at room temperature for 18 h and evaporated in vacuo. The residue was treated with saturated aqueous sodium chloride and extracted with diethyl ether (20 ml×3). The combined extracts were dried over magnesium sulfate and evaporated in vacuo to give a colorless solid of **5** (0.306 g, 66%) after crystallization from ethanol: Colorless prisms (ethanol); mp 145—146 °C; IR (KBr) 2935, 1728, 1336, 1150, and 1064 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=2.37 (3H, s, Ts), 3.19 (3H, s, 4-COOMe), 3.27 (1H, t, J_{4-3}=J_{4-5}=8.8 Hz, H-4), 3.31, 3.37 (each 3H, s, OMe), 3.35 (1H, ddd, J_{3-4}=8.8, J_{3-2}=7.7, and J_{3-CH}=4.4 Hz, H-3), 3.84 (3H, s, 2-COOMe), 4.24 (1H, d, J_{CH-3}=4.4 Hz, 3-CH), 4.47 (1H, d, J_{2-3}=7.7 Hz, H-2), 5.16 (1H, d, J_{5-4}=8.8 Hz, H-5), and 7.2—7.6 (9H, m, Ph and Ar); ^{13}C NMR ($CDCl_3$) δ=21.51 (Ts), 47.11, 50.41, 51.58, 52.63 (C-3, C-4, and 2×COOMe), 55.52 (MeO), 62.19 (C-2), 65.46 (C-5), 104.02 (3-CH), 127.60, 127.79, 127.93, 128.06, 129.27, 134.86, 137.94, 143.74 (each Ph and Ar), 169.61, and 172.18 (each COOMe); MS *m/z* (rel intensity, %) 491 (M^+, 1), 432 (34), 336 (38), 305 (19), and 304 (base peak). Found: C, 58.49; H, 5.88; N, 2.79%. Calcd for $C_{24}H_{29}NO_8S$: C, 58.64; H, 5.95; N, 2.85%.

Cycloaddition of 8 Leading to 9. To a solution of methyl *N*-benzylideneglycinate (0.177 g, 1 mmol) in dry THF (4 ml) were added successively under nitrogen lithium bromide (0.13 g, 1.5 mmol), triethylamine (0.17 ml, 1.2 mmol), and **8** (0.272 g, 1 mmol). The mixture was stirred at room temperature for 24 h, quenched with saturated aqueous ammonium chloride (10 ml), and extracted with dichloromethane (20 ml×3). The combined extracts were dried over magnesium sulfate and evaporated in vacuo. The residue was triturated with diethyl ether and the precipitate was filtered off. The filtrate was evaporated in vacuo to give **9** (0.353 g, 79%) which was purified by column chromatography on silica gel by using diethyl ether as an eluent.

9: Colorless liquid; IR (neat) 3400, 2968, 1728, 1596, 1500, 1340, and 1160 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.69 (1H, ddt, J_{gem}=12.4, J=7.8, and 4.6 Hz, one of H-7'), 1.8—1.9 (2H, m, H-6'), 2.15 (1H, ddt, J_{gem}=12.4, J=7.8, and 4.6 Hz, the other of H-7'), 2.78 (1H, dt, J_{gem}=8.8 and $J_{5'-6'}$=7.8 Hz, one of H-5'), 2.90 (3H, s, 4-COOMe), 3.02 (1H, dd, J_{gem}=8.8 and $J_{1'-7a'}$=7.1 Hz, one of H-1'), 3.2—3.3 (2H, m, H-3 and the other of H-5'), 3.36 (1H, dd, J_{4-5}=8.1 and J_{4-3}=5.5 Hz, H-4), 3.72 (1H, dd, J_{gem}=8.8 and $J_{1'-7a'}$=7.3 Hz, the other of H-1'),

3.91 (3H, s, 2-COOMe), 3.98 (1H, m, H-7a′), 4.06 (1H, d, J_{2-3}=8.1 Hz, H-2), 4.72 (1H, d, J_{5-4}=8.1 Hz, H-5), 4.74 (1H, d, $J_{3'-3}$=3.2 Hz, H-3′), and 6.6—7.4 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=25.40 (C-6′), 31.40 (C-7′), 50.88 (C-5′), 51.29 (C-4), 52.08, 52.30 (each COOMe), 54.73 (C-1′), 57.09 (C-3), 62.62, 63.01 (C-2 and C-7a′), 65.31 (C-5), 82.57 (C-3′), 113.01, 116.84, 126.69, 127.28, 128.02, 129.10, 139.15, 146.10 (each Ph), 172.67, and 173.51 (each COOMe); MS *m/z* (rel intensity, %) 449 (M^+, 16), 264 (15), 188 (16), 187 (base peak), 159 (40), 158 (15), 117 (12), 107 (12), 104 (16), 91 (17), and 77 (18). Found: C, 69.48; H, 6.90; N, 9.37%. Calcd for $C_{26}H_{31}N_3O_4$: C, 69.47; H, 6.95; N, 9.35%.

Cycloaddition of 8 Leading to 10. A similar procedure using *t*-butyl *N*-benzylideneglycinate (0.177 g, 1 mmol) in THF (5 ml), lithium bromide (0.13 g, 1.5 mmol), triethylamine (0.17 ml, 1.2 mmol), and **8** (0.272 g, 1 mmol) under the reaction conditions shown in Table 1 gave **10** (0.464 g, 94%) which was purified by column chromatography on silica gel with diethyl ether as an eluent.

10: Pale yellow liquid; IR (neat) 3403, 2903, 1712, 1588, and 1132 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.46 (1H, m, one of H-7′), 1.61 (9H, s, COOBu-*t*), 1.8—1.9 (2H, m, H-6′), 2.12 (1H, m, the other of H-7′), 2.78 (1H, dt, J_{gem}=8.8 and $J_{5'-6'}$=7.1 Hz, one of H-5′), 2.86 (3H, s, 4-COOMe), 2.99 (1H, dd, J_{gem}=8.8 and $J_{1'-7a'}$=7.3 Hz, one of H-1′), 3.2—3.3 (2H, m, H-3 and the other of H-5′), 3.36 (1H, dd, J_{4-5}=8.1 and J_{4-3}=5.9 Hz, H-4), 3.70 (1H, dd, J_{gem}=8.8 and $J_{1'-7a'}$=7.3 Hz, the other of H-1′), 3.94 (1H, d, J_{2-3}=8.0 Hz, H-2), 3.97 (1H, m, H-7a′), 4.72 (1H, d, J_{5-4}=8.1 Hz, H-5), 4.73 (1H, d, $J_{3'-3}$=2.4 Hz, H-3′), and 6.6—7.3 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=25.40 (C-6′), 28.18 (*t*-Bu), 31.36 (C-7′), 50.70 (C-5′), 51.49 (C-4), 52.37 (COOMe), 54.74 (C-1′), 57.12 (C-3), 62.99, 63.38 (C-2 and C-7a′), 65.38 (C-5), 81.71 (*t*-BuO), 82.76 (C-3′), 112.94, 116.73, 126.63, 127.17, 127.94, 128.97, 139.77, 146.10 (each Ph), 172.32, and 172.52 (each COO); MS *m/z* (rel intensity, %) 491 (M^+, 19), 188 (15), 187 (base peak), and 159 (16). Found: C, 70.78; H, 7.33; N, 8.53%. Calcd for $C_{29}H_{37}N_3O_4$: C, 70.85; H, 7.58; N, 8.55%.

Tosylation of 9 Leading to 11. To a solution of **9** (1.65 g, 3.672 mmol) in chloroform (50 ml) were added *p*-toluenesulfonyl chloride (0.84 g, 4.406 mmol) and triethylamine (0.61 ml, 4.406 mmol). The mixture was stirred overnight at room temperature and evaporated in vacuo. The residue was triturated with diethyl ether (30 ml) and the precipitate was removed off by filtration. The filtrate was evaporated in vacuo and the residue was chromatographed on silica gel with hexane-ethyl acetate (2:1 v/v) to give **11** (1.47 g, 66%).

11: Colorless solid; mp 137.5—139 °C; $[\alpha]_D^{20}$=−58.9° (*c* 1.00, $CHCl_3$); IR (KBr) 3400, 2935, 1720, 1592, 1336, and 1150 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.6—1.7 (1H, m, one of H-7′), 1.8—1.9 (2H, m, H-6′), 2.0—2.2 (1H, m, the other of H-7′), 2.38 (3H, s, Ts), 2.56 (3H, s, 4-COOMe), 2.7—2.8 (1H, m, one of H-5′), 2.82 (1H, t, J_{gem}=$J_{1'-7a'}$=8.4 Hz, one of H-1′), 3.2—3.3 (2H, m, H-4 and the other of H-5′), 3.4—3.5 (2H, m, H-3 and the other of H-1′), 3.6—3.7 (1H, m, H-7a′), 3.97 (3H, s, 2-COOMe), 4.64 (1H, d, $J_{3'-3}$=2.9 Hz, H-3′), 4.66 (1H, d, J_{2-3}=9.5 Hz, H-2), 5.16 (1H, d, J_{5-4}=9.5 Hz, H-5), and 6.4—7.7 (14H, m, Ph and Ar); ^{13}C NMR ($CDCl_3$) δ=21.51 (Ts), 25.37 (C-6′), 30.87 (C-7′), 48.15 (C-5′), 50.77 (C-4), 51.20, 52.71 (each COOMe), 55.02 (C-1′), 56.57 (C-3), 62.73, 63.64 (C-2 and C-7a′), 65.21 (C-5), 80.17 (C-3′), 112.75, 117.13, 127.08, 127.38, 127.81, 128.06, 129.05, 129.23, 134.94, 138.14, 143.71, 145.83 (each Ph and Ar), 168.68, and 172.54 (each COO); MS *m/z* (rel intensity, %) 603 (M^+, 3), 449 (2), 272 (2), 224 (3), 188 (15), 187 (base peak), and 106 (1). Found: C, 64.98; H, 6.23; N, 6.46%. Calcd for $C_{33}H_{37}N_3O_6S$: C, 65.59; H, 6.18; N, 6.96%.

Acetal Exchange of 11 Leading to (−)-5. A solution of **11** (0.2 g, 0.331 mmol) in methanol (15 ml) containing concentrated sulfuric acid (0.5 ml) was refluxed for 20 h. The mixture was neutralized with saturated aqueous sodium hydrogencarbonate, diluted with water (30 ml), and extracted with dichloromethane (30 ml×3). The combined extracts were dried over magnesium sulfate and evaporated in vacuo. The residue was chromatographed on silica gel by using hexane-ethyl acetate (2:1 v/v) as an eluent to give (−)-**5** (0.144 g, 89%) after crystallization from ethanol. $[\alpha]_D^{20}$=−40.90° (*c* 1.00, $CHCl_3$).

Cycloaddition of 8 Leading to 12 and 13. To a solution of LDA, freshly prepared from butyllithium (1.5 M in hexane, 1 M=1 mol dm^{-3}, 0.35 ml, 0.529 mmol) and diisopropylamine (0.054 g, 0.529 mmol) in dry THF, were added successively at −78 °C under nitrogen *N*-benzylideneaminoacetonitrile (0.076 g, 0.529 mmol in THF (1 ml)) and **8** (0.12 g, 0.441 mmol in THF (1 ml)). The mixture was stirred at −78 °C for 1 h, quenched at this temperature with saturated aqueous ammonium chloride, and extracted with diethyl ether (40 ml×3). The combined extracts were dried over magnesium sulfate and evaporated in vacuo to give a 13:76:4:7 mixture (^{1}H NMR) of **12**, **13a**, **13b**, and **13c** (0.183 g, 100%), from which pure **12** was obained on trituration with ethanol (0.018 g, 10%).

12: Colorless needles (ethanol); mp 132.5—134.5 °C; IR (KBr) 3387, 2968, 1714, 1596, 1348, 1160, and 756 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.6—1.8 (1H, m, one of H-7′), 1.8—2.1 (2H, m, H-6′), 2.14 (1H, m, the other of H-7′), 2.76 (1H, m, one of H-5′), 2.78 (3H, s, COOMe), 2.99 (1H, dd, J_{gem}=8.8 and $J_{1'-7a'}$=7.0 Hz, one of H-1′), 3.21 (1H, ddd, J_{gem}=9.5, $J_{5'-6'}$=6.0, and 4.4 Hz, the other of H-5′), 3.35 (1H, dd, J_{3-2}=9.5 and J_{3-4}=8.8 Hz, H-3), 3.58 (1H, m, H-4), 3.62 (1H, dd, J_{gem}=8.8 and $J_{1'-7a'}$=7.3 Hz, the other of H-1′), 3.92 (1H, m, H-7a′), 4.17 (1H, d, J_{5-4}=9.5 Hz, H-5), 4.67 (1H, d, J_{2-3}=9.5 Hz, H-2), 4.68 (1H, d, $J_{3'-4}$=3.7 Hz, H-3′), and 6.6—7.3 (10H, m, Ph); ^{13}C NMR ($CDCl_3$) δ=25.28 (C-6′), 31.12 (C-7′), 49.47, 50.86, 50.99 (C-3, C-5, and C-5′), 51.23 (COOMe), 54.47 (C-1′), 56.70 (C-4), 63.07 (C-7a′), 64.04 (C-2), 80.24 (C-3′), 113.03 (CN), 117.04, 119.92, 127.04, 127.66, 128.00, 129.25, 139.19, 145.74 (each Ph), and 170.79 (COOMe); MS *m/z* (rel intensity, %) 416 (M^+, 1), 188 (15), and 187 (base peak). Found: C, 72.36; H, 6.57; N, 13.19%. Calcd for $C_{25}H_{28}N_4O_2$: C, 72.09; H, 6.78; N, 13.45%.

13a+13b+13c: These were obtained only as mixtures. Based on the ^{1}H and ^{13}C NMR spectra of samples containing different isomer ratios, their structures were tentatively assigned. ^{1}H NMR ($CDCl_3$) **13a**: δ=1.7—1.9 (3H, m, H-6′ and one of H-7′), 2.13 (1H, m, the other of H-7′), 2.55 (1H, m, one of H-5′), 3.01 (3H, s, 4-COOMe), 3.03 (1H, dd, J_{gem}=9.2 and $J_{1'-7a'}$=7.3 Hz, one of H-1′), 3.10 (1H, m, the other of H-5′), 3.48 (1H, dd, J_{4-5}=9.5 and J_{4-3}=7.0 Hz, H-4), 3.64 (1H, dd, J_{gem}=9.2 and $J_{1'-7a'}$=7.3 Hz, the other of H-1′), 3.90 (1H, m, H-3), 4.63 (1H, d, $J_{3'-3}$=7.0 Hz, H-3′), 5.66 (1H, dt, J_{5-4}=9.5 and J_{5-2}=J_{5-3}=2.2 Hz, H-5), 6.6—7.3 (10H, m, Ph), and 7.76 (1H, dd, J_{2-5}=2.2 and J_{2-3}=1.1 Hz, H-2). **13b**: δ=3.13 (3H, s, 4-COOMe), 5.55 (1H, m, H-5), and 7.83 (1H, dt, J_{2-5}=2.6 and J_{2-3}=J_{2-4}=1.1 Hz, H-2). **13c**: δ=3.25 (3H, s,

4-COOMe), 5.72 (1H, m, H-5), and 7.74 (1H, br, H-2). ^{13}C NMR ($CDCl_3$) δ=24.71 (C-6′), 30.33 (C-7′), 50.51 (C-3), 51.13 (COOMe), 53.89, 54.47 (C-4 and C-5′), 59.71 (C-1′), 61.86 (C-7a′), 78.20 (C-5), 81.54 (C-3′), 112.84, 117.15, 127.38, 127.92, 129.25, 129.30, 137.72, 146.50 (each Ph), 168.56 (COOMe), and 171.83 (C-2).

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