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STEREOSELECTIVE SYNTHESIS OF A NOVEL TETRACYCLIC β-LACTAM

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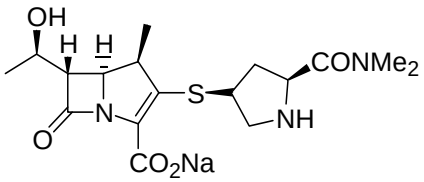
Abstract - Stereocontrolled total synthesis of a novel tetracyclic β-lactam (**3**) has been achieved in ten steps. The key transformations in this approach are the regioselective ring opening of β-epoxide (**5β**) and the stereoselective construction of ketoazetidinone (**11**) from methoxyketo-γ-lactam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

Since the discovery of thienamycin by Merck scientists[1] 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 Perboni[9] 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]



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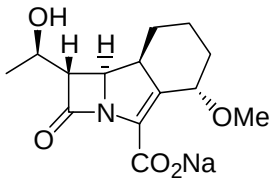

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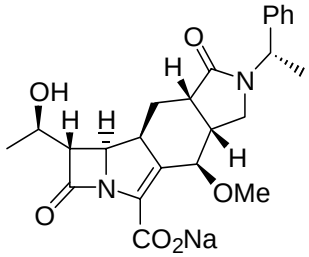

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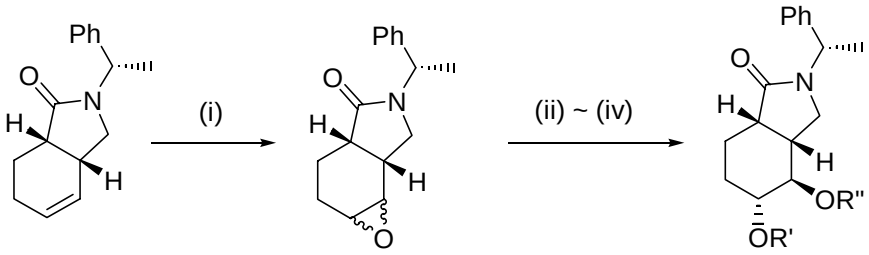
As a part of our research program to explore a new class of β-lactams,[14] we report a stereocontrolled total synthesis of novel tetracyclic β-lactam (**3**) from the commercially available 4-acetoxyazetidinone (**10**).

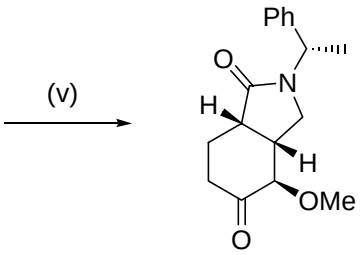
Our initial approach directed toward the preparation of methoxyketo-γ-lactam (**9**) was quite successfully carried out as outlined in Scheme 1. Bicyclic γ-lactam (**4**) prepared by the known intramolecular Diels-

Alder reaction,[15] was treated with *m*CPBA to give a mixture of epoxides (**5**)(β / α = 3 / 1), which could be easily separated by flash chromatography. Regiospecific ring opening reaction of the β-epoxide (**5β**) by acetic acid in the presence of a catalytic amount of Ti(O-*i*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.



4 **5** (β / α = 3 / 1)

6. R' = Ac, R'' = H
7. R' = Ac, R'' = Me
8. R' = H, R'' = Me



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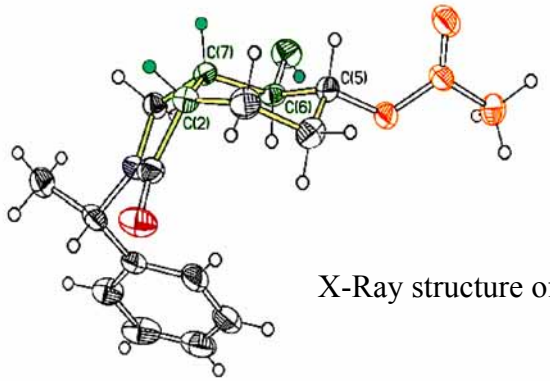
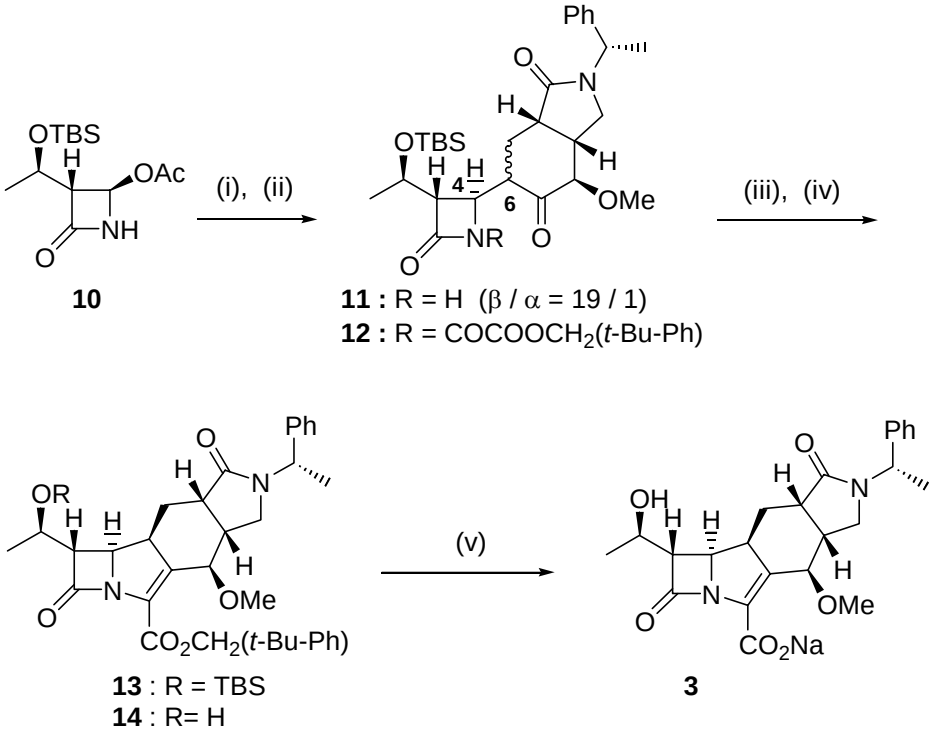


X-Ray structure of **6**

Scheme 1. Reagents : (i) *m*CPBA, reflux (96%); (ii) AcOH, Ti(O-*i*Pr), rt (90%); (iii) MeI, Ag_2O, rt (92%); (iv) NaOMe, 0 ^oC (90%); (v) $(CF_3CO)_2O$, DMSO, Et_3N, -78 ^oC (94%)

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-acetoxyazetidine (**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 (β / α = 19 / 1) in ^{1}H-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**, $SnCl_4$, DIPEA, -25 - 0 ^oC (77%); (ii) $ClCOCO_2$(*t*-Bu-Ph), K_2CO_3,TEA, 0 ^oC (62%); (iii) $P(OEt)_3$, xylene, reflux (87%); (iv) NH_4F_2H, NMP, rt (77%); (v) 10% Pd/C, H_2, 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 ^{1}H-NMR spectrum(J = 2.3 Hz). The signal of the methoxy group of the β-isomer (**11β**) was shifted to lower field by approximately 0.2 ppm relative to that of the α-isomer (**11α**) in ^{1}H-NMR analysis.

With a multigram quantity of desired **11β** 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 **11β** 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 (**5β**) and the stereoselective synthesis of ketoazetidinone (**11**) by $SnCl_4$-mediated alkylation.

EXPERIMENTAL

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

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.

*(3a*S*, 6a*R*)-5-[(1*S*)-1-Phenylethyl]octahydro-4*H*-oxireno[2, 3-e]isoindol-4-ones* (**5α** and **5β**)
To a solution of (3a*R*, 7a*S*)-2-[(1*S*)-1-phenylethyl]-2, 3, 3a, 6, 7, 7a-hexahydro-1*H*-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. $Na_2S_2O_3$ solution. The mixture was extracted with CH_2Cl_2 (20 mL x 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 **5α** and 3.89 g (73%) of **5β** to the as a colorless oil. **5α**: ^{1}H-NMR($CDCl_3$) 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}C-NMR($CDCl_3$) 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 $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found C, 74.66; H, 7.47; N, 5.32. **5β**: ^{1}H-NMR($CDCl_3$) 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}C-NMR($CDCl_3$) 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 $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found C, 74.61; H, 7.47; N, 5.40.

*(3a*R*, 4*R*, 5*S*, 7a*S*)-4-Hydroxy-1-oxo-2-[(1*S*)-1-phenylethyl]octahydro-1*H*-isoindol-5-yl acetate* (**6**)
To a solution of **5β** (3.0 g, 11.65 mmol) in 6.7 mL of AcOH was added Ti(O-*i*Pr)$_4$ (1.72 mL, 5.83 mmol). The reaction mixture was stirred for 6 h at 32 ^{o}C and then concentrated. The mixture was extracted with EtOAc (20mL x 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 ^{o}C; ^{1}H-NMR($CDCl_3$) 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}C-NMR($CDCl_3$) 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 $C_{18}H_{23}NO_4$; 317.1627, found 317.1629; Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 67.90; H, 7.23; N, 4.52.

*(3a*R*, 4*R*, 5*S*, 7a*S*)-4-Methoxy-1-oxo-2-[(1*S*)-1-phenylethyl]octahydro-1*H*-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 CH_2Cl_2. The precipitates were removed by filteration. The filterate was diluted with 30 mL of EtOAc (10 mL x 3) and the extract was washed with H_2O and brine, dried over anhydrous $MgSO_4$, 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 ctystals. mp 84-87 °C; ^{1}H-NMR($CDCl_3$) 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); ^{13}C-NMR($CDCl_3$) 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($CDCl_3$) cm^{-1} 2935, 2879, 1739, 1684, 1424, 1237, 704; HRMS(EI, 70eV) Calcd for $C_{19}H_{25}NO_4$; 331.1784, found 331.1782; Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found C, 69.07; H, 7.47; N, 4.25.

*(3a*R, *4*R, *5*S, *7a*S*)-5-Hydroxy-4-methoxy-2-[(1*S*)-1-phenylethyl]octahydro-1*H*-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 H_2O and brine, dried over anhydrous $MgSO_4$, 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. ^{1}H-NMR($CDCl_3$) 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); ^{13}C-NMR($CDCl_3$) 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($CDCl_3$) cm^{-1} 3464, 1743, 1692, 1374, 1243; HRMS(EI, 70eV) Calcd for $C_{17}H_{23}NO_3$; 289.1678, found 289.1677; Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found C, 70.48; H, 7.96; N, 4.81.

*(3a*R, *4*R, *7a*S*)-4-Methoxy-2-[(1*S*)-1-phenylethyl]hexahydro-1*H*-isoindole-1, 5(4*H*)-dione* (**9**)
To a solution of trifluoroacetic anhydride (0.59 mL, 4.15 mmol) in 6 mL of CH_2Cl_2 under N_2 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 CH_2Cl_2 was added to the above solution and stirring was continued for 30 min at the same temperature. To the above mixture was added Et_3N (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. NH_4Cl solution and extracted with 10 mL of EtOAc (10 mL x 2). The combined organic 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 = 4/1) provided 535 mg (90%) of **9** as a colorless oil. ^{1}H-NMR($CDCl_3$) 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); ^{13}C-NMR($CDCl_3$) 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

$C_{17}H_{21}NO_3$; 287.1521, found 287.1521; Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found C, 71.11; H, 7.37; N, 4.84.

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

To a solution of **9** (108 mg, 0.38 mmol) in 2 mL of CH_2Cl_2 under N_2 at –25 °C was added $SnCl_4$ (0.13 mL, 1.13 mmol) for 10 min. The solution was stirred for 10 min at –25 °C and then 4-acetoxyazetidinone (**10**) (109 mg, 0.38 mmol) in 0.5 mL of CH_2Cl_2 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. $NaHCO_3$ solution, and brine. The mixture was dried over anhydrous $MgSO_4$, 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, ^{1}H-NMR spectral analysis based on methoxy integration) ^{1}H-NMR($CDCl_3$) 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, 11α), 3.29(d, *J* = 9.4 Hz, 1H), 3.10(s, 3H, OMe, 11β), 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); ^{13}C-NMR($CDCl_3$) 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 $C_{28}H_{42}N_2O_5Si$: C, 65.34; H, 8.22; N, 5.44. Found C, 65.53; H, 8.21; N, 5.32.

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

To a solution of **11** (260 mg, 0.51 mmol) in 2 mL of CH_2Cl_2 was added K_2CO_3 (70 mg, 0.51 mmol) and Et_3N (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 CH_2Cl_2 was added. The reaction mixture was stirred for 1 h, then quenched with 2 mL of phosphate buffer solution (pH = 7.0). The aquoues layer was separated and extracted with 5 mL of EtOAc (50 mL x 2). The combined organic extracts were washed with H_2O and brine, dried over anhydrous $MgSO_4$, 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. ^{1}H-NMR($CDCl_3$) 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); ^{13}C-NMR($CDCl_3$) 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 $C_{41}H_{56}N_2O_8Si$: C, 67.18; H, 7.70; N, 3.82. Found C, 67.19; H, 7.70; N, 5.29.

4-tert-*Butylbenzyl (3a*R, *4*R, *8*S, *8a*S, *8b*S, *9a*S)-8-{(1*R*)-1-(*tert-butyldimethylsilyloxy)ethyl}-4-methoxy-1, 7-dioxo-2-[(1*S*)-1-phenylethyl]-2, 3, 3a, 4, 7, 8, 8a, 8b, 9, 9a-decahydro-1*H-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 H_2O and brine, dried over anhydrous $MgSO_4$, 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. ^{1}H-NMR($CDCl_3$) 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); ^{13}C-NMR($CDCl_3$) 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 $C_{41}H_{56}N_2O_6Si$; 700.3907, found 700.3901; Anal. Calcd for $C_{41}H_{56}N_2O_6Si$: C, 70.25; H, 8.05; N, 4.00. Found C, 70.19; H, 8.06; N, 3.98.

4-tert-*Butylbenzyl (3a*R, *4*R, *8*S, *8a*S, *8b*S, *9a*S)*-8-[(1*R)*-1-hydroxyethy]-4-methoxy-1, 7-dioxo-2-[(1*S)*-1-phenylethyl]-2, 3, 3a, 4, 7, 8, 8a, 8b, 9, 9a-decahydro-1*H*-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 $(NH_4)HF_2$ (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 H_2O and brine, dried over anhydrous $MgSO_4$, filtered, then concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc) provided 97 mg (77%) of **14** as a colorless oil. ^{1}H-NMR($CDCl_3$) 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); ^{13}C-NMR($CDCl_3$) 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 $C_{35}H_{42}N_2O_6$; 586.3043, found 586.3039; Anal. Calcd for $C_{35}H_{42}N_2O_6$: C, 71.65; H, 7.22; N, 4.77. Found C, 71.58; H, 7.22; N, 4.73.

*Sodium (3a*R, *4*R, *8*S, *8a*S, *8b*S, *9a*S)*-8-[(1*R)*-1-hydroxyethy]-4-methoxy-1, 7-dioxo-2-[(1*S)*-1-phenylethyl]-2, 3, 3a, 4, 7, 8, 8a, 8b, 9, 9a-decahydro-1*H*-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 Et_3N (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 filterate 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 H_2O. The organic layer was separated and extracted with H_2O. Purification of the combined aqueous phase by reverse phase column chromatography (MeCN/H_2O = 1/10) provided 17

mg (50%) of **3** as a white amorphous solid. ^{1}H-NMR(D_2O) 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}C-NMR($CDCl_3$) 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 $C_{24}H_{27}N_2O_6Na$; 462.1767, found 462.1754; Anal. Calcd for $C_{24}H_{27}N_2O_6Na$: C, 62.33; H, 5.88; N, 6.06. Found C, 62.31; H, 5.89; N, 6.04.

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