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Highly Diastereoselective Enolate Addition of O-Protected α-Hydroxyacetate to (S_R)-*tert*-Butanesulfinylimines: Synthesis of Taxol Side Chain

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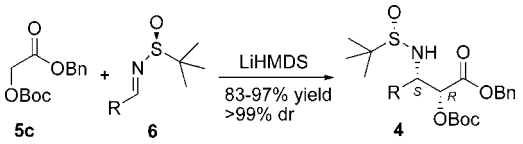
Received November 5, 2005



The taxol side chain (S_R,2*R*,3*S*)-*N*-*tert*-butanesulfinyl-*O*-Boc-3-phenylisoserine benzyl ester **4c** was synthesized through a lithium enolate addition of *O*-Boc-α-hydroxyacetate benzyl ester **5c** to benzylidene (S_R)-*tert*-butanesulfinamide **6a** in excellent yield and diastereoselectivity. By similar approach, a series of enantiopure 3-substituted isoserine benzyl esters **4** useful for the semi-syntheses of taxol derivatives were also prepared in high to excellent yields and diastereoselectivities. The diastereoselective addition mechanism was discussed on the basis of the experimental observation.

Introduction

Taxol **1**,[1] isolated from *Taxus brevifolia*, is considered the most promising anticancer drug. Considering the complexity of taxol and the fact that the content of taxol in the bark of *T. brevifolia* is only about 0.03%, the major barrier for medical usage of taxol is resource limitation. Mass production by total synthesis[2] and by isolation from the natural resource no doubt is not economical and has sacrificed the rare species of *T. brevifolia*. For this reason, extensive efforts have been focused on semi-synthesis[3] of taxol by the condensation of commercially available 14-β-hydroxy-10-deacetylbacctin III **2** with a side chain such as *N*-benzoyl-(2*R*, 3*S*)-3-phenylisoserine **3** (Figure 1). Therefore, over the last 20 years, the efficient synthesis of enantiopure side chain **3** has attracted much attention from academic community as well as industry.[4] In this article, we report a highly diastereoselective enolate addition of *O*-Boc-α-hydroxyacetate to benzylidene (S_R)-*tert*-butanesulfinamide to lead directly to the formation of *N*,*O*-protected (S_R,2*R*,3*S*)-3-phenylisoserine ester **4c** in excellent yield. The efficiency and applicable scope of *tert*-butanesulfinylimine enolate addition to prepare a series of enantiopure 3-substituted isoserines **4** were well demonstrated.

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10.1021/jo052298n CCC: $33.50
Published on Web 01/13/2006

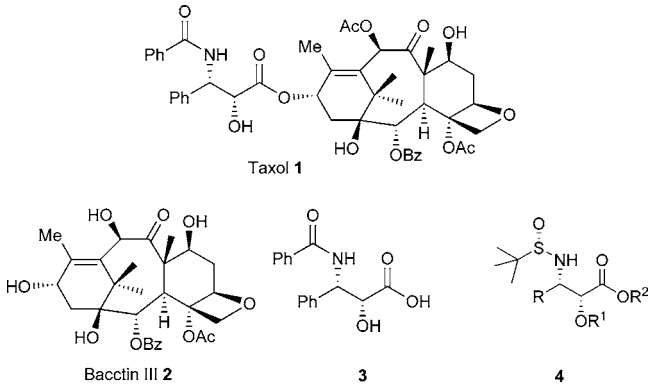
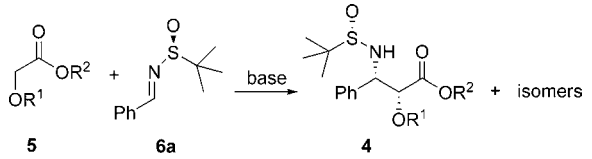


FIGURE 1. Structure of taxol, bacctin III, and taxol side chains.

SCHEME 1. Diastereoselective Addition of 5 to *tert*-Butanesulfinylimine 6a



Results and Discussion

In recent years, Davis, Ellman, and co-workers have demonstrated well the diastereoselective sulfinylimine enolate addition reaction as one of the important reactions of C−C bond formation for preparing chiral β-amino acid ester and α,β-diamino acid ester.[5,6] In continuing our study on chiral *tert*-butanesulfinamide chemistry,[7] we envisioned that enantiopure 3-phenylisoserine ester **4** with a (2*R*,3*S*) configuration may be directly assembled by the diastereoselective addition of an enolate of *O*-protected α-hydroxyacetate **5** to enantiopure *tert*-butanesulfinylimine **6a**, although theoretically four isomers will be formed in the addition reaction (Scheme 1).

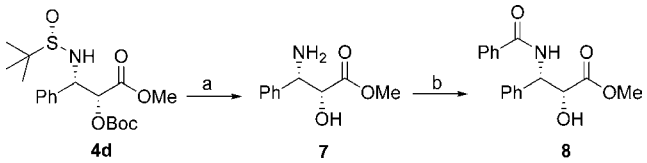
Initial experiments showed that the addition reaction of imine **6a** with a series of lithium enolates of benzyl acetates **5** (R^1 = Et_3Si, $^tBuMe_2Si$, Bn, *p*-$MeOC_6H_4$, ^tBuCO, and Bz, R^2 = Bn), generated by the reaction of **5** with LDA at −78 °C in THF, respectively, gave unexceptionally a complicated mixture in low yield. When the hydroxyl-protecting group of benzyl acetate **5** was changed to a carbonate group (**5a**, R^1 = MeOCO, R^2 = Bn), we were pleased to find that the major *syn*-adduct **4a** with a (2*R*,3*S*) configuration was isolated in 45% yield and moderate diastereoselectivity (Table 1, entry 1).[8] With the size increase of R^1 from methoxy carbonyl group to *tert*-butoxy carbonyl group, the yield and diastereoselectivity were greatly improved (Table 1, entries 1−3). Only one adduct, **4c**, was observed and was isolated in 86% yield when acetate **5c** (R^1 = Boc, R^2 = Bn) was used. After screening a couple of bases (Table 1, entries 3−6), the best result was achieved using 5 equiv of LiHMDS as a base and 5 equiv of **5c** at −78 °C in THF. Under the best condition, we were able to isolate **4c** (R^1 = Boc, R^2 = Bn) in 97% yield as sole adduct (Table 1, entry 6). Attempts to raise the reaction temperature and reduce the quantity of lithium enolate of **5c** unfortunately resulted in lower yields, although the diastereoselectivities were kept the same (Table 1, entries 7 and 8). Methyl acetate **5d** gave a similar result compared with benzyl acetate **5c** (Table 1, entry 9).

TABLE 1. Diastereoselective Addition of 5 to (S_R)-*N*-(Benzylidene)-*tert*-butanesulfinamide 6a[a]

entry	acetate **5**	R^1	R^2	base	yield of **4**[b]	dr
1	**5a**	MeOCO	Bn	LDA	**4a** (45)	88:12:0:0[c]
2	**5b**	Cbz	Bn	LDA	**4b** (56)	—[d]
3	**5c**	Boc	Bn	LDA	**4c** (86)	>99:0:0:0[e]
4	**5c**	Boc	Bn	BuLi	**4c** (36)	>99:0:0:0[e]
5	**5c**	Boc	Bn	^{t}BuLi	**4c** (43)	>99:0:0:0[e]
6	**5c**	Boc	Bn	LiHMDS	**4c** (97)	>99:0:0:0[e]
7[f]	**5c**	Boc	Bn	LiHMDS	**4c** (50)	>99:0:0:0[e]
8[g]	**5c**	Boc	Bn	LiHMDS	**4c** (85)	>99:0:0:0[e]
9	**5d**	Boc	Me	LiHMDS	**4d** (96)	>99:0:0:0[e]

[a] All reactions were conducted at −78 °C in THF using 1 equiv of **6a**, 5 equiv of **5**, and 5 equiv of base unless specifically indicated. [b] Isolated yield. In parentheses, percent value. [c] The dr value was based on isolated isomers, and the absolute configuration of minor isomer was not identified. [d] Other isomers were isolated as an inseparable and unidentified mixture contaminated with byproducts. [e] A dr value of >99% indicated that other isomers were not observed. [f] At −45 °C. [g] At −78 °C, 3 equiv of **5c** and LiHMDS were used.

SCHEME 2 [a]



[a] Reagents and conditions: (a) 6 N HCl in MeOH, 1 h, 96%. (b) PhCOCl/$NaHCO_3$, aq. THF, 85%.

The absolute stereochemistry of major adduct **4** was verified by converting **4d** into the known methyl ester of (2*R*,3*S*)-3-benzoyl-3-phenylisoserine (−)-**8** with the same rotation and identical ^{1}H NMR spectrum compared with that of the literature data (Scheme 2). (−)-**8**, mp: 183−184 °C, $[\alpha]^{25}_D$ −48.8 (*c* 1.25, MeOH) {lit.[1d] $[\alpha]^{23}_D$ −49.6 (MeOH), lit.[9] $[\alpha]^{23}_D$ −48.0 (MeOH)}. The absolute configuration of the major adduct was further unambiguously confirmed by the X-ray crystallographic analysis of **4c** as S_R,2*R*,3*S*.[10]

It was interesting to find the applicable scope and efficiency of current imine enolate addition strategy for the preparation of enantiopure isoserine **4** with different substituents at position-3, since taxol analogues with a variety of substituents instead of phenyl group at position-3 of the side chain have shown equal or even better anticancer profile, and some of them are being studied in different stages of clinical trials.[11]

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(8) The syn-adducts with a typical double doublet ascribed to H-3 were readily differentiated from the anti-adducts with a typical triplet in the ^{1}H NMR spectrum.

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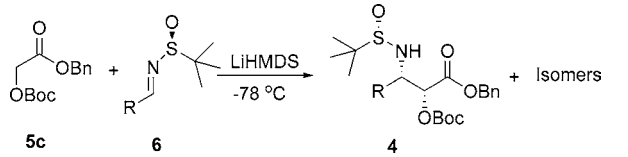
(10) A colorless crystal of **4c** ($C_{25}H_{31}N_1O_6S_1$, mp 148−149 °C) suitable for X-ray analysis was obtained by crystallization from acetone/petroleum 1:3. The crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, CCDC 276473, and are also available in Supporting Information (the ORTEP/X-ray figure of **4c** is shown in Supporting Information).

TABLE 2. Diastereoselective Addition of 5c to (S_R)-*tert*-Butanesulfinylimines 6



5c **6** **4**

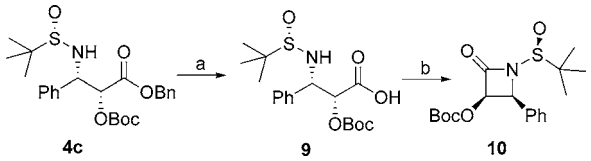
entry	6	R	4	yield[a]	dr[c]
1	**6b**	4-ClC_6H_4	**4e**	96	>99:0:0:0
2	**6c**	3,4-$(MeO)_2C_6H_3$	**4f**	89	>99:0:0:0
3	**6d**	4-$MeOC_6H_4$	**4g**	96[b]	91:9:0:0[c]
4	**6e**	2-BrC_6H_4	**4h**	89	93:5:2:0[c]
5	**6f**	4-$NO_2C_6H_4$	**4i**	98	>99:0:0:0
6	**6g**	2-pyridinyl	**4j**	94	97:3:0:0[c]
7	**6h**	3-pyridinyl	**4k**	84	>99:0:0:0
8	**6i**	4-pyridinyl	**4l**	83	>99:0:0:0
9	**6j**	2-furyl	**4m**	84[b]	91:9:—[d]
10	**6k**	2-thienyl	**4n**	97	>99:0:0:0
11	**6l**	$C_6H_4(CH_2)_2$	**4o**	89	>99:0:0:0
12	**6m**	*i*Pr	**4p**	95	98:2:0:0[c]
13	**6n**	cyclopropyl	**4q**	96	>99:0:0:0

[a] Isolated yield. [b] Inseparable mixture of two isomers in 11:1 ratio. [c] The ratio was based on ^{1}H NMR integration of crude product; a dr value of >99% indicated that other isomers were not observed, and the absolute configuration of minor isomer was not identified. [d] Other isomers were isolated as an inseparable and unidentified mixture contaminated with byproducts.

As shown in Table 2, the additions of **5c** to both aromatic and alkyl imines **6** were completed within 6 h to afford the desired *syn*-**4** as the major adduct in high to excellent yields and diastereoselectivities under our best conditions. The ratio was determined by careful ^{1}H NMR analyses of the crude product and each purified minor component. For most of the addition reactions, the reactions were very clean and only one adduct was detected by TLC analysis after quenching the reactions. The reactions with electron-rich imines such as **6c**, **6d**, **6j**, and **6k** proceeded rapidly and were completed within 1 h (Table 2, entries 2, 3, 9, and 10), whereas the electron-poor imines **6f**−**6i** exhibited a lower reactivity and required a longer reaction time (4−6 h) (Table 2, entries 5−8). For the addition reaction generating minor isomers (Table 2, entries 4, 6, and 12), the major adduct *syn*-**4** was easily separated from its minor isomers by chromatography purification. The exception was the reaction with imines **6d** and **6j**, where the major adducts **4g** and **4m** were isolated, respectively, as an inseparable mixture contaminated with one minor isomer (Table 2, entries 3 and 9).

The *N*,O-protected isoseric acid and *β*-lactam were commonly used for the *semi-synthsis* of taxol.[2b,4l,12] With adduct **4c** in hands, our attention was then focused on preparing the isoseric acid **9** and *β*-lactam **10** by selective manipulating of the protecting groups in **4c**. Acid **9** and *β*-lactam **10** were readily synthesized by the following two steps. Thus, hydrogenolysis of **4c** under 1 atm of hydrogen pressure for 12 h in the presence of 5% $Pd(OH)_2$ (Pearlman's catalyst) afforded **9** in 94% yield. When **9** was treated with 1.5 equiv of 2-chloro-1-methylpyridinium iodide and Et_3N in MeCN at 60 °C for 6 h, the *β*-lactam **10** was obtained in 45% yield as well as some unidentified byproducts (Scheme 3).

SCHEME 3 [a]



4c **9** **10**

[a] Reagents and conditions: (a) 10% $Pd(OH)_2$, 1 atm H_2 in MeOH, 12 h, 94% yield. (b) 1.5 equiv of 2-chloro-1-methylpyridinium iodide and Et_3N in MeCN at 60 °C, 45% yield.

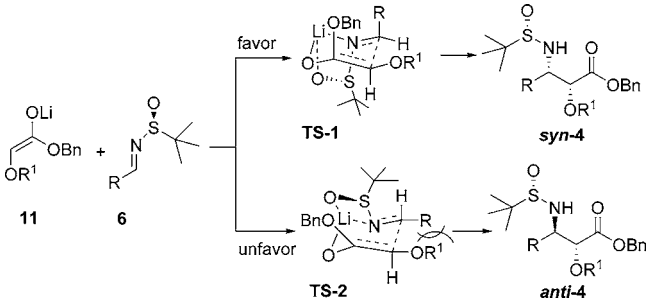


FIGURE 2. Plausible mechanism for the lithium enolate imine addition.

To provide a rationale for the observed excellent diastereoselectivity using lithium enolate of *O*-Boc-α-hydroxyacetate **11** as a nucleophile, a tentative mechanism was suggested (Figure 2), which adopted the six/four-membered bicyclic transition state proposed by Davis, Ellman, and co-workers in their asymmetric addition reaction of lithium enolate to sulfinylimine.[6a,d] Both *trans*-enolate **11** and imine **6** were linked together through lithium chelation to form six/four-membered bicyclic transition states **TS-1** and **TS-2**. **TS-1** should be the favored low-energy transition state, since the cis relationship between *a*-orientation R and *e*-orientation R^1 in **TS-1** has less steric hindrance and allows the easier access of C-2 to C-3, compared with the trans relationship between both *e*-orientation R and R^1 in **TS-2**. With the size increase of R^1 from methoxy carbonyl group to *tert*-butoxy carbonyl group, the addition reaction should be more likely to occur through **TS-1** to afford *syn*-**4** as the dominating adduct. The suggested mechanism explained well our experimental observation (Table 1, entries 1−3).

Conclusion

We have described that the enantiopure 3-substituted isoserine **4** with a (S_R,2*R*,3*S*) absolute stereochemistry can be readily prepared in high to excellent yields by the diastereoselective enolate addition of *O*-Boc-α-hydroxyacetate **5** with (S_R)-*tert*-butanesulfinylimine **6**. To the best of our knowledge, the current method provides the most straightforward access to enantiopure 3-substituted isoserine **4**, which is useful for the semi-syntheses of taxol and its derivatives.

Experimental Section

General Procedure for the Addition of O-Protected α-Hydroxyacetate 5 with (S_R)-*tert*-Butanesulfinylimine 6. Under N_2, to a solution of *O*-protected α-hydroxyacetate **5** (10.0 mmol) in 25 mL of dry THF was added a solution of base (10.0 mmol) at −78 °C. After being stirred for 1 h at −78 °C, the mixture was added to (S_R)-*tert*-butanesulfinylimine **6** (2.0 mmol in 5 mL of dry THF and was stirred at −78 °C for 1−6 h until imine **6** was completely consumed and checked by TLC analysis. The reaction mixture was

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quenched at −78 °C with saturated NH_4Cl solution and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried with anhydrous $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by chromatography to give adduct **4** and other isomers. The results were shown in Tables 1 and 2.

(*S*$_R$,2*R*,3*S*)-*N*-*tert*-Butanesulfinyl-*O*-methoxycarbonyl-3-phenylisoserine Benzyl Ester 4a: Purified by chromatography (acetone/petroleum 1:4, R_f 0.4) as viscous oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.41 (m, 10H), 5.27 (d, J = 2.8 Hz, 1 H), 5.21 (d, J = 12.4 Hz, 1H), 5.14 (d, J = 12.4 Hz, 1H), 5.03 (dd, J = 10.0, 2.8 Hz, 1H), 4.13 (d, J = 9.6 Hz, 1H), 3.76 (s, 3H), 1.14 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 154.6, 137.7, 134.67, 134.60, 128.58, 128.52, 128.4, 128.3, 128.2, 127.0, 78.6, 67.6, 60.2, 56.6, 55.2, 22.3 ppm; HRMS-ESI calcd for $C_{22}H_{27}N_1Na_1O_4S_1$ (M + Na)$^+$ 456.1457, found 456.1451.

Isomer of 4a: Purified by chromatography (acetone/petroleum 1:4, R_f 0.35) as viscous oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19−7.39 (m, 10H), 5.39 (d, J = 5.2 Hz, 1H), 5.10 (d, J = 12.4 Hz, 1H), 5.03 (d, J = 12.4 Hz, 1H), 4.91 (t, J = 5.2 Hz, 1H), 4.22 (d, J = 4.8 Hz, 1H), 3.79 (s, 3H), 1.16 (s, 9H) ppm; ^{1}HRMS-ESI calcd for $C_{22}H_{27}N_1Na_1O_4S_1$ (M + Na)$^+$ 456.1457, found 456.1454.

(*S*$_R$,2*R*,3*S*)-*N*-*tert*-Butanesulfinyl-*O*-Cbz-3-phenylisoserine Benzyl Ester 4b: Purified by chromatography (acetone/petroleum 1:7, R_f 0.2) as viscous oil, IR (KBr) 3300, 2959, 1750, 1498, 1455, 1385, 1270, 1242, 1073, 1040 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.40 (m, 15H), 5.32 (d, J = 2.8 Hz, 1H), 5.18 (d, J = 12.4 Hz, 1H), 5.15 (d, J = 12.4 Hz, 1H), 5.12 (d, J = 12.4 Hz, 1H), 5.09 (d, J = 12.4 Hz, 1H), 5.03 (dd, J = 9.6, 2.8 Hz, 1H), 4.12 (d, J = 9.6 Hz, 1H), 1.12 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 154.1, 137.7, 134.7, 128.6, 128.58, 128.53, 128.4, 128.21, 128.13, 127.1, 78.7, 70.3, 67.6, 60.3, 56.7, 22.6, 22.5 ppm; HRMS-ESI calcd for $C_{28}H_{31}N_1Na_1O_6S_1$ (M + Na)$^+$ 532.1770, found 532.1764.

(*S*$_R$,2*R*,3*S*)-*N*-*tert*-Butanesulfinyl-*O*-Boc-3-phenylisoserine Benzyl Ester 4c: Purified by chromatography (acetone/petroleum 1:8, R_f 0.2) as a white solid, recrystallized from acetone and petroleum; X-ray (see CIF file); mp 148−149 °C; $[\alpha]^{25}_D$ +1.0° (*c* 1.0, EtOH); IR (KBr) 3296, 2975, 1746, 1497, 1458, 1426, 1395, 1366, 1291, 1243, 1208, 1160, 1113, 1046, 1009, 956, 862 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.41 (m, 10H), 5.27 (d, J = 0.8 Hz, 1H), 5.17 (s, 2H), 5.01 (d, J = 9.6 Hz, 1H), 4.14 (d, J = 9.6 Hz, 1H), 1.39 (s, 9H), 1.15 (s, 9 H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 152.1, 137.8, 134.6, 128.5, 128.4, 128.0, 127.1, 83.3, 77.6, 67.4, 60.4, 56.6, 27.4, 22.3 ppm; Anal. Calcd for $C_{25}H_{33}N_1O_6S_1$: C, 63.13; H, 6.99; N, 2.95. Found: C, 63.08; H, 6.98; N, 3.08; HRMS-ESI calcd for $C_{25}H_{33}N_1Na_1O_6S_1$ (M + Na)$^+$ 498.1926, found 498.1921.

(*S*$_R$,2*R*,3*S*)-*N*-*tert*-Butanesulfinyl-*O*-Boc-3-phenylisoserine Methyl Ester 4d: Purified by chromatography (acetone/petroleum 1:8, R_f 0.2) as a white solid, mp 85−87 °C; $[\alpha]^{25}_D$ +8.6° (*c* 1.2, $CHCl_3$); IR (KBr) 3345, 2957, 1745, 1499, 1461, 1393, 1370, 1352, 1310, 1280, 1162, 1136, 1080, 1018, 951 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.43 (m, 5H), 5.25 (d, J = 2.8 Hz, 1H), 5.01 (dd, J = 10.0, 2.8 Hz, 1H), 4.16 (d, J = 10.0 Hz, 1H), 3.78 (s, 3H), 1.41 (s, 9H), 1.19 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 152.2, 138.0, 128.6, 128.1, 127.1, 83.4, 60.3, 56.7, 52.4, 27.5, 22.6, 22.4 ppm; Anal. Calcd for $C_{19}H_{29}N_1O_6S_1$: C, 57.14; H, 7.32; N, 3.51. Found: C, 57.10; H, 7.30; N, 3.64; HRMS-ESI calcd for $C_{19}H_{29}N_1Na_1O_6S_1$ (M + Na)$^+$ 422.1613, found 422.1608.

Correlation of the Absolute Configurations by Chemical Transformation. Adduct **4d** (0.202 g, 0.5 mmol) was dissolved in 10 mL of 6 M HCl in MeOH overnight. The mixture was poured into an ice-cooled saturated $NaHCO_3$ solution and was extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were combined and dried with anhydrous Na_2SO_4. The solvent was removed under vacuum to afford 0.098 g of crude **7** (96% yield), which was pure enough for the next step. The crude **7** was dissolved in 15 mL of THF. To the THF solution, saturated $NaHCO_3$ (5 mL) and benzoyl chloride (1.0 mmol) were added successively at 0 °C. After being stirred for 2 h at 0 °C, the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried, and the solvent was removed under vacuum to give a residue, which was purified by chromatography to give **8** (0.123 g, 82% overall yield two steps).

(2*R*,3*S*)-3-Phenylisoserine Methyl Ester 7. The analytic sample was purified by chromatography (acetone/petroleum 1:4, R_f 0.2) as a white solid, mp 103−105 °C, $[\alpha]^{25}_D$ +10.6° (*c* 1.0, MeOH); IR (KBr) 3367, 3308, 3070, 2855, 2707, 1730, 1449, 1434, 1365, 1280, 1198, 1160, 1082, 922 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.26 (m, 5H), 4.30 (m, 2H), 3.80 (s, 3H), 2.00 (s, br, 2H)-ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 141.9, 128.4, 127.5, 126.6, 75.0, 57.8, 52.3 ppm.

(2*R*,3*S*)-*N*-Benzoyl-3-phenylisoserine Methyl Ester 8: Purified by chromatography (acetone/petroleum 1:4, R_f 0.5) as a white solid, mp 183−184 °C, $[\alpha]^{25}_D$ −48.8 (*c* 1.3, MeOH) {lit.[1d] $[\alpha]^{23}_D$ −49.6 (MeOH), lit.[9] $[\alpha]^{23}_D$ −48.0 (MeOH)}. ^{1}H NMR was identical to literature report.[1d,9] IR (KBr) 3391, 3367, 1735, 1639, 1580, 1521, 1489, 1449, 1292, 1261, 1208, 1111 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (m, 2H), 7.27−7.56 (m, 8H), 6.98 (d, J = 8.8 Hz, 1H), 5.74 (dd, J = 9.2, 0.8 Hz, 1H), 4.64 (dd, J = 4.0, 2.4 Hz, 1H), 3.85 (s, 3H), 3.27 (d, J = 3.6 Hz, 1H) ppm.

Synthesis of *β*-Lactam 10. Adduct **4c** (1.255 g, 2.6 mmol) in 20 mL of MeOH was subjected to hydrogenolysis under 1 atm hydrogen pressure in the presence of 10% of $Pd(OH)_2$ for 12 h. After we removed the $Pd(OH)_2$ by filtration, we evaporated the mixture to dryness. The residue was purified by chromatography (CH_2Cl_2/MeOH/AcOH 10:1:0.1, R_f 0.3) to afford acid **9** (0.931 g, 93% yield). Under N_2, a mixture of acid **7** (0.820 g, 2.1 mmol), Et_3N (0.323 g, 3.2 mmol), and 2-chloro-1-methylpyridinium iodide (0.800 g, 3.2 mmol) in 15 mL of dry MeCN was refluxed for 6 h. The solvent was removed by evaporation, and the residue was subjected to chromatography (acetone/petroleum 1:8, R_f 0.2) to give *β*-lactam **10** (0.347 g, 45% yield).

(*S*$_R$,2*R*,3*S*)-*N*-*tert*-Butanesulfinyl-*O*-Boc-3-phenylisoserine Acid 9: mp 144−146 °C; $[\alpha]^{25}_D$ +23.0° (*c* 1.2, $CHCl_3$); IR (KBr) 3357, 2980, 1741, 1610, 1452, 1372, 1351, 1309, 1279, 1249, 1229, 1166, 1132, 1098, 1006 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40 (d, J = 7.6 Hz, 2H), 7.27 (t, J = 7.6 Hz, 2H), 7.22 (m,1H), 6.32 (br, 1H), 4.85 (s, 1H), 4.70 (dd, J = 9.2, 4.0 Hz, 1H), 1.34 (s, 9H), 1.09 (s, 9H)ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 170.0, 152.8, 140.9, 128.2, 127.9, 127.1, 80.9, 78.8, 67.2, 58.8, 56.2, 27.7, 25.3, 22.6 ppm; Anal. Calcd for $C_{18}H_{27}N_1O_6S_1$: C, 56.08; H, 7.06; N, 3.63. Found: C, 55.71; H, 7.06; N, 3.85; HRMS-ESI calcd for $C_{18}H_{27}N_1Na_1O_6S_1$ (M + Na)$^+$ 408.1457, found 408.1451.

(*S*$_R$,3*R*,4*S*)-*N*-*tert*-Butanesulfinyl-3-(*tert*-butoxycarbonate)-4-phenyl-*β*-lactam 10: White solid, mp 125−127 °C; $[\alpha]^{25}_D$ +56.2° (*c* 1.2, $CHCl_3$); IR (KBr) 2979, 1792, 1745, 1458, 1369, 1278, 1252, 1130, 1101, 1047, 1014 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.45 (m, 5H), 5.74 (d, J = 6.0 Hz, 1H), 5.36 (d, J = 6.0 Hz, 1H), 1.16 (s, 9H), 1.03 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 150.6, 133.0, 129.7, 129.1, 128.4, 83.6, 57.7, 57.3, 27.1, 22.3 ppm; Anal. Calcd for $C_{18}H_{25}NO_5S$: C, 58.83; H, 6.86; N, 3.81. Found; C, 58.77; H, 6.94; N, 3.86; HRMS-ESI calcd for $C_{18}H_{25}N_1Na_1O_5S_1$ (M + K)$^+$ 406.1091, found 406.1098.

Acknowledgment. This work was supported by the National Natural Science Foundation of China (No. 20372048 and No. 20572072), Ministry of Education (NCET, RFDP and EYTP), Sichuan Province Government (No. 04ZQ026-011 and 05JY029-025-1), and Sichuan University (2005CF01).

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of compounds **4**, **7**−**10**, and X-ray crystallographic data for **4c** as a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052298N