Supporting Information

Synthesis of 3-Thia-1-dethiacephems via Regioselective Iodocyclization Reaction

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EXPERIMENTAL

General
All reactions were performed in round-bottom flask fitted with balloon filled with nitrogen, otherwise specified. Transfer of air- and moisture-sensitive liquids were performed via cannula under a positive pressure of nitrogen. TLC analysis was performed on Merck TLC (silica gel 60F$_{254}$ on glass plate). Evaporation and condensation were carried out in vacuo. Silica gel (60-120 mesh) manufactured by Fisher Scientific was used for column chromatography. Visualization of TLC was carried out by using Iodine or by charring solutions such as molybdenum, anisaldehyde, ninhydrin and H$_2$SO$_4$. Dry tetrahydrofuran (THF) was purchased from S D Fine Chemical Ltd and was further dried using molecular sieves (3 Å) prior to use. Dichloromethane (DCM) distilled from CaO$_2$ prior to use. DMF was deoxygenated prior to use. Iodine was purchased from Fisher Scientific chemicals private Ltd. Propargyl bromide, m-tolyl isothiocyanate, p-tolyl isothiocyanate, and (3R,4R)-(+-)4-acetoxy-3-[(R)-(tert-butyldimethylsilyloxy)ethyl]-azetidinone were purchased from TCI chemicals. Phenyl isothiocyanate, p-chlorophenyl isothiocyanate and m-chlorophenyl isothiocyanate were purchased from Wako Pure Chemical Industries Ltd. NaH was purchased from Nacalai Tesque Inc. o-Tolyl isothiocyanate, o-chlorophenyl isothiocyanate, p-methoxy isothiocyanate, p-fluoro isothiocyanate, p-nitro isothiocyanate, p-trifluoromethyl isothiocyanate, p-cyano isothiocyanate and Indium were purchased from Aldrich Chemical Company.

IR spectra were measured on SHIMADZU FT-IR8400 or JASCO FT/IR-410 Fourier Transform Infrared Spectrometer. The $^1$H NMR spectra were measured on JEOL:JNM ECX-400 P or Bruker Advance II-400 spectrometers in CDCl$_3$. Chemical shifts of protons are reported in δ values referred to TMS as an internal standard, and the following abbreviation were used as follows: s: singlet, d: doublet, t: triplet, m: multiplet. The $^{13}$C NMR spectra was obtained from the JEOL:JNM ECX-400 P spectrometers in CDCl$_3$. MS was measured on a JEOL JMS-700 or Thermo Scientific Q-Exactive, Accela 1250 pump.

Abbreviations

TBS = tert-Butyldimethylsilyl.
General procedure for the preparation of N'-substituted- N-homopropargyl-N-acyl-thioureas (3):

To a suspension of NaH (60% in mineral oil, 0.561 mmol) in 5 mL of THF at -10 ºC was added 4-(propargyl)-2-azetidinone 1 (100 mg, 0.374 mmol) in 2 mL THF over 5 min. The mixture was stirred at -10 ºC for an additional 15 min and isothiocyanate 2 (0.561 mmol) in 2 mL THF was added dropwise. The reaction mixture was stirred for 5–10 h and the excess of NaH was quenched with 2 N HCl. The organic layer was washed with water. The aqueous layer was extracted 3 times with 10 mL of diethyl ether each. The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified by column chromatography (SiO₂: hexane/ethyl acetate = 20/1) to give the corresponding products 3a–m.

The isolated yield and the spectra data for 3a-3m are as follows:

(3S,4R)-3-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-N-(4-chlorophenyl)-2-oxo-4-(prop-2-yn-1-yl)azetidine-1-carbothioamide (3a).

Yield: 155 mg (95%); colourless liquid. IR (Neat): 831, 1068, 1134, 1250, 1328, 1379, 1494, 1543, 1600, 1720, 1768, 3304 cm⁻¹. ¹H NMR (CDCl₃): δ 0.07 (s, 3H), 0.10 (s, 3H), 0.85 (s, 9H), 1.28 (d, J = 6.1 Hz, 3H), 2.08 (t, J = 2.7 Hz, 1H), 3.02–3.19 (m, 2H), 3.24 (t, J = 2.7 Hz, 1H), 4.31–4.40 (m, 1H), 4.53–4.58 (m, 1H), 7.34 (d, J = 8.5 Hz, 2H), 7.55 (d, J = 8.5 Hz, 2H), 10.19 (brs, 1H). ¹³C NMR (CDCl₃): δ -5.41, -4.09, 17.6, 21.3, 22.2, 25.4, 53.4, 61.0, 64.5, 71.7, 78.4, 125.2, 128.9, 131.7, 135.7, 162.2, 175.8. HRMS: m/z = 437.1486, calcd. for C₂₁H₃₀N₂O₂SSiCl, found 437.1482 [M+ H]⁺.
(3S,4R)-3-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-2-oxo-N-phenyl-4-(prop-2-yn-1-yl)azetidine-1-carbothioamide (3b).

Yield: 139 mg (92%); colourless liquid. IR (Neat): 837, 1136, 1267, 1313, 1379, 1460, 1550, 1656, 1749, 2224, 3443 cm⁻¹. ¹H NMR (CDCl₃): δ 0.10 (s, 3H), 0.12 (s, 3H), 0.88 (s, 9H), 1.31 (d, J = 6.3 Hz, 3H), 2.10 (t, J = 2.7 Hz, 1H), 3.05–3.19 (m, 2H), 3.25 (t, J = 2.9 Hz, 1H), 4.32–4.39 (m, 1H), 4.54–4.59 (m, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 7.59 (d, J = 7.6 Hz, 2H), 10.23 (brs, 1H). ¹³C NMR (CDCl₃): δ -5.34, -4.06, 17.7, 21.4, 22.3, 25.5, 53.4, 61.0, 64.6, 71.7, 78.6, 124.1, 126.6, 128.8, 137.2, 167.3, 175.96. HRMS: m/z = 402.1797, calcd. for C₂₁H₃₀N₂O₂SSi, found 402.1808 [M⁺].

(3S,4R)-3-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-2-oxo-4-(prop-2-yn-1-yl)-N-(o-tolyl)azetidine-1-carbothioamide (3c).

Yield: 148 mg (95%); white solid; mp: 90–91°C. IR (KBr): 765, 1054, 1217, 1305, 1537, 1590, 1760, 2935, 3273 cm⁻¹. ¹H NMR (CDCl₃): δ 0.11 (s, 3H), 0.12 (s, 3H), 0.90 (s, 9H), 1.31 (d, J = 6.3 Hz, 3H), 2.09 (s, 1H), 2.31 (s, 3H), 3.05–3.30 (m, 3H), 4.35–4.43 (m, 1H), 4.56–4.62 (m, 1H), 7.24–7.30 (m, 3H), 7.65 (d, J = 8.3 Hz, 1H), 9.98 (brs, 1H). ¹³C NMR (CDCl₃): δ -5.23, -4.12, 17.9, 21.4, 22.4, 25.6, 53.2, 61.1, 64.5, 71.7, 78.5, 126.3, 126.4, 127.5, 130.7, 133.5, 135.7, 167.1, 176.7. HRMS: m/z = 417.2032, calcd. for C₂₂H₃₃N₂O₂SSi, found 417.2027 [M+ H⁺].

(3S,4R)-3-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-2-oxo-4-(prop-2-yn-1-yl)-N-(m-tolyl)azetidine-1-carbothioamide (3d).
Yield: 142 mg (91%); colourless liquid. IR (Neat): 835, 1066, 1134, 1257, 1381, 1464, 1562, 1612, 1759, 2114, 2292, 3306 cm⁻¹. ¹H NMR (CDCl₃): δ 0.10 (s, 3H), 0.12 (s, 3H), 0.88 (s, 9H), 1.31 (d, J = 6.2 Hz, 3H), 2.10 (t, J = 2.6 Hz, 1H), 2.39 (s, 3H), 3.06–3.19 (m, 2H), 3.25 (t, J = 2.9 Hz, 1H), 4.32–4.39 (m, 1H), 7.08 (d, J = 7.6 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 7.38–7.44 (m, 2H), 10.19 (brs, 1H). ¹³C NMR (CDCl₃): δ -5.34, -4.09, 17.7, 21.4, 22.3, 25.5, 29.6, 53.4, 60.98, 64.6, 71.7, 78.6, 121.1, 124.6, 127.4, 128.6, 137.1, 138.8, 167.2, 175.9.

HRMS: m/z = 416.1954, calcd. for C₂₂H₃₂N₂OSSi, found 416.1971 [M⁺].

(3S,4R)-3-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-2-oxo-4-(prop-2-yn-1-yl)-N-(p-tolyl)azetidine-1-carbothioamide (3e).

Yield: 148 mg (95%); colourless liquid. IR (Neat): 829, 1076, 1282, 1462, 1541, 1600, 1728, 1770, 2926, 3313 cm⁻¹. ¹H NMR (CDCl₃): δ 0.07 (s, 3H), 0.08 (s, 3H), 0.85 (s, 9H), 1.28 (d, J = 6.2 Hz, 3H), 2.06 (t, J = 2.6 Hz, 1H), 2.34 (s, 3H), 3.08–3.14 (m, 2H), 3.21 (t, J = 2.7 Hz, 1H), 4.30–4.39 (m, 1H), 4.50–4.58 (m, 1H), 7.17 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 8.1 Hz, 2H), 10.11 (brs, 1H). ¹³C NMR (CDCl₃): δ -5.32, -4.05, 17.7, 21.1, 21.4, 22.3, 25.5, 53.4, 61.0, 64.6, 71.7, 78.7, 124.2, 129.4, 134.6, 136.5, 167.2, 176.1. HRMS: m/z = 416.1954, calcd. for C₂₂H₃₂N₂O₂SSi, found 416.1965 [M⁺].

(3S,4R)-3-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-N-(2-chlorophenyl)-2-oxo-4-(prop-2-yn-1-yl)azetidine-1-carbothioamide (3f).

Yield: 150 mg (92%); white solid; mp 95–96°C; IR (KBr): 766, 1219, 1319, 1520, 1594, 1756, 2403, 2892, 3303 cm⁻¹. ¹H NMR (CDCl₃): δ 0.08 (s, 3H), 0.10 (s, 3H), 0.85 (s, 9H), 1.30 (d, J = 6.3 Hz, 3H), 2.08 (s, 1H), 3.05–3.22 (m, 2H), 3.25 (s, 1H), 4.32–4.42 (m, 1H), 4.56–4.59 (m, 1H), 7.17–7.33 (m, 2H), 7.45 (d, J = 8.3 Hz, 1H), 8.38 (d, J = 8.3 Hz, 1H), 10.45 (brs, 1H). ¹³C NMR (CDCl₃): δ -5.24, -4.15, 17.7, 21.3, 22.4, 25.6, 53.4, 61.1, 64.6, 71.8, 78.5, 125.7, 126.8,
127.1, 129.5, 134.5, 166.8, 175.7. HRMS: \( m/z = 437.1486 \), calcd. for \( \text{C}_{21}\text{H}_{30}\text{N}_{2}\text{O}_{2}\text{ClSSi} \), found 437.1480 \([\text{M+H}]^+\).

\( (3S,4R)-3-((R)-1-((\text{tert-butyldimethylsilyl})\text{oxy})\text{ethyl})-\text{N}-(\text{3-chlorophenyl})-2\text{-oxo-4-(prop-2-yn-1-yl)azetidine-1-carbothioamide} \) (3g).

Yield: 150 mg (92%); colourless liquid. IR (Neat): 831, 1078, 1128, 1290, 1325, 1477, 1541, 1666, 1749, 2203, 2943, 3435 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 0.08 (s, 3H), 0.10 (s, 3H), 0.85 (s, 9H), 1.28 (d, \( J = 6.3 \) Hz, 3H), 2.08 (t, \( J = 2.3 \) Hz, 1H), 3.02–3.18 (m, 2H), 3.24 (t, \( J = 2.7 \) Hz, 1H), 4.30–4.42 (m, 1H), 4.52–4.58 (m, 1H), 7.22 (d, \( J = 8.1 \) Hz, 1H), 7.31 (d, \( J = 8.1 \) Hz, 1H), 7.45 (d, \( J = 8.1 \) Hz, 1H), 7.72 (s, 1H), 10.22 (brs, 1H). \(^{13}\)C NMR (CDCl\(_3\)): \( \delta \) 5.34, 4.06, 17.7, 21.3, 22.3, 25.5, 53.5, 61.1, 64.6, 71.8, 78.4, 121.9, 123.9, 126.5, 129.8, 134.4, 138.3, 167.3, 175.8.

HRMS: \( m/z = 436.1408 \), calcd. for \( \text{C}_{21}\text{H}_{29}\text{ClN}_{2}\text{O}_{2}\text{SSi} \), found 436.1433 \([\text{M+H}]^+\).

\( (3S,4R)-3-((R)-1-((\text{tert-butyldimethylsilyl})\text{oxy})\text{ethyl})-\text{N}-(\text{3-chlorophenyl})-2\text{-oxo-4-(prop-2-yn-1-yl)azetidine-1-carbothioamide} \) (3h).

Yield: 133 mg (85%); colourless liquid. IR (Neat): 835, 1066, 1143, 1257, 1354, 1462, 1537, 1766, 2090, 2926, 3313 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): \( \delta \) 0.01 (s, 3H), 0.06 (s, 3H), 0.82 (s, 9H), 1.25 (d, \( J = 6.3 \) Hz, 3H), 2.04 (t, \( J = 2.6 \) Hz, 1H), 3.02–3.20 (m, 3H), 3.47 (t, \( J = 5.2 \) Hz, 2H), 4.26–4.34 (m, 1H), 4.46–4.52 (m, 1H), 4.73 (dd, \( J = 5.2 \) & 15.0 Hz, 1H), 4.86 (dd, \( J = 5.2 \) & 15.0 Hz, 1H), 7.27–7.38 (m, 5H), 8.75 (brs, 1H). \(^^{13}\)C NMR (CDCl\(_3\)): \( \delta \) -5.14, -3.94, 17.8, 21.6, 22.5, 25.7, 48.5, 53.5, 61.2, 64.7, 71.8, 78.8, 127.99, 128.0, 128.9, 136.5, 167.1, 177.99. HRMS: \( m/z = 416.1954 \), calcd. for \( \text{C}_{22}\text{H}_{32}\text{N}_{2}\text{O}_{2}\text{SSi} \), found 416.1964 \([\text{M+H}]^+\).

\( (3S,4R)-3-((R)-1-((\text{tert-butyldimethylsilyl})\text{oxy})\text{ethyl})-\text{N}-(\text{4-methoxyphenyl})-2\text{-oxo-4-(prop-2-yn-1-yl)azetidine-1-carbothioamide} \) (3i).
Yield: 142 mg (88%); yellow solid; mp 70–73°C. IR (KBr): 768, 834, 1025, 1134, 1251, 1316, 1382, 1521, 1607, 1757, 2857, 2942, 3296 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 0.08 (s, 3H), 0.10 (s, 3H), 0.87 (s, 9H), 1.29 (d, \(J = 6.4\) Hz, 3H), 2.08 (t, \(J = 2.5\) Hz, 1H), 3.12–3.15 (m, 2H), 3.23 (t, \(J = 2.7\) Hz, 1H), 3.82 (s, 3H), 4.34–4.39 (m, 1H), 4.54–4.57 (m, 1H), 6.91 (d, \(J = 8.8\) Hz, 2H), 7.42 (d, \(J = 8.8\) Hz, 2H), 10.0 (brs, 1H). \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) -5.34, -4.04, 17.7, 21.5, 22.3, 25.5, 53.4, 55.4, 61.1, 64.6, 71.7, 78.7, 114.1, 126.1, 129.98, 158.1, 167.2, 176.5. HRMS: m/z = 433.1981, calcd. for C\(_{22}\)H\(_{33}\)N\(_2\)O\(_3\)SSi, found 433.1976 [M+H]^+.

(3S,4R)-3-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-N-(4-fluorophenyl)-2-oxo-4-(prop-2-yn-1-yl)azetidine-1-carbothioamide (3j).

Yield: 137 mg (87%); white solid; mp 83–89°C. IR (KBr): 763, 836, 1063, 1140, 1219, 1319, 1378, 1520, 1615, 1757, 2892, 3021, 3304 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 0.08 (s, 3H), 0.10 (s, 3H), 0.86 (s, 9H), 1.29 (d, \(J = 6.4\) Hz, 3H), 2.08 (t, \(J = 2.7\) Hz, 1H), 3.06–3.18 (m, 2H), 3.24 (t, \(J = 2.7\) Hz, 1H), 4.34–4.40 (m, 1H), 4.55–4.58 (m, 1H), 7.08 (t, \(J = 8.6\) Hz, 2H), 7.50 (dd, \(J = 8.8, 3.9\) Hz, 2H), 10.11 (brs, 1H). \(^{13}\)C NMR (CDCl\(_3\)): \(\delta\) -5.37, -4.04, 17.7, 21.4, 22.3, 25.5, 53.4, 61.1, 64.6, 71.7, 78.5, 115.7 (d, \(^2J_{C,F} = 23.1\) Hz), 126.3 (d, \(^3J_{C,F} = 8.5\) Hz), 133.0 (d, \(^4J_{C,F} = 3.1\) Hz), 160.8 (d, \(^1J_{C,F} = 246\) Hz), 167.3, 176.5. HRMS: m/z = 421.1781, calcd. for C\(_{21}\)H\(_{30}\)N\(_2\)O\(_2\)SSiF, found 421.1776 [M+H]^+.

(3S,4R)-3-((R)-1-((tert-butyldimethylsilyl)oxy)ethyl)-N-(4-cyanophenyl)-2-oxo-4-(prop-2-yn-1-yl)azetidine-1-carbothioamide (3k).
Yield: 146 mg (91%); white solid; mp 138–140°C. IR (KBr): 835, 1070, 1120, 1215, 1330, 1357, 1499, 1620, 1765, 2218, 2988, 3307 cm$^{-1}$. $^1$H NMR (CDCl$_3$): $\delta$ 0.06 (s, 3H), 0.09 (s, 3H), 0.82 (s, 9H), 1.28 (d, $J = 6.4$ Hz, 3H), 2.08 (t, $J = 2.5$ Hz, 1H), 3.05–3.21 (m, 2H), 3.27 (t, $J = 2.5$ Hz, 1H), 4.55–4.58 (m, 1H), 7.66 (d, $J = 8.3$ Hz, 2H), 7.85 (d, $J = 8.3$ Hz, 2H), 10.46 (brs, 1H). $^{13}$C NMR (CDCl$_3$): $\delta$ -5.39, -4.06, 17.6, 21.2, 22.2, 25.4, 53.2, 61.1, 64.6, 71.9, 78.2, 109.1, 118.4, 122.9, 132.9, 141.3, 144.7, 167.4, 175.2. HRMS: m/z = 428.1828, calcd. for C$_{22}$H$_{30}$N$_3$O$_2$SSi, found 428.1828 [M+H]$^+$. 

(3$S,4R$)-3-((R)-1-((tert-butyldimethylsilyloxy)ethyl)-2-oxo-4-(prop-2-yn-1-yl)-N-(4-(trifluoromethyl)phenyl)azetidine-1-carbothioamide (3l).

Yield: 151 mg (86%); white solid; mp 140–142°C. IR (KBR): 764, 837, 1065, 1124, 1256, 1315, 1368, 1549, 1611, 1759, 2943, 3302 cm$^{-1}$. $^1$H NMR (CDCl$_3$): $\delta$ 0.07 (s, 3H), 0.10 (s, 3H), 0.84 (s, 9H), 1.29 (d, $J = 6.4$ Hz, 3H), 2.09 (t, $J = 2.7$ Hz, 1H), 3.05–3.20 (m, 2H), 3.27 (t, $J = 2.8$ Hz, 1H), 3.36–3.40 (m, 1H), 4.57–4.60 (m, 1H), 7.64 (d, $J = 8.5$ Hz, 2H), 7.80 (d, $J = 8.5$ Hz, 2H), 10.38 (brs, 1H). $^{13}$C NMR (CDCl$_3$): $\delta$ -5.39, -4.06, 17.7, 21.3, 22.2, 25.5, 53.5, 61.1, 64.6, 71.9, 78.4, 123.3, 123.8 (q, $^1$J$_{CF3} = 272$ Hz), 126.0 (d, $^3$J$_{C-F} = 3.8$ Hz), 127.97 (q, $^2$J$_{C-F} = 33.5$ Hz), 140.3, 144.7, 167.4, 175.6. HRMS: m/z = 471.1749, calcd. for C$_{22}$H$_{30}$N$_2$O$_2$SSiF$_3$, found 471.1748 [M+H]$^+$. 

(3$S,4R$)-3-((R)-1-((tert-butyldimethylsilyloxy)ethyl)-N-(4-nitrophenyl)-2-oxo-4-(prop-2-yn-1-yl)azetidine-1-carbothioamide (3m).
Yield: 137 mg (82%); brown solid; mp 102–104°C. IR (KBr): 768, 845, 1008, 1117, 1225, 1303, 1422, 1525, 1583, 1760, 2862, 2942, 3298 cm\(^{-1}\). 1H NMR (CDCl\(_3\)): δ 0.06 (s, 3H), 0.09 (s, 3H), 0.82 (s, 9H), 1.29 (d, \(J = 6.1\) Hz, 3H), 2.09 (t, \(J = 2.4\) Hz, 1H), 3.02–3.07 (m, 1H), 3.15–3.21 (m, 1H), 3.29 (t, \(J = 3.1\) Hz, 1H), 3.36–3.40 (m, 1H), 4.57–4.60 (m, 1H), 7.93 (d, \(J = 9.1\) Hz, 2H), 8.25 (d, \(J = 9.1\) Hz, 2H), 10.6 (brs, 1H). \(^{13}\)C NMR (CDCl\(_3\)): δ -5.39, -4.05, 17.6, 21.1, 22.2, 25.4, 53.6, 61.1, 64.6, 71.97, 78.1, 122.5, 124.6, 143.1, 144.7, 167.5, 175.2. HRMS: m/z = 448.1726, calcd. for C\(_{21}\)H\(_{30}\)N\(_3\)O\(_4\)SSi, found 448.1721 [M+H]\(^+\).
**Table 1.** Optimization conditions for the iodocyclization reaction of 3a.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Electrophile</th>
<th>Time (h)</th>
<th>Yield (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>CH(_2)Cl(_2)</td>
<td>I(_2) (1.0)</td>
<td>36.0</td>
<td>38</td>
</tr>
<tr>
<td>2.</td>
<td>CH(_2)Cl(_2)</td>
<td>I(_2) (1.25)</td>
<td>28.0</td>
<td>56</td>
</tr>
<tr>
<td>3.</td>
<td>CH(_2)Cl(_2)</td>
<td>I(_2) (1.5)</td>
<td><strong>8.0</strong></td>
<td><strong>66</strong></td>
</tr>
<tr>
<td>4.</td>
<td>CHCl(_3)</td>
<td>I(_2) (1.5)</td>
<td>8.0</td>
<td>44</td>
</tr>
<tr>
<td>5.</td>
<td>THF</td>
<td>I(_2) (1.5)</td>
<td>9.5</td>
<td>46</td>
</tr>
<tr>
<td>6.</td>
<td>CH(_3)CN</td>
<td>I(_2) (1.5)</td>
<td>9.0</td>
<td>42</td>
</tr>
<tr>
<td>7.</td>
<td>Toluene</td>
<td>I(_2) (1.5)</td>
<td>14.0</td>
<td>56</td>
</tr>
<tr>
<td>8.</td>
<td>DMF</td>
<td>I(_2) (1.5)</td>
<td>26.0</td>
<td>7</td>
</tr>
<tr>
<td>9.</td>
<td>DMSO</td>
<td>I(_2) (1.5)</td>
<td>6.5</td>
<td>29</td>
</tr>
<tr>
<td>10.</td>
<td>CH(_3)OH</td>
<td>I(_2) (1.5)</td>
<td>24.0</td>
<td>19</td>
</tr>
<tr>
<td>11.</td>
<td>CH(_2)Cl(_2)</td>
<td>NIS (1.5)</td>
<td>1</td>
<td>12(^c)</td>
</tr>
<tr>
<td>12.</td>
<td>CH(_2)Cl(_2)</td>
<td>ICl (1.5)</td>
<td>6</td>
<td>35</td>
</tr>
</tbody>
</table>

\(^a\) All iodocyclization reactions were carried out at r.t. on 0.114 mmol of 3a.

\(^b\) Isolated yields.

\(^c\) Reaction resulted in formation of multiple spots.
Typical procedure for the synthesis of 3-thia-1-dethiacephem (4):

To a solution of 3 (50 mg, 1 equiv.) in CH$_2$Cl$_2$ (2 mL) was added I$_2$ (1.5 equiv.) at room temperature. After stirring at this temperature (6 to 12 h), the reaction mixture was extracted with CH$_2$Cl$_2$ and washed with saturated Na$_2$S$_2$O$_3$ and NaHCO$_3$. The organic phase was washed with brine, dried over Na$_2$SO$_4$, filtered and evaporated in vacuo. The residue was chromatographed on silica gel using ether/hexane (2:8) as eluent to give corresponding product 3-Thia-1-dethiacephems 4a–m.

The isolated yield and the spectra data for 4a-4m are as follows:

3-Thia-1-dethiacephem (4a).

Yield: 42 mg (66%); white solid; mp 137–139°C. IR (KBr): 777, 835, 1068, 1122, 1211, 1336, 1483, 1585, 1620, 1778, 2929 cm$^{-1}$. $^1$H NMR (CDCl$_3$): δ 0.11 (s, 3H), 0.12 (s, 3H), 0.91 (s, 9H), 1.31 (d, $J = 6.3$ Hz, 3H), 2.38 (t, $J = 14.3$ Hz, 1H), 3.18 (d, $J = 3.3$ Hz, 1H), 3.47 (dd, $J = 3.3$ & 14.8 Hz, 1H), 4.00 (dt, $J = 2.7$ & 12.1 Hz, 1H), 4.28–4.36 (m, 1H), 6.36 (d, $J = 1.4$ Hz, 1H), 6.82 (d, $J = 8.3$ Hz, 2H), 7.26 (d, $J = 8.3$ Hz, 2H). $^{13}$C NMR (CDCl$_3$): δ -4.91, -4.03, 18.0, 22.7, 25.8, 25.98, 29.8, 38.7, 52.0, 65.5, 66.3, 74.3, 122.5, 129.1, 130.0, 134.7, 140.96, 145.5, 163.3. HRMS: m/z = 562.0374, calcd. for C$_{21}$H$_{28}$ClIN$_2$O$_2$SSi, found 562.0401 [M$^+$].
Yield: 46 mg (70%); white solid; mp 168–170°C. IR (KBr): 776, 1015, 1138, 1357, 1460, 1597, 1640, 1790, 2950 cm⁻¹. ¹H NMR (CDCl₃): δ 0.11 (s, 3H), 0.12 (s, 3H), 0.91 (s, 9H), 1.31 (d, J = 6.4 Hz, 3H), 2.39 (t, J = 14.9 Hz, 1H), 3.15 (dd, J = 2.7 & 5.5 Hz, 1H), 3.42 (dd, J = 3.2 & 14.9 Hz, 1H), 3.99 (dt, J = 2.9 & 12.0 Hz, 1H), 4.27–4.36 (m, 1H), 6.32 (d, J = 1.1 Hz, 1H), 6.87 (d, J = 7.6 Hz, 2H), 7.11 (t, J = 7.6 Hz, 1H), 7.30 (t, J = 7.6 Hz, 2H). ¹³C NMR (CDCl₃): δ -4.89, -4.01, 18.0, 22.7, 25.9, 29.8, 38.8, 52.1, 65.6, 66.2, 73.9, 121.1, 124.7, 128.98, 135.1, 140.3, 147.02, 163.3. HRMS: m/z = 528.0764, calcd. for C₂₁H₂₉N₂O₂SSi, found 528.0740 [M⁺].

3-Thia-1-dethiacephem (4c).

Yield: 43 mg (66%); white solid; mp 192°C. IR (KBr): 761, 1113, 1213, 1356, 1590, 1627, 1785, 2404, 2943, 3050 cm⁻¹. ¹H NMR (CDCl₃): δ 0.13 (s, 3H), 0.15 (s, 3H), 0.93 (s, 9H), 1.31 (d, J = 6.1 Hz, 3H), 2.15 (s, 3H), 2.35–2.42 (m, 1H), 3.18 (t, J = 2.6 Hz, 1H), 3.45 (dd, J = 3.2 & 14.9 Hz, 1H), 3.95–4.05 (m, 1H), 4.30–4.40 (m, 1H), 6.31 (d, J = 1.6 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 7.04 (t, J = 7.1 Hz, 1H), 7.10–7.20 (m, 2H). ¹³C NMR (CDCl₃): δ -5.07, -4.11, 17.7, 17.9, 22.6, 25.8, 38.5, 51.5, 65.2, 66.2, 73.6, 120.1, 124.6, 126.2, 128.98, 130.4, 135.1, 139.6, 145.7, 163.3. HRMS: m/z = 543.0998, calcd. for C₂₂H₃₂N₂O₂SSi, found 543.0993 [M+H]⁺.

3-Thia-1-dethiacephem (4d).
Yield: 36 mg (55%); white solid; mp 162–164°C. IR (KBr): 777, 1010, 1134, 1357, 1459, 1597, 1633, 1791, 2953 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): \(\delta 0.12\) (s, 3H), \(0.13\) (s, 3H), \(0.92\) (s, 9H), \(1.32\) (d, \(J = 6.1\) Hz, 3H), \(2.30–2.44\) (m, 4H), \(3.16\) (dd, \(J = 2.6\) & \(5.5\) Hz, 1H), \(3.44\) (dd, \(J = 3.2\) & \(14.9\) Hz, 1H), \(4.00\) (dt, \(J = 3.2\) & \(11.9\) Hz, 1H), \(6.33\) (d, \(J = 1.7\) Hz, 1H), \(6.66–6.73\) (m, 2H), \(6.94\) (d, \(J = 7.6\) Hz, 1H), \(7.20\) (t, \(J = 7.6\) Hz, 1H). \(^13\)C NMR (CDCl\(_3\)): \(\delta -4.89\), -4.03, 17.9, 20.97, 22.6, 25.8, 38.7, 51.98, 65.5, 66.1, 73.7, 120.8, 129.5, 134.1, 135.2, 139.9, 146.9, 163.1. HRMS: \(m/z = 542.0920\), calcd. for \(C_{22}H_{31}IN_2O_2SSi\), found 542.0906 [\(M^+\)].

3-Thia-1-dethiacephem (4e).

Yield: 41 mg (63%); white solid; mp 89–90°C. IR (KBr): 777, 833, 1068, 1139, 1251, 1352, 1590, 1627, 1683, 1790, 2929 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): \(\delta 0.11\) (s, 3H), \(0.12\) (s, 3H), \(0.91\) (s, 9H), \(1.31\) (d, \(J = 6.2\) Hz, 3H), \(2.30–2.46\) (m, 4H), \(3.15\) (dd, \(J = 2.7\) & \(5.4\) Hz, 1H), \(3.43\) (dd, \(J = 3.3\) & \(15.3\) Hz, 1H), \(3.97\) (dt, \(J = 3.3\) & \(12.2\) Hz, 1H), \(4.27–4.35\) (m, 1H), \(5.31\) (d, \(J = 1.8\) Hz, 1H), \(6.77\) (d, \(J = 8.5\) Hz, 2H), \(7.10\) (d, \(J = 8.5\) Hz, 2H). \(^13\)C NMR (CDCl\(_3\)): \(\delta -4.99\), -4.11, 17.9, 20.97, 22.6, 25.8, 38.7, 51.98, 65.5, 66.1, 73.7, 120.8, 129.5, 134.1, 135.2, 139.9, 144.4, 163.1. HRMS: \(m/z = 542.0920\), calcd. for \(C_{22}H_{31}IN_2O_2SSi\), found 542.0912 [\(M^+\)].

3-Thia-1-dethiacephem (4f).

Yield: 40 mg (62%); white solid; mp 170°C. IR (KBr): 762, 1215, 1360, 1467, 1622, 1789, 2403, 2941, 3019 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): \(\delta 0.12\) (s, 3H), \(0.14\) (s, 3H), \(0.92\) (s, 9H), \(1.32\) (d, \(J = 6.2\) Hz, 3H), \(2.39\) (td, \(J = 2.7\) & \(5.7\) Hz, 1H), \(3.20\) (t, \(J = 2.7\) Hz, 1H), \(3.45\) (dd, \(J = 3.3\) & \(12.9\) Hz, 1H), \(4.00–4.08\) (m, 1H), \(4.30–4.40\) (m, 1H), \(6.34\) (s, 1H), \(6.89\) (dd, \(J = 2.7\) & \(7.5\) Hz, 1H), \(7.05\) (td, \(J = 2.7\) & \(7.5\) Hz, 1H), \(7.20\) (td, \(J = 2.7\) & \(7.5\) Hz, 1H), \(7.37\) (dd, \(J = 2.7\) & \(7.5\) Hz, 1H).
$^{13}$C NMR (CDCl$_3$): $\delta$ -5.07, -4.14, 17.9, 22.6, 25.7, 38.4, 51.6, 65.2, 66.3, 74.0, 122.2, 125.4, 127.2, 129.8, 134.6, 142.0, 144.1, 163.1. HRMS: $m/z = 563.0552$, calcd. for C$_{21}$H$_{29}$N$_2$O$_2$ClISSi, found 563.0447 [M+H]$^+$. 

3-Thia-1-dethiacephem (4g).

Yield: 46 mg (72%); white solid; mp 186–188°C. IR (KBr): 763, 1215, 1457, 1629, 1789, 2406, 2961, 3018 cm$^{-1}$. $^1$H NMR (CDCl$_3$): $\delta$ 0.12 (s, 6H), 0.92 (s, 9H), 1.32 (d, $J = 6.2$ Hz, 3H), 2.29-2.48 (m, 1H), 3.18 (dd, $J = 2.7$ & 5.7 Hz, 1H), 3.44 (dd, $J = 3.3$ & 14.9 Hz, 1H), 4.01 (dt, $J = 3.3$ & 12.9 Hz, 1H), 4.26–4.38 (m, 1H), 6.37 (d, $J = 1.7$ Hz, 1H), 6.72–6.82 (m, 1H), 6.89 (t, $J = 2$ Hz, 1H), 7.05–7.12 (m, 1H), 7.20 (d, $J = 8.2$ Hz, 1H). $^{13}$C NMR (CDCl$_3$): $\delta$ -5.05, -4.15, 17.9, 22.6, 25.1, 38.5, 51.8, 65.3, 66.2, 74.3, 119.4, 121.2, 124.6, 129.9, 134.5, 141.2, 148.1, 163.2. HRMS: $m/z = 563.0552$, calcd. for C$_{21}$H$_{29}$N$_2$O$_2$ClISSi, found 563.0447 [M+H]$^+$. 

3-Thia-1-dethiacephem (4h).

Yield: 27 mg (41%); white solid; mp 106–108°C. IR (KBr): 770, 1073, 1139, 1215, 1331, 1461, 1628, 1780, 2402, 2892, 3021 cm$^{-1}$. $^1$H NMR (CDCl$_3$): $\delta$ 0.10 (s, 3H), 0.11 (s, 3H), 0.92 (s, 9H), 1.30 (d, $J = 6.3$ Hz, 3H), 2.22-2.40 (m, 1H), 3.08 (d, $J = 6.3$ Hz, 1H), 3.44 (d, $J = 6.3$ Hz, 1H), 3.93 (dd, $J = 3.2$ & 14.9 Hz, 1H), 4.25–4.30 (m, 1H), 4.58 (d, $J = 6.3$ Hz, 1H), 4.72 (d, $J = 6.3$ Hz, 1H), 6.47 (s, 1H), 7.18-7.36 (m, 5H). $^{13}$C NMR (CDCl$_3$): $\delta$ -5.05, -4.12, 17.9, 22.6, 25.7, 38.95, 51.8, 54.3, 65.5, 65.8, 74.2, 126.7, 127.4, 128.3, 134.7, 138.8, 139.7, 163.2. HRMS: $m/z = 543.0998$, calcd. For C$_{22}$H$_{32}$N$_2$O$_2$ISSi, found 543.0993 [M+H]$^+$. 

3-Thia-1-dethiacephem (4i).
Yield: 42 mg (65%); yellow solid; mp 98-100°C. IR (KBr): 762, 833, 1071, 1139, 1243, 1357, 1503, 1621, 1786, 2943 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): \(\delta 0.12\) (s, 3H), 0.13 (s, 3H), 0.92 (s, 9H), 1.32 (d, \(J = 6.1\) Hz, 3H), 2.39 (t, \(J = 14.1\) Hz, 1H), 3.15 (dd, \(J = 2.7 \& 5.6\) Hz, 1H), 3.45 (dd, \(J = 3.2 \& 14.6\) Hz, 1H), 3.79 (s, 3H), 3.98 (dt, \(J = 2.8 \& 11.99\) Hz, 1H), 4.28–4.34 (m, 1H), 6.33 (d, \(J = 1.9\) Hz, 1H), 6.81–6.87 (m, 4H). \(^1\)C NMR (CDCl\(_3\)): \(\delta -5.02\), -4.15, 17.9, 22.6, 25.7, 38.7, 51.9, 55.3, 65.5, 66.0, 73.7, 114.1, 122.1, 135.1, 139.99, 140.1, 156.7, 163.1. HRMS: m/z = 559.0948, calcd. for C\(_{22}\)H\(_{32}\)IN\(_2\)O\(_2\)Si, found 559.0942 [M+H]\(^+\).

3-Thia-1-dethiacephem (4j).

Yield: 48 mg (74%); white solid; mp 78–80°C. IR (KBr): 755, 838, 1093, 1215, 1354, 1502, 1623, 1786, 2956, 3019 cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): \(\delta 0.12\) (s, 3H), 0.13 (s, 3H), 0.92 (s, 9H), 1.32 (d, \(J = 6.3\) Hz, 3H), 2.39 (t, \(J = 14.3\) Hz, 1H), 3.18 (dd, \(J = 2.7 \& 5.5\) Hz, 1H), 3.45 (dd, \(J = 3.4 \& 14.5\) Hz, 1H), 3.99 (dt, \(J = 3.1 \& 11.9\) Hz, 1H), 4.29–4.35 (m, 1H), 6.36 (d, \(J = 1.9\) Hz, 1H), 6.85 (dd, \(J = 3.9 \& 8.8\) Hz, 2H), 7.00 (t, \(J = 8.6\) Hz, 2H). \(^1\)C NMR (CDCl\(_3\)): \(\delta -5.04\), -4.13, 17.9, 22.6, 25.7, 38.6, 51.9, 65.4, 66.1, 74.1, 115.65 (d, \(2J_{C,F} = 23\) Hz), 122.4 (d, \(3J_{C,F} = 7.7\) Hz), 134.7, 140.8, 142.9 (d, \(4J_{C,F} = 2.3\) Hz), 159.99 (d, \(1J_{C,F} = 242\) Hz), 163.2. HRMS: m/z = 547.0748, calcd. for C\(_{21}\)H\(_{29}\)FIN\(_2\)O\(_2\)Si, found 547.0742 [M+H]\(^+\).

3-Thia-1-dethiacephem (4k).
Yield: 50 mg (77%); colourless liquid. IR (KBr): 764, 837, 1017, 1136, 1246, 1360, 1460, 1588, 1629, 1725, 1793, 2225, 2935, 3409 cm$^{-1}$. $^1$H NMR (CDCl$_3$): δ 0.12 (s, 6H), 0.91 (s, 9H), 1.31 (d, $J = 6.4$ Hz, 3H), 2.40 (t, $J = 14.4$ Hz, 1H), 3.21 (dd, $J = 2.0$ & $2.9$ Hz, 1H), 3.47 (dd, $J = 3.4$ & $14.7$ Hz, 1H), 4.03 (dt, $J = 3.2$ & $11.99$ Hz, 1H), 4.31–4.36 (m, 1H), 6.40 (d, $J = 1.5$ Hz, 1H), 6.96 (d, $J = 8.3$ Hz, 2H), 7.60 (d, $J = 8.3$ Hz, 2H). $^{13}$C NMR (CDCl$_3$): δ -5.09, -4.16, 17.9, 22.5, 25.7, 38.4, 51.8, 65.2, 66.3, 74.8, 107.8, 119.0, 121.9, 133.1, 133.9, 141.3, 150.9, 163.2. HRMS: m/z = 554.0794, calcd. for C$_{22}$H$_{29}$IN$_3$O$_2$SSi, found 554.0793 [M+H]$^+$. 

3-Thia-1-dethiacephem (4I).

Yield: 47 mg (75%); white solid; mp 80-82°C. IR (KBr): 762, 838, 1016, 1066, 1121, 1321, 1413, 1607, 1791, 2942, 3011 cm$^{-1}$. $^1$H NMR (CDCl$_3$): δ 0.12 (s, 3H), 0.13 (s, 3H), 0.92 (s, 9H), 1.32 (d, $J = 6.3$ Hz, 3H), 2.40 (t, $J = 14.4$ Hz, 1H), 3.20 (dd, $J = 2.5$ & $5.1$ Hz, 1H), 3.46 (dd, $J = 3.4$ & $14.5$ Hz, 1H), 4.03 (dt, $J = 3.02$ & $11.95$ Hz, 1H), 4.30–4.36 (m, 1H), 6.38 (d, $J = 1.7$ Hz, 1H), 6.97 (d, $J = 8.3$ Hz, 2H), 7.56 (d, $J = 8.4$ Hz, 2H). $^{13}$C NMR (CDCl$_3$): δ -5.09, -4.16, 17.9, 22.6, 25.7, 38.5, 51.8, 65.3, 66.2, 74.4, 121.3, 124.23 (q, $^1$J$_{CF} = 272$ Hz), 126.16 (d, $^3$J$_{CF} = 3.1$ Hz), 126.53 (q, $^2$J$_{CF} = 33$ Hz), 134.3, 141.1, 149.97, 163.2. HRMS: m/z = 597.0716, calcd. for C$_{22}$H$_{29}$F$_3$IN$_3$O$_2$SSi, found 597.0710 [M+H]$^+$. 

3-Thia-1-dethiacephem (4m).

Yield: 51 mg (80%); white solid; mp 80-82°C. IR (KBr): 764, 843, 1067, 1215, 1340, 1470, 1586, 1626, 1791, 2943, 3021 cm$^{-1}$. $^1$H NMR (CDCl$_3$): δ 0.12 (s, 3H), 0.13 (s, 3H), 0.92 (s, 9H), 1.31 (d, $J = 6.1$ Hz, 3H), 2.41 (t, $J = 14.4$ Hz, 1H), 3.23 (dd, $J = 2.9$ & $4.6$ Hz, 1H), 3.47 (dd, $J = 3.4$ & $14.5$ Hz, 1H), 4.05 (dt, $J = 3.1$ & $11.99$ Hz, 1H), 4.31–4.37 (m, 1H), 6.41 (d, $J = 1.5$ Hz, 1H), 6.99 (d, $J = 8.8$ Hz, 2H), 8.19 (d, $J = 8.8$ Hz, 2H). $^{13}$C NMR (CDCl$_3$): δ -5.09, -4.16, 17.9, 22.5, 25.7, 38.3, 51.8, 65.2, 66.3, 74.9, 121.7, 124.9, 133.8, 141.5, 144.5, 152.9, 163.2. HRMS: m/z = 574.0693, calcd. for C$_{22}$H$_{29}$IN$_3$O$_4$SSi, found 574.0687 [M+H]$^+$. 

S16
Supporting Information

Synthesis of 3-Thia-1-dethiacephems via Regioselective Iodocyclization Reaction

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TBSO
Me

N
N

H
H

3e

HMQC NMR
Chloroform-d
TBSO
Me
H
H
I
N
S
N
O
N
4a
Ph
Cl

Chloroform-d

2.06 1.92 0.89 1.00 1.00 1.01 1.00 1.06 1.00 4.05 9.59 6.00
4e