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DIASTEREOFACE-DISCRIMINATION REACTION OF LITHIUM OR TITANIUM ESTER ENOLATES WITH A CHIRAL IMINE LEADING TO STEREODIVERGENT SYNTHESIS OF β-LACTAMS

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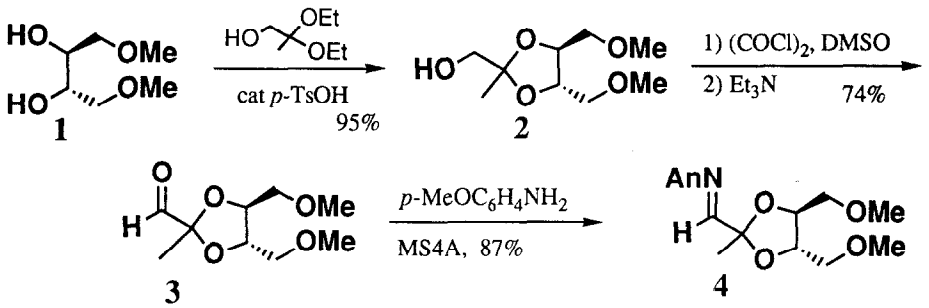
Summary: Diastereoselective addition reaction of ester enolates to a chiral imine possessing (4*S*,5*S*)-4,5-dimethoxymethyl-2-methyl-1,3-dioxolane ring as a chiral auxiliary is reported, in which varying metal enolates resulted in the selective formation of (4*S*)- or (4*R*)-β-lactam. Namely, addition of the lithium enolates provided (4*S*)-β-lactams, whereas the triisopropoxytitanium enolates effected selective formation of (4*R*)-β-lactams, demonstrating a successful example where the titanium ester enolates were employed for the addition reaction to imine. Possible intermediates leading to (4*S*)- and (4*R*)-isomers are also discussed, and different coordination abilities of titanium and lithium metals to the chiral auxiliary are postulated to reflect the reversal of the selectivities.

Introduction

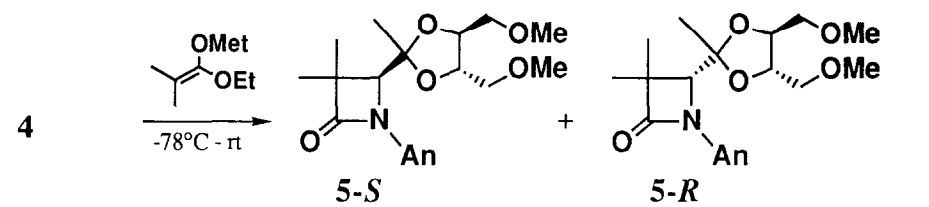
Widespread existence of naturally occurring and synthetic β-lactam antibiotics stimulates the development of new efficient routes to them in optically active forms. Optically active monocyclic 2-azetidinones possessing substituents at 3- and/or 4-positions are an important class of compounds for the synthesis of a series of β-lactam antibiotics such as penicillins, cephalosporins, monobactams, carbapenams, and so on, and a variety of synthetic routes to construct β-lactam skeleton has been developed.[1] Since the discovery of ester-imine condensation reaction to β-lactams by Gilman and Speeter,[2] this methodology to construct β-lactams has received considerable relative attention[3] due to the following features; one step construction of β-lactam ring; availability and variety of ester enolates and imines leading to β-lactams substituted at 3- and/or 4-positions; readily controllable relative stereochemistry at 3- and 4-positions. Although the asymmetric version of such reactions affords chiral 2-azetidinons,[4] unavailability of both enantiomers of chiral auxiliaries from natural sources involving amino acids often results in the production of only one of the two enantiomers. Therefore, it is highly desirable to prepare either enantiomer of 2-azetidinone from a single starting material. Recent reports describing the addition of metal ester enolates from either side of the diastereoface by varying the metal species[5] as well as our earlier studies concerning diastereoface-differentiating addition of organometallics[6] have prompted us to embark on a project that deals with diastereoface-differentiating addition reaction of nucleophiles to imines.[7] In this article the stereoselective construction of both diastereomers of 2-azetidinones substituted at 3- and/or 4-positions from a single chiral imine by taking advantage of different metal species of ester enolates is reported.[8] In particular, generation and application of the triisopropoxytitanium ester enolates for the addition to imines have been exploited.

Results and Discussion

The starting chiral imine **4** possessing an auxiliary derived from (2*S*,3*S*)-tartaric acid was prepared in the following manner: (2*S*,3*S*)-1,4-Dimethoxy-2,3-butanediol **1** prepared as reported previously[9] was subjected to ketal exchange reaction with 2,2-diethoxypropanol[10] derived from piruvate followed by Swern oxidation[11] to give the aldehyde **3**, which in turn condensed with *p*-anisidine to afford the chiral imine **4** in good overall yield.



Addition reaction of ester enolate to the imine **4** was examined using metal enolates of ethyl isobutyrate as a



An = *p*-MeOC$_6$H$_4$-

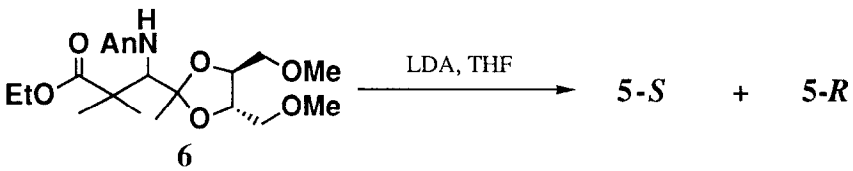
Table 1. Addition Reaction of Metal Enolates of Ethyl Isobutyrate to the Chiral Imine 4

Entry	Met	Solvent	Yield/%[a]	**5-*S* : 5-*R*[b]**
1	Li	THF	78	93 : 7
2	Li	Et_2O	81	93 : 7
3	Li	DME	96	99 : 1
4	Li	$PhCH_3$	79	84 : 16
5	Na	THF	10	95 : 5[c]
6	MgBr	THF	0	- : -
7	$SnBu_3$	THF	0	- : -
8	SnCl	THF	0	- : -
9	$AlEt_2$	THF	0	- : -
10	$ZrClCp_2$	THF	0	- : -
11	ZnCl	THF	84	85 : 15
12	$Ti(O^iPr)_3$	THF	80	8 : 92
13	$Ti(O^iPr)_3$	Et_2O	94	4 : 96
14	$Ti(O^iPr)_3$	DME	91	7 : 93
15	$Ti(O^iPr)_3$	$PhCH_3$	96	11 : 89

[a] Isolated yields. [b] The ratios were determined by capillary GLC (SE-30, 50m). [c] The ratio after cyclization of uncyclized adduct **6** to 2-azetidinone with lithium diisopropyl amide in THF.

model. First, the lithium enolate was subjected to the addition reaction to the imine **4**. The lithium enolate was prepared from ethyl isobutyrate and lithium diisopropylamide (LDA) in THF at -78 °C for 15 min. Then a solution of the imine **4** in THF was added at -78 °C, and the mixture was allowed to stand at room temperature for 12 hr. After normal workup followed by purification on TLC, the directly cyclized 2-azetidinone was obtained. The diastereomeric ratio of (4*S*)-isomer (**5-*S***) to (4*R*)-isomer (**5-*R***) was determined by capillary GLC analysis, and the results are shown in Table 1. Among the solvents examined relatively polar solvents such as Et_2O, THF, and DME gave better selectivities, whereas in toluene the selectivity decreased. When one equivalent of the lithium enolate was used, the reaction did not reach completion, and some of the imine was recovered unaffected. Satisfactory yields were obtained when six equivalents of the enolate were used in THF, Et_2O, and $PhCH_3$. In DME the enolate appeared to be more reactive towards the imine **4** than in THF or Et_2O, and excellent yield and selectivity were obtained with three equivalents of the enolate.

As to other metal enolates, the sodium enolate prepared using sodium hexamethyldisilazide gave mainly the adduct **6** in 61% yield along with the expected azetidinone **5-*S*** and **5-*R*** in a yield of 10%. The adduct **6** readily underwent cyclization upon treatment with LDA in THF, in which the ratio of the two diastereomers was 95 : 5. Other metal enolates were prepared *via in situ* transmetallation of the lithium enolate with one



6

equivalent of metal halides and used for the addition to the imine **4**. Magnesium (MgBr),[12] stannyl ($SnBu_3$ or SnCl),[13] aluminum ($AlEt_2$),[14] and zirconium ($ZrClCp_2$) enolates[15] did not give the azetidinone nor the adduct, whereas the zinc (ZnCl) enolate[16] afforded the azetidinone in good yield with an isomeric ratio of 85 : 15.

Reversal of the diastereoselectivity was realized by switching the metal enolate to triisopropoxytitanium analogue prepared *via in situ* transmetallation of the lithium enolate with $ClTi(O^iPr)_3$,[17a] in which the (*R*)-isomer was obtained predominantly. In the titanium case ether is the solvent of choice and the product yield was also dependent on the amount of the enolate used. For example, with two equivalents of the enolate in ether the reaction did not give the desired product at all, whereas with four equivalents of the enolate in ether the β-lactam was obtained in 73% yield with an isomeric ratio of **5-*S*** : **5-*R*** = 5 : 95. Satisfactory yield and selectivity were obtained with six equivalents of the titanium enolate in ether. The transmetallation from lithium to triisopropoxytitanium was found to be rapid as verified by the following experiments: The product ratio obtained from the reaction involving the transmetallation at -78 °C for 15 min and that obtained with the transmetallation conducted at -30 °C for 3 hr were exactly the same. Furthermore, addition of the lithium enolate to the pre-complexed chiral imine **4** with one equivalent of chlorotitanium triisopropoxide gave **5-*S*** and **5-*R*** in 85% yield in a ratio of 9 : 91. However, the addition of $Ti(O^iPr)_4$ to the lithium enolate did not result in the reversal of diastereoselectivity, implying that the complete transmetallation and not the ate-type complex[17b-d] may be crucial for the changeover of the diastereoselectivity.

A series of both diastereomers of 3,3-disubstituted azetidinone was prepared using α,α-disubstituted ester enolates, and the results are summarized in Table 2. As shown, Li enolates always gave (4*S*)-isomer in good yields with excellent selectivity, whilst with the Ti enolate (4*R*)-isomers were obtained predominantly. Yields

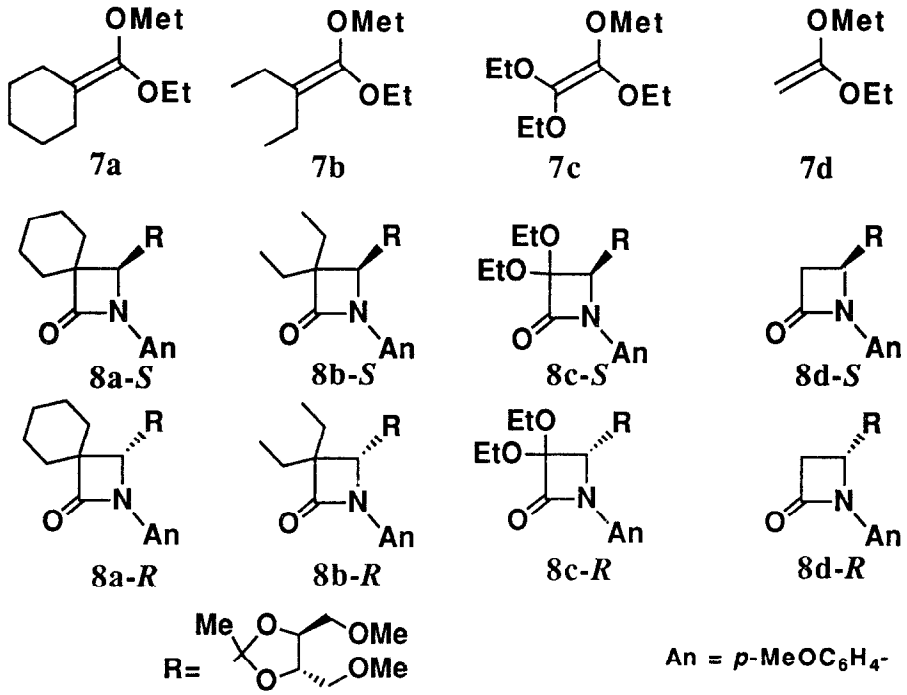


Table 2. Addition Reaction of Various Ester Enolate to the Chiral Imine 4

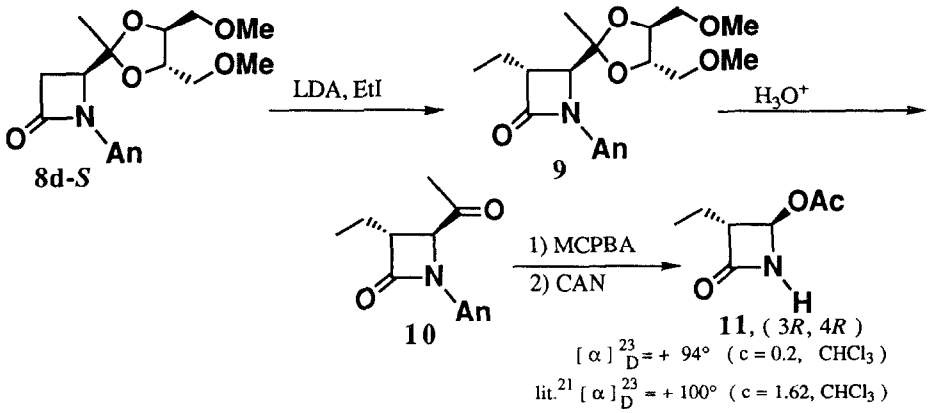
Entry	Enolate	Met	Solvent	Yield/%[a]	8-*S* : 8-*R*
16	**7a**	Li	DME	85[b]	98 : 2[e]
17	**7a**	$Ti(O^iPr)_3$	Et_2O	82[c]	8 : 92[e]
18	**7b**	Li	DME	72[c]	98 : 2[e]
19	**7b**	$Ti(O^iPr)_3$	Et_2O	76[c]	5 : 95[f]
20	**7c**	Li	DME	55[c]	85 : 15[f]
21	**7c**	$Ti(O^iPr)_3$	Et_2O	19[d]	9 : 91[f]
22	**7d**	Li	DME	42[b]	87 : 13[f]
23	**7d**	$Ti(O^iPr)_3$	Et_2O	85[c]	99 : 1[f]

[a] Isolated yields. [b] Three equivalents of ester enolate were used. [c] Six equivalents of ester enolate were used. [d] Fifteen equivalents of ester enolate were used. [e] The ratios were determined by HPLC (n-Hexane : Ethyl Acetate = 3 : 1). [f] The ratios were determined by capillary GLC (SE-30, 50m).

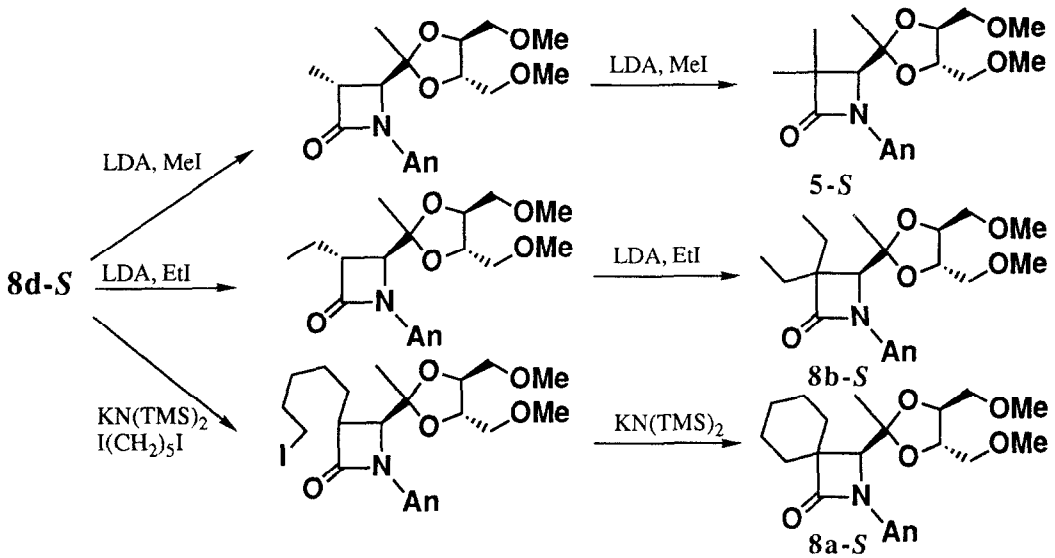
were affected by the steric bulk of the enolates especially with the titanium enolates. In strong contrast to α,α-disubstituted ester enolates, in the case of ethyl acetate no changeover of the diastereoselectivity was observed between Ti and Li enolates. This means that the bulky substituents in those acetate derivatives play an important role in the present diastereoface-discriminations.

The stereochemistry at C-4 in newly formed β-lactams was determined as follows. The β-lactam **8d** without any substituents at 3-position prepared from the titanium enolate of ethyl acetate was transformed into the lithium enolate upon treatment with LDA at -78 °C followed by ethylation with ethyl iodide to give **9**.[18] Removal of the chiral auxiliary was carried out under the acidic conditions with aq HCl in acetone.[19] The

Baeyer-Villiger oxidation with *m*-CPBA in refluxing benzene, followed by oxidative cleavage of methoxyphenyl group with ceric ammonium nitrate in aq acetonitrile[20] gave the known 2-azetidinone **11**.[21] The spectroscopic data and the sign of the optical rotation were in good accordance with those reported.

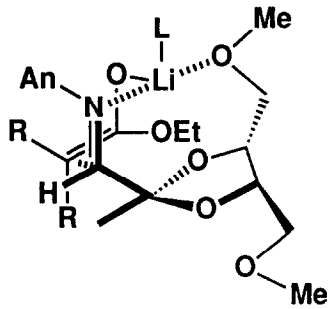


On the other hand, di-alkylation reaction of **8d-*S*** in the same manner[18] afforded β-lactams **5-S** and **8a~b-*S***. Analyses of the products by ^{1}H NMR and chromatographies established the stereochemistry of the C-4 of the β-lactams derived from lithium enolates to be the *S*-configuration.

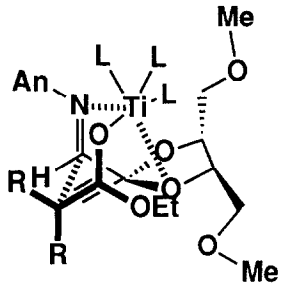


The diastereoface-discrimination studied here appears to be most probably explicable in terms of the following intermediates. Based on the six-membered chair-like cyclic transition states analogous to the aldol reaction[22] and the different coordination states of the enolate metals, the lithium enolate which prefers the tetra-coordinated state forms the intermediate **12-*S*** by the coordination to the methoxy oxygen, leading to the (4*S*)-isomer *via si*-facial attack, whereas the titanium enolate forms a well precedented[17b-d] hexa-coordinated

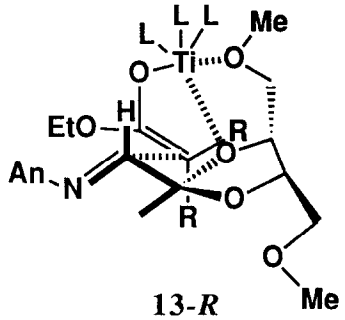
intermediate **12-*R*** involving a coordination to the dioxolane ring, resulting in the formation of (4*R*)-isomer *via* *re*-facial attack. On the other hand, considering the most stable conformer of the imine **4** as well as the steric bulk of the chiral auxiliary and in particular that of the titanium enolate possessing relatively highly coordinating titanium metal, one may not exclude another plausible transition state **13-*R*** where the enolate is located in the least hindered position, leading to the formation of (4*R*)-isomers.



12-*S*



12-*R*



13-*R*

In summary, we have developed a new method for the stereodivergent construction of β-lactam skeletons possessing substituents at 3- and 4-positions from a single chiral imine by taking advantage of different coordination states of the enolate metals, and in particular, demonstrated that titanium ester enolates are efficient ester enolate species for the addition to imines.[23] Almost complete reversal of the diastereoface-discrimination with respect to the C-4 of the β-lactam skeleton attained in the present system coupled with flexibility in the selection of the enolates and ready removal of the chiral auxiliary may offer a useful and practical addition to the existing methodologies.

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Experimental

Infrared spectra of neat film samples (unless otherwise noted) were determined on a JASCO IR-810 spectrometer. ^{1}H NMR spectra were taken on a JEOL JNM-EX270 or JNM-RX60SI spectrometer using tetramethylsilane as an internal standard. Gas liquid phase chromatography (GLC) was performed on a Hitachi G-3000 instrument using an SE-30 (50 m) column. High performance liquid chromatography (HPLC) was carried out on a Hitachi L-4000 detector and a Hitachi L-6000 pump using a Finepak SIL column. Optical rotations were measured with a Union PM-101 polarimeter. Exact mass spectra were taken on a Hitachi M80 spectrometer. Tetrahydrofuran (THF) and diethyl ether were freshly distilled from sodium diphenyl ketyl immediately before use. Dichloromethane was distilled from CaH_2 and stored over molecular sieves 4A. 1,2-Dichloromethane (DME) and toluene were distilled successively from CaH_2 and sodium, and stored over sodium. All the melting points and boiling points were uncorrected. Preparative TLC plates were prepared with Merck Kiesel Gel PF_{254}. Column chromatography was carried out with Wakogel C-300.

(4S,5S)-2-Hydroxymethyl-2-methyl-4,5-dimethoxy-1,3-dioxolane (2)

A mixture of (2*S*,3*S*)-1,4-dimethoxy-2,3-butanediol (14 g, 94 mmol) prepared according to the described procedure,[9] 2,2-diethoxy-1-propanol[10] (13 g, 94 mmol), and *p*-toluenesulfonic acid (3.5 g, 18 mmol) in the presence of molecular sieves 4A (50 g) in benzene (300 ml) was heated at reflux for 4 hr. Then solid sodium bicarbonate (1 g) was added to the mixture, which was filtered through a pad of celite followed by evaporation of the solvent to give an oil. Distillation of the crude oil gave the title compound as a colorless oil (17.6 g,

91%). Bp, 90 °C/0.1 mmHg; NMR (CCl_4) δ 1.36 (s, 3H), 3.41 (s, 6H), 3.10-3.80 (m, 6H), and 3.82-4.43 (m, 2H); IR (neat) 3290, 3000, 2800, 1450, 1260, and 1040 cm^{-1}.

(4*S*,5*S*)-2-Formyl-2-methyl-4,5-dimethoxy-1,3-dioxolane (3)

To a solution of oxalyl chloride (4.5 g, 35 mmol) in dichloromethane (100 ml) was added slowly dimethylsulfoxide (5.5 g, 70 mmol) at -78°C. After 15 min a solution of (4S,5S)-2-hydroxymethyl-2-methyl-4,5-dimethoxy-1,3-dioxolane (6.6 g, 32 mmol) in dichloromethane (20 ml) was added at -78°C. After stirring at -78°C for 1 hr, triethylamine (16.3 g, 16 mmol) was added at that temperature, and the whole mixture was stirred at room temperature for 8 hr. Then addition of water (50 ml) followed by extraction with chloroform, drying with Na_2SO_4, and concentration of the combined extracts gave an oil, which was distilled to give the title compound (4.8 g, 74 %). Bp, 70 °C/0.5 mmHg; NMR (CCl_4) δ 1.36 (s, 6H), 3.10-3.78 (m 4H), 3.80-4.35 (m 2H), and 9.28 (s, 1H); IR (neat) 3140, 3000, 2980, 1680, 1500, and 1000 cm^{-1}; $[\alpha]_D^{23}$ -23.3°(c 0.47, MeOH). Anal. Calcd for $C_9H_{16}O_5$: C, 52.93; H, 7.90. Found: C, 52.69; H, 8.01.

(4*S*,5*S*)-4,5-Dimethoxymethyl-2-(*N*-*p*-methoxyphenyl)iminomethyl-2-metyl-1,3-dioxolane (4)

A mixture of (4S,5S)-2-formyl-2-methyl-4,5-dimethoxy-1,3-dioxolane (429 mg, 2.1 mmol) and *p*-anisidine (259 mg, 2.1 mmol) in dichloromethane (8 ml) was stirred in the presence of molecular sieves 4A (3g) at room temperature for 16 hr. After filtration of molecular sieves, the crude solution was successively concentrated and distilled to give the title compound (570 mg, 88 %), as a yellow oil. Bp, 130 °C/0.2 mmHg; NMR (CCl_4) δ 1.53 (s, 3H), 3.33 (s, 6H), 3.26-3.60 (m, 4H), 3.73 (s, 3H), 3.90-4.16 (m, 2H), 6.73 (d, 2H, J = 9.0 Hz), 6.98 (d, 2H, J = 9.0 Hz), and 7.56 (s, 1H); IR (neat) 3125, 3100, 2800, 1675, 1460, 1380, 1320, and 990 cm^{-1}; $[\alpha]_D^{23}$ -6.0 ° (c 0.94, MeOH). Anal. Calcd for $C_{16}H_{23}NO_5$: C, 61.12; H, 7.49; N, 4.53. Found: C, 59.84; H, 7.78; N, 4.40.

(4*S*)-4-[(4*S*,5*S*)-4.5-Dimethoxymethyl-2-methyl-1,3-dioxolan-2-yl]-1-*p*-methoxyphenyl-3,3-dimethyl-2-azetidinone (5-*S*) (General Procedure for the Reaction of the Imine 4 and Li-Enolate)

A DME solution (3 ml) of LDA was prepared from diisopropylamine (158 mg, 1.5 mmol) and *n*-BuLi (0.96 ml, 1.55N in *n*-hexane). To LDA was added a solution of ethyl isobutyrate (201 mg, 1.5 mmol) in DME (3 ml) at -78°C. After stirring at -78°C for 15 min, a solution of the imine **4** (155 mg, 0.5 mmol) in DME (3 ml) was added at the same temperature, and the mixture was allowed to stand at room temperature for 12 hr. Then the mixture was quenched by adding a saturated aq NaCl (5 ml). Extraction of the entire mixture with ethyl acetate followed by drying (Na_2SO_4) and concentration of the combined extracts gave an oil, which was purified on TLC to give the title compound (182 mg, 96 %) as a yellow oil. The ratio of (4S)- vs (4R)-isomers was determined by GLC to be 99 : 1. NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.42 (s, 3H), 1.43 (s, 3H), 3.16-3.24 (m, 1H), 3.29-3.41 (m, 10H, including two singlets at 3.31 and 3.33 ppm), 3.78 (s, 3H), 3.98 (s,1H), 4.01-4.82 (m, 1H), 6.84 (d, 2H, J = 9.2 Hz) and 7.51 (d, 2H, J = 9.2 Hz); IR (neat) 2890, 1750, 1520, 1470, 1400, 1380, 1300, 1250, 1150, and 1100 cm^{-1}. Anal. Calcd for $C_{20}H_{29}NO_6$: C, 63.30; H, 7.70; N, 3.69. Found: C, 62.96; H, 8.09; N, 3.50.

(4*R*)-4-[(4*S*,5*S*)-4.5-Dimethoxymethyl-2methyl-1,3-dioxolan-2-yl]-1-*p*-methoxyphenyl-3,3-dimethyl-2-azetidinone (5-*R*) (General Procedure for the Reaction of the Imine 4 and Ti-Enolate)

The lithium enolate of ethyl isobutyrate (201 mg, 1.5 mmol) in ether (3 ml) was prepared as described above. To the enolate was added chlorotitanium triisopropoxide[17a] (1.5 ml, 1.01N in *n*-pentane) at -78°C, and the mixture was stirred at that temperature for 15 min. Then a solution of the imine **4** (78 mg, 0.25 mmol) in ether (2 ml) was added dropwise at -78 °C, and the mixture was allowed to stand at room temperature for 12 hr. The workup and purification were carried out as described above to give the title compound as a yellow oil (89 mg, 94 %). The ratio of (4*S*)- vs (4*R*)-isomers was determined by GLC to be 4 : 96; NMR ($CDCl_3$) δ 1.40 (s, 3H), 1.42 (s, 3H), 1.43 (s, 3H), 3.07-3.12 (m, 1H), 3.24 (s, 3H), 3.33-3.39 (m, 4H, including a singlet at 3.36 ppm), 3.47-3.48 (m, 2H), 3.59-3.64 (m, 1H), 3.78 (s, 3H), 3.91-3.98 (m, 5H, including a singlet at 3.95 ppm), 6.85 (d, 2H, J = 9.2 Hz), and 7.46 (d, 2H, J = 9.2 Hz); IR (neat) 2925, 1750, 1515, 1460, 1390, 1380, 1245, 1140, and 1080 cm^{-1}. Anal. Calcd for $C_{20}H_{29}NO_6$: C, 63.30; H, 7.70; N, 3.69. Found: C, 63.48; H, 8.05; N, 3.63.

(4*S*)-3-[(4*S*,5*S*)-4.,5-Dimethoxymethyl-2-methyl-1,3-dioxolan-2-yl]-2-*p*-methoxyphenyl-2-azaspiro[3.5]nonan-1-one (8a-*S*)

This compound was prepared by the reaction of the Li enolate of ethyl cyclohexaxanecarboxylate with the imine **4**. The ratio of (4*S*)- vs (4*R*)-isomers was determined by HPLC to be 98 : 2; NMR (CCl_4) δ 1.35 (s, 3H), 1.31-2.00 (m, 10H) 3.32 (s, 6H), 2.90-3.58 (m, 5H), 3.73 (s, 3H), 3.58-4.23 (m, 2H), 6.75 (d, 2H, J

= 8.0 Hz), and 7.40 (d, 2H, J = 8.0 Hz); IR (neat) 3020, 2925, 2850, 1745, 1520, 1460, 1390, and 1250 cm^{-1}. Exact MS. Calcd for $C_{23}H_{33}NO_6$: (*m/e*) 419.2299. Found: (*m/e*) 419.2287.

(4*R*)-3-[(4*S*,5*S*)-4,5-Dimethoxymethyl-2-methyl-1,3-dioxolan-2-yl]-2-*p*-methoxyphenyl-2-azaspiro[3.5]nonane-1-one (8a-*R*)

This compound was prepared by the reaction of the Ti enolate of ethyl cyclohexaxanecarboxylate with the imine **4**. The ratio of (4*S*)- vs (4*R*)-isomers was determined by HPLC to be 8 : 92; NMR (CCl_4) δ 1.33 (s, 3H), 1.00-2.50 (m, 10H), 3.20 (s, 3H), 3.33 (s, 3H), 3.00-3.23 (m, 5H), 3.70 (s, 3H), 3.23-4.00 (m, 2H), 6.73 (d, 2H, J = 8.0 Hz), and 7.43 (d, 2H, J = 8.0 Hz); IR (neat) 3075, 2925, 2850, 1740, 1515, 1450, 1380, 1300, and 1250 cm^{-1}. Exact MS. Calcd for $C_{23}H_{33}NO_6$: (*m/e*) 419.2299. Found: (*m/e*) 419.2297.

(4*S*)-4-[(4*S*,5*S*)-4,5-Dimethoxymethyl-2-methyl-1,3-dioxolan-2-yl]-1-*p*-methoxyphenyl-3,3-diethyl-2-azetidinone (8b-*S*)

This compound was prepared by the reaction of the Li enolate of ethyl 2-ethylbutyrate with the imine **4**. The ratio of (4*S*)- vs (4*R*)-isomers was determined by GLC to be 98 : 2; NMR ($CDCl_3$) δ 0.97 (t, 3H, J = 7.3 Hz), 1.12 (t, 3H, J = 7.3 Hz), 1.42 (s, 3H), 1.48-2.35 (m, 4H), 3.17-3.56 (m, 4H), 3.30 (s, 3H), 3.35 (s, 3H), 3.78 (s, 3H), 3.98-4.18 (m, 3H), 6.84 (d, 2H, J = 9.2 Hz), and 7.49 (d, 2H, J = 9.2 Hz); IR (neat) 2925, 1750, 1590, 1520, 1460, 1390, 1300, 1250, and 1140 cm^{-1}. Exact MS. Calcd for $C_{22}H_{33}NO_6$: (*m/e*) 407.2299. Found: (*m/e*) 407.2298.

(4*R*)-4-[(4*S*,5*S*)-4,5-Dimethoxymethyl-2-methyl-1,3-dioxolan-2-yl]-1-*p*-methoxyphenyl-3,3-diethyl-2-azetidinone (8b-*R*)

This compound was prepared by the reaction of the Ti enolate of ethyl 2-ethylbutyrate with the imine **4**. The ratio of (4*S*)- vs (4*R*)-isomers was determined by GLC to be 5 : 95; NMR ($CDCl_3$) δ 0.97 (t, 3H, J = 7.3 Hz), 1.12 (t, 3H, J = 7.3 Hz), 1.40 (s, 3H), 1.55-1.75 (m, 2H), 1.80-1.96 (m, 1H), 2.25-2.40 (m, 1H), 2.55-2.63 (m, 1H), 3.04-3.09 (m, 1H), 3.25 (s, 3H), 3.35 (s, 3H), 3.45-3.61 (m, 3H), 3.81 (s, 3H), 3.89-3.98 (m, 2H), 6.84 (d, 2H, J = 8.9 Hz), and 7.42 (d, 2H, J = 8.9 Hz); IR (neat) 2940, 1745, 1515, 1460, 1380, 1300, 1250, and 1140 cm^{-1}. Exact MS. Calcd for $C_{22}H_{33}NO_6$: (*m/e*) 407.2299. Found: (*m/e*) 407.2296.

(4*S*)-4-[(4*S*,5*S*)-4,5-Dimethoxymethyl-2-methyl-1,3-dioxolan-2-yl]-1-*p*-methoxyphenyl-3,3-diethoxy-2-azetidinone (8c-*S*)

This compound was prepared by the reaction of the Li enolate of ethyl 2,2-diethoxyacetate with the imine **4**. The ratio of (4*S*)- vs (4*R*)-isomers was determined by GLC to be 85 : 15; NMR (CCl_4) δ 1.13 (t, 6H, J = 6.0 Hz), 1.37 (s, 3H), 3.28 (s, 6H), 3.29-4.38 (m, 11H), 3.75 (s, 3H), 6.66 (d, 2H, J = 8.4 Hz), and 7.48 (d, 2H, J = 8.4 Hz); IR (neat) 2920, 1745, 1520, and 1110 cm^{-1}. Exact MS. Calcd for $C_{22}H_{33}NO_8$: (*m/e*) 439.2197. Found: (*m/e*) 439.2196.

(4*R*)-4-[(4*S*,5*S*)-4,5-Dimethoxymethyl-2-methyl-1,3-dioxolan-2-yl]-1-*p*-methoxyphenyl-3,3-diethoxy-2-azetidinone (8c-*R*)

This compound was prepared by the reaction of the Ti enolate of ethyl 2,2-diethoxyacetate with the imine **4**. The ratio of (4*S*)- vs (4*R*)-isomers was determined by GLC to be 9 : 91; NMR (CCl_4) δ 1.23 (t, 6H, J = 6.0 Hz), 1.37 (s, 3H), 3.27 (s, 6H), 3.30-4.30 (m, 11H), 3.73 (s, 3H), 6.73 (d, 2H, J = 9.0 Hz), and 7.53 (d, 2H, J = 9.0 Hz); IR (neat) 2920, 1745, 1520, and 1110 cm^{-1}. Exact MS. Calcd for $C_{22}H_{33}NO_8$: (*m/e*) 439.2197. Found: (*m/e*) 439.2210.

(4*S*)-4-[(4*S*,5*S*)-4,5-Dimethoxymethyl-2-methyl-1,3-dioxolan-2-yl]-1-*p*-metoxyphenyl-2-azetidinone (8d-*S*)

This compound was prepared by the reaction of the Ti or Li enolate of ethyl acetate with the imine **4**. The ratios of (4*S*)- vs (4*R*)-isomers were determined by GLC to be 99 : 1 (with Ti enolate) and 87 : 13 (with Li enolate), respectively; NMR ($CDCl_3$) δ 1.40 (s, 3H), 2.94 (dd, 1H, J = 2.6 and 14.8 Hz), 3.08 (dd, 1H, J = 5.7 and 14.8 Hz), 3.32 (s, 3H), 3.38 (s, 3H), 3.39-3.44 (m, 4H), 3.49-3.56 (m, 1H), 3.79 (s, 3H), 4.04-4.11 (m, 1H), 4.22 (dd, 1H, J = 2.6 and 5.7 Hz), 6.85 (d, 2H, J = 9.0 Hz), and 7.52 (d, 2H, J = 9.0 Hz); IR ($CHCl_3$) 2925, 1750, 1640, 1510, 1400, 1295, 1240, 1140, and 1110 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_6$: C, 61.52; H, 7.17; N, 3.99. Found: C, 61.31; H, 7.35; N, 3.75.

(3*R*,4*S*)-4-[(4*S*,5*S*)-4,5-Dimethoxymethyl-2-methyl-1,3-dioxolan-2-yl]-1-*p*-methoxyphenyl-3-ethyl-2-azetidinone (9)

To a solution of diisopropylamine (121 mg, 1.2 mmol) in THF (4 ml) was added *n*-BuLi (1.86 ml, 1.55 N in *n*-hexane) at -78°C and the mixture was stirred at that temperature for 15 min. To the solution of LDA was added a solution of (4*S*)-4-[(4*S*,5*S*)-4,5-dimethoxymethyl-2-methyl-1,3-dioxolan-2-yl]-1-*p*-methoxyphenyl-2-azetidinone (294 mg, 1.0 mmol) in THF (2 ml) and the orange mixture was stirred at -78°C for 30 min. A

solution of ethyl iodide (655 mg, 4.2 mmol) in THF (1 ml) was added and the reaction mixture was allowed to stand at room temperature for 1 hr. After quenching of the reaction with saturated aq NaCl solution followed by extraction with ethyl acetate, the combined extracts were dried ($MgSO_4$) and concentrated to leave an oil, which was purified on TLC to give the title compound (220 mg, 84 %) as a yellow oil; NMR (CCl_4) δ 1.05 (t, 3H), 2.94 (dd, 1H, J = 2.6 and 14.8 Hz), 3.08 (dd, 1H, J = 5.7 and 14.8 Hz), 3.32 (s, 3H), 3.38 (s, 3H, J = 7.0 Hz), 1.32 (s, 3H), 1.43-2.00 (m, 2H), 2.80-4.15 (m, 8H), 3.28 (s, 6H), 3.73 (s, 3H), 6.70 (d, 2H, J = 9.0 Hz), and 7.40 (d, 2H, J = 9.0 Hz); IR (neat) 2945, 2850, 1750, 1520, 1460, 1390, 1300, 1250, 1150, and 1100 cm^{-1}. Anal. Calcd for $C_{20}H_{29}NO_6$: C, 63.30; H, 7.70; N, 3.69. Found: C, 62.97; H, 8.05; N, 3.51.

(3*R*,4*S*)-4-Acetyl-3-ethyl-1-*p*-methoxyphenyl-2-azetidinone (10)

A solution of (3*R*,4*S*)-4-[(4*S*,5*S*)-4,5-dimethoxymethyl-2-methyl-1,3-dioxolan-2-yl]-1-*p*-methoxy-phenyl-3-ethyl-2-azetidinone (82 mg, 0.22 mmol) in acetone (10 ml) was treated with HCl (2 ml, 1.2 N) at reflux for 6 days. After normal workup, the crude oil was purified on TLC to give the title compound (32 mg, 58 %) ; NMR (CCl_4) δ 1.11 (t, 3H, J = 7.4 Hz), 1.63-2.00 (m, 2H), 2.20 (s, 3H), 3.14 (td, J = 3.8 and 2.5 Hz), 3.79 (s, 3H), 4.15 (d, 1H, J = 2.5 Hz), 6.87 (d, 2H, J = 9.0 Hz), and 7.22 (d, 2H, J = 9.0 Hz); IR (neat) 2960, 2930, 1750, 1720, 1520, 1460, 1400, 1360, 1300, 1250, 1180, 1160, 1120, and 1030 cm^{-1}. $[\alpha]_D^{23}$ -126° (c 0.64, MeOH).

(3*R*,4*S*)-4-Acetoxy-3-ethyl-1-*p*-methoxyphenyl-2-azetidinone

A mixture of (3*R*,4*S*)-4-acetyl-3-ethyl-1-*p*-methoxyphenyl-2-azetidinone (32 mg, 0.13 mmol) and *m*-chloroperbenzoic acid (67 mg, 0.39 mmol) in benzene (2 ml) was heated at reflux for 14 hr. Then, aq NaCl solution (2 ml) was added. After normal workup, the crude oil was purified on TLC to give the title compound (34 mg, 100 %) ; NMR (CCl_4) δ 1.10 (t, 3H, J = 9.0 Hz), 1.60-2.10 (m, 2H), 2.13 (s, 3H), 3.17 (td, J = 7.0 and 2.0 Hz), 3.78 (s, 3H), 6.19 (d, 1H, J = 2.0 Hz), 6.87 (d, 2H, J = 9.0 Hz), and 7.34 (d, 2H, J = 9.0 Hz); IR (neat) 2950, 1750, and 1740 cm^{-1}. $[\alpha]_D^{23}$ -70.6° (c 0.68, MeOH).

(3*R*,4*S*)-4-Acetoxy-3-ethyl-2-azetidinone (11)

To a solution of (3*R*,4*S*)-4-acetoxy-3-ethyl-1-*p*-methoxyphenyl-2-azetidinone (34 mg, 0.13 mmol) in acetonitrile (1 ml) was added a solution of ceric ammonium nitrate (197 mg, 0.36 mmol) in water (1 ml) at 0°C, and the mixture was stirred at 0 °C for 30 min. Water (5 ml) was added and the entire mixture was extracted with ethyl acetate. The combined extracts were washed with 40% aqueous $NaHSO_3$. Normal workup followed by purification on TLC gave the title compound (9 mg, 43 %) ; NMR ($CDCl_3$) δ 1.05 (t, 3H, J = 7.3 Hz), 1.65-1.90 (m, 2H), 2.12 (s, 3H), 3.14-3.19 (m, 1H), 5.54 (br s, 1H), and 6.57 (br s, 1H); IR (neat) 2975, 1775, 1750, 1740, 1460, 1380, 1240, 1175, and 1040 cm^{-1}. $[\alpha]_D^{23}$ +94° (c 0.18, $CHCl_3$). The spectroscopic properties were identical with the reported data.[21]

Dimethylation of (4*S*)-4-[(4*S*,5*S*)-4,5-Dimethoxymethyl-2-methyl-1,3-dioxolan-2-yl]-1-p-methoxyphenyl-2-azetidinone (5-*S* from 8d-*S*)

Methylation of (4*S*)-4-[(4*S*,5*S*)-4,5-dimethoxymethyl-2-methyl-1,3-dioxolan-2-yl]-1-*p*-methoxyphenyl-2-azetidinone (0.25 mmol) was carried out with LDA (0.3 mmol) in THF followed by treatment with methyl iodide (0.75 mmol) in the same manner as in the case of ethylation of (3*R*,4*S*)-4-[(4*S*,5*S*)-4,5-dimethoxymethyl-2-methyl-1,3-dioxolan-2-yl]-1-*p*-methoxyphenyl-3-ethyl-2-azetidinone described above. The monomethylated product was further methylated under the same conditions as monomethylation. After normal workup and purification, (4*R*)-4-[(4*S*,5*S*)-4,5-dimethoxymethyl-2-methyl-1,3-dioxolan-2-yl]-1-*p*-methoxyphenyl-3,3-dimethyl-2-azetidinone was obtained. The spectroscopic properties were identical with those obtained from the reaction between the Li enolate of ethyl isobutyrate and the imine **4**.

Diethylation of (4*S*)-4-[(4*S*,5*S*)-4,5-Dimethoxymethyl-2-methyl-1,3-dioxolan-2-yl]-3-ethyl-1-*p*-methoxyphenyl-2-azetidinone (8b-*S* from 8d-*S*)

The monoethylated product was further ethylated under the same conditions as monoethylation described above. After normal workup and purification, (4*R*)-4-[(4*S*,5*S*)-4,5-dimethoxymethyl-2-methyl-1,3-dioxolan-2-yl]-1-*p*-methoxyphenyl-3,3-diethyl-2-azetidinone was obtained. The spectroscopic properties were identical with those obtained from the reaction between the Li enolate of ethyl 2-ethylbutyrate and the imine **4**.

Spiro-annulation of (4*S*)-4-[(4*S*,5*S*)-4,5-Dimethoxymethyl-2-methyl-1,3-dioxolan-2-yl]-1-*p*-methoxyphenyl-2-azetidinone to (4*S*)-3-[(4*S*,5*S*)-4,5-Dimethoxymethyl-2methyl-1,3-dioxolane-2-yl]-2-p-methoxyphenyl-2-azaspiro[3.5]nonane-1-one (8a-*S* from 8d-*S*)

To a solution of (4*S*)-4-[(4*S*,5*S*)-4,5-dimethoxymethyl-2-methyl-1,3-dioxolan-2-yl]-1-*p*-methoxyphenyl-2-azetidinone (32 mg, 0.091 mmol) in THF (1 ml) was treated with potassium hexamethyldisilazide (0.5 M in toluene, 0.236 ml, 0.12 mmol) at -78°C for 1 hr followed by treatment with 1,5-diiodopentane (88 mg, 0.27

mmol) in the same manner as in the case of ethylation. The crude mixture was further treated with potassium hexamethyldisilazide (0.5 M in toluene, 0.236 ml, 0.12 mmol) at 0°C for 2 hr. After normal workup and purification, (4*S*)-3-[(4*S*,5*S*)-4,5-dimethoxymethyl-2-methyl-1,3-dioxolan-2-yl]-2-*p*-methoxyphenyl-2-aza-spiro[3.5]nonane-1-one (4 mg, 10 %) was obtained. The spectroscopic properties were identical with those obtained from the reaction between the Li enolate of ethyl cyclohexanecarboxylate and the imine **4**.

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