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Highly Stereocontrolled Asymmetric Syntheses of Taxol and Taxotère C-13 Side Chain Analogues[1]

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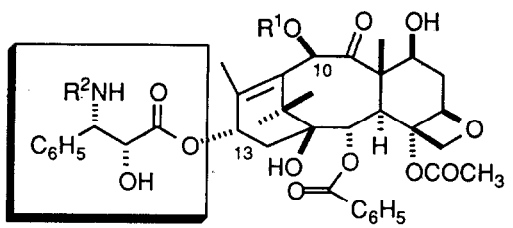
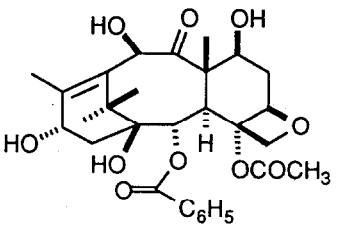
Abstract: Asymmetric aldol reaction of (+)-tricarbonyl(η^6-2-trimethylsilylbenzaldehyde)chromium(0) complex (**4**) with titanium enolate of *S-tert*-butyl benzyloxyethanethioate (**10**) provided, after consecutive desilylation and decomplexation, *anti*-aldol product **15** in a highly stereoselective manner. *Anti*-product **15** was subsequently converted to (2R,3S)-*N*-benzoyl- and *N-tert*-butoxycarbonyl-3-phenylisoserine methyl esters (**23** and **24**), C-13 side chain analogues of taxol (**1**) and taxotère (**2**).

Taxol (**1**), isolated from the bark of *Taxus brevifolia*,[2,3] is a complex diterpene and the most exciting anti-cancer natural product.[4] Although taxol (**1**) is obtainable in very low yield from natural resources, its synthetic precursor, 10-deacetylbaccatin III (**3**),[5] has been shown to be more readily available from *Taxus baccata*. Alternatively, taxotère (**2**),[6] a semisynthetic analogue of taxol (**1**), can be supplied from relatively abundant 10-deacetylbaccatin III (**3**)[5] through esterification of its C-13 hydroxyl group. Taxotère (**2**) was proved to be so far the most powerful and promising cancer chemotherapeutic agent among the known taxanes[7](natural and unnatural). A (2R,3S)-*N*-acyl-3-phenylisoserine moiety, a common structural feature of the C-13 side chain of these two anticancer agents taxol (**1**) and taxotère (**2**) has been found to be crucial for the strong anticancer



N-Acyl-(2R,3S)-3-phenyl-isoserine moiety



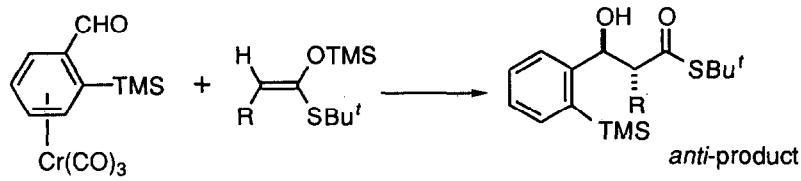
Taxol : **1** R^1= Ac, R^2= C_6H_5CO 10-Deacetylbaccatin III : **3**

Taxotère : **2** R^1= H, R^2= ^{t}BuOCO

activity.[6,8] With the availability of 10-deacetylbaccatin III (**3**), many efforts[9,10] have recently been made for the

development of efficient synthesis of (2R,3S)-*N*-acyl-3-phenylisoserine derivatives. We describe herein a highly stereoselective alternative for the preparation of (2R,3S)-*N*-benzoyl- and *N*-*tert*-butoxycarbonyl-3-phenylisoserine methyl esters where a homochiral tricarbonyl(η^6-trimethylsilylbenzaldehyde)chromium(0) complex was chosen as a chiral starting material.

Recent efforts from this laboratory[11] disclosed that the chiral chromium-complexed aldehyde **4**[11,12] emerged as an important chiral synthon producing optically active *anti*-aldol products **7**[13] when exposed to acyclic *O*-silyl ketene *O,S*-acetals **5** possessing an alkyl group at its C_2-position. We envisioned that *anti*-aldol product **8** would be selectively formed if aldol reaction of the chiral chromium-complexed aldehyde **4** with *O*-silyl ketene *O,S*-acetal **6**, derived from *S*-*tert*-butyl benzyloxyethanethioate (**10**), proceeded as the case for the acetal **5**. *Anti*-aldol product **8**, thus prepared, would be in turn converted to the desired *N*-acyl-3-phenylisoserine derivatives through conventional manipulations.



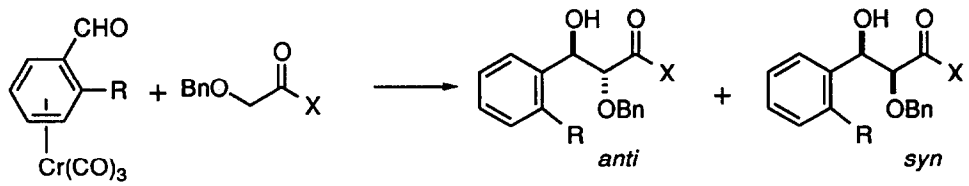
(+)-**4**

5 : R = alkyl
6 : R = benzyloxy

7 : R = alkyl
8 : R = benzyloxy

At the inception of this study, therefore, aldol reaction of racemic chromium-complexed aldehyde **4**[14] with *O*-silyl ketene *O,S*-acetal **6** was executed so as to estimate the sense of stereoselectivity. Benzyloxy-substituted *O,S*-acetal **6** was prepared from **10** according to the literature.[15] Aldol reaction between racemic chromium-complexed aldehyde **4** and *O,S*-acetal **6** was carried out in methylene chloride (CH_2Cl_2) at various temperature in the presence of Lewis acid. The reaction, however, didn't give condensation products and resulted in the recovery of the starting aldehyde **4**. An unexpected result forced us to investigate the aldol reaction of **4** with *S*-*tert*-butyl benzyloxyethanethioate (**10**) under several conditions from reactive as well as stereoselective points of view. Treatment of the chromium-complexed aldehyde **4** with lithium enolate of **10** in tetrahydrofuran (THF) afforded, after decomplexation with cerium (IV) ammonium nitrate (CAN), aldol products **8** and **11** in 63% yield. Stereochemical assignment of these aldol condensation products was made by ^{1}H NMR spectral consideration based on the literature precedents.[16] The ratio of *anti* to *syn*[17] (**8** to **11**) in the aldol mixture was determined to be 20 to 80 by the ^{1}H NMR spectral analysis. Preferential formation of *syn*-isomer **11** over *anti*-isomer **8** may be interpreted in terms of the cyclic chair-like transition sate, since lithium enolate of **10** could be considered to exist as a mixture of (*E*)- and (*Z*)-enolates in the ratio of 67 to 33 judging from the *E* : *Z* ratio of *O*-silyl ketene *O,S*-acetal **6** (*E* : *Z* = 67 : 33).[15] Therefore, the ratio of (*E*)-enolate to (*Z*)-enolate would reflect that of **11** to **8**.

Although the aldol reaction occurred in sharp contrast to the case of benzyloxy-substituted *O*-silyl ketene *O,S*-acetal **6**, the undesired *syn*-isomer **11** became a main product. Variation of lithium enolate of **10** to the



4 : R = TMS **10** : X = SBu^t **8** : R = TMS, X = SBu^t **11** : R = TMS, X = SBu^t

9 : R = H **12** : X = OMe **13** : R = TMS, X = OMe **14** : R = TMS, X = OMe

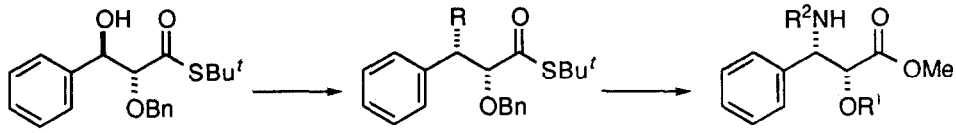
15 : R = H, X = SBu^t **16** : R = H, X = SBu^t

corresponding titanium enolate generated *in situ* by treatment of the former with chlorotitanium triisopropoxide[18] in THF brought about reverse sense of stereoselectivity to yield aldol products **8** and **11** in a highly *anti*-selective manner (**8** : **11** = 95 : 5) in 64% yield. Titanium enolate prepared by metal exchange method[18] furnished satisfactory stereoselectivity and chemical yield as well. However the procedure was too capricious to make itself practical. We conjectured this caprice was due in large part to an insufficient metal exchange from lithium to titanium counterion. In order to remedy the above situation, we tried to prepare titanium enolate of *S-tert*-butyl benzyloxyethanethioate (**10**) directly according to the literature procedure.[19] To a solution of **10** in dry CH_2Cl_2 at -78°C was added successively titanium tetrachloride ($TiCl_4$) and triethylamine. The resulting titanium enolate subsequently reacted with the chromium-complexed aldehyde **4** to give, after decomplexation, aldol products **8** and **11** in 91% yield as a mixture of *anti*- and *syn*-isomers in a ratio of 95 to 5. The ratio of **8** to **11** (95 : 5) was the same as that observed in the best case of lithium-titanium exchange method. It is noteworthy that this procedure provided high selectivity (*anti* : *syn* = 95 : 5) as well as high yield with reliable reproducibility. Aldol reaction of **4** with titanium enolate of methyl benzyloxyacetate (**12**) also worked under the similar condition described for that of thioester **10** to produce aldol products **13** and **14**[16] in 66% yield. However, *anti*-selectivity was no longer to be found (**13** : **14** = 38 : 62) in contrast to the case of thioester **10**. This result may be in line with previous observation[11b, 20] where *O*-silyl ketene *O,S*-acetals revealed much better *anti*-selectivity than the corresponding *O*-silyl ketene acetals in aldol reactions in the presence of Lewis acid.

It became apparent that the *ortho* trimethylsilyl (TMS) group of the complex **4** did not play an important role for achievement of high *anti*-selectivity. When tricarbonyl(η^6-benzaldehyde)chromium(0) complex (**9**)[21] was submitted to aldol reaction under the identical condition for **4**, *anti*-aldol product **15** was obtained predominantly (**15** : **16** = 92 : 8) in 67% yield. Inspection of the role of chromium tricarbonyl species for *anti*-selectivity was performed with the corresponding non-complexed aldehydes. 2-Trimethylsilylbenzaldehyde and benzaldehyde were independently treated with titanium enolate of **10** under the similar condition described for **4** except for CAN treatment to furnish aldol products in a highly stereocontrolled fashion in 52 and 91% yields, respectively. Ratios of *anti* to *syn* (**8** to **11** and **15** to **16**) were shown to be >98 to <2 and 97 to 3, respectively. Control experiments clearly indicated that chromium complexation isn't mandatory for observed *anti*-selectivity, either. Thus, we developed highly *anti*-selective aldol reactions between benzaldehyde derivatives with or without chromium complexation and titanium enolate of *S-tert*-butyl benzyloxyethanethioate (**10**).

To sum up these results; (i) the aldol reactions of benzaldehyde derivatives with titanium enolate of **10** constantly afforded the aldol products in a highly *anti*-selective fashion; (ii) chromium complexation and the *ortho* TMS group on the benzene ring are not necessary for *anti*-selectivity, though both of them are obviously essential to synthesize chiral *anti*-aldol product required for the C-13 side chains of taxol (**1**) and taxotère (**2**). Because of the uncertainty about the nature of the trichlorotitanium enolates,[18,19] the reaction mechanism of this *anti*-selective aldol reactions has not yet been elucidated. However, it would be expected that (*E*)-titanium enolate could exclusively be formed by intramolecular chelation between the carbonyl functionality and oxygen atom of benzyloxy group through titanium atom.[22] (E)-enolate, thus formed, would react with the aldehyde counterparts through the cyclic boat-like transition state[23] in which the aldehyde oxygen could coordinate with titanium atom resulting in *anti*-aldol products. It appeared shortly after our preliminary results[1] that an Italian group[23] reported similar *anti*-selective aldol reactions of alkyl and aryl aldehydes with titanium enolate derived from *S*-aryl benzyloxyethanethioate.

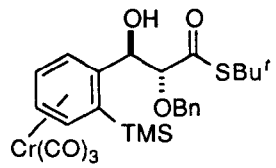
With *anti*-aldol product **15** in racemic form in hand, we set about converting it into (2R*,3S*)-*N*-acyl-3-phenylisoserine derivatives. Introduction of the azido functionality with stereo-inversion could be realized by exposure of **15** containing a small amount of **16** (**15** : **16** = 92 : 8) to the Mitsunobu condition (hydrazoic acid / triphenylphosphine / diethyl azodicarboxylate)[24] to give *syn*-azido compound **17**.[25] The azido functionality of **17** was subsequently reduced with triphenylphosphine and water[26] producing the amino derivative **18**,[25] which underwent benzoylation with benzoyl chloride and *N,N*-dimethylaminopyridine (DMAP) to afford pure **19** in 53% overall yield from **15**. Thallium trinitrate[27] effected transesterification of the thioester **19** to the corresponding methyl ester to provide **21** in 90% yield. Reductive debenzylation of **21** with 10% Pd-C under a hydrogen atmosphere yielded (2R*,3S*)-*N*-benzoyl-3-phenylisoserine methyl ester (**23**)[10a] in 89% yield. A synthesis of the desired racemic 3-phenylisoserine analogue was, thus, achieved in a highly stereocontrolled way.



15

17 : R = N_3
18 : R = NH_2
19 : R = NHBz
20 : R = NHBoc

21 : R^1= Bn, R^2= Bz
22 : R^1= Bn, R^2= Boc
23 : R^1= H, R^2= Bz
24 : R^1= H, R^2= Boc



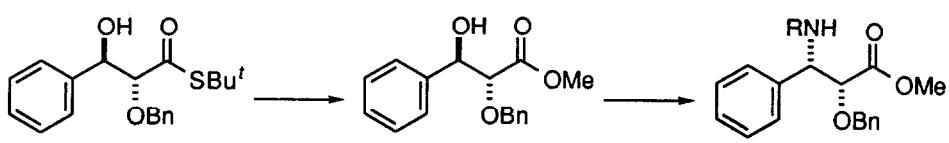
25

Bz = benzoyl, Boc = *tert*-butoxycarbonyl

On the basis of an efficient transformation of **15** to **23** in racemic form, we addressed our endeavor to the asymmetric synthesis of an optically active methyl ester **23**, a taxol (**1**) C-13 side chain analogue. Optically active aldol product **15** was prepared as follows. Upon treatment with titanium enolate of *S*-*tert*-butyl benzyloxyethanethioate (**10**) in CH_2Cl_2, the optically active chromium-complexed aldehyde (+)-**4**[11] gave

condensation product **25**[28] with chromium complexation in 93%yield. The chromium-complexed **25** was submitted to the desilylating condition composed of *n*-tetrabutylammonium fluoride and hydrofluoric acid to afford the desilylated product, the chromium moiety of which was subsequently removed by irradiation leading to the optically active **15** in 63% yield as an inseparable mixture of chiral **15** and **16** in a ratio of 95 to 5. By the analogy of racemic series, the optically active **15**[28] was transformed into the benzoylamino derivative **19** through successive introduction of the azido functionality, reduction, and benzoylation. Chromatography of the crude product furnished pure (+)-**19** in 63% overall yield from **15**. It should be stated that (+)-**19** is completely free from the corresponding *syn*-isomers. Enantiomeric excess (e.e.)[29] of (+)-**19** was determined to be more than 98% that implies, in this paper, no peaks due to an antipode could be detected in the ^{1}H NMR spectrum. Conversion of (+)-**19** into methyl ester (-)-**21** proceeded in a quantitative yield. Final debenzylation of (-)-**21** afforded (-)-(2R,3S)-*N*-benzoyl-3-phenylisoserine methyl ester (**23**)[10a] in 78% yield. ^{1}H NMR spectral analysis showed **23** comprises one enantiomer and is optically pure.[30]

By taking advantage of optically active amino derivative **18**, we tried to prepare the optically active (2R,3S)-*N*-*tert*-butoxycarbonyl-3-phenylisoserine methyl ester (**24**),[9b] taxotère (**2**) C-13 side chain. The amino derivative **18**, prepared from **17** by reduction, was acylated with 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile[31] and triethylamine in aqueous dioxane to furnish, after chromatographic purification, (+)-**20** in 69% overall yield from the optically active thioester **15**. Transesterification of (+)-**20** to (+)-**22** was somewhat troublesome because of contamination with several by-products, although (+)-**22** was isolated in 64% yield by column chromatography. This step suffered from inconvenience of work-up procedure, since brownish red fine metal suspensions were formed as the reaction proceeded. It was not the case when thallium trinitrate was employed for conversion of **19** to **21** where colorless solids, presumably thallium (II) salts arisen from thallium trinitrate, were precipitated and easily filtered off. According to the procedure described for **21**, debenzylation of (+)-**22** was carried out to give (-)-(2R,3S)-*N*-*tert*-butoxycarbonyl-3-phenylisoserine methyl ester (**24**)[10a] in 70% yield with >98% e.e.[29]



15 **26** **21** : R = Bz
22 : R = Boc

An alternative protocol was further devised to overcome disadvantage encountered during conversion of **20** to **22**. The optically active *anti*-aldol product **15** (containing a small amount of **16**)[28] was first transesterified by thallium trinitrate in methanol to afford the methyl ester **26** in 83% yield. Methyl ester **26** was exposed to successive treatment with the Mitsunobu condition, reduction, and *tert*-butoxycarbonylation as mentioned earlier to give (+)-**22** in 65% yield. In addition, methyl ester **26** was transformed into (-)-**21** in 60% overall yield from **26**. The latter protocol through **26** was much easier than the former one involving **17** and **18** from manipulation point of view.

In summary, we could accomplish highly stereocontrolled asymmetric syntheses of taxol (**1**) and taxotère (**2**) side chain analogues **23** and **24** from the optically active chromium-complexed aldehyde **4**. This procedure provides a new entry to a highly stereoselective asymmetric synthesis of (2R,3S)-*N*-acyl-3-phenylisoserine derivatives.

Experimental Section

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were measured with a JASCO-102 spectrometer in $CHCl_3$ unless otherwise stated, mass spectra (MS) and high resolution mass spectra with a Hitachi M-80 mass spectrometer, optical rotations with a JASCO DIP-181 digital polarimeter, ^1H NMR spectra with a JEOL JNM-GSX 500 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard, and ^{13}C NMR spectra with a JEOL EX-270 and JNM-GSX 500 spectrometers in $CDCl_3$ with $CDCl_3$ (77.00 ppm) as an internal reference. CH_2Cl_2 was freshly distilled from P_2O_5, and THF from sodium diphenylketyl prior to use. Aldol reactions were performed in oven-dried glasswares under an inert atmosphere of nitrogen. Silica gel (silica gel 60, 230 - 400 mesh, Nacalai Tesque) and alumina (Aluminiumoxid 90, Aktivitätsstufe II-III, 70-230 mesh, Merck) were used for chromatography. Organic extracts were dried over anhydrous Na_2SO_4.

Reaction of (±)-4 with Titanium Enolate of 10. *Method A* —— To a solution of **10** (140 mg, 0.58 mmol) in dry CH_2Cl_2 (3 ml) was added dropwise a solution of $TiCl_4$ in dry CH_2Cl_2 (1.0 M solution; 0.86 ml, 0.86 mmol) at -78°C. After being stirred for 5 min, triethylamine (0.12 ml, 0.86 mmol) was added dropwise to the reaction mixture, which was then kept at the same temperature for 30 min. A solution of **4** (150 mg, 0.48 mmol) in dry CH_2Cl_2 (4 ml) was added to the titanium enolate solution over a period of 5 min at -78°C. Stirring was continued for an additional hour at the same temperature and the reaction was quenched by addition of 5% $NaHCO_3$ solution. The reaction mixture was diluted with CH_2Cl_2 (50 ml), washed with water, dried, and concentrated to leave the aldol products with chromium complexation. The crude aldol products were dissolved in MeOH (3 ml), to which CAN (729 mg, 1.33 mmol) was added portionwise at 0°C. The reaction mixture was stirred at 0°C for 30 min and MeOH was evaporated off. The residue was taken up in CH_2Cl_2, washed with water and brine, dried and concentrated to dryness. Chromatography of the residual oil with hexane-acetone (20/1) afforded a mixture of *S-tert*-butyl (2R*,3R*)- and (2R*,3S*)-2-benzyloxy-3-hydroxy-3-(2-trimethylsilylphenyl)propanethioate (**8** and **11**) (181 mg, 91%, **8** : **11** = 95 : 5) as a colorless oil; MS *m/z* 238

(M^+ - TMS-$PhCH_2O$, 33), 182 (25), 163 (42), 147 (12), 91 (100), 73 (15), 57 (51); IR 3500 (OH), 1660 (C=O) cm^{-1}; ^1H NMR δ 7.52-7.49 (m, 2H, aromatic H), 7.37-7.34 (m, 1H, aromatic H), 7.31-7.28 (m, 1H, aromatic H), 7.22-7.19 (m, 3H, aromatic H), 6.97-6.95 (m, 2H, aromatic H), 5.25 (dd, 0.05H, *J*=3.9, 5.4 Hz, C_3-H), 5.12 (dd, 0.95H, *J*=2.9, 7.8 Hz, C_3-H), 4.70 (d, 0.05H, *J*=10.8 Hz, benzylic H), 4.53 (d, 0.95H, *J*=11.2 Hz, benzylic H), 4.24 (d, 0.05H, *J*=10.8 Hz, benzylic H), 4.10 (d, 0.95H, *J*=11.2 Hz, benzylic H), 3.98 (d, 0.05 H, *J*=5.4 Hz, C_2-H), 3.94 (d, 0.95 H, *J*=7.8 Hz, C_2-H), 3.05 (d, 0.95H, *J*=2.9 Hz, OH), 2.71 (d, 0.05H, *J*=3.9 Hz, OH), 1.50 (s, 8.55H, *t*-Bu), 1.46 (s, 0.45H, *t*-Bu), 0.31 (s, 0.45H, TMS), 0.30 (s, 8.55H, TMS); ^{13}C NMR δ (for *anti*-product **8**) 203.65, 145.21, 139.57, 136.62, 134.30, 129.25, 128.12, 128.09, 127.75, 127.39, 126.54, 87.66, 73.75, 73.55, 47.71, 29.72, 0.96. *Anal.* Calcd for $C_{23}H_{32}O_3SSi$: C, 66.30; H, 7.74. Found: C, 66.17; H, 7.79. *Method B* —— To a solution of lithium diisopropylamide in THF (4 ml), prepared from diisopropylamine (0.06 ml, 0.457 mmol) and 1.6M *n*-butyllithium in hexane solution (0.29 ml, 0.457 mmol), was added dropwise a solution of **10** (99 mg, 0.416 mmol) in THF (2 ml) at -78°C. After being stirred at the same temperature for 30 min, chlorotitanium triisopropoxide (95%, 0.39 ml, 0.512 mmol) was added to the reaction mixture (a pale yellow solution turned to bright orange). The reaction temperature was then transferred to -40°C and kept there for 2 h. The reaction mixture was again cooled down to -78°C, to which a solution of (±)-**4** (43.5 mg, 0.138 mmol) in THF (1.5 ml) was added. The reaction mixture was maintained at -78°C for 2 h, quenched by addition of saturated NH_4F solution and allowed to warm up to room temperature. The THF solution was diluted with ethyl acetate, which was washed with water and brine, dried, and concentrated to dryness. Decomplexation of the residue with CAN, followed by chromatographic purification gave a mixture of **8** and **11** (37.1 mg, 64%, **8** : **11** = 95 : 5).

Reaction of (±)-4 with Lithium Enolate of 10. —— To a solution of lithium diisopropylamide in THF (3 ml), prepared from diisopropylamine (0.03 ml, 0.176 mmol) and 1.6M *n*-butyllithium in hexane solution (0.13 ml, 0.177 mmol), was added dropwise a solution of **10** (42 mg, 0.177 mmol) in THF (1 ml) at -78°C. After being stirred at the same temperature for 30 min, a solution of **4** (18.5 mg, 0.059 mmol) in THF (1.5 ml) was added to the reaction mixture and kept there for an additional hour. The reaction mixture was diluted with ethyl acetate (30 ml), which was washed with water and brine, dried, and concentrated to dryness. Decomplexation of the residue with CAN (66.5 mg, 0.12 mmol) under the condition described above gave a mixture of **8** and **11** (15.5 mg, 63%, **8** : **11** = 20 : 80).

Reaction of (±)-4 with Titanium Enolate of 12. According to *Method A* described for reaction of (±)-**4** with titanium enolate of **10**, (±)-**4** (84 mg, 0.27 mmol) was treated with titanium enolate of **12**, prepared from **12** (58 mg, 0.32 mmol), $TiCl_4$ (1.0M CH_2Cl_2 solution; 0.64 ml, 0.64 mmol), and triethylamine (0.09ml, 0.64 mmol). Prior to treatment with CAN, the aldol products with chromium complexation were separated by column chromatography with hexan-acetone (10/1) to give fraction-1 (57 mg) and fraction-2 (35 mg). Faction-2 (35 mg) was exposed to CAN (116 mg, 0.21 mmol) in MeOH (2 ml) to give methyl (2R*,3R*)-2-benzyloxy-3-hydroxy-3-(2-trimethylsilylphenyl)propanoate (**13**, 24 mg, 25% from **4**) as a colorless oil; MS *m/z* 358 (M^+, 0.4), 235 (36), 191 (16), 180 (100), 163 (100), 149 (23), 105 (7), 91 (100), 73 (35); IR 3550 (OH), 1735 (C=O) cm^{-1}; ^1H NMR δ 7.52 (dd, 1H, *J*=1.5, 7.8 Hz, aromatic H), 7.47 (d, 1H, *J*=7.8 Hz, aromatic H), 7.35 (dt, 1H, *J*=1.5, 7.8 Hz, aromatic-H), 7.30-7.23 (m, 4H, aromatic H), 7.08-7.06 (m, 2H, aromatic H), 5.24 (dd, 1H, *J*=3.9, 6.8 Hz, C_3-H), 4.60 (d, 1H, *J*=11.7 Hz, benzylic H), 4.28 (d, 1H, *J*=11.7 Hz, benzylic H), 4.13

(d, 1H, *J*=6.8 Hz, C_2-H), 3.71 (s, 3H, OCH_3), 2.76 (d, 1H, *J*=3.9 Hz, OH), 0.31 (s, 9H, TMS); ^{13}C NMR δ 171.50, 145.02, 139.18, 136.66, 134.49, 129.27, 128.21, 128.18, 127.91, 127.51, 126.02, 81.78, 73.37, 72.89, 51.93, 0.80. *Anal.* Cald for $C_{20}H_{26}O_4Si$: C, 67.01; H, 7.31. Found: C, 67.36; H, 7.37. Fraction-1 (57 mg) was exposed to CAN (190 mg, 0.35 mmol) in MeOH (3 ml) to give methyl (2R*,3S*)-2-benzyloxy-3-hydroxy-3-(2-trimethylsilylphenyl)propanoate (**14**, 39 mg, 41% from **4**) as a colorless oil; MS *m/z* 358 (M^+, 3.7), 235 (11), 191 (6), 180 (100), 163 (100), 105 (21), 91 (100), 73 (54); IR 3550 (OH), 1735 (C=O) cm^{-1}; ^1H NMR δ 7.60 (d, 1H, *J*=7.8 Hz, aromatic H), 7.50 (dt, 1H, *J*=1.5, 7.8 Hz, aromatic H), 7.40 (dt, 1H, *J*=1.5, 7.8 Hz, aromatic H), 7.32-7.25 (m, 4H, aromatic H), 7.18-7.16 (m, 2H, aromatic H), 5.24 (t, 1H, *J*=5.4 Hz, C_3-H), 4.73 (d, 1H, *J*=11.7 Hz, benzylic H), 4.41 (d, 1H, *J*=11.7 Hz, benzylic H), 4.15 (d, 1H, *J*=5.4 Hz, C_2-H), 3.67 (s, 3H, OCH_3), 2.89 (d, 1H, *J*=5.4 Hz, OH), 0.31 (s, 9H, TMS); ^{13}C NMR δ 170.85, 144.60, 138.28, 136.57, 134.59, 129.06, 128.39, 128.30, 128.05, 127.55, 127.51, 81.35, 73.69, 73.21, 52.04, 0.65. *Anal.* Cald for $C_{20}H_{26}O_4Si$: C, 67.01; H, 7.31. Found: C, 66.79; H, 7.32.

Reaction of 9 with Titanium Enolate of 10. According to *Method A* described for reaction of (±)-**4** with titanium enolate of **10**, **9** (77 mg, 0.32 mmol) was treated with titanium enolate of **10**, prepared from **10** (91 mg, 0.38 mmol), $TiCl_4$ (1.0M CH_2Cl_2 solution; 0.69 ml, 0.69 mmol), and triethylamine (0.08 ml, 0.69 mmol), to provide after CAN (606 mg, 1.11 mmol) treatment *S-tert*-butyl (2R*,3R*)- and (2R*,3S*)-2-benzyloxy-3-hydroxy-3-phenylpropanethioate (**15** and **16**)(72 mg, 67%, **15** : **16** = 92 : 8) as a colorless oil; MS *m/z* 238 (M^+ - $PhCH_2O$, 34), 182 (23), 147 (8), 107 (12), 91 (100), 57 (22); IR 3550 (OH), 1665 (C=O) cm^{-1}; ^1H NMR δ 7.37-7.23 (m, 8H, aromatic H), 7.14-7.12 (m, 2H, aromatic H), 4.96 (t, 0.08H, *J*=5.2 Hz, C_3-H), 4.90 (dd, 0.92H, *J*=3.7, 6.7 Hz, C_3-H), 4.72 (d, 0.08H, *J*=11.0 Hz, benzylic H), 4.63 (d, 0.92H, *J*=11.0 Hz, benzylic H), 4.35 (d, 0.08H, *J*=11.0 Hz, benzylic H), 4.20 (d, 0.92H, *J*=11.0 Hz, benzylic H), 3.94 (d, 0.08H, *J*=5.2 Hz, C_2-H), 3.93 (d, 0.92H, *J*=6.7 Hz, C_2-H), 3.12 (d, 0.92H, *J*=3.7 Hz, OH), 2.95 (d, 0.08H, *J*=5.2 Hz, OH), 1.45 (s, 8.28H, *t*-Bu), 1.43 (s, 0.72H, *t*-Bu); ^{13}C NMR δ (for *anti*-product **15**) 202.83, 139.43, 136.69, 128.33, 128.12, 128.09, 128.06, 127.95, 127.24, 87.54, 74.93, 73.95, 47.59, 29.64. *Anal.* Calcd for $C_{20}H_{24}O_3S$: C, 69.74; H, 7.02. Found: C, 69.38; H, 7.02.

Reaction of 2-Trimethylsilylbenzaldehyde with Titanium Enolate of 10. —— Titanium enolate of **10**, generated from **10** (139 mg, 0.58 mmol), $TiCl_4$ (1M CH_2Cl_2 solution; 0.88 ml, 0.88 mmol) and triethylamine (0.13 ml, 0.88 mmol), was treated with 2-trimethylsilylbenzaldehyde (87 mg, 0.49 mmol) under the condition (*Method A*) described for the reaction of **4** except for CAN treatment to furnish, after chromatographic purification, **8** (106 mg, 52%).

Reaction of Benzaldehyde with Titanium Enolate of 10. —— Titanium enolate of **10**, generated from **10** (135 mg, 0.57 mmol), $TiCl_4$ (1M CH_2Cl_2 solution; 0.85 ml, 0.85 mmol) and triethylamine (0.12 ml, 0.85 mmol), was treated with benzaldehyde (50 mg, 0.47 mmol) under the condition (*Method A*) described for the reaction of **4** except for CAN treatment to furnish, after chromatographic purification , a mixture of **15** and **16** (148 mg, 91%, **15** : **16** = 97 : 3).

***S-tert*-Butyl (2R*,3S*)-3-Benzoylamino-2-benzyloxy-3-phenylpropanethioate (19).** —— To a solution of (±)-**15** (528 mg, 1.53 mmol, **15** : **16** = 92 : 8) and triphenylphosphine (806 mg, 3.06 mmol) in

dry benzene (7 ml) were successively added a solution of hydrazoic acid (*ca.* 4% solution; 2.5 ml, 2.30 mmol) and diethyl azodicarboxylate (534 mg, 3.06 mmol) in dry benzene (2 ml) at room temperature. After being stirred for 1 h, benzene was evaporated off and the residue was passed through a silica gel pad (with hexane-ethyl acetate = 50/1) to remove excess reagents. The curde azido compound **17** (450 mg, *syn* : *anti* = 92 : 8), thus obtained, was dissolved in THF (8 ml), to which triphenylphosphine (384 mg, 1.46 mmol) and water (two drops) were added. The reaction mixture was heated at 60°C for 15 h. Addition of Na_2SO_4 to the reaction mixture and the THF was evaporated off. The residue was passed through a silica gel pad (with hexane-ethyl acetate = 10/1) to leave the crude amino derivative **18** (351 mg, *syn* : *anti* = 92 : 8). This crude amino derivative **18** was used for the next step. Benzoyl chloride (287 mg, 2.04 mmol) was added to a mixture of **18** (351 mg, 1.02 mmol) and DMAP (250 mg, 2.04 mmol) in dry CH_2Cl_2 (5 ml) at 0°C. The reaction mixture was stirred at room temperature for 1 h, diluted with CH_2Cl_2, washed with water, dried, and concentrated to dryness. Chromatography of the residue with hexane- acetone (10/1) afforded pure amide (±)-**19** (364 mg, 53% overall yield from **15**) as colorless needles, mp 118-118.5°C (hexane-acetone); MS *m/z* 447 (M^+, 0.4), 330 (11), 238 (9), 211 (12), 105 (89), 91 (100), 77 (23), 57 (16); IR 3450 (NH), 1670 (C=O) cm^{-1}; ^1H NMR δ 7.85-7.83 (m, 2H, aromatic H), 7.53-7.41 (m, 3H, aromatic H), 7.32-7.20 (m, 9H, aromatic H), 7.14-7.12 (m, 2H, NH and aromatic H), 5.66 (dd, 1H, *J*=2.3, 8.9 Hz, C_3-H), 4.71, (d, 1H, *J*=11.6 Hz, benzylic H), 4.32 (d, 1H, *J*=11.6 Hz, benzylic H), 4.17 (d, 1H, *J*=2.3 Hz, C_2-H), 1.43 (s, 9H, *t*-Bu); ^{13}C NMR δ 201.26, 166.48, 138.74, 136.33, 134.32, 131.55, 128.53, 128.40, 128.39, 128.19, 128.10, 127.56, 127.18, 126.81, 86.62, 73.99, 55.29, 47.86, 29.67. *Anal.* Calcd for $C_{27}H_{29}NO_3Si$: C, 72.45; H, 6.53; N, 3.13. Found: C, 72.49; H, 6.55; N, 3.11.

Methyl (2R*,3S*)-Benzoylamino-2-benzyloxy-3-phenylpropanoate (21). —— To a solution of **19** (120 mg, 0.27 mmol) in dry MeOH (3 ml) was added TTN•trihydrate (417 mg, 0.94 mmol) at 27°C. The reaction mixture was stirred at the same temperature overnight. The resulting precipitates were filtered off by suction and the filtrate was evaporated off. Chromatography of the residue with hexane-acetone (10/1) afforded (±)-**21** (94 mg, 90%) as colorless needles, mp 125-125.5°C (hexane-acetone); MS *m/z* 389 (M^+, 0.2), 210 (100), 106 (12), 91 (50), 77 (38); IR 3450 (NH), 1735 (C=O), 1660 (C=O) cm^{-1}; ^1H NMR δ 7.81-7.80 (m, 2H, aromatic H), 7.52-7.49 (m, 1H, aromatic H), 7.45-7.42 (m, 2H, aromatic H), 7.36-7.26 (m, 5H, aromatic H), 7.25-7.18 (m, 4H, aromatic H), 7.05-7.03 (m, 2H, NH and aromatic H), 5.69 (dd, 1H, *J*=2.4, 8.8 Hz, C_3-H), 4.75 (d, 1H, *J*=11.7 Hz, benzylic H), 4.35 (d, 1H, *J*=11.7 Hz, benzylic H), 4.32 (d, 1H, *J*=2.4 Hz, C_2-H), 3.78 (s, 3H, OCH_3); ^{13}C NMR δ 170.75, 166.86, 138.89, 136.54, 134.26, 131.63, 128.58, 128.44, 128.35, 127.97, 127.94, 127.62, 127.14, 126.74, 79.82, 72.78, 55.04, 52.38. *Anal.* Calcd for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60. Found: C, 73.95; H, 5.99; N, 3.55.

Methyl (2R*,3S*)-3-Benzoylamino-2-hydroxy-3-phenylpropanoate (23). —— 10% HCl solution (two drops) was added to a mixture of (±)-**21** (41 mg, 0.11 mmol) and 10% Pd-C (10 mg) in EtOH (3 ml). The reaction mixture was heated at 60°C under a hydrogen atmosphere for 1 h. After removal of the catalyst, the filtrate was evaporated off and the residue was taken up in ethyl acetate, which was washed with saturated $NaHCO_3$ solution and water, dried, and concentrated to dryness. Chromatography of the residue with hexane-acetone (5/1) afforded (±)-**23** (28 mg, 89%) as colorless needles, mp 161-162°C [$CHCl_3$-($^iPr)_2O$]; MS *m/z* 299 (M^+, 1), 283 (9), 238 (96), 182 (52), 163 (55), 147 (20), 91 (100); IR 3370 (OH and NH), 1735 (C=O), 1640 (C=O) cm^{-1}; ^1H NMR δ 7.78-7.76 (m, 2H, aromatic H), 7.53-7.50 (m, 1H, aromatic H), 7.46-7.34 (m, 6H,

aromatic H), 7.32-7.29 (m, 1H, aromatic H), 6.97 (d, 1H, *J*=9.0 Hz, NH), 5.75 (dd, 1H, *J*=2.0, 9.0 Hz, C_3-H), 4.64 (dd, 1H, *J*=2.0, 3.9 Hz, C_2-H), 3.85 (s, 3H, OCH_3), 3.27 (d, 1H, *J*=3.9 Hz, OH); ^{13}C NMR δ 173.40, 166.83, 138.69, 134.07, 131.77, 128.75, 128.64, 127.96, 127.04, 126.88, 73.19, 54.79, 53.30. *Anal.* Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.13, H, 5.79; N, 4.67.

(2R,3R,1'S,2'R)-Tricarbonyl[*S-tert*-butyl 2-benzyloxy-3-hydroxy-3-(2-trimethylsilylphenyl)propanethioate]chromium(0) (25). —— According to the procedure (*Method A*) except for decomplexation process described for (±)-**4** with titanium enolate of **10**, (+)-**4** (299 mg, 0.95 mmol) was treated with titanium enolate of **10**, prepared from **10** (284 mg, 1.19 mmol), $TiCl_4$ (1.0M CH_2Cl_2 solution; 1.8 ml, 1.8 mmol), and triethylamine (0.25 ml, 1.79 mmol), to provide the chromium-complexed aldol product **25** (489 mg, 93%, *anti* : *syn* = 95 : 5) as a yellow oil; MS *m/z* 552 (M^+, 2), 468 (40), 314 (23), 230 (71), 163 (100), 91 (91), 57 (77); IR 1970 (C≡O), 1890 (C≡O), 1660 (C=O) cm^{-1}; ^1H NMR δ 7.28-7.22 (m, 3H, aromatic H), 7.10-7.06 (m, 2H, aromatic H), 5.60 (dt, 0.05H, *J*=1.0, 6.4 Hz, aromatic H), 5.55 (dd, 0.05H, *J*=1.0, 6.4 Hz, aromatic H), 5.48 (dt, 0.95H, *J*=1.0, 6.4 Hz, aromatic H), 5.38 (dd, 0.95H, *J*=1.0, 6.4 Hz, aromatic H), 5.33 (dd, 0.05H, *J*=1.0, 6.4 Hz, aromatic H), 5.28 (dd, 0.95H, *J*=1.0, 6.4 Hz, aromatic H), 5.19 (dt, 0.95H, *J*=1.0, 6.4 Hz, aromatic H), 5.13 (dt, 0.05H, *J*=1.0, 6.4 Hz, aromatic H), 5.00 (dd, 0.05H, *J*=1.5, 5.4 Hz, C_3-H), 4.82 (d, 0.05H, *J*=11.7 Hz, benzylic H), 4.80 (dd, 0.95H, *J*=2.6, 6.9 Hz, C_3-H), 4.71 (d, 0.95H, *J*=11.7 Hz, benzylic H), 4.29 (d, 0.95H, *J*=11.7 Hz, benzylic H), 4.23 (d, 0.05H, *J*=11.7 Hz, benzylic H), 3.86 (d, 0.05H, *J*=5.4 Hz, C_2-H), 3.71 (d, 0.95H, *J*=6.9 Hz, C_2-H), 3.08 (d, 0.05H, *J*=1.5 Hz, OH), 2.76 (d, 0.95H, *J*=2.6 Hz, OH), 1.54 (s, 0.45H, *t*-Bu), 1.51 (s, 8.55H, *t*-Bu), 0.32 (s, 8.55H, TMS), 0.29 (s, 0.45H, TMS); ^{13}C NMR δ (for *anti*-product) 233.08, 200.95, 135.90, 128.79, 128.45, 128.32, 118.71, 100.09, 99.39, 94.52, 91.07, 88.23, 87.26, 73.07, 71.27, 48.48, 29.76, 1.01. *Anal.* Calcd for $C_{26}H_{32}CrO_6SSi$: C, 56.50; H, 5.84. Found: C, 56.57; H, 6.07.

***S-tert*-Butyl (2R,3R)-2-Benzyloxy-3-hydroxy-3-phenylpropanethioate (15).** —— To a solution of **25** (460 mg, 0.832 mmol, *anti* : *syn* = 95 : 5) in THF / CH_3CN (1/1, 50 ml) was added a solution of TBAF and hydrofluoric acid in aqueous THF (0.9 ml, prepared from 0.85 ml of 1.0M TBAF in THF solution and 0.05 ml of 47% hydrofluoric acid) at -78°C. After being stirred at -15°C for 15 min, the reaction mixture was gradually warmed up to room temperature. The reaction mixture was diluted with ethyl acetate and washed with water and brine, dried, and concentrated to leave the desilylated product, which was subsequently dissolved in diethyl ether (300 ml). The etheral solution was irradiated with high-pressure mercury lamp through a Pyrex filter for 2 h and the resulting precipitates were filtered off. The filtrate was concentrated and chromatographed with hexane-ethyl acetate (20/1) to give **15** (182 mg, 63%, **15** : **16** = 95 : 5). *Anal.* Calcd for $C_{20}H_{24}O_3S$: C, 69.74; H, 7.02. Found: C, 69.59; H, 6.96.

***S-tert*-Butyl (2R,3S)-3-Benzoylamino-2-benzyloxy-3-phenylpropanethioate (19).** —— According to the procedure that described for conversion of (±)-**15** into (±)-**19**, (+)-**19** (127 mg, 63%) was obtained from the optically active **15** (155 mg, 0.45 mmol, *anti* : *syn* = 95 : 5). (+)-**19** : colorless crystals, mp 138-139°C (hexane-acetone); $[\alpha]_D^{23}$ +58.5° (*c* 0.41, $CHCl_3$).[29] *Anal.* Calcd for $C_{27}H_{29}NO_3S$: C, 72.45; H, 6.53; N, 3.13. Found: C, 72.49; H, 6.55; N, 3.11.

Methyl (2R,3S)-3-Benzoylamino-2-benzyloxy-3-phenylpropanoate (21). —— According to the procedure that described for conversion of (±)-**19** into (±)-**21**, (-)-**21** (49.6 mg, 100%) was obtained from (+)-**19** (57 mg, 0.13 mmol). (+)-**21** : colorless needles, mp 103-105°C [$CHCl_3$-($^iPr)_2O$]; $[\alpha]_D^{22}$ -5.3° (*c* 0.41, $CHCl_3$).[29] *Anal.* Calcd for $C_{24}H_{23}NO_4$: C, 74.02; H, 5.95; N, 3.60. Found: C, 73.90; H, 6.05; N, 3.59.

Methyl (2R,3S)-Benzoylamino-2-hydroxy-3-phenylpropanoate (23). —— According to the procedure that described for conversion of (±)-**21** into (±)-**23**, (-)-**23** (18.2 mg, 78%) was obtained from (-)-**21** (30.3 mg, 0.08 mmol). (-)-**23** : colorless needles, mp 180-182°C [$CHCl_3$ - ($iPr)_2O$](lit.[10a] mp 184-185°C); $[\alpha]_D^{20}$ -48.1° (*c* 0.28, MeOH)[30][lit.[10a] $[\alpha]_D^{24}$ -48° (*c* 1.0, MeOH)]. *Anal.* Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.07; H, 5.70; N, 4.59.

***S-tert*-Butyl (2R,3S)-2-Benzyloxy-3-*tert*-butoxycarbonylamino-3-phenylpropanethioate (20).** —— According to the procedure that described for conversion of (±)-**15** into (±)-**19**, the optically active **15** (81 mg, 0.24 mmol, *anti* : *syn* = 95 : 5) was transformed into the optically active amino derivative **18** (72 mg). The crude amino derivative **18** (72 mg, 0.21 mmol) and triethylamine (0.04 ml, 0.29 mmol) were dissolved in 25% aqueous dioxane (1.5 ml), to which 2-(*tert*-butoxycarbonyloxyimino)-2-phenylacetonitrile (129 mg, 0.52 mmol) was added. The reaction mixture was stirred at room temperature for 20 h and diluted with ethyl acetate (10 ml) that was washed with water and brine, dried, and concentrated to dryness. Chromatography of the residue on alumina with hexane-ethyl acetate (10/1) afforded (+)-**20** (72 mg, 69% overall yield from **15**)as colorless needles, mp 88-89°C (hexane); $[\alpha]_D^{24}$ +90.2° (*c* 0.32, $CHCl_3$); MS *m/z* 443 (M^+, 1), 388 (2), 314 (12), 270 (41), 226 (34), 206 (87), 150 (100), 106 (55), 91 (67), 57 (23); IR 1710 (C=O), 1670 (C=O) cm^{-1}; ^1H NMR δ 7.32-7.26 (m, 8H, aromatic H), 7.12-7.10 (m, 2H, aromatic H), 5.58 (br-s, 1H, NH), 5.20 (d, 1H, *J*=5.9 Hz, C_3-H), 4.63 (d, 1H, *J*=11.2 Hz, benzylic H), 4.19 (d, 1H, *J*=11.2 Hz, benzylic H), 4.01 (br-s, 1H, C_2-H), 1.48 (s, 9H, *t*-Bu), 1.39 (br-s, 9H, *t*-Bu); ^{13}C NMR δ 201.13, 154.88, 139.62, 136.44, 128.32, 128.28, 128.18, 128.00, 127.35, 126.69, 87.12, 79.48, 74.05, 56.19, 47.57, 29.69, 28.30. *Anal.* Calcd for C25H33NO4S: C, 67.69; H, 7.50; N, 3.16. Found: C, 67.74; H, 7.61; N, 3.19.

Methyl (2R,3S)-2-benzyloxy-3-*tert*-butoxycarbonylamino-3-phenylpropanoate (22). —— According to the procedure that described for conversion of (±)-**19** into (±)-**21**, (+)-**22** (9.6 mg, 64%) was obtained from (+)-**20** (17 mg, 0.04 mmol). (+)-**22** : colorless crystals, mp 61-62°C (hexane); $[\alpha]_D^{24}$ +44.9° (c 0.27, $CHCl_3$); MS *m/z* 385 (M^+, 0.3), 270 (13), 206 (100), 150 (100), 106 (100), 91 (100), 57 (100); IR 1740 (C=O), 1705 (C=O) cm^{-1}; ^1H NMR δ 7.34-7.27 (m, 6H, aromatic H), 7.24-7.18 (m, 2H, aromatic H), 7.00-6.98 (m, 2H, aromatic H), 5.59 (d, 1H, *J*=6.8 Hz, NH), 5.23 (d, 1H, *J*=6.8 Hz, C_3-H), 4.68 (d, 1H, *J*=11.7 Hz, benzylic H), 4.27 (d, 1H, *J*=11.7 Hz, benzylic H), 4.15 (br-s, 1H, C_2-H), 3.78 (s, 3H, OCH_3), 1.41 (s, 9H, *t*-Bu); ^{13}C NMR δ 170.73, 155.13, 139.45, 136.59, 128.31, 128.25, 127.87, 127.84, 127.41, 126.61, 80.17, 79.71, 72.75, 56.06, 52.23, 28.23. *Anal.* Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.71; H, 7.12; N, 3.63.

Methyl (2R,3S)-2-Hydroxy-3-*tert*-butoxycarbonylamino-3-phenylpropanoate (24). —— According to the procedure that described for conversion of (±)-**21** into (±)-**23**, (-)-**24** (26.8 mg, 70%) was obtained from (+)-**22** (50 mg, 0.13 mmol). (-)-**24** : colorless crystals, mp 131.5-132°C (CH_2Cl_2-cyclohexane)

(lit.[10a] mp 130.5-131.5°C); $[\alpha]_D^{25}$ -6.9° (*c* 0.25, $CHCl_3$)[29] [lit.[10a] $[\alpha]_D^{24}$ -7° (*c* 1.2, $CHCl_3$)]; MS *m/z* 295 (M^+, 10), 239 (39), 206 (100), 150 (100), 106 (100), 57 (100); IR 3500 (OH), 1730 (C=O), 1705 (C=O) cm^{-1}; ^1H NMR δ 7.36-7.34 (m, 4H, aromatic H), 7.30-7.29 (m, 1H, aromatic H), 5.39 (d, 1H, *J*=9.3 Hz, NH), 5.22 (d, 1H, *J*=9.3 Hz, C_3-H), 4.47 (br-s, 1H, C_2-H), 3.84 (s, 3H, OCH_3), 3.14 (br-s, 1H, OH), 1.42 (s, 9H, *t*-Bu); ^{13}C NMR δ 173.39, 155.10, 139.07, 128.58, 127.69, 126.68, 79.89, 73.49, 56.03, 53.03, 28.22. *Anal.* Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.65; H, 7.13; N, 4.60.

Methyl (2R,3R)-2-Benzyloxy-3-hydroxy-3-phenylpropanoate (26). —— According to the procedure that described for conversion of (±)-**19** into (±)-**21**, the optically active **15** (151 mg, 0.44 mmol, *anti* : *syn* = 95 : 5) was treated with TTN•trihydrate (682 mg, 1.53 mmol) in MeOH (2 ml). Work-up and chromatography of the residue with hexane-acetone (10/1) afforded **26** (104 mg, 83%, *anti* : *syn* = 95 : 5) as a colorless oil; MS *m/z* 286 (M^+, 0.1), 180 (100), 162 (100), 131 (27), 119 (20), 107 (100), 91 (100); IR 3500 (OH), 1740 (C=O) cm^{-1}; ^1H NMR δ 7.37-7.26 (m, 8H, aromatic H), 7.17-7.15 (m, 2H, aromatic H), 5.00-4.98 (m, 1H, C_3-H), 4.69 (d, 0.05H, *J*=11.2 Hz, benzylic H), 4.67 (d, 0.95H, *J*=11.7 Hz, benzylic H), 4.43 (d, 0.05H, *J*=11.2 Hz, benzylic H), 4.35 (d, 0.95H, *J*=11.7 Hz, benzylic H), 4.12 (d, 0.95H, *J*=6.3 Hz, C_2-H), 4.07 (d, 0.05H, *J*=5.4 Hz, C_2-H), 3.68 (s, 0.95H, OCH_3), 3.65 (s, 0.05H, OCH_3), 2.97 (d, 0.05H, *J*=5.9 Hz, OH), 2.87 (d, 0.95H, *J*=4.4 Hz, OH); ^{13}C NMR δ (for *anti*-product) 171.10, 129.52, 136.75, 128.39, 128.25, 128.12, 128.03, 128.00, 126.72, 81.80, 74.22, 73.01, 51.95. High resolution mass calcd for $C_{17}H_{18}O_4$, 286.1203, found 286.1127.

Conversion of 26 into (-)-21. —— According to the procedure that described for conversion of (±)-**15** into (±)-**19**, (-)-**21** (64mg, 60%) was obtained from **26** (78 mg, 0.27 mmol, *anti* : *syn* = 95 : 5) by successive Mitsunobu reaction, reduction, and benzoylation.

Conversion of 26 into (+)-22. —— According to the procedure that described for conversion of **15** into (+)-**20**, (+)-**22** (42mg, 65%) was obtained from **26** (48 mg, 0.17 mmol, *anti* : *syn* = 95 : 5) by successive Mitsunobu reaction, reduction, and *tert*-butoxycarbonylation.

References and Notes

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