

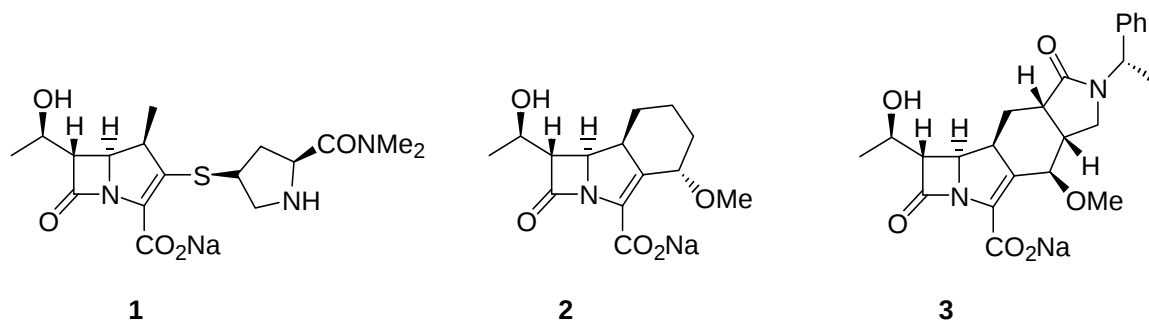
STERESELECTIVE SYNTHESIS OF A NOVEL TETRACYCLIC β -LACTAM

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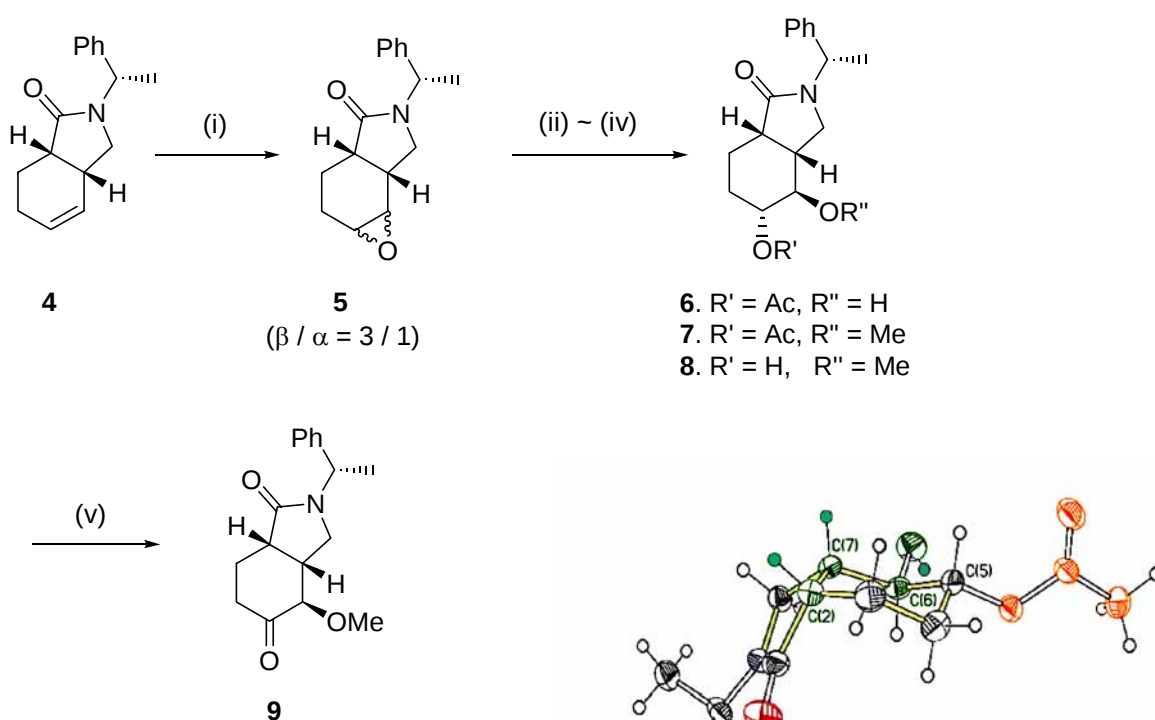
Abstract - Stereocontrolled total synthesis of a novel tetracyclic β -lactam (**3**) has been achieved in ten steps. The key transformations in this approach are the regioselective ring opening of β -epoxide (**5 β**) and the stereoselective construction of ketoazetidinone (**11**) from methoxyketo- γ -lactam (**9**) and 4-acetoxiazetidinone (**10**).

Since the discovery of thienamycin by Merck scientists¹ in 1976, great advances have been made in the chemistry and biology of carbapenem antibiotics.² The introduction of a substituent into the 1-position of carbapenem skeleton considerably improves the DHP-1 stability,³ as exemplified by meropenem (**1**),⁴ biapenem,⁵ and BO-2727.⁶ Christensen,⁷ Tamburini,⁸ and Perboni⁹ have described tricycle carbapenems. The most promising tricyclic carbapenem, sanfetrinem (**2**), has shown excellent activity against a wide range of bacteria and is now under clinical trials.¹⁰ Recently, some tetracycline β -lactams were also published by Sendai,¹¹ Gerlach,¹² and Schmidt.¹³

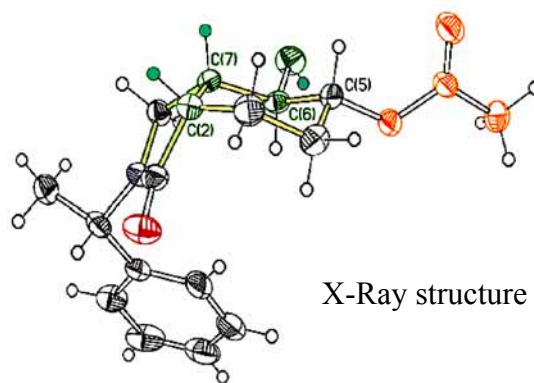


As a part of our research program to explore a new class of β -lactams,¹⁴ we report a stereocontrolled total synthesis of novel tetracyclic β -lactam (**3**) from the commercially available 4-acetoxiazetidinone (**10**). Our initial approach directed toward the preparation of methoxyketo- γ -lactam (**9**) was quite successfully carried out as outlined in Scheme 1. Bicyclic γ -lactam (**4**) prepared by the known intramolecular Diels-

Alder reaction,¹⁵ was treated with *m*CPBA to give a mixture of epoxides (**5**)($\beta / \alpha = 3 / 1$), which could be easily separated by flash chromatography. Regiospecific ring opening reaction of the β -epoxide (**5 β**) by acetic acid in the presence of a catalytic amount of $\text{Ti}(\text{O-}i\text{Pr})_4$ led to the objective acetoxy alcohol (**6**), which was treated with methyl iodide to afford the corresponding methyl ether derivative (**7**). The absolute configuration of **6** was confirmed by single crystal X-Ray analysis. After cleavage of the acetyl group of **7** with a catalytic amount of NaOMe in MeOH, Swern oxidation of the resultant alcohol (**8**) afforded the desired methoxyketo- γ -lactam (**9**) in a good yield.

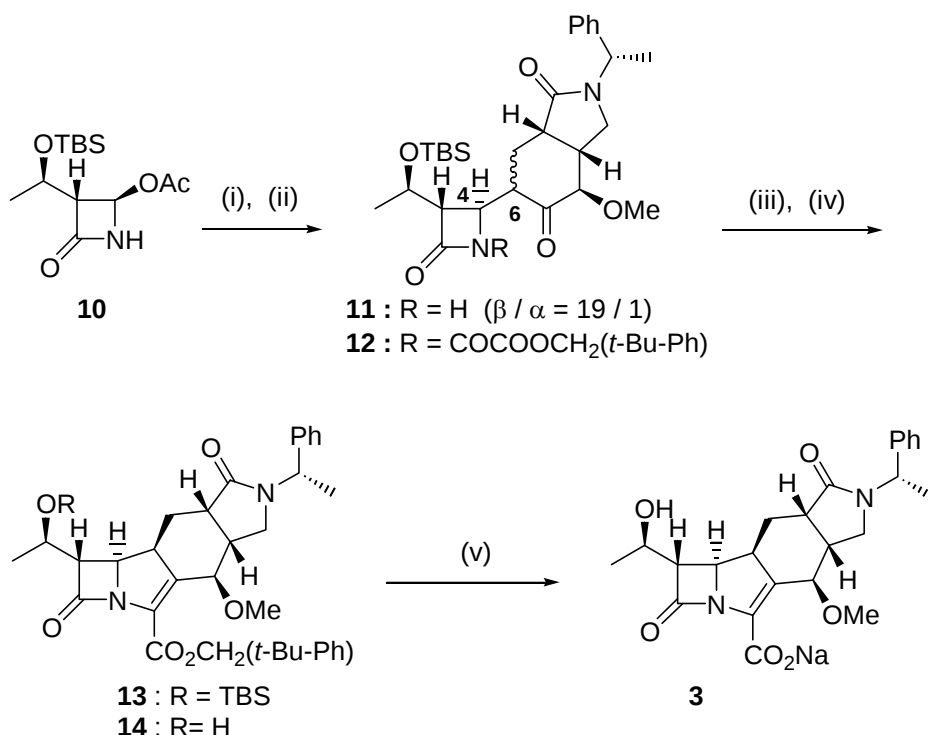


Scheme 1. Reagents : (i) *m*CPBA, reflux (96%); (ii) AcOH, $\text{Ti}(\text{O-}i\text{Pr})_4$, rt (90%); (iii) MeI, Ag_2O , rt (92%); (iv) NaOMe, 0°C (90%); (v) $(\text{CF}_3\text{CO})_2\text{O}$, DMSO, Et_3N , -78°C (94%)



X-Ray structure of **6**

Ketoazetidinone (**11**), a key intermediate in the synthesis of tetracyclic β -lactam (**3**), could be accessible by stereoselective construction of the C4-C6 bond *via* the reaction of an enolate of methoxyketo- γ -lactam (**9**) and 4-acetoxiazetidine (**10**) using the methodology developed by Rossi.¹⁶ Thus, ketone (**9**) was allowed to react with **10** in the presence of SnCl_4 and DIPEA giving rise to ketoazetidinone (**11**) with high diastereoselectivity ($\beta / \alpha = 19 / 1$) in ^1H -NMR spectral analysis. This diastereoselectivity is probably due to the steric effect induced by the *tert*-butyldimethylsilyloxyethyl side chain of **10** and the bulky tin tetrachloride chelated with the methoxy group of **9**.



Scheme 2. Reagents : (i) **9**, SnCl₄, DIPEA, -25 - 0 °C (77%);
(ii) ClCOCO₂(*t*-Bu-Ph), K₂CO₃, TEA, 0 °C (62%); (iii) P(OEt)₃,
xylene, reflux (87%); (iv) NH₄F₂H, NMP, rt (77%); (v) 10% Pd/C,
H₂, SEH, rt (50%)

The configuration at C-6 position of **11** was determined by 2D-spectra(COSY), NOE experiments (4.9% enhancement between C4 and C6 protons) and coupling constant of ¹H-NMR spectrum($J = 2.3$ Hz). The signal of the methoxy group of the β -isomer (**11 β**) was shifted to lower field by approximately 0.2 ppm relative to that of the α -isomer (**11 α**) in ¹H-NMR analysis.

With a multigram quantity of desired **11 β** in hand, we pursued the synthesis of tetracyclic β -lactam using P(OEt)₃-mediated ring closure.¹⁷ Acylation of the β -lactam nitrogen of **11 β** with (*tert*-butylbenzyloxy)oxalyl chloride produced the corresponding oxalimide (**12**), which was treated with P(OEt)₃ in xylene to provide the protected tetracyclic β -lactams (**13**). Desilylation with ammonium hydrogen difluoride followed by hydrogenolysis in the presence of sodium 2-ethylhexanoate (SEH) afforded the desired tetracyclic β -lactam (**3**) as a white amorphous solid, after purification by reverse phase column chromatography.

In conclusion, we have accomplished a stereoselective ten-steps synthesis of novel tetracyclic β -lactam (**3**) in *ca.* 6.5% overall yield. But tetracyclic β -lactam (**3**) was not fruitful from a viewpoint of the antibacterial activities. The key steps of the synthesis are the regioselective ring opening of epoxide (**5 β**) and the stereoselective synthesis of ketoazetidinone (**11**) by SnCl₄-mediated alkylation.

EXPERIMENTAL

General: NMR spectra were recorded on Varian Gemini 200 spectrometers operating at 200 MHz (¹H)

and 50 MHz (^{13}C) in deuteriochloroform (CDCl_3) and deuterium oxide (D_2O). Tetrahydrofuran and ether were distilled from sodium-benzophenone ketyl at atmospheric pressure immediately prior to use. Methylene chloride and dimethyl sulfoxide (DMSO) were distilled from calcium hydride. All other reagents and solvents used were reagent grade.

(3aS, 6aR)-5-[(1S)-1-Phenylethyl]octahydro-4H-oxireno[2, 3-e]isoindol-4-ones (5 α and 5 β)

To a solution of (3aR, 7aS)-2-[(1S)-1-phenylethyl]-2, 3, 3a, 6, 7, 7a-hexahydro-1H-isoindol-1-one (**4**) (5.0 g, 20.71 mmol) in 40 mL of CH_2Cl_2 was added *m*CPBA (7.15 g, 41.42 mmol). The reaction mixture was heated at reflux for 2 h in the apparatus fitted with a dean-stark water separator. The reaction mixture was cooled, then quenched with 10 mL of saturated aq. $\text{Na}_2\text{S}_2\text{O}_3$ solution. The mixture was extracted with CH_2Cl_2 (20 mL $\times$ 3). The combined extracts were washed with saturated aq. NaHCO_3 solution and brine, dried over anhydrous MgSO_4 , filtered, then concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc/Hexane = 2/1) provided 1.22 g (23%) of **5 α** and 3.89 g (73%) of **5 β** to the as a colorless oil. **5 α** : $^1\text{H-NMR}(\text{CDCl}_3)$ δ 7.29-7.21(m, 5H), 5.45(q, J = 7.1 Hz, 1H), 3.40(t, J = 9.0 Hz, 1H), 3.22(s, 1H), 2.70(dd, J = 4.1, 9.0 Hz, 1H), 2.27-2.02(m, 2H), 1.76-1.63(m, 2H), 1.50(d, J = 7.1 Hz, 3H), 1.92(m, 1H); $^{13}\text{C-NMR}(\text{CDCl}_3)$ δ 174.9, 139.4, 128.2, 127.1, 126.5, 52.4, 50.1, 48.3, 43.0, 39.1, 29.8, 22.3, 17.7, 16.0; MS (EI, 70eV) m/z 257(M^+); Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_2$: C, 74.68; H, 7.44; N, 5.44. Found C, 74.66; H, 7.47; N, 5.32. **5 β** : $^1\text{H-NMR}(\text{CDCl}_3)$ δ 7.29(m, 5H), 5.47(q, J = 6.9 Hz, 1H), 3.46(dd, J = 7.9, 10.6 Hz, 1H), 3.04(s, 1H), 2.72(d, J = 9.0 Hz, 2H), 2.56(d, J = 3.9 Hz, 2H), 1.98-1.60(m, 4H), 1.47(d, J = 7.1 Hz, 3H); $^{13}\text{C-NMR}(\text{CDCl}_3)$ δ 174.1, 140.1, 128.4, 127.4, 126.5, 54.2, 52.4, 48.8, 44.1, 39.1, 30.1, 20.6, 16.2, 15.7; IR(CDCl_3) cm^{-1} 2978, 2938, 1684, 1428, 778, 701; MS(EI, 70eV) m/z 257(M^+); Anal. Calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_2$: C, 74.68; H, 7.44; N, 5.44. Found C, 74.61; H, 7.47; N, 5.40.

(3aR, 4R, 5S, 7aS)-4-Hydroxy-1-oxo-2-[(1S)-1-phenylethyl]octahydro-1H-isoindol-5-yl acetate (6)

To a solution of **5 β** (3.0 g, 11.65 mmol) in 6.7 mL of AcOH was added $\text{Ti}(\text{O-}i\text{Pr})_4$ (1.72 mL, 5.83 mmol). The reaction mixture was stirred for 6 h at 32 $^\circ\text{C}$ and then concentrated. The mixture was extracted with EtOAc (20mL $\times$ 3). The combined extracts were washed with saturated aq. NaHCO_3 solution, H_2O and brine, dried over anhydrous MgSO_4 , filtered, then concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc/Hexane = 3/1) provided 3.63 g (98%) of **6** as colorless crystals. mp 169-172 $^\circ\text{C}$; $^1\text{H-NMR}(\text{CDCl}_3)$ δ 7.32-7.16(m, 5H), 5.38(q, J = 7.3 Hz, 1H), 4.43(dt, J = 3.7, 10.4 Hz, 1H), 3.33(dd, J = 5.1, 10.0 Hz, 1H), 2.99(d, J = 10.0 Hz, 1H), 2.87(t, J = 10.0 Hz, 1H), 2.52(t, J = 6.4 Hz, 1H), 2.36(d, J = 6.6 Hz, 1H), 2.14-2.07(m, 2H), 1.93(s, 3H), 1.73(dd, J = 3.2, 12.4 Hz, 1H), 1.53(m, 1H), 1.44(d, J = 6.6 Hz, 3H), 1.15(m, 1H); $^{13}\text{C-NMR}(\text{CDCl}_3)$ δ 173.5, 170.8, 139.9, 128.3, 127.3, 126.8, 75.8, 72.2, 49.1, 43.7, 41.6, 41.1, 26.4, 21.0, 20.7, 15.7 IR(CDCl_3) cm^{-1} 3362, 3006, 2954, 2873, 1740, 1661; HRMS(EI, 70eV) Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_4$; 317.1627, found 317.1629; Anal. Calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 67.90; H, 7.23; N, 4.52.

(3aR, 4R, 5S, 7aS)-4-Methoxy-1-oxo-2-[(1S)-1-phenylethyl]octahydro-1H-isoindol-5-yl acetate (7)

To a solution of **6** (3.0 g, 9.45 mmol) in 15 mL of DMF was added MeI (4.76 mL, 75.62 mmol) and Ag_2O

(3.72 g, 16.07 mmol). The reaction mixture was stirred for 48 h at 30 °C and then diluted with 15 mL of CH₂Cl₂. The precipitates were removed by filtration. The filtrate was diluted with 30 mL of EtOAc (10 mL x 3) and the extract was washed with H₂O and brine, dried over anhydrous MgSO₄, filtered, then concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc/Hexane = 1/1) provided 3.07 g (98%) of **7** as yellow crystals. mp 84-87 °C; ¹H-NMR(CDCl₃) δ 7.33-7.14(m, 5H), 5.38(q, *J* = 7.3 Hz, 1H), 4.41(dt, *J* = 3.7, 10.4 Hz, 1H), 3.29(dd, *J* = 5.1, 10.0 Hz, 1H), 2.96(s, 3H), 2.91(d, *J* = 10.0 Hz, 1H), 2.86(m, 1H), 2.52(t, *J* = 6.7 Hz, 1H), 2.34(d, *J* = 6.7 Hz, 1H), 2.21-2.04(m, 2H), 1.94(s, 3H), 1.77(dd, *J* = 3.0, 12.3 Hz, 1H), 1.55(m, 1H), 1.43(d, *J* = 6.7 Hz, 3H), 1.17(m, 1H); ¹³C-NMR(CDCl₃) δ 173.6, 170.7, 139.2, 128.5, 127.9, 127.2, 76.1, 72.2, 68.5, 49.1, 44.7, 42.1, 41.7, 26.5, 21.9, 21.2, 15.5; IR(CDCl₃) cm⁻¹ 2935, 2879, 1739, 1684, 1424, 1237, 704; HRMS(EI, 70eV) Calcd for C₁₉H₂₅NO₄; 331.1784, found 331.1782; Anal. Calcd for C₁₉H₂₅NO₄: C, 68.86; H, 7.60; N, 4.23. Found C, 69.07; H, 7.47; N, 4.25.

(3aR, 4R, 5S, 7aS)-5-Hydroxy-4-methoxy-2-[(1S)-1-phenylethyl]octahydro-1H-isoindol-1-one (8)

To a solution of **7** (3.07 g, 9.26 mmol) in 20 mL of MeOH was added NaOMe (1.0 g, 18.52 mmol) at 0 °C. After stirring for 1 h at 10 °C, the reaction mixture was diluted with 10 mL of EtOAc and poured with ice water. The separated organic layer was washed with H₂O and brine, dried over anhydrous MgSO₄, filtered, then concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc/Hexane = 5/1) provided 2.45 g (91%) of **8** as a colorless oil. ¹H-NMR(CDCl₃) δ 7.33-7.14(m, 5H), 5.38(q, *J* = 7.3 Hz, 1H), 4.41(dt, *J* = 3.7, 10.4 Hz, 1H), 3.29(dd, *J* = 5.1, 10.0 Hz, 1H), 2.96(s, 3H), 2.92(d, *J* = 10.0 Hz, 1H), 2.86(m, 1H), 2.52(t, *J* = 6.7 Hz, 1H), 2.34(d, *J* = 6.7 Hz, 1H), 2.21-2.04(m, 2H), 1.77(dd, *J* = 3.0, 12.3 Hz, 1H), 1.55(m, 1H), 1.43(d, *J* = 6.7 Hz, 3H), 1.17(m, 1H); ¹³C-NMR(CDCl₃) δ 201.3, 173.6, 139.2, 128.5, 127.9, 127.2, 76.1, 72.2, 68.7, 49.1, 44.7, 42.1, 41.7, 26.5, 21.9, 21.2, 15.5; IR(CDCl₃) cm⁻¹ 3464, 1743, 1692, 1374, 1243; HRMS(EI, 70eV) Calcd for C₁₇H₂₃NO₃; 289.1678, found 289.1677; Anal. Calcd for C₁₇H₂₃NO₃: C, 70.56; H, 8.01; N, 4.84. Found C, 70.48; H, 7.96; N, 4.81.

(3aR, 4R, 7aS)-4-Methoxy-2-[(1S)-1-phenylethyl]hexahydro-1H-isoindole-1, 5(4H)-dione (9)

To a solution of trifluoroacetic anhydride (0.59 mL, 4.15 mmol) in 6 mL of CH₂Cl₂ under N₂ at -78 °C was added DMSO (0.44 mL, 6.21 mmol). The solution was stirred for 30 min at -78 °C and then **8** (600 mg, 2.07 mmol) in 2 mL of CH₂Cl₂ was added to the above solution and stirring was continued for 30 min at the same temperature. To the above mixture was added Et₃N (1.21 mL, 8.69 mmol) at -78 °C. The mixture was stirred for another 1 h and warmed to rt. The mixture was treated with 5 mL of saturated aq. NH₄Cl solution and extracted with 10 mL of EtOAc (10 mL x 2). The combined organic extracts were washed with saturated aq. NaHCO₃ solution and brine, dried over anhydrous MgSO₄, filtered, then concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc/Hexane = 4/1) provided 535 mg (90%) of **9** as a colorless oil. ¹H-NMR(CDCl₃) δ 7.35-7.25(m, 5H), 5.58(q, *J* = 7.1 Hz, 1H), 3.38(dd, *J* = 5.3, 10.3 Hz, 1H), 2.94(s, 3H), 2.91(d, *J* = 11.8 Hz, 1H), 2.74(m, 1H), 2.57-2.40(m, 2H), 2.33-2.24(m, 2H), 1.91(m, 1H), 1.52(d, *J* = 7.3 Hz, 3H); ¹³C-NMR(CDCl₃) δ 208.7, 172.8, 139.9, 128.5, 127.7, 127.0, 83.0, 59.0, 49.0, 44.1, 42.8, 41.4, 36.9, 23.9, 15.1; HRMS (EI, 70eV) Calcd for

C₁₇H₂₁NO₃; 287.1521, found 287.1521; Anal. Calcd for C₁₇H₂₁NO₃: C, 71.06; H, 7.37; N, 4.87. Found C, 71.11; H, 7.37; N, 4.84.

(3aR, 4R, 6R, 7aS)-6-[(2S, 3S)-3-[(1R)-(tert-Butyldimethylsilyloxy)ethyl]-4-oxoazetidinyl]-4-methoxy-2-[(1S)-1-phenylethyl]hexahydro-1H-isoindole-1,5(4H)-dione (**11**)

To a solution of **9** (108 mg, 0.38 mmol) in 2 mL of CH₂Cl₂ under N₂ at –25 °C was added SnCl₄ (0.13 mL, 1.13 mmol) for 10 min. The solution was stirred for 10 min at –25 °C and then 4-acetoxiazetidinone (**10**) (109 mg, 0.38 mmol) in 0.5 mL of CH₂Cl₂ was added. The reaction mixture was warmed to 0 °C and DIPEA (0.17 mL, 0.99 mmol) was added for 15 min. The mixture was stirred for 10 h, then quenched with cold saturated Rochelle salt solution, saturated aq. NaHCO₃ solution, and brine. The mixture was dried over anhydrous MgSO₄, filtered, then concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc/ Hexane = 4/1) provided 151 mg (77%) of **11** as a colorless oil. (β / α = 19 / 1, ¹H-NMR spectral analysis based on methoxy integration) ¹H-NMR(CDCl₃) δ 7.39-7.23(m, 5H), 6.34(s, 1H), 5.51(q, *J* = 7.3 Hz, 1H), 4.20(m, 1H), 3.90(d, *J* = 7.3 Hz, 1H), 3.41(q, *J* = 10.2 Hz, 1H), 3.31(s, OMe, 1H), 3.29(d, *J* = 9.4 Hz, 1H), 3.10(s, 3H, OMe, 1H), 2.96(m, 1H), 2.89-2.74(m, 2H), 2.68-2.52(m, 2H), 2.28(m, 1H), 2.02(m, 1H), 1.53(d, *J* = 6.5 Hz, 3H), 0.86(s, 9H), 0.07(s, 6H); ¹³C-NMR(CDCl₃) δ 208.8, 173.7, 168.1, 139.5, 128.6, 127.7, 127.0, 82.1, 64.8, 62.7, 59.2, 51.2, 49.5, 49.0, 43.9, 39.7, 38.6, 29.7, 22.6, 17.8, 15.6, -4.2, -5.2; MS(CI, 70eV) 515(M+1); Anal. Calcd for C₂₈H₄₂N₂O₅Si: C, 65.34; H, 8.22; N, 5.44. Found C, 65.53; H, 8.21; N, 5.32.

4-tert-Butylbenzyl [(2S, 3S)-2-[(3aS, 5R, 7R, 7aR)-7-methoxy-3, 6-dioxo-2-[(1S)-1-phenylethyl]octahydro-1H-isoindol-5-yl]-3-[(1R)-1-(tert-butyldimethylsilyloxy)ethyl]-4-oxoazetidinyl](oxo)acetate (**12**)

To a solution of **11** (260 mg, 0.51 mmol) in 2 mL of CH₂Cl₂ was added K₂CO₃ (70 mg, 0.51 mmol) and Et₃N (0.20 mL, 1.53 mmol) at 0 °C. The solution was stirred for 10 min at same temperature and then (tert-butylbenzyloxy)oxalyl chloride (322 mg, 1.26 mmol) in 0.5 mL of CH₂Cl₂ was added. The reaction mixture was stirred for 1 h, then quenched with 2 mL of phosphate buffer solution (pH = 7.0). The aqueous layer was separated and extracted with 5 mL of EtOAc (50 mL x 2). The combined organic extracts were washed with H₂O and brine, dried over anhydrous MgSO₄, filtered, then concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc/ Hexane = 1/1) provided 289 mg (62%) of **12** as a colorless oil. ¹H-NMR(CDCl₃) δ 7.41-7.25(m, 9H), 5.50(q, *J* = 7.3 Hz, 1H), 5.30(s, 2H), 4.71(m, 1H), 4.29(m, 1H), 3.17(d, *J* = 11.4 Hz, 1H), 2.98-2.86(m, 2H), 2.63(m, 1H), 2.50(m, 1H), 2.35(m, 1H), 1.70(m, 1H), 1.54(d, *J* = 7.1 Hz, 3H), 1.30(s, 3H), 1.23(d, *J* = 5.9 Hz, 3H), 0.79(s, 9H), 0.60(s, 3H), 0.07(s, 3H); ¹³C-NMR(CDCl₃) δ 206.9, 173.5, 163.4, 159.6, 156.6, 151.8, 139.5, 130.7, 128.9, 128.6, 127.6, 126.7, 125.4, 81.7, 76.4, 68.5, 65.0, 61.0, 59.3, 53.2, 49.0, 47.1, 44.0, 39.4, 34.5, 34.3, 31.3, 22.0, 21.6, 17.6, 15.6, -4.5, -5.3; Anal. Calcd for C₄₁H₅₆N₂O₈Si: C, 67.18; H, 7.70; N, 3.82. Found C, 67.19; H, 7.70; N, 5.29.

4-tert-Butylbenzyl (3aR, 4R, 8S, 8aS, 8bS, 9aS)-8-[(1R)-1-(tert-butyldimethylsilyloxy)ethyl]-4-methoxy-1, 7-dioxo-2-[(1S)-1-phenylethyl]-2, 3, 3a, 4, 7, 8, 8a, 8b, 9, 9a-decahydro-1H-azeto[2,1-a]pyrrolo[3,4-

f]isoindole-5-carboxylate (**13**)

To a solution of **12** (200 mg, 0.27 mmol) in 1.5 mL of xylene was added P(OEt)₃ (0.24 mL, 1.36 mmol) and hydroquinone (2 mg, 0.01 mmol). The reaction mixture was heated at reflux for 4 h. The mixture was cooled to rt and concentrated. The residue was diluted with 5 mL of EtOAc, washed with H₂O and brine, dried over anhydrous MgSO₄, filtered, then concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc/Hexane = 1/1) provided 166 mg (87%) of **13** as a colorless oil. ¹H-NMR(CDCl₃) δ 7.41-7.25(m, 9H), 5.38(q, *J* = 6.3 Hz, 1H), 5.17(s, 2H), 4.69(s, 1H), 4.23-4.13(m, 2H), 3.11(s, 3H), 3.02(q, *J* = 3.3 Hz, 2H), 2.83-2.65(m, 2H), 2.49(m, 1H), 2.08(m, 1H), 1.50(d, *J* = 6.9 Hz, 3H), 1.32(s, 9H), 1.19(d, *J* = 6.1 Hz, 3H), 0.84(s, 9H), 0.06(s, 3H), 0.05(s, 3H); ¹³C-NMR(CDCl₃) δ 175.2, 173.8, 160.6, 151.1, 144.4, 139.3, 131.9, 128.6, 127.7, 126.4, 125.2, 72.0, 66.8, 65.5, 63.5, 60.4, 56.1, 54.2, 49.1, 42.1, 40.2, 39.6, 34.4, 31.2, 28.9, 25.6, 22.1, 17.8, 16.4, 16.0, -4.4, -5.2; HRMS(CI, 70eV) Calcd for C₄₁H₅₆N₂O₆Si; 700.3907, found 700.3901; Anal. Calcd for C₄₁H₅₆N₂O₆Si: C, 70.25; H, 8.05; N, 4.00. Found C, 70.19; H, 8.06; N, 3.98.

4-tert-Butylbenzyl (3aR, 4R, 8S, 8aS, 8bS, 9aS)-8-[(1R)-1-hydroxyethyl]-4-methoxy-1, 7-dioxo-2-[(1S)-1-phenylethyl]-2, 3, 3a, 4, 7, 8, 8a, 8b, 9, 9a-decahydro-1H-azeto[2,1-a]pyrrolo[3,4-f]isoindole-5-carboxylate (**14**)

To a solution of **13** (150 mg, 0.21 mmol) in 1 mL of DMF and 0.3 mL of NMP was added (NH₄)HF₂ (61 mg, 1.07 mmol). The reaction mixture was stirred for 78 h at rt, then diluted with 3 mL of EtOAc and poured with ice water. The combined organic extracts were washed with H₂O and brine, dried over anhydrous MgSO₄, filtered, then concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc) provided 97 mg (77%) of **14** as a colorless oil. ¹H-NMR(CDCl₃) δ 7.42-7.40(m, 5H), 7.21-7.18(m, 4H), 5.17(s, 2H), 4.94(d, *J* = 6.4 Hz, 1H), 4.43(d, *J* = 6.7 Hz, 1H), 4.19(m, 1H), 3.75(m, 1H), 3.70(s, 2H), 3.48(m, 1H), 3.28(s, 3H), 3.03-2.91(m, 1H), 2.89-2.81(m, 2H), 2.37(m, 1H), 2.17(s, 1H), 1.47(d, *J* = 6.9 Hz, 3H), 1.32(d, *J* = 6.5 Hz, 3H), 1.22(s, 9H); ¹³C-NMR(CDCl₃) δ 173.8, 165.5, 163.8, 151.2, 134.4, 129.4, 127.3, 126.5, 126.3, 125.8, 113.1, 79.8, 67.2, 63.4, 59.8, 58.4, 57.2, 50.2, 48.4, 44.3, 43.7, 41.8, 34.6, 31.3, 28.5, 20.9, 20.4; HRMS(CI, 70eV) Calcd for C₃₅H₄₂N₂O₆; 586.3043, found 586.3039; Anal. Calcd for C₃₅H₄₂N₂O₆: C, 71.65; H, 7.22; N, 4.77. Found C, 71.58; H, 7.22; N, 4.73.

Sodium (3aR, 4R, 8S, 8aS, 8bS, 9aS)-8-[(1R)-1-hydroxyethyl]-4-methoxy-1, 7-dioxo-2-[(1S)-1-phenylethyl]-2, 3, 3a, 4, 7, 8, 8a, 8b, 9, 9a-decahydro-1H-azeto[2,1-a]pyrrolo[3,4-f]isoindole-5-carboxylate (**3**)

To a solution of **14** (42 mg, 0.07 mmol) in 0.5 mL of propanol was added 10% Pd/C (13 mg) and Et₃N (24 μL, 0.11 mmol). The reaction mixture was stirred under a balloon pressure of hydrogen for 1 h at rt. The reaction mixture was filtered through a pad of celite. The pad was washed with 5 mL of acetone and the combined filtrate and washing were concentrated. The residue was dissolved in 2 mL of acetone and SEH (14 mg, 0.08 mmol) was added. The mixture was stirred for 30 min and concentrated. The residue was diluted with ether and H₂O. The organic layer was separated and extracted with H₂O. Purification of the combined aqueous phase by reverse phase column chromatography (MeCN/H₂O = 1/10) provided 17

mg (50%) of **3** as a white amorphous solid. $^1\text{H-NMR}(\text{D}_2\text{O})$ δ 5.13(q, $J = 6.9$ Hz, 1H), 4.11-4.03(m, 2H), 3.52-3.46(m, 2H), 2.98(dd, $J = 2.9, 5.9$ Hz, 2H), 2.61(m, 2H), 1.89(m, 1H), 1.45(d, $J = 7.1$ Hz, 3H), 1.26(d, $J = 6.3$ Hz, 3H); $^{13}\text{C-NMR}(\text{CDCl}_3)$ δ 174.1, 168.6, 164.1, 138.9, 136.2, 127.3, 126.5, 126.3, 114.3, 79.3, 69.9, 60.0, 58.1, 57.4, 52.2, 43.8, 28.3, 20.9; HRMS (CI, 70eV) Calcd for $\text{C}_{24}\text{H}_{27}\text{N}_2\text{O}_6\text{Na}$; 462.1767, found 462.1754; Anal. Calcd for $\text{C}_{24}\text{H}_{27}\text{N}_2\text{O}_6\text{Na}$: C, 62.33; H, 5.88; N, 6.06. Found C, 62.31; H, 5.89; N, 6.04.

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