Asymmetric Synthesis of γ-Keto-δ-lactam Derivatives: Application to the Synthesis of a Conformationally Constrained Surrogate of Ala-Ser Dipeptide

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Received July 27, 2001

Optically active δ-lactams (2-piperidones) are common structural subunits and building blocks of a wide variety of naturally occurring piperidine and indolizidine alkaloids,[1] which possess valuable biological and pharmacological properties.[2] Thus, many saturated and unsaturated 2-piperidones have been used as chiral key intermediates in the preparation of numerous natural and synthetic compounds[3] with significant anticancer,[4] anti-HIV,[5] anti-inflamatory,[6] and glycosidase inhibition[7] activities. Consequently, the development of synthetic methods for the efficient preparation of various optically active δ-lactams is the subject of particular interest and research activity.[8] As a part of our ongoing studies on the synthesis of chiral piperidine derivatives,[9] we envisioned the framework of α,β-unsaturated-γ-keto-δ-lactam **3** as a flexible intermediate for the convenient enantioselective preparation of various δ-lactam building blocks amenable for the synthesis of various biologically active piperidine alkaloids. We have also used this core structure for the efficient preparation of the corresponding 3-amino-2-piperidone derivative. The latter as unnatural amino acid belongs to a class of compounds that exhibit important biological activities[10] and are being elaborated with increasing frequency as small ring constrained nonpeptide scaffolds, in the design and synthesis of peptidomimetics.[11] In this context, we also report the efficient enantioselective preparation of a novel conformationally constrained surrogate of Ala-Ser dipeptide, in which the conformational restriction is caused by a bond between the β-carbon of alanine and γ-carbon of serine. Such constrained pseudopeptides are very interesting targets because of their potential for probing various recognition events in protein chemistry and biology.[12]

Previously reported syntheses of α,β-unsaturated γ-keto-δ-lactam structural motif include the kinetic resolution of a 2-furfurylamine,[13] its transformation to the corresponding dihydropyridone and further oxidation to δ-lactam. Recently, we developed a new synthetic methodology for the enantioselective transformation of D-glucal to chiral 2-furylsulfonamide **1** and its subsequent oxidative cyclization to (2*S*)-hydroxymethyl-dihydropyridone **2**.[14] Continuing our investigations on the applications of this methodology, we describe herein the efficient synthesis of diversely substituted δ-lactam derivatives in a limited number of steps and avoiding the kinetic resolution step.

As chiral key intermediate in our syntheses we used the of α,β-unsaturated-γ-keto-δ-lactam **3**, which was obtained in almost quantitative yield by Jones oxidation of 6-hydroxy-1,6-dihydro-2*H*-pyridin-3-one **2**, or directly from *N*-furfurylsulfonamide **1** upon prolonged exposure to a large excess of *m*-CPBA (Scheme 1). Hydrogenation of **3** with Zn powder and acetic acid furnished the corresponding saturated 3,5-dione **4**, which may be elaborated in the enantioselective synthesis of (−)-prosopinine, according to a recently reported synthetic route.[15]

Modified Luche reduction of ketolactam **3** furnished the allylic alcohol **5** as a single diastereomer (Scheme 2). The diastereoselectivity of this reduction step is attributed to the apparent hydride attack on the less hindered face of the molecule (Figure 1). Subsequent catalytic hydrogenation and benzylation provided compound **7**, a key intermediate of the chiral synthesis of (+)-spectaline.[16]

The configuration of compound **6** was elucidated by 2D COSY and NOESY studies. Thus, the strong NOE

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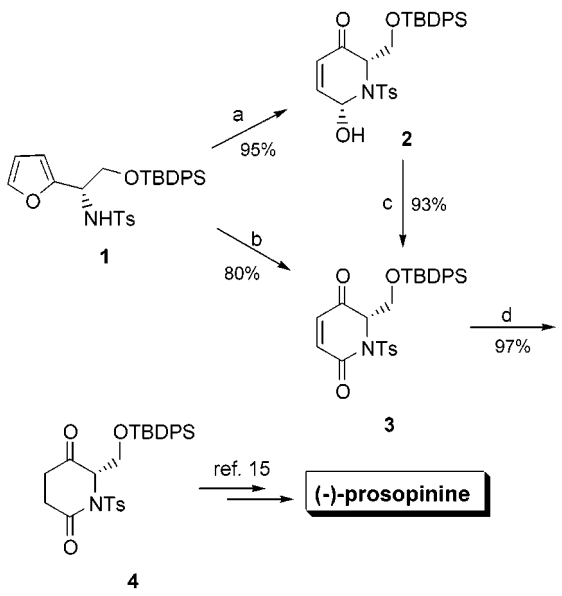
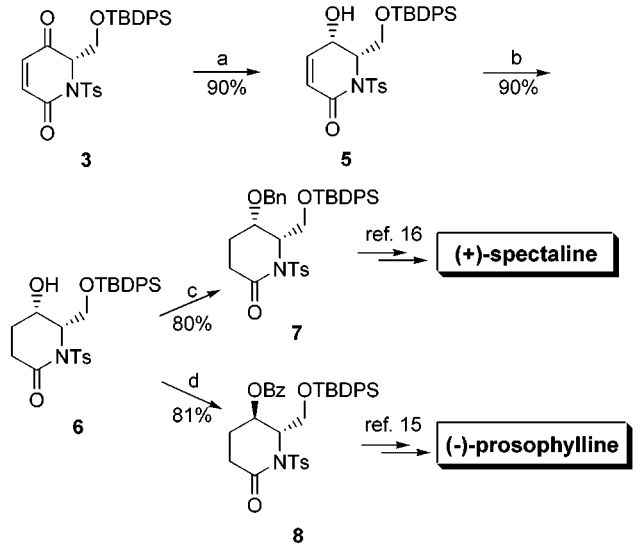
10.1021/jo0159688 CCC: $20.00 © 2001 American Chemical Society
Published on Web 10/17/2001

Scheme 1[a]



[a] Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 2 h; (b) large excess of *m*-CPBA, CH_2Cl_2, 6 h; (c) Jones reagent, Me_2CO; (d) Zn, AcOH, CH_2Cl_2.

Scheme 2[a]



[a] Reagents and conditions: (a) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH; (b) H_2, Pd/C, EtOAc; (c) NaH, BnBr, Bu_4NI, THF; (d) DEAD-TPP, $PhCO_2H$, THF.

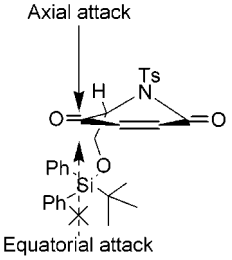


Figure 1. Spatial view of the hydride attack on compound **3**.

correlation between H-5_{ax} and H-3_{ax} and the small coupling constant between the β H-6 and H-5 are indicative of a $^4C_1$ chairlike conformation and the equatorial disposition of the hydroxy group (Figure 2).

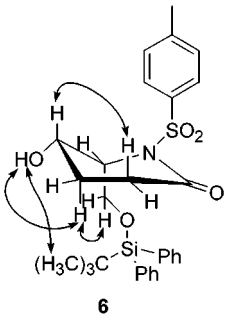
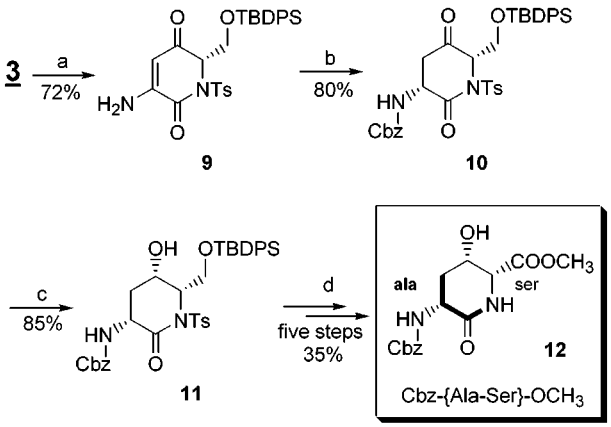


Figure 2. NOE correlations in **6**.

Scheme 3[a]



On the other hand, compound **6** by a Mitsunobu reaction provided the diastereomeric lactam **8** which is the key intermediate for the chiral synthesis of (−)-prosophylline.[15]

Treatment of unsaturated dione **3** with an excess of hydrazoic acid (prepared in situ) in a 1:1 mixture of AcOH/AcONa provided in high yield the corresponding aminoenyl derivative **9** through a 1,4-reductive addition mechanism, previously reported for of α,*β*-unsaturated dicarbonyl systems and naphthoquinones (Scheme 3).[17]

Catalytic hydrogenation of compound **9** proved troublesome, since this system is inert under usual conditions, while under more vigorous conditions (high pressure, PtO_2 catalyst, etc.) produced a variety of byproducts. The hydrogenation was carried out efficiently only by an ultrasound promoted reaction, using Zn powder in acetic acid and provided the corresponding aminodione which is unstable to the workup. Thus, the product was reacted in situ with benzyl chloroformate to give the very stable compound **10** as the 6*S*, 3*R* diastereomer ($[\alpha]^{22}_D = -13.3$ (*c* 0.3, EtOAc) in 80% overall yield. Reduction with $NaBH_4$ produced diastereoselectively the corresponding hydroxylated derivative **11** which by a series of consecutive protection, oxidation and deprotections furnished smoothly the desired target Ala-Ser surrogate **12**. This dipeptide, except of an amide bond, contains a conformational restriction through a bond between the *β*-carbon of alanine and *γ*-carbon of serine.

The stereochemistry of key intermediate 5-hydroxy-3-carbobenzoxyamino-2-pyridone **11** was unambiguously assigned considering the strong 1,3-diaxial NOE interac-

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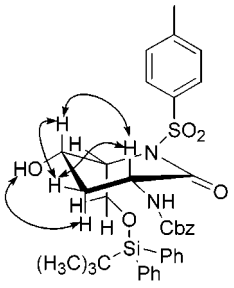

11

Figure 3. NOE correlations in **11**.

tion between the H-3 and H-5, which is indicative of the diequatorial orientation of the corresponding substituents (Figure 3). Moreover, the observed NOEs between H-3, H-5, and H-4_{eq}, the small enhancement between H-4_{ax} and OH in conjunction with coupling constants of H-5, reveal the assigned configuration.

In summary, we have demonstrated the usefulness of of α,β-unsaturated-γ-keto-δ-lactam **3** as chiral key intermediate for the enantio- and diastereocontrolled access to various δ-lactams, eliminating the need for kinetic resolution of 2-furyltosylamines or dihydropyridones. Furthermore, the same intermediate was used for the convenient synthesis of chiral 3-amino-2-pyridone derivatives and a novel conformationally constrained Ala-Ser dipeptide surrogate. Studies on the use of these chiral building blocks for the preparation of natural and synthetic alkaloids, as well as other peptidomimetics are currently underway.

Experimental Section

General Methods. All reactions were carried out under argon unless otherwise noted. Solvents were dried by distillation prior to use. Tetrahydrofuran was distilled from sodium-benzophenone and methylene chloride over CaH_2 immediately prior to use. (*S*)-(1-Furan-2-yl-2-*tert*-butyldiphenylsilyloxy)-*N*-(toluene-4-sulfonyl)ethylamine **1** ($[\alpha]^{22}_D = -18.7°$ (*c* = 1.35, MeOH); mp = 107−108 °C) and (2*S*,6*S*)-2-(*tert*-butyldiphenylsilyloxymethyl)-6-hydroxy-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridine-3-one **2** ($[\alpha]^{22}_D = +27.9°$ (*c* = 0.98, MeOH), mp = 97−98 °C) were prepared according to the literature procedure.[14] IR spectra were recorded on a Nicolet Magna 750 series II spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on Bruker AC-200 or DRX-400 spectrometers (200 and 400 MHz, respectively) using TMS as internal standard. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at ambient temperature. TLC was conducted on Merck glass plates coated with silica gel 60 F_{254}. Flash column chromatography was performed using Merck silica gel 60 (230−400 mesh ASTM).

(6*S*)-6-(*tert*-Butyldiphenylsilanyloxymethyl)-1-(toluene-4-sulfonyl)-1,6-dihydropyridine-2,5-dione 3. To an ice-cold solution of compound **2** (0.8 g, 1.5 mmol) in acetone (10 mL) was added dropwise Jones reagent (0.5 mL). After being stirred for 20 min, the solid inorganic byproducts were eliminated by decantation and the liquid layer was concentrated to a residue that was partitioned in EtOAc and water. The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated. The residue was crystallized from cold diethyl ether to afford 0.76 g of compound **3** (95%): mp 200−201 °C dec; $[\alpha]^{22}_D = +13.2$ (*c* 1.6, EtOAc); IR (neat) ν 1725 (C=O), 1690 cm^{-1} (NC=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (s, 9H, C−CH_3), 2.44 (s, 3H, CH_3), 4.15 (m, 2H, CH_2), 5.01 (m, 1H, H-6), 6.68 (d, *J* = 10.2 Hz, 1H, H-3), 6.73 (d, *J* = 10.2 Hz, 1H, H-4), 7.25 (d, *J* = 8.6 Hz, 2H, ArH), 7.41 (m, 10H, ArH), 7.91 (d, *J* = 8.6 Hz, 2H, ArH). Anal. Calcd for $C_{29}H_{31}NO_5SSi$: C, 65.26; H, 5.85; N, 2.62. Found: C, 65.39; H,6.01; N, 2.71.

(6*S*)-6-(*tert*-Butyldiphenylsilanyloxymethyl)-1-(toluene-4-sulfonyl)piperidine-2,5-dione 4. To a stirred solution of compound **3** (0.5 g, 0.95 mmol) and AcOH (5 mL) in CH_2Cl_2 (7 mL) was added well-powdered zinc dust (0.32 g) portionwise. After 2 h of stirring, the mixture was filtered from Celite and the filtrate was washed with $NaHCO_3$. The aqueous layer was backwashed with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and chromatographed using hexane/EtOAc (4:1) yielding the desired product which was crystallized from hexane (0.49 g, 97%): mp 135−135 °C; $[\alpha]^{22}_D = +3.1$ (*c* 0.45, EtOAc); IR(neat) ν 1715 (C=O), 1636 cm^{-1} (NC=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 9H, C−CH_3), 1.45 (m, 1H, H-4), 2.40 (s, 3H, $ArCH_3$), 2.53−2.80 (m, 3H, H-4, H-3), 3.93 (dd, *J* = 10.6, 3.1 Hz, 1H, CH_{2a}), 4.29 (dd, *J* = 10.6, 3.1 Hz, 1H, CH_{2b}), 4.89 (s, 1H, H-6), 7.25 (m, 2H, ArH), 7.39−7.49 (m, 10H, ArH), 7.89 (d, *J* = 8.2 Hz, 2H, ArH). Anal. Calcd for $C_{29}H_{33}NO_5SSi$: C, 65.02; H, 6.21; N, 2.61. Found: C, 65.22; H, 6.13; N, 2.71.

(6*S*,5*S*)-6-(*tert*-Butyldiphenylsilanyloxymethyl)-5-hydroxy-1-(toluene-4-sulfonyl)-5,6-dihydro-1*H*-pyridin-2-one 5. To a stirred solution of compound **3** (0.73 g, 1.34 mmol) and $CeCl_3 \cdot 7H_2O$ (0.25 g, 0.67 mmol) in methanol (15 mL) at −50 °C was added portionwise $NaBH_4$ (0.18 g, 4.67 mmol). After 40 min of stirring at that temperature, the reaction was quenched with saturated aqueous NH_4Cl (15 mL) and extracted repetitively with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and chromatographed (EtOAc/hexane 1:4) to afford 0.57 g of compound **5** (80%) as white solid: mp 155−157 °C; $[\alpha]^{22}_D = -1.75$ (*c* 0.65 EtOAc); IR (neat) ν 3440 (OH), 1676 cm^{-1} (NC=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 9H, CCH_3), 2.34 (s, 3H, $ArCH_3$), 3.87 (dd, *J* = 10.6, 4.1 Hz, 1H, CH_{2a}), 4.07 (dd, *J* = 10.6, 8.9 Hz, 1H, CH_{2b}), 4.15 (d, *J* = 7.5 Hz, 1H, OH), 5.04 (m, 1H, H-5), 5.06 (m, 1H, H-6), 5.68 (dd, *J* = 10.2, 2.4 Hz, 1H, H-4), 6.69 (dt, *J* = 10.2, 1.7 Hz, 1H, H-3), 7.11 (d, *J* = 7.5 Hz, 2H, ArH), 7.40 (m, 2H, ArH), 7.46 (m, 4H, ArH), 7.57 (dd, *J* = 7.5, 1.3 Hz, 2H, ArH), 7.67 (d, *J* = 8.5 Hz, 4H, ArH). Anal. Calcd for $C_{29}H_{33}NO_5SSi$: C, 65.02; H, 6.21; N, 2.61. Found: C, 65.29; H, 6.17; N, 2.44.

(6*S*,5*S*)-6-(*tert*-Butyldiphenylsilanyloxymethyl)-5-hydroxy-1-(toluene-4-sulfonyl)piperidin-2-one 6. A solution of compound **5** (0.5 g, 0.93 mmol) in MeOH (10 mL) was hydrogenated over 10% Pd/C (0.05 g) under 1 bar pressure for 40 min. The mixture was filtered over Celite and partitioned between EtOAc and water. The aqueous layer was backwashed with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated The yellowish slurry was chromatographed (EtOAc/hexane 1:4) to give compound **6** (0.53 g, 90%) as a white solid that was crystallized from diethyl ether/hexane to afford white crystals: mp 168−170 °C; $[\alpha]^{22}_D = +1.13$ (*c* 6.2, EtOAc); IR (neat) ν 3407 (OH), 1686 cm^{-1} (NC=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 9H, CCH_3), 1.99 (m, 1H, C-4_{eq}), 2.12 (m, 1H, C-4_{ax}), 2.37 (s, 3H, $ArCH_3$), 2.44 (m, 1H, 8.5 Hz, 1H, H-3_{eq}), 2.55 (ddd, *J* = 18.1, 7.9, 3.1 Hz, 1H, H-3_{ax}), 3.25 (d, *J* = 6.8 Hz, 1H, OH), 3.91 (dd, *J* = 10.9, 7.9 Hz, 1H, CH_{2a}), 4.14 (dd, *J* = 10.9, 3.4 Hz, 1H, CH_{2b}), 4.18 (m, 1H, H-5), 4.68 (dt, *J* = 7.9, 3.4 Hz, 1H, H-6), 7.16 (d, *J* = 8.5 Hz, 2H, ArH), 7.32−7.51 (m, 6H, ArH), 7.62 (dd, *J* = 6.5, 1.0 Hz, 2H, ArH), 7.68 (dd, *J* = 7.9, 1.7 Hz, 2H, ArH), 7.73 (d, *J* = 8.3 Hz, 2H, ArH). Anal. Calcd for $C_{29}H_{35}NO_5SSi$: C, 64.77; H, 6.56; N, 2.60. Found: C, 64.86; H, 6.41; N, 2.75.

(5*S*,6*S*)-5-Benzyl-6-(*tert*-butyldiphenylsilanyloxymethyl)-1-(toluene-4-sulfonyl)piperidin-2-one 7. To an ice-cold stirred solution of compound **6** (0.24 g, 0.44 mmol) in THF (1 mL) was added portionwise sodium hydride (12.6 mg, 0.53 mmol). The reaction mixture was allowed to warm to 15 °C and stirred for an additional 20 min. Then a catalytic amount of Bu_4NI (8 mg, 0.022 mmol) and benzyl bromide (74 μL, 0.66 mmol) were added. After 2 h of stirring at that temperature, the reaction was quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and chromatographed (EtOAc/hexane 1:4) to give 0.22 g of compound **7** as white crystals (80%): mp 152−153 °C; $[\alpha]^{22}_D = +14.5$ (*c* 1.2, MeOH); IR (neat) ν 1686 cm^{-1} (NC=O); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.98 (s, 9H, CCH_3), 2.15−2.25 (m, 2H, H-4), 2.32 (m, 1H, H-3), 2.40 (s, 3H, $ArCH_3$), 2.45 (m, 1H, H-3), 3.91 (dd, *J* = 10.9, 9.9 Hz, 1H, CH_{2a}), 3.92 (m, 1H, H-5), 4.14 (dd, *J* = 10.9, 3.4 Hz, 1H, CH_{2b}), 4.52 (d, *J* = Hz, 1H,

CH_2Ar), 4.71 (d, J = Hz, 1H, CH_2Ar), 4.90 (m, 1H, H-6) 7.21 (d, J = 8.3 Hz, 2H, ArH). 7.25−7.51 (m, 10H, ArH), 7.59 (m, 3H, ArH), 7.69 (d, J = 8.3 Hz, 2H, ArH), 7.92 (d, J = 8.3 Hz, 2H, ArH). Anal. Calcd for $C_{36}H_{41}NO_5SSi$: C, 68.87; H, 6.58; N, 2.23. Found: C, 69.01; H, 6.44; N, 2.11.

(2*S*,3*R*)-Benzoic Acid 2-(*tert*-Butyldiphenylsilanyloxymethyl)-6-oxo-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridin-3-yl Ester 8. To a solution of compound **6** (0.29 g, 0.53 mmol), triphenylphosphine (0.17 g, 0.64 mmol), and benzoic acid (80 mg, 0.64 mmol) in dry THF (3 mL) was added dropwise diethyl azodicarboxylate (DEAD) (0.1 mL, 0.64 mmol). After the mixture was stirred for 2 h, the solvent was evaporated, and the residue was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was separated, dried over $MgSO_4$, and chromatographed (EtOAc/hexane 9:1) yielding 0.28 g of **8** which was crystallized from hexane (81%): mp 142−144 °C; $[\alpha]^{22}_D = -4.5$ (*c* 0.95, EtOAc); IR (neat) ν 1730 (OC═O), 1650 cm^{-1} (NC═O); ^1H NMR (200 MHz, $CDCl_3$) δ 0.98 (s, 9H, CCH_3), 1.42 (m, 1H, H-4), 1.65 (m, 1H, H-4), 1.9 (m, 2H, H-3), 2.35 (s, 3H, $ArCH_3$), 3.95 (dd, J = 10.2, 5.1 Hz, 1H, CH_{2a}), 4.02 (dd, J = 10.2, 5.1 Hz, 1H, H-6), 4.09 (tr, J = 10.2 Hz, 1H, CH_{2b}), 5.40 (s, 1H, H-5), 6.92 (d, J = 7.9 Hz, 2H, ArH), 7.32 (m, 3H, ArH), 7.4 (m, 4H, ArH), 7.52 (m, 3H, ArH), 7.59 (m, 3H, ArH), 7.72 (m, J = 7.9 Hz, 2H, ArH), 7.92 (d, J = 7.9 Hz, 2H, ArH). Anal. Calcd for $C_{36}H_{39}NO_6SSi$: C, 67.37; H, 6.12; N, 2.18. Found: C, 67.51; H, 6.01; N, 2.25.

(6*S*)-3-Amino-6-(*tert*-butyldiphenylsilanyloxymethyl)-1-(toluene-4-sulfonyl)-1,6-dihydropyridine-2,5-dione 9. A stirred solution of compoumd **3** (0.25 g 0.49 mmol) in methanol (5 mL) was buffered by the addition of a 1:1 mixture AcOH/AcONa. Then sodium azide (0.22 g, 3.43 mmol) was added portionwise and the reaction was run for 12 h. The mixture was partitioned in EtOAc and water. The organic extract was washed with water, brine, dried over $MgSO_4$ and chromatographed (EtOAc/hexane 1:2) to afford 0.19 g of compound **9** as white solid which was crystallized from diethyl ether/hexane (72%): mp 205−206 °C dec; $[\alpha]^{22}_D = -4.1$ (*c* 0.54, EtOAc); IR (neat) ν 3465, 3310 (NH_2), 1700 (C═O), 1630 cm^{-1} (NC═O); ^1H NMR (400 MHz, $CDCl_3$) δ 0.82 (s, 9H, C−CH_3), 2.38 (s, 3H, $ArCH_3$, 4.07 (d, J = 10 Hz, 1H, CH_{2b}), 4.11 (d, J = 10 Hz, 1H, CH_{2a}), 4.85 (s, 1H, H-6), 5.29 (s br, 2H, NH), 5.76 (s, 1H, H-4), 7.19−7.40 (m, 10H, ArH), 7.48 (d, J = 8 Hz, 2H, ArH), 7.87 (d, J = 8 Hz, 2H, ArH). Anal. Calcd for $C_{29}H_{32}N_2O_5SSi$: C, 63.48; H, 5.88; N, 5.11. Found: C, 63.52; H, 5.99; N, 4.85.

(3*R*,6*S*)-[6-(*tert*-Butyldiphenylsilanyloxymethyl)-2,5-dioxo-1-(toluene-4-sulfonyl)piperidin-3-yl]carbamic Acid Benzyl Ester 10. A solution of compound **9** (0.52 g, 0.95 mmol), AcOH (5 mL), and well-powdered zinc dust (0.32 g) in CH_2Cl_2 (7 mL) was sonicated in an ultrasound bath at 35 °C for 30 min. Then the reaction mixture was filtered over Celite, the pH was adjusted to 8 by addition of Et_3N, and CbzCl (0.17 mL, 1.2 mmol) was added. The reaction mixture was stirred for 30 min, quenched with saturated aqueous NH_4Cl, and extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, and chromatographed (EtOAc/hexane 1:4) to give 0.52 g of compound **10** as white crystals (80%): mp 178−179 °C; $[\alpha]^{22}_D = -13.3$ (*c* 0.3 EtOAc); IR (neat) ν 3440 (OH), 3310 (NH), 1720 (C═O), 1640 cm^{-1} (NC═O); ^1H NMR (400 MHz, $CDCl_3$) δ 0.97 (s, 9H, CCH_3), 2.44 (s, 3H, $ArCH_3$), 2.64 (dd, J = 16.2, 14.1 Hz, 1H, H-4_{ax}), 3.30 (dd, J = 16.2, 5.3 Hz, 1H, H-4_{eq}), 4.00 (dd, J = 11.0, 2.6 Hz, 1H, CH_{2a}), 4.33 (dd, J = 11.0, 1.8 Hz, 1H, CH_{2b}), 4.91 (br s, 1H, H-6), 5.06 (s, 2H, CH_2), 5.08 (m, 1H, H-3), 5.51 (d, J = 4 Hz, 1H, NH), 7.28−7.54 (m, 17H, ArH), 7.85 (d, J = 8.3 Hz, 2H, ArH). Anal. Calcd for $C_{37}H_{40}N_2O_7SSi$: C, 64.89; H, 5.89; N, 4.09. Found: C, 65.01; H, 5.75; N, 3.99.

(3*R*,5*S*,6*S*)-[6-(*tert*-Butyldiphenylsilanyloxymethyl)-5-hydroxy-2-oxo-1-(toluene-4-sulfonyl)piperidin-3-yl]carbamic Acid Benzyl Ester 11. To an ice-cold stirred solution of compound **10** (0.1 g, 0.146 mmol) in methanol (3 mL) was added portionwise $NaBH_4$ (11 mg, 0.292 mmol), while the pH of the reaction was adjusted and maintained to 5−6 by addition of acetic acid. After 40 min of stirring at that temperature, the reaction was quenched with water and extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, and chromatographed (EtOAc/hexane 1:4) to afford 80 mg of the compound **11** (80%): $[\alpha]^{22}_D = +1.1$ (*c* 0.2, EtOAc); IR (neat) ν 3360 (OH), 1715 (OC═O), 1645 cm^{-1} (NC═O); ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 9H, CCH_3), 2.16 (q, J = 10.5 Hz, 1H, H-4_{ax}), 2.34 (s, 3H, $ArCH_3$), 2.60 (ddd, J = 10.5, 5.5, 4.0 Hz, 1H, H-4_{eq}), 3.36 (m, 1H, CH_{2a}), 3.51 (m, 2H, H-6, CH_{2b}), 4.54 (dd, J = 10.5, 7.0 Hz, 1H, H-3), 4.88 (dd, J = 10.5, 5.5 Hz, 1H, H-5), 4.93 (s, 1H, OH), 5.06 (s, 2H, CH_2), 5.36 (d, J = 7.0 Hz, 1H, NH), 7.10 (d, J = 8 Hz, 2H, ArH), 7.34−7.51 (m, 15H, ArH), 7.56 (d, J = 8 Hz, 2H, ArH). Anal. Calcd for $C_{37}H_{42}N_2O_7SSi$: C, 64.70; H, 6.16; N, 4.08. Found: C, 64.86; H, 6.31; N, 4.03.

(2*R*,3*S*,5*R*)-5-Benzyloxycarbonylamino-3-hydroxy-6-oxopiperidine-2-carboxylic acid methyl ester 12: mp 121−123 °C; $[\alpha]^{22}_D = -1.8$ (*c* 0.2, EtOAc); IR (neat) ν 3350 (OH), 1735, 1715 (OC═O), 1640 cm^{-1} (NC═O); ^1H NMR (400 MHz, $CDCl_3$) δ 2.20 (q, J = 10.1 Hz, 1H, H-4_{ax}), 2.40 (ddd, J = 10.1, 5, 3.8 Hz, 1H, H-4_{eq}), 3.55 (s, 3H, CH_3), 4.51 (dd, J = 10.1, 7 Hz, 1H, H-5), 4.74 (m, 2H, H-2, 3), 4.90 (s, 1H, OH), 5.15 (s, 2H, CH_2), 5.30 (d, J = 7 Hz, 1H, NH), 7.25 (m, 5H, ArH). Anal. Calcd for $C_{15}H_{18}N_2O_6$: C, 55.90; H, 5.63; N, 8.69. Found: C, 56.11; H, 5.43; N, 8.75.

JO0159688