ORIGINAL ARTICLE

Synthesis of Thienamycin methyl ester from 2-deoxy-D-ribose via Kinugasa reaction

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A novel synthesis of thienamycin is described. The crucial step of the synthesis is based on Cu(I)-mediated Kinugasa cycloaddition/rearrangement cascade reaction between terminal acetylene derived from D-lactic acid and suitable, partially protected, five-membered cyclic nitrone obtained from 2-deoxy-D-ribose. The reaction was performed in the presence of tetramethylguanidine as a base to provide 5,6-*trans* substituted carbapenam as the main product. Thus obtained carbapenam **11** with (5*R*,6*S*) configuration at the azetidinone ring was subsequently subjected to oxidation/deprotection/oxidation reaction sequence to afford the β-keto ester **20**, which was directly transformed into *N,O*-protected methyl ester of thienamycin.

INTRODUCTION

Carbapenems are important β-lactam antibiotics which, owing to high antibacterial activity and resistance to β-lactamase, continually attract the interest of industrial and academic laboratories.[1–13] Recently we have shown that the Kinugasa reaction between D-lactic acid-derived acetylene **2** and five-membered cyclic nitrone **1** obtained from 2-deoxy-D-ribose[14–17] offers an attractive entry into carbapenems.[18] The main drawback of this strategy has been related to the undesired *cis* configuration of H-5 and H-6 protons in the major adducts **4** or **6** (Scheme 1). We have demonstrated that the stereogenic center at C-6 of the alcohol **4** can be epimerized in the presence of 2 equiv. KHMDS to provide the *trans* isomer **5** in 55% yield (Scheme 1). Epimerization performed on compound with protected side-chain hydroxyl **6** caused β-elimination to the *exo* double bond.

As effective *cis*/*trans* epimerization requires a free hydroxyl group in the side chain and seeing that Kinugasa reaction involving commercially available alcohol **2** and its *t*-butyldiphenysilyl-protected derivative **3**[19] was low yielding, we decided to change the side-chain hydroxyl group protection and reaction conditions. After conducting several experiments we found that the protection of alcohol **2** as *t*-butyldimethylsilyl derivative **8**[20] and the use of 1,1,3,3-tetramethyl-guanidine as the base offered better yield and higher content of the *trans* isomer **10** which allowed for its easy separation (Scheme 1). This observation was important for the further synthesis of thienamycin because one of the structural features present in carbapenem antibiotics is the *trans* configuration in the four-membered β-lactam ring.

RESULTS AND DISCUSION

Selective debenzylation of the primary hydroxyl group[21] in **10** by hydrogenolysis under the pressure of 6 bar H_2 provided a mixture of
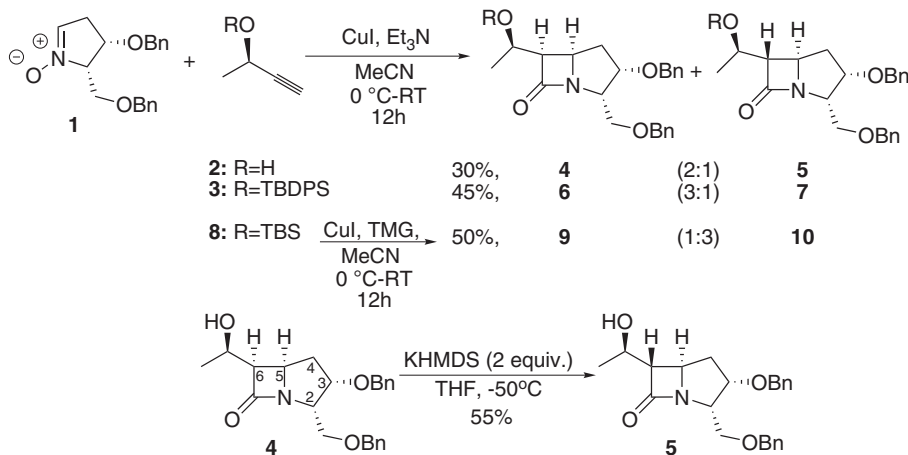
two regioisomers **11** and **12** (6:1), however, in a low yield (35%) only. Higher pressure led to debenzylation of both groups to afford **13** in low yield. The same deprotection of both benzyl groups can be achieved by a reduction with sodium in liquid ammonia (Figure 1).[22]

This results prompted us to use partly deprotected nitrone **14** in the Kinugasa reaction with **8**. Nitrone **14** was obtained from **1** by a modification of a known method,[23,24] using the complex of BCl_3 with dimethyl sulfide. Under such milder conditions, only the primary hydroxyl group was deprotected in 50% yield (Scheme 2).

The reaction of **14** with **8** gave a mixture of *cis* and *trans* carbapenams **15** and **11** in a ratio of about 1:3 and with 54% overall yield. The *trans* adduct **11** was separated by chromatography. The primary hydroxyl group was oxidized to the aldehyde using Dess–Martin periodinane[25] in 91% yield and subsequently the crude product was oxidized with sodium chlorite under Pinnick–Lindgren[26,27] conditions to afford the carboxylic acid function, which was in turn methylated with diazomethane[28] to afford ester **18** (Scheme 3).

The benzyl protecting group was then removed using palladium hydroxide on carbon to afford the alcohol **19** in 97% yield. The structure and configuration of alcohol **19** was confirmed by X-ray crystallography. Compound **19** was then oxidized to ketone **20** using Dess–Martin reagent (Scheme 4). It's important to know that the similar keto-*p*-nitrobenzyl ester **20a** has already been transformed into thienamycin by the Hannesian group.[29]

The transformation of the ketone **20** into thienamycin derivative **21** according to a known procedure required the enolization of the carbonyl group followed by phosphorylation of the enol hydroxyl and subsequent addition of *N*-acetylcysteamine.[29] The best result was obtained for diethyl chlorophosphate as a phosphorylation agent. We also found that the enolization of ketone **20** required quite a long time.

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Scheme 1 Synthesis of carbapenams via Kinugasa reaction with Et$_3$N and 1,1,3,3-tetramethylguanidine as a base. Attempted epimerization at C-6.
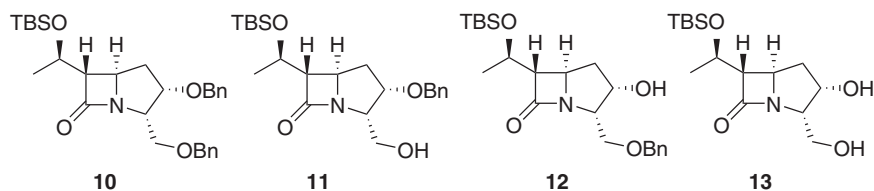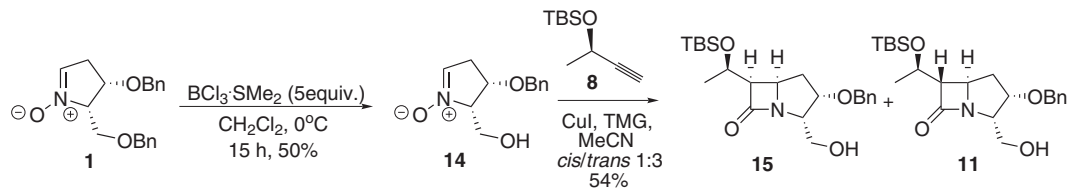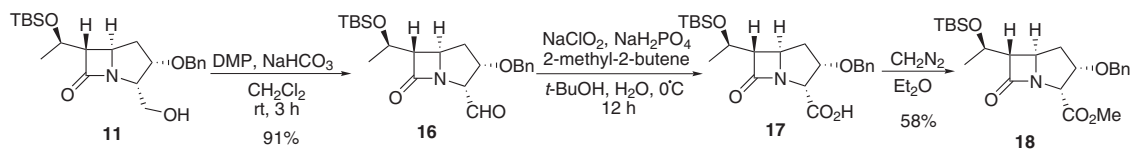

Figure 1 Selective debenzylation of the primary hydroxyl group.

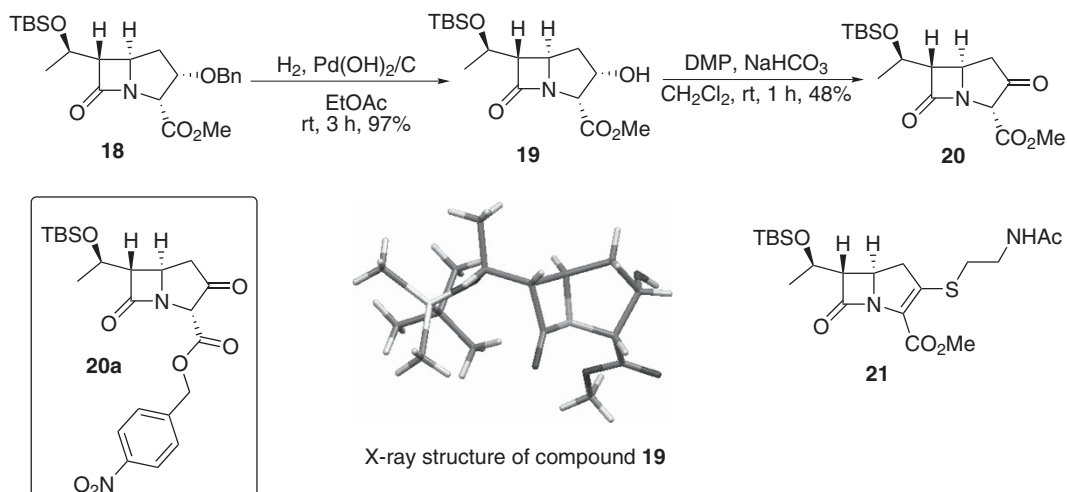**Scheme 2** Deprotection of nitrone **1** and Kinugasa reaction with alkyne **8**.

Scheme 3 Preparation of carbapenam **18**.

Otherwise phosphorylation did not occur and compound **21** was not formed. Particularly when treating **20** with diphenyl chlorophosphate, we observed the opening of the pyrrolidine ring *via* retro-Dieckmann reaction and formation of thioester **22** (Scheme 5).

In conclusion, we have demonstrated that the cyclic five-membered nitrone **1**, easily available from 2-deoxy-D-ribose represents an attractive substrate for the stereocontrolled synthesis of thienamycin —an important natural carbapenem antibiotic. The configuration of the stereogenic center next to the nitrogen atom has a decisive role in the asymmetric induction at the C-5 carbon atom of the carbapenam scaffold. The predominance of the isomer with anti configuration of H-5 and H-6 protons was achieved by the use of tetramethylguanidine as a base in the Kinugasa reaction.

EXPERIMENTAL PROCEDURE

Scheme 4 Synthesis of ketone 20. A full color version of this scheme is available at *The Journal of Antibiotics* journal online.
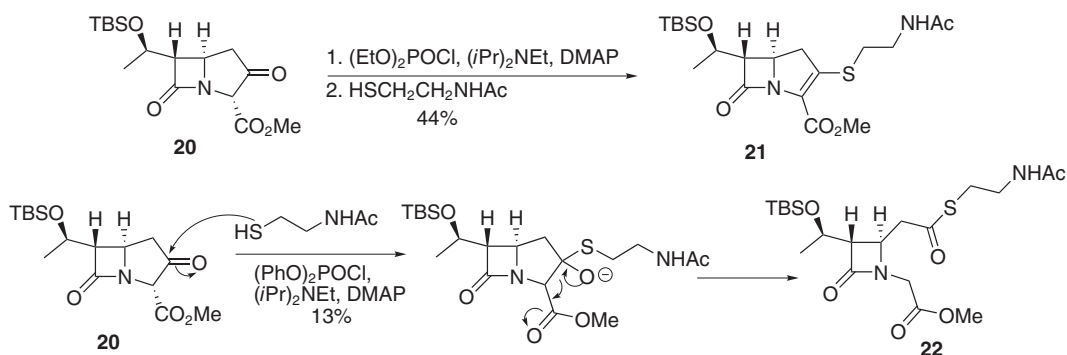
Scheme 5 Synthesis of protected thienamycin 21 and side reactions in the phosphorylation-addition sequence.

Thin-layer chromatography (TLC) was performed on aluminum sheets silica gel 60 F$_{254}$ from Merck. Column chromatography (CC) was carried out using Merck silica gel (230–400 mesh) or Florisil (100–200 mesh). The TLC spots were visualized in UV (254 nm) and by treatment with alcoholic solution of ninhydrine, aqueous solution of KMnO$_4$ or with ceric sulphate/phosphomolybdic acid solution.

All solvents were dried and purified applying standard techniques.

(2S,3S)-3-(benzyloxy)-2-((benzyloxy)methyl)-3,4-dihydro-2H-pyrrole-1-oxide (1) Compound 1 was prepared according to literature methods

Step 1: To a solution of 3,5-di-O-benzyl-2-deoxy-D-ribofuranoside[15] (8.91 g, 28.3 mmol)[16] in dry toluene (70 ml) was added MgSO$_4$ (10.3 g) under argon. The suspension was stirred at reflux temperature for 5 min, and then O-tert-butyldiphenylsilylhydroxylamine (8.6 g, 32 mmol) and pyridinium p-toluenesulfonate (98 mg) were added. The reaction mixture was heated at the same temperature for 30 min, and then it was filtered. The filtrate was washed with a saturated aqueous solution of NaHCO$_3$ and with brine and dried over MgSO$_4$ to give a residue, which was use in the next step without further purification.

Step 2: To a solution of oxime with previous step (12.0 g, 21.2 mmol) in CH$_2$Cl$_2$ (70 ml) placed at 0 °C under argon atmosphere were added successively triethylamine (4.5 ml, 32.8 mmol) and mesyl chloride (1.9 ml, 24.6 mmol). The solution was stirred for 30 min, and then water (15 ml) was added. The aqueous layer was extracted three times with CH$_2$Cl$_2$. The organic layers were washed with brine, dried over MgSO$_4$, and concentrated under vacuum to give a residue, which upon short column chromatography over silica gel (pentane/AcOEt 9/1, 4/1, then 1/1) yielded the desired unstable mesylate (13.4 g, 97.6%:

3/1 mixture of E/Z isomers) as an yellow oil. To a solution of mesylate (13.4 g, 20.7 mmol) in THF (400 ml) placed at 0 °C under argon was added tetrabutylammonium fluoride (24.2 ml, 1 M solution in THF, 24.2 mmol). The reaction mixture was stirred for 5 min at 0 °C, and then the solvent was removed under vacuum. The residue was dissolved in ethyl acetate, water was added, and the aqueous layer was extracted three times with ethyl acetate. The organic layers were washed with brine, dried over MgSO$_4$, and concentrated under vacuum to give a residue, which was use in the next step without further purification.

Step 3: To a solution of crude oxime with previous step (6.2 g, 18.8 mmol) in a 4:1 mixture of methanol and water (200 ml) were added NaHCO$_3$ (8.5 g, 102.0 mmol) and hydroxylamine hydrochloride (6.7 g, 96.5 mmol). The reaction mixture was heated overnight at reflux temperature. After concentration under vacuum, the residue was dissolved in CH$_2$Cl$_2$, and water was added. The aqueous layer was extracted three times with CH$_2$Cl$_2$, and the organic layers were washed with brine, dried over MgSO$_4$ and concentrated under vacuum to give a residue, which upon column chromatography over silica gel (acetone/DCM 1/9 then methanol/DCM 5/95) yielded the nitrone 1 (5.1 g, 87%) as an olive syrup.

[α]$_D$+23,7 (c 1, CHCl$_3$), IR (film) ν: 737, 1113, 2866, 3062, 3239 cm^{-1}

^{1}H NMR (600 MHz, CDCl$_3$) δ: 2.74–2.78 (m, 1H, H-3), 2.79-2.85 (ddd J = 2.6 Hz, 7,1 Hz, 17,9 Hz, 1H, H-3), 4.00–4.05 (m, 1H, H-5), 4.07–4.12 (m, 2H, CH$_2$OBn), 4.45–4.50 (m, 1H, H-4), 4.54–4.62 (m, 2H, 2 × CH$_2$Ph), 6.85–6.88 (m, 1H, H-2). ^{13}C NMR (150 MHz, CDCl$_3$) δ: 35.03, 64.86, 72.20, 73.63, 73.66, 74.32, 127.56, 127.60, 127.66, 127.94, 128.31, 128.50, 133.23, 137.41, 137.99.

HR MS (ESI): m/z [M+Na]$^+$calculated. for C$_{19}$H$_{21}$NO$_3$Na: 334,1419; found: 334,1427

(2*S*,3*S*)-3-Benzyloxy-2-hydroxymethyl-3,4-dihydro-2*H*-pyrrole-*N*-oxide (14)

To a solution of nitrone **1** (0.46 g, 1.50 mmol) in CH_2Cl_2 (30 ml), cooled to 0 °C, BCl_3•Me_2S complex (1 ml, 7.50 mmol) was added. The reaction mixture was stirred at room temperature overnight. Subsequently the mixture was evaporated, treated with methanol and evaporated again (4 × 10 ml). The crude mixture was purified by silica gel chromatography to afford the nitrone **14** (0.17 g, 0.75 mmol) in 50% yield.

Colorless syrup; $[\alpha]_D$+23,7 (*c* 1, CHCl_3), IR (film) *ν*: 1453, 2925, 3030, 3334 cm^{-1}

^{1}H NMR (600 MHz, CDCl_3) *δ*: 2.70-2.77 (m, 1H, H-4), 2.85–2.94 (m, 1H, H-4), 4.01–4.07 (m, 1H, C*H*HOH), 4.09–4.15 (m, 2H, H-2, OH), 4.20-4.45 (m, 1H, CH*H*OH), 4.43-4.62 (m, 3H, CH_2Ph, H-3), 6.89 (s, 1H, H-5), 7.24–7.40 (m, 5H, Ar). ^{13}C NMR (150 MHz, CDCl_3) *δ*: 34.93, 60.35, 71.78, 73.53, 76.79, 127.60, 128.26, 128.52, 128.68, 136.72.

HR MS (ESI): m/z [M+Na]$^+$calculated for $C_{12}H_{15}NO_3Na$: 244,1086; found: 244,1088

(2*S*,3*S*,5*R*,6*S*,1'*R*)-3-Benzyloxy-6-[1'-(*tert*-butyldimethylosiloxy)ethyl]-2-(hydroxymethyl)-1-azabicyclo[3.2.0]heptan-7-one (15) and (2*S*,3*S*,5*R*,6*R*,1'*R*)-3-benzyloxy-6-[1'-(*tert*-butyldimethylosiloxy)ethyl]-2-(hydroxymethyl)-1-azabicyclo [3.2.0]heptan-7-one (11)

To a suspension of CuI (0.5 mmol, 95 mg) in dry, degassed MeCN (3 ml), 253 µl (2.0 mmol) of 1,1,3,3-tetramethylguanidine was added. After cooling to 0 °C a solution of acetylene **8**[20] (92 mg, 0.5 mmol) in 1 ml of MeCN was added and thus obtained mixture was stirred for 15 min. Then a solution of nitrone **14** (221 mg, 1.0 mmol) in MeCN (2 ml) was added slowly and the mixture was kept at 0 °C for additional 15 min. After removal of the cooling bath, the mixture was stirred at ambient temperature under an inert atmosphere for 24 h. The progress of the reaction was monitored by TLC. Removal of the solvent gave a residue, which was chromatographed on silica gel (hexane/AcOEt 4:6 v/v) to afford a mixture of **15** and **11** in ratio 1:3 (110 mg, 54%, according to ^{1}H NMR of crude reaction mixture).

Compound **11**; colorless syrup; $[\alpha]_D$ +64,3 (*c* 1, CHCl_3); IR (film) *ν*: 1099, 1757, 2856, 3437 cm^{-1}; ^{1}H NMR (600 MHz, CDCl_3) *δ*: 0.06 (s, 6H, Si(CH_3)_2), 0,87 (s, 9H, *t*-Bu), 1.22 (d, J = 6.1 Hz, 3H, CH_3), 1.68-1.73 (m, 1H, H-4), 2.31-2.36 (m, 1H, H-4), 2.80 (dd, J = 2.0 Hz, 6,0 Hz, 1H, H-6), 3.73 (d, J = 5.6 Hz, 2H,CH_2OH), 3,86-3.89 (m, 1H, H-5), 4.00 (q,1H, J = 5.8 Hz, H-2), 4,15-4.20 (m, 1H, C*H*OSi), 4.44-4.46 (m, 1H, H-3,), 4.45–4.64(m, 2H, CH_2Ph), 7.28–7.32 (m, 3H, Ar), 7.34-7.37 (m, 2H, Ar); ^{13}C NMR (150 MHz, CDCl_3) *δ*: −4.94, −4.22, 17,95, 22,61, 25,68, 53.81, 61.28, 62.65, 65.23, 66.18, 72.33, 84.95, 127.57, 128.64, 137.33, 177.16; HR MS(ESI) m/z [M+Na]$^+$ calculated for $C_{22}H_{35}NO_4SiNa$: 428.2233; found: 428.2234.

Compound **15**: colorless syrup; $[\alpha]_D$ +39,1 (*c* 1, CHCl_3); IR (film) *ν*: 1092, 1744, 2926, 3400 cm^{-1}; ^{1}H NMR (600 MHz, CDCl_3) *δ*: 0.06 (s, 6H, Si(CH_3)_2), 0,88 (s, 9H, *t*-Bu), 1.20 (d, J = 6.2 Hz, 3H, CH_3), 1.82-1.87 (m, 1H, H-4), 2.15–2.20 (m, 1H, H-4), 3.39(dd, J = 5.7 Hz, 7,7 Hz, 1H, H-6), 3.71–3.78 (m, 2H, CH_2OH), 3.90(q, J = 5.7 Hz, 1H, H-2), 3.91-3.95 (m, 1H, H-5), 4.00–4.05 (m, 1H, C*H*Si), 4.42–4.45(m, 1H, H-3), 4.46–4.63(m, 2H, CH_2Ph), 7.35–7.37(m, 5H, Ar); ^{13}C NMR (150 MHz, CDCl_3) *δ*: −4.55, −4.33, 22.84, 25.81, 29.68, 32.08, 54.20, 58.12, 61.52, 61.94, 65.36, 72.27, 84.66, 126.97, 127.64, 128.55, 140.87, 178.37; HR MS(ESI) m/z [M+Na]$^+$calculated. for $C_{22}H_{35}NO_4SiNa$: 428.2233; found: 428.2227.

(2*R*,3*S*,5*R*,6*S*,1'*R*)-3-Benzyloxy-6-[1'-(*tert*-butyldimethylsiloxy)ethyl]-2-methoxycarbonyl-1-azabicyclo[3.2.0]heptan-7-one (18)

To a solution of **11** (166 mg, 0.4 mmol) in CH_2Cl_2 (15 ml) sodium bicarbonate (134 mg, 1.6 mmol) and Dess–Martin periodinane (340 mg, 0.8 mmol) were added. The reaction mixture was stirred at room temperature for 1 h. Subsequently, a saturated solution of $Na_2S_2O_3$ was added. The water phase was extracted with CH_2Cl_2 (3×). The combined extracts were washed with brine and dried over MgSO_4. The solution was evaporated and the crude aldehyde **16** was used in the next step without purification.

The crude **16** was dissolved in *t*-BuOH (6 ml) and treated with 2-methyl-2-butene (6 ml). Subsequently $NaClO_2$ (0.21 g, 2.3 mmol) and a solution of NaH_2PO_4 (0.26 g, 1.90 mmol) in water (11 ml) were added. The reaction mixture was stirred overnight at room temperature. NH_4Cl was added and the aqueous solution was extracted with ethyl acetate (3X). The combined extracts were dried over MgSO4, filtered and evaporated. The crude acid **17** was dissolved in Et_2O (20 ml), cooled to 0 °C and treated with a solution of diazomethane. After 5 min the mixture was treated with drop of acetic acid and evaporated. The product was purified on a silica gel column using hexane-EtOAc, 6:4 v/v as an eluant to give **18** in 58% yield.

Colorless syrup; $[\alpha]_D$ +121,1(*c* 1, CHCl_3); IR (film) *ν*: 1099, 1746, 1792, 2929, cm^{-1}; ^{1}H NMR (500 MHz, CDCl_3) *δ*: 0.08 (s, 6H, Si(CH_3)_2), 0,89 (s, 9H, *t*-Bu), 1.24 (d, J = 6.0, 3H, CH_3), 1.62-1.69 (m, 1H, H-4),2.32-2.38 (m, 1H, H-4), 2.82 (dd, J = 2.1 Hz, 6,4 Hz, 1H, H-6), 3.70 (s, 3H, CO_2CH_3), 4.03-4.08 (m, 1H, H-5), 4.19-4.25 (m, 1H, CHOSi), 4.55 (s, 2H, OCH_2Ph), 4.57-4.61 (m, 1H, H-3), 4.61-4.64 (m, 1H, H-2), 7.25-7.36 (m, 5H, Ar); ^{13}C NMR (150 MHz, CDCl_3) *δ*: -4.21, 17.93, 22.62, 25.69, 36.02, 52.03, 55.28, 63.70, 65.34, 66.25, 72.61, 85.47, 127.54, 127.88, 128.42, 137.33, 168.59, 175.88.

HR MS(ESI) m/z [M+Na]$^+$calculated. for $C_{23}H_{35}NO_5SiNa$: 456.2182; found: 456.2185.

(2*R*,3*S*,5*R*,6*S*,1'*R*)-6-[1'-(*tert*-Butyldimethylsiloxy)ethyl]-3-hydroxy-2-methoxycarbonyl-1-azabicyclo[3.2.0]heptan-7-one (19)

Compound **18** (0.10 g, 0,30 mmol) in ethyl acetate (10 ml) was treated with Pd(OH)_2 (0.15 g) and hydrogenated under 1 atm H_2 at room temp. for 3 h. Subsequently the catalyst was filtered off through a short path of celite. The solution was evaporated and purified on a silica gel column using hexane/EtOAc 4:6 v/v as an eluent to give **19** (0.10 g, 0.29 mmol) in 97% yield.

Colorless crystals; $[\alpha]_D$ +103, 8 (*c* 1, CHCl_3); m.p. = 151–153 °C; IR (film) *ν*: 1718, 1735, 2927, 3337 cm^{-1}; ^{1}H NMR (500 MHz, CDCl_3) *δ*: 0.09 (s, 6H, Si(CH_3)_2), 0,89 (s, 9H, *t*-Bu), 1.25 (d, J = 6.2 Hz, 3H, CH_3), 1.69-1.70 (m, 1H, H-4), 2.34–2.36 (m, 1H, H-4), 2.69 (bs,1H, OH), 2.85 (dd, J = 1.8 Hz, 5,8 Hz, 1H, H-6), 3.77(s, 3H, CO_2CH_3), 4.09–4.10 (m, 1H, H-5), 4.24–4.26 (m, 1H, C*H*OSi), 4.5 (d, J = 4.8 Hz, 1H, H-2), 4.94-4.95 (m, 1H, H-3); ^{13}C NMR (150 MHz, CDCl_3) *δ*: − 4.99, − 4.22, 17.94, 22.64, 25.67, 39.41, 52.45, 55.33, 64.56, 64.84, 66.00, 79.06, 169.91, 176.13.

HR MS(ESI) m/z [M+Na]$^+$calculated for $C_{16}H_{29}NO_5SiNa$: 366.1713; found: 366.1707.

Crystallographic data: $C_{16}H_{29}NO_5Si$, MW = 343.49 Da, 0.40 × 0.40 × 0.05, monoclinic, space group. P = 21, Z = 2, T = 100(2) K, a = 7.3250(2), b = 7.5160(2), c = 17.4905(5) Å, V = 962.89(5) Å^3, λ(Cu, Kα) = 1.54184 Å, µ = 1.271 mm^{-1}.Intensity data were collected on SuperNova area detector system. The structure was solved by direct mehods and refined by the full-matrix least-squares on F^2 (SHELXL-97). A total of 2389 reflections were measured and 2345 were independent. Final R1 = 0.0479, wR2 = 0.1325 (2389 references; I > 2σ(I), and GOF = 1.080 (for all data, R1 = 0.0483, wR2 = 0.1333).

(2*R*,5*R*,6*S*,4'*R*)-6-[1'-(*tert*-Butyldimethylosiloxy)ethyl]-2-methoxycarbonyl-1-azabicyclo[3.2.0]heptan-3,7-di-one (20)

To a solution of compound **19** (84 mg, 0,24 mmol) in CH_2Cl_2 (10 ml), $NaHCO_3$ (81 mg, 0.96 mmol) and Dess–Martin periodinane (0.20 g, 0.48 mmol) were added. The reaction mixture was stirred at room temperature for 40 min. Subsequently, saturated aqueous solution of $Na_2S_2O_3$ was added. The aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with brine, dried over MgSO_4 and evaporated. The product was purified on a silica gel column with hexane–EtOAc, 4:6 (v/v) as the eluent to afford **20** (40 mg, 0.11 mmol) in 48% yield.

Colorless crystals m.p. 151–154 °C; $[\alpha]_D$ +125,5 (*c* 1, CHCl_3); IR (film) *ν*: 1256, 1770, 2856, 2929 cm^{-1}; ^{1}H NMR (600 MHz, CDCl_3) *δ*: 0.08 (s, 6H, Si(CH_3)_2), 0,90 (s, 9H, *t*-Bu), 1.26 (d, J = 6.2 Hz, 3H, CH_3), 2.40 (dd, J = 7.7 Hz, 18,8 Hz, 1H, H-4), 2.86 (dd, J = 6.9 Hz, 18.8 Hz, 1H, H-4), 3.10 (dd, J = 2.0 Hz, 5,1 Hz, 1H, H-6), 3.75 (s, 3H, CO_2CH_3), 4.11-4.15 (m, 1H, H-5), 4.30 (dq, J = 6.15 Hz, 1H, CHOSi), 4.64 (s, 1H, H-2); ^{13}C NMR (150 MHz, CDCl_3) *δ*: -5.09, -4.25, 17.88, 22.59, 25.58, 27.14, 41.17, 46,87, 50.98, 53.02, 63.93, 65.35, 68.76, 165.46, 172.47, 207.32.

HR MS(ESI) *m/z* [M+Na]⁺calculated. for $C_{16}H_{27}NO_5SiNa$: 364.1556; found: 364.1557

(5R,6S,1'R)-Methyl 3-[(2-acetamidoetyl)thio]-6-[1'-(tert-butyldimethylsiloxy)ethyl]-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (21)

Compound **20** (14 mg, 0.04 mmol) in acetonitrile (2 ml) was cooled to 0 °C and treated with *N,N*-diisopropylethylamine (8 µl, 0.05 mmol), diethyl chlorophosphate (7 µl, 0.05 mmol) and catalytic amount of DMAP. The mixture was stirred for 1 h at room temperature. Subsequently it was cooled to 0 °C and treated with a another portion of *N,N*-diisopropylethylamine (11 µl, 0.06 mmol) and *N*-acetylcysteamine (6,5 µl, 0.06 mmol). The mixture was stirred overnight at room temperature. Subsequently it was evaporated under reduced pressure and purified on a silica gel column using toluene-*i*-propanol, 4:1(v/v) as an eluent to afford **21** (8 mg, 0.018 mmol) in 44% yield.

Easily solidifing syrup; [α]$_D$+52,3 (*c* 0.69, CHCl₃); IR (film) *v*: 1659, 1748, 1758, 2898, 2929, 2953 cm⁻¹;

¹H NMR (600 MHz, CDCl₃) δ: 0.06 (s, 6H, Si(C*H₃*)₂), 0,90 (s, 9H, *t*-Bu), 1.24 (d, *J* = 6.1 Hz, 3H, CH₃), 1.97 (s, 3H, CH₃), 2.88-2.94 (m, 1H, SC*H*H), 2.99-3.06 (m, 2H, SCH*H*, H-4), 3.10 (dd, *J* = 2.7 Hz, 6,1 Hz,1H, H6), 3.22-3.29 (m, 1H, H-4), 3.39-3.49 (m, 2H, C*HH*NHAc), 3.81(s, 3H, CO₂C*H₃*), 4.14-4.21 (m, 2H, H5, C*H*OSi), 5.96 (bs, 1H, N*H*Ac);

¹³C NMR (150 MHz, CDCl₃) δ: -4.93, -4.26, 17.94, 22.51, 23.17, 25.62, 25.68, 31.87, 39.70, 40.10, 52.16, 52.64, 66.23, 67.38, 124.92, 145.93, 161.90, 170.44, 175.98.

HR MS(ESI) *m/z* [M+Na]⁺ calculated. for $C_{20}H_{34}N_2O_5SNaSi$: 465.1855; found: 465.1858

(3S,4R,1'R)-4-(2''-acetamidoethyltiocarbonylmethyl)-3-[1'-(tert-butylodimethylsiloxy) ethyl]-azetidin-2-one (22)

Compound **20** (45 mg, 0,13 mmol) in acetonitrile (2 ml) was cooled to 0 °C and treated with *N,N*-diisopropylethylamine (25 µl, 0.14 mmol), diphenyl chlorophosphate (30 µl, 0.14 mmol) and a catalytic amount of DMAP. After 1 h an another portion of *N,N*-diisopropylethyloamine (25 µl, 0.14 mmol) and *N*-acetylcysteamine (15 µl, 0.14 mmol) were added. The mixture was stirred overnight. Subsequently it was evaporated under reduced pressure and the residue was purified by chromatography using hexane-acetone, 4:6 (v/v) as an eluent to give **22** (8 mg, 0.017 mmol) in 13% yield.

Syrup; [α]$_D$ +12,3 (*c* 0,6, CH₂Cl₂); IR (film) *v*: 1660, 1682, 1748 2930, 2954, 3202 cm⁻¹; ¹H NMR (600 MHz, C₆D₆) δ: − 0.01 (s, 3H, Si(C*H₃*)₂), 0.08 (s, 3H, Si(C*H₃*)₂), 0,88 (s, 9H, *t*-Bu), 1.07 (d, *J* = 6.1 Hz, 3H, CH₃), 1.47(s, 3H, Ac), 2.56 (dd, *J* = 2.4 Hz, 6,1 Hz, 1H, H-3), 2.58–2.73 (m, 4H, SCH₂, CH₂COS), 3.03-3.12 (m, 2H, CH₂NH), 3.19 (s, 3H, CO₂C*H₃*), 3.89 (m, 2H, NC*H₂*CO₂), 4.04–4.10 (m, 1H, C*H*OSi), 4.10-4.14 (m, 1H, H-4), 4.72 (bs, 1H, NH); ¹³C NMR (150 MHz, CDCl₃) δ: − 5.22, − 4.63, 22.28, 22.30, 25.58, 28.60, 38.70, 42.20, 47.61, 51.32, 52.13, 63.71, 66.03, 128.05, 166.53, 168.53, 168.88, 197.08.

HR MS(ESI) *m/z* [M+Na]⁺ calculated for $C_{20}H_{36}N_2O_6SiNaS$: 483.1961; found: 483.1958.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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