STEREOSELECTIVE SYNTHESIS OF A NOVEL TETRACYCLIC β-LACTAM

Do Kyu Pyun,a Hee Jung Jung, Hyun Jung Kwak, Jae Hak Kim Eun Jung Kim, Bong Jin Kim, Moon Hwan Kim, and Cheol Hae Lee*

Korea Research Institute of Chemical Technology P.O.Box 107, Yusung, Taejon 305-600, Korea
Department of Chemistry, Sogang University, Seoul, 121-742, Korea a

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 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-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\textsuperscript{15} was treated with \textit{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 \(\beta\)-epoxide (5\(\beta\)) by acetic acid in the presence of a catalytic amount of Ti(O-iPr)\(_4\) 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-\(\gamma\)-lactam (9) in a good yield.

\[\text{Scheme 1. Reagents: (i) \textit{m}CPBA, reflux (96%); (ii) AcOH, Ti(O-iPr), rt (90%); (iii) MeI, Ag}_2\text{O, rt (92%); (iv) NaOMe, 0\degree\text{C (90%); (v) (C}_3\text{F}_3\text{CO})_2\text{O, DMSO, Et}_3\text{N, -78\degree\text{C (94%)}}.}\]

Ketoazetidinone (11), a key intermediate in the synthesis of tetracyclic \(\beta\)-lactam (3), could be accessible by stereoselective construction of the C4-C6 bond via the reaction of an enolate of methoxyketo-\(\gamma\)-lactam (9) and 4-acetoxyazetidine (10) using the methodology developed by Rossi.\textsuperscript{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 \(^1\text{H-NMR}\) spectral analysis. This diastereoselectivity is probably due to the steric effect induced by the \textit{tert}-butylidimethylsilyloxyethyl side chain of 10 and the bulky tin tetrachloride chelated with the methoxy group of 9.
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 $\beta$-isomer (11$\beta$) was shifted to lower field by approximately 0.2 ppm relative to that of the $\alpha$-isomer (11$\alpha$) in $^1H$-NMR analysis.

With a multigram quantity of desired 11$\beta$ in hand, we pursued the synthesis of tetracyclic $\beta$-lactam using P(OEt)$_3$-mediated ring closure. Acylation of the $\beta$-lactam nitrogen of 11$\beta$ with (tert-butylbenzylxyloxy)oxalyl chloride produced the corresponding oxalimide (12), which was treated with P(OEt)$_3$ in xylene to provide the protected tetracyclic $\beta$-lactams (13). Desilylation with ammonium hydrogen difluoride followed by hydrogenolysis in the presence of sodium 2-ethylhexanoate (SEH) afforded the desired tetracyclic $\beta$-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 $\beta$-lactam (3) in ca. 6.5% overall yield. But tetracyclic $\beta$-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$\beta$) 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 ($^1H$)
and 50 MHz \((^{13}\text{C})\) in deuteriochloroform (CDCl\(_3\)) and deuterium oxide (D\(_2\)O). 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.

\((3\text{aS}, 6\text{aR})-5\text{a}-\text{[1S)-1-Phenylethyl]octahydro-4H-oxireno[2, 3-e]isoindol-4-ones (5a and 5b)}\)

To a solution of \((3\text{aR}, 7\text{aS})-2\text{a}-\text{[1S)-1-phenylethyl]-2, 3, 3\text{a, 6, 7, 7a-hexahydro-1H-isoindol-1-one (4)}\) (5.0 g, 20.71 mmol) in 40 mL of CH\(_2\)Cl\(_2\) was added mCPBA (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\(_2\)S\(_2\)O\(_3\) solution. The mixture was extracted with CH\(_2\)Cl\(_2\) (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 5\text{a} and 3.89 g (73%) of 5\text{b} to the as colorless oil.

5\text{a}:
\[1\text{H-NMR(CDCl}_3\] \(\delta 7.29-7.21\text{(m, 5H)}, 5.45\text{(q, }J = 7.1\text{ Hz, 1H)}, 3.40\text{(t, }J = 9.0\text{ Hz, 1H)}, 3.22\text{(s, 1H)}, 2.70\text{(dd, }J = 4.1, 9.0\text{ Hz, 2H)}, 2.27-2.02\text{(m, 2H)}, 1.76-1.63\text{(m, 2H)}, 1.50\text{(d, }J = 7.1\text{ Hz, 3H)}, 1.92\text{(m, 1H)}; \]
\[13\text{C-NMR(CDCl}_3\] \(\delta 174.9, 139.4, 128.2, 127.1, 126.5, 52.4, 50.1, 48.3, 43.0, 39.1, 29.8, 22.3, 17.7, 16.0; MS (EI, 70eV) m/z 257(M\)+); 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.

5\text{b}:
\[1\text{H-NMR(CDCl}_3\] \(\delta 7.29\text{(m, 5H)}, 5.47\text{(q, }J = 6.9\text{ Hz, 1H)}, 3.46\text{(dd, }J = 7.9, 10.6\text{ Hz, 1H)}, 3.04\text{(s, 1H)}, 2.72\text{(d, }J = 9.0\text{ Hz, 2H)}, 2.56\text{(d, }J = 3.9\text{ Hz, 2H)}, 1.98-1.60\text{(m, 4H)}, 1.47\text{(d, }J = 7.1\text{ Hz, 3H}); \]
\[13\text{C-NMR(CDCl}_3\] \(\delta 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.

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

To a solution of 5\text{b} (3.0 g, 11.65 mmol) in 6.7 mL of AcOH was added Ti(O-iPr\(_4\)) (1.72 mL, 5.83 mmol). The reaction mixture was stirred for 6 h at 32 °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\(_2\)O 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 °C; \[1\text{H-NMR(CDCl}_3\] \(\delta 7.32-7.16\text{(m, 5H)}, 5.38\text{(q, }J = 7.3\text{ Hz, 1H)}, 4.43\text{(dt, }J = 3.7, 10.4\text{ Hz, 1H)}, 3.33\text{(dd, }J = 5.1, 10.0\text{ Hz, 1H)}, 2.99\text{(d, }J = 10.0\text{ Hz, 1H)}, 2.87\text{(t, }J = 10.0\text{ Hz, 1H)}, 2.52\text{(t, }J = 6.4\text{ Hz, 1H)}, 2.36\text{(d, }J = 6.6\text{ Hz, 1H)}, 2.14-2.07\text{(m, 2H)}, 1.93\text{(s, 3H)}, 1.73\text{(dd, }J = 3.2, 12.4\text{ Hz, 1H)}, 1.53\text{(m, 1H)}, 1.44\text{(d, }J = 6.6\text{ Hz, 3H)}, 1.15\text{(m, 1H)}; \]
\[13\text{C-NMR(CDCl}_3\] \(\delta 173.5, 170.8, 139.9, 128.3, 127.3, 126.8, 75.8, 72.2, 49.1, 43.7, 41.6, 41.1, 26.4, 21.0, 20.7, 15.7\text{ IR(CDCl}_3\) 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.

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

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\(_2\)O
(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-isooindol-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), 1.94(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 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
\(C_{17}H_{21}NO_3\); 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.

\((3aR, 4R, 6R, 7aS)-6\)\{\(2S, 3S\)\}-3\{\(1R\)-\(\text{tet}-\text{Butyldimethylsilyloxy}\)ethyl\}-4-oxoazetidinyl\}-4-methoxy-2-\{\(1S\)-1-phenylethyl\}hexahydrop-1H-isouindole-1,5(4H)-dione \((11)\)

To a solution of \(9\) (108 mg, 0.38 mmol) in 2 mL of \(\text{CH}_2\text{Cl}_2\) under \(\text{N}_2\) at –25 \(^\circ\)C was added \(\text{SnCl}_4\) (0.13 mL, 1.13 mmol) for 10 min. The solution was stirred for 10 min at –25 \(^\circ\)C and then 4-acetoxyazetidinone \((10)\) (109 mg, 0.38 mmol) in 0.5 mL of \(\text{CH}_2\text{Cl}_2\) was added. The reaction mixture was warmed to 0 \(^\circ\)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. \(\text{NaHCO}_3\) solution, and brine. The mixture was dried over anhydrous \(\text{MgSO}_4\), 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. (\(\beta/\alpha = 19/1, 1\)H-NMR spectral analysis based on methoxy integration) \(1\)H-NMR (\(\text{CDCl}_3\)) \(\delta\) 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, \(1\)α), 3.29 (d, \(J = 9.4\) Hz, 1H), 3.10 (s, 3H, OMe, \(1\)β), 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 (\(\text{CDCl}_3\)) \(\delta\) 208.8, 173.7, 168.1, 167.0, 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 \(C_{28}H_{42}N_2O_5\text{Si}\): C, 65.34; H, 8.22; N, 5.44. Found C, 65.53; H, 8.21; N, 5.32.

\(4\)-\(\text{tert}-\text{Butylbenzyl}\) \((/2S, 3S)\)-2\{\(3aS, 5R, 7R, 7aR\)\}-7-methoxy-6-dioxo-2\{\(1S\)-1-phenylethyl\}octahydro-1H-isouindole-5-yl\}3\{\(1R\)-\(\text{tert}-\text{Butyldimethylsilyloxy}\)ethyl\}-4-oxoazetidinyl\}(oxo)acetate \((12)\)

To a solution of \(11\) (260 mg, 0.51 mmol) in 2 mL of \(\text{CH}_2\text{Cl}_2\) was added \(\text{K}_2\text{CO}_3\) (70 mg, 0.51 mmol) and \(\text{Et}_3\text{N}\) (0.20 mL, 1.53 mmol) at 0 \(^\circ\)C. The solution was stirred for 10 min at same temperature and then \(\text{tert}-\text{butylbenzyl}oxy\)oxalyl chloride (322 mg, 1.26 mmol) in 0.5 mL of \(\text{CH}_2\text{Cl}_2\) 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 \(\text{H}_2\text{O}\) and brine, dried over anhydrous \(\text{MgSO}_4\), 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 (\(\text{CDCl}_3\)) \(\delta\) 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 (\(\text{CDCl}_3\)) \(\delta\) 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 \(C_{41}H_{56}N_2O_8\text{Si}\): C, 67.18; H, 7.70; N, 3.82. Found C, 67.19; H, 7.70; N, 5.29.

\(4\)-\(\text{tert}-\text{Butylbenzyl}\) \((/2S, 3S)\)-2\{\(3aS, 8S, 8aS, 8bS, 9aS\)\}-8\{\(1R\)-\(\text{tert}-\text{Butyldimethylsilyloxy}\)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-
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.

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), 3.03-3.191(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.

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. $^1$H-NMR(D$_2$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); $^{13}$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, 60.8, 58.1, 57.4, 52.2, 43.8, 28.3, 20.9; HRMS (CI, 70eV) Calcd for C$_{24}$H$_{27}$N$_2$O$_6$Na; 462.1767, found 462.1754; Anal. Calcd for C$_{24}$H$_{27}$N$_2$O$_6$Na: C, 62.33; H, 5.88; N, 6.06. Found C, 62.31; H, 5.89; N, 6.04.

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