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ORIGINAL ARTICLE

Formal synthesis of Thienamycin

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A formal synthesis of Thienamycin from ethyl (*E*)–crotonate and a cyclic five-membered nitrone derived from 2-deoxy-D-ribose is described. The synthesis involves 1,3-dipolar cycloaddition, cleavage of the N–O bond in the adduct, and intramolecular *N*-acylation to afford a bicyclic carbapenam skeleton. Subsequent transformations of the five-membered ring substituents provide the title compound.
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INTRODUCTION

In 1979, Tufariello *et al.*[1] reported a simple and effective synthesis of the basic skeleton of the racemic carbapenem antibiotic Thienamycin[2–5] which continually attracts the interest of industrial and academic laboratories owing to its high antibacterial activity and resistance to β-lactamase enzymes.[6–14] Due to the *endo* approach of methyl (*E*)-crotonate to the cyclic five-membered nitrone, the relative configuration of the three stereogenic centers formed during the 1,3-dipolar cycloaddition step is the same as in protected antibiotic **1** (Scheme 1).[1]

A few years later we expanded on Tufariello's idea[1] to carry out the stereocontrolled formation of *N*,4-diaryl and aryl–alkyl β-lactams from α,β-unsaturated sugar-derived lactones and corresponding open-chain nitrones.[15] The obtained results have prompted us recently to apply that strategy for the effective synthesis of Ezetimibe, a potent inhibitor of cholesterol absorption.[16,17]

Very recently, we have reported a synthesis of protected Thienamycin (**1**) using the Kinugasa reaction[18,19] involving the cyclic nitrone **3** derived from 2-deoxy-D-ribose and its partly deprotected derivative **4** with terminal acetylene **2** derived from D-lactic acid.[20,21] The *cis* substitution of the four-membered ring, characteristic of the main product of the Kinugasa reaction, was the major drawback of this synthetic strategy. This was partly overcome, however, by the application of tetramethylguanidine as the base instead of trimethylamine. This change effected the preferential formation of the *trans* Kinugasa adduct **5** which, however, required chromatographic separation from the accompanying *cis* isomer (Scheme 2).[21]

The synthesis of nitrone **3** prompted us to employ it in 1,3-dipolar cycloaddition reaction with unsaturated sugar-derived γ- and δ-lactones.[22] The obtained results followed our previous observations made for other five-membered ring nitrones derived from tartaric and malic acids.[23] Owing to the preferential anti-exo cycloaddition, the final β-lactams exhibited the undesired *syn* configuration of the four-membered ring protons.[22]

RESULTS AND DISCUSSION

Nitrone **3** seemed to be a very attractive substrate for Tufariello's synthesis of Thienamycin,[1] since it was expected to promote the desired absolute configuration of all stereogenic centers in the 1,3-dipolar cycloadduct, the same as in the target antibiotic, whereas substituents in the pyrrolidine ring should have allowed straightforward introduction of the carboxylic acid and cysteamine moieties present in **1**.[22]

1,3-Dipolar cycloaddition of ethyl crotonate and nitrone **3** in a toluene solution took 24 h at 40 °C, providing adduct **6** as the only product in 95% yield. The structure and configuration of **6** were proved by NMR. The N–O bond cleavage in **6** was performed using a standard procedure with zinc and 10% hydrochloric acid to afford amino alcohol **7**. Subsequently, the hydroxyl group in **7** was silylated with *tert*-butyldiphenylsilyl chloride to give product **8** which was treated with *t*-butyl magnesium bromide to afford the bicyclic β-lactam **9** in 90% yield. Since the hydroxyl group liberated during the reduction of the N–O bond required protection, we could not use the partially deprotected nitrone **4** for the 1,3-dipolar cycloaddition step due to the higher reactivity of the primary hydroxyl group.[22]

Regioselective monodebenzylation of **9** by hydrogenolysis or the treatment with BCl_3/dimethyl sulfide complex failed. Numerous carefully performed experiments provided a mixture of compound **10** with deprotected primary hydroxyl and fully deprotected compound **11**. The best result of the deprotection of the primary hydroxyl was achieved with BCl_3/dimethyl sulfide at − 20 °C, but the reaction was capricious, affording **10** in yields varying between 20 and 70%. It should be stressed that the debenzylation of both hydroxyl groups in **9** with BCl_3 yielded **11** in 95% yield.

Looking for discrimination of the hydroxyl groups in the five-membered ring of compound **11**, we investigated regioselective oxidation (Scheme 3). Oxidation of **11** with MnO_2 in dichloromethane gave hydroxy ketone **12** in 54% yield after 24 h, whereas PCC yielded the same product after 30 min in 60% yield. Swern oxidation of **11** provided unsaturated aldehyde **13** in 22% yield. Compound **12** could offer an entry to possible modifications of the

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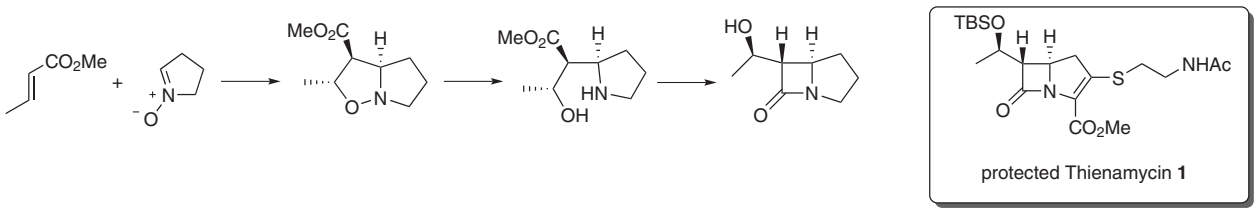
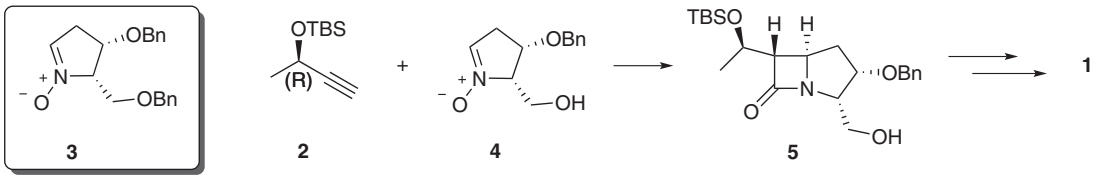
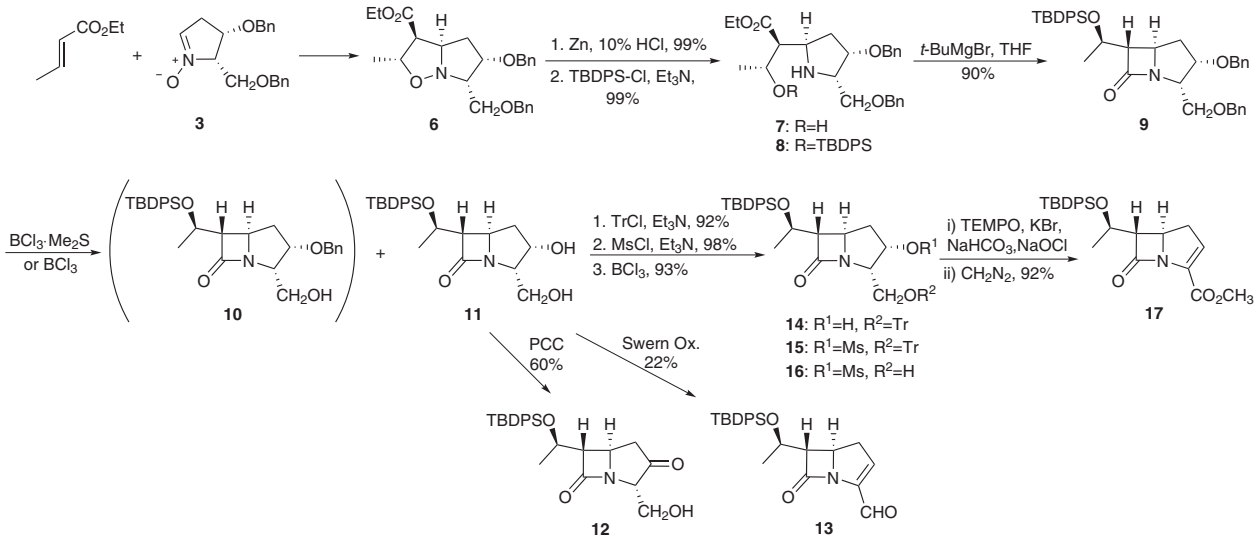


Scheme 1 Tufariello's synthesis of the basic skeleton of Thienamycin.



Scheme 2 Synthesis of protected Thienamycin using the Kinugasa reaction.



Scheme 3 Synthesis of protected Thienamycin following Tufariello's strategy.

carbapenem structure. Low yield of aldehyde **13** rendered its oxidation to unsaturated carboxylic acid (which had previously been transformed into Thienamycin **1**) unpractical.[24] Methyl ester of acid **17** could be easily obtained by a standard five-step procedure involving tritylation of **11**, mesylation of the trityl derivative **14**, detritylation of **15**, oxidation of the hydroxymethyl group in **16** to a carboxylic acid followed by β-elimination of the mesylate, and final methylation of the acid with diazomethane to afford **17**.

Due to issues with regioselective debenzylation, we synthesized nitrone **18** with the primary hydroxyl group protected using a PMB group. The reaction sequence involved the silylation of the terminal hydroxymethyl in methyl 2-deoxy-D-riboside with TBDPS–Cl, benzylation of the other hydroxyl,[25] desilylation, and *p*-methoxybenzylation of the primary hydroxyl group. Subsequent standard transformations following known procedures provided nitrone **18** in 47% overall yield (Supplementary Information).

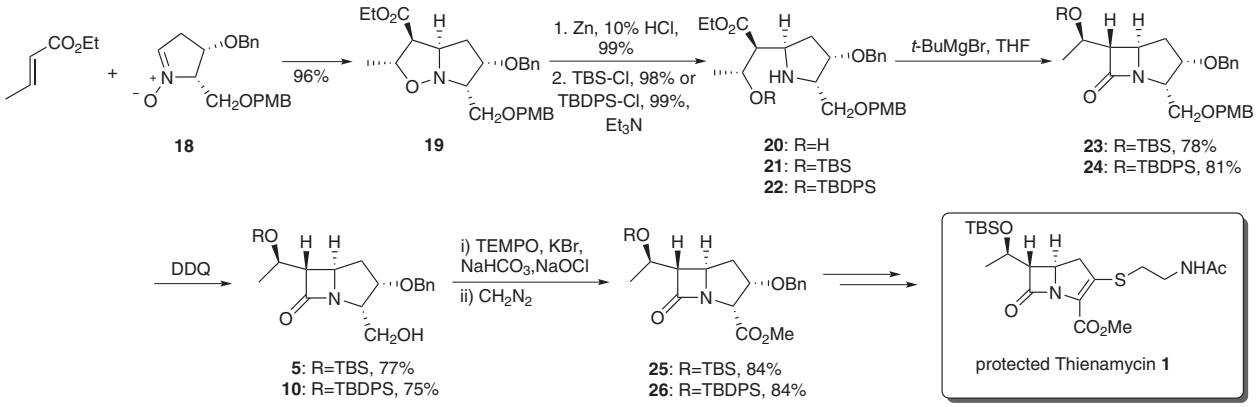
Cycloaddition of nitrone **18** and ethyl crotonate provided adduct **19** which subsequently was subjected to the cleavage of the N–O bond to afford amino alcohol **20** which was then subjected to the protection of the hydroxyl group with *t*-butyldimethylsilyl or *t*-butyldiphenylsilyl to give **21** and **22**, respectively, which were transformed into corresponding β-lactams **23** and **24** (Scheme 4). Deprotection of the hydroxymethyl group in **23** with CAN effected desilylation in the side chain as well, whereas removal of the PMB group with DDQ proceeded well to provide carbapenams **5** and **10**. Hydroxymethyl groups in compounds **5** and **10** were oxidized with TEMPO and sodium hypochlorite to afford acids which were treated with diazomethane without purification to give the corresponding methyl esters **25** and **26** in 84% overall yield (Scheme 4). Compound **25** had already been transformed in our laboratory into protected Thienamycin **1**[20] using a protocol described by Hanessian[26] and others.[11,27,28]

CONCLUSION

It was shown that the application of five-membered ring nitrones derived from 2-deoxy-D-ribose **3** and **18** to Tufariello's strategy[1] offers a very attractive entry to carbapenem antibiotics, offering high stereoselectivity and good yields of all steps. This was demonstrated by the formal synthesis of protected Thienamycin **1**.

EXPERIMENTAL PROCEDURE

Melting points were determined using Köfler hot-stage apparatus with a microscope and were uncorrected. Proton and carbon NMR spectra were



Scheme 4 Intermediates in the synthesis of protected Thienamycin involving PMB-protected nitrone **18**.

recorded on a Varian VNMRS Spectrometer at 600 MHz and 150 MHz, respectively, in $CDCl_3$ or C_6D_6. Infrared spectra were obtained on an FT–IR–1600 Perkin–Elmer spectrophotometer. Optical rotations were measured with a JASCO J–2000 digital polarimeter. High resolution mass spectra were recorded on an ESI–TOF Mariner spectrometer (Perspective Biosystem). Thin layer chromatography (TLC) was performed on aluminum silica gel 60 F_{254} sheets from Merck. Column chromatography (CC) was carried out using Merck silica gel (230–400 mesh). The TLC spots were visualized by UV (254 nm) and by treatment with an alcoholic solution of ninhydrine, aqueous solution of $KMnO_4$ or with ceric sulfate/phosphomolybdic acid solution. All solvents were dried and purified applying standard techniques.

The standard sequence of transformations of methyl 2-deoxy-D-riboside into nitrone **18** is described in the Supplementary Information.[25] Compounds **21** and **23** were obtained following procedures described for **7** and **8**, whereas compound **26** was obtained according to the procedure for **25**.[29]

Ethyl (2*R*,3*S*,3a*R*,5*S*,6*S*)-5-benzyloxy-6-benzyloxymethyl-2-methylhexahydro-pyrrolo[1,2-b]isoxazole-3-carboxylate (6)

Nitrone **3** (1.50 g, 4.8 mmol) was dissolved in dry toluene (60 ml) in an argon atmosphere and ethyl crotonate (3 eq. 1.65 g, 14.4 mmol) was added. The reaction was carried out for 24 h at 40 °C. The reaction progress was monitored by TLC and independently by NMR (the sample of the crude reaction mixture was evaporated and examined). Subsequently, the solvent was evaporated and the residue was purified on a silica gel column using hexane:AcOEt 7:3 v/v as the eluent to afford **6**, 2.0 g (95%).

Colorless syrup; $[\alpha]_D$ +139 (*c* 3.2, $CHCl_3$);

IR (film) $\nu = 1731\ cm^{-1}$;

^1H NMR (600 MHz, $CDCl_3$) δ 7.35–7.26 (m, 10H, Ar), 4.61, 4.55 (2d, *J* = 11.8 Hz, 2H, Bn), 4.59, 4.49 (2d, *J* = 12.2 Hz, 2H, Bn), 4.29 (m, 1H, H-3a), 4.28–4.24 (m, 2H, H-2, H-5), 4.19 (2dq, *J* = 10.7, 7.1, 2H, OCH_2CH_3), 3.94 (t, *J* = 9.1 Hz, 1H, C*H*HOBn), 3.77 (dd, *J* = 9.1, 4.8 Hz, 1H, CH*H*OBn), 3.40 (dt, *J* = 9.1, 4.8 Hz, 1H, H-6), 3.09 (dd, *J* = 10.2, 9.0 Hz, 1H, H-3), 2.09 (ddd, *J* = 13.7, 8.0, 6.8 Hz, 1H, H-4), 1.72 (ddd, *J* = 13.7, 9.9, 4.3 Hz, 1H, H-4), 1.35 (d, *J* = 5.8 Hz, 3H, $CHCH_3$), 1.29 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3).

^{13}C NMR (150 MHz, $CDCl_3$) δ 170.0, 138.3, 138.3, 128.3, 128.3, 128.3, 127.8, 127.5, 127.5, 127.3, 78.1, 73.5, 71.8, 71.6, 70.9, 68.5, 64.2, 60.8, 57.1, 33.1, 16.5, 14.2.

HRMS calcd for $C_{25}H_{32}NO_5$ $[M+H]^+$ 426.2280, found 426.2284.

Ethyl (2′*S*,3′*R*)-2′-(2*R*,4*S*,5*S*)-(4-benzyloxy-5-benzyloxymethyl-pyrrolidin-2-yl)-3′-hydroxy-butanoate (7)

Adduct **6** (42 mg, 0.1 mmol) in acetonitrile (2.0 ml) was treated with 10% HCl (0.2 ml) and Zn powder (10 eq. 65 mg, 1.0 mmol). The mixture was stirred for 1 h at room temperature. The reaction progress was monitored by TLC. After 1 h an additional portion of acid and Zn powder was added to complete the reaction. Subsequently, the solution of **7** was filtered and the precipitate was washed with AcOEt. The mixture was then neutralized with sodium bicarbonate and extracted with AcOEt. The extract was dried (Na_2SO_4) and evaporated to afford **7**, 42 mg (99%), which was used for the next step without chromatographic purification.

Colorless syrup; $[\alpha]_D$ +27.6 (*c* 2.4, $CHCl_3$);

IR (film) $\nu = 3330$, $1726\ cm^{-1}$;

^1H NMR (600 MHz, $CDCl_3$) δ 7.35–7.25 (m, 10H, Ar), 4.54, 4.50 (2d, *J* = 11.8 Hz, 2H, Bn), 4.54, 4.43 (2d, *J* = 11.8 Hz, 2H, Bn), 4.21 (dq, *J* = 8.7, 6.1 Hz, 1H, H-3′), 4.18 (m, 1H, H-4), 4.12 (m, 2H, OCH_2CH_3), 3.89 (ddd, *J* = 8.7, 8.0, 4.3 Hz, 1H, H-2), 3.63 (dd, *J* = 8.1, 3.9 Hz, 1H, C*H*HOBn), 3.60–3.53 (m, 2H, H-5, CH*H*OBn), 2.59 (dd, *J* = 8.8, 4.3 Hz, 1H, H-2′), 2.11 (ddd, *J* = 13.8, 9.1, 5.8 Hz, 1H, H-3), 1.99 (ddd, *J* = 13.8, 7.6, 3.6 Hz, 1H, H-3), 1.25 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.17 (d, *J* = 6.1 Hz, 3H, $CHCH_3$);

^{13}C NMR (150 MHz, $CDCl_3$) δ 172.3, 138.2, 138.1, 128.4, 128.4, 127.7, 127.7, 127.6, 127.4, 78.9, 73.2, 71.6, 68.1, 66.3, 60.4, 59.9, 55.6, 54.6, 32.6, 21.9, 14.2;

HRMS calcd for $C_{25}H_{34}NO_5$ $[M+H]^+$ 428.2437, found 428.2438.

Ethyl (2′*S*,3′*R*)-2′-(2*R*,4*S*,5*S*)-(4-benzyloxy-5-benzyloxymethyl-pyrrolidin-2-yl)-3′-*tert*-butyldiphenylsilyloxy-butanoate (8)

Compound **7** (42 mg, ~0.1 mmol) was dissolved in dichloromethane (2.0 ml), cooled to 0 °C and treated with Et_3N (2 eq. 20 mg), and with *tert*-butyl(chloro) diphenylsilane (1.2 eq. 33 mg, 1.2 mmol). The reaction mixture was stirred overnight, and then filtered, dried (Na_2SO_4), evaporated, and purified on silica gel using hexane/AcOEt 7:3 v/v as the eluent to afford **8**, 66 mg (99%).

Colorless syrup; $[\alpha]_D$ +36.9 (*c* 3.2, $CHCl_3$);

IR (film) ν 1725 cm^{-1};

^1H NMR (600 MHz, $CDCl_3$) δ 7.74–7.20 (m, 20H, Ar), 4.51, 4.49 (2d, *J* = 12.2 Hz, 2H, Bn), 4.44, 4.36 (2d, *J* = 12.0 Hz, 2H, Bn), 4.18 (m, 2H, OCH_2CH_3), 3.93 (bs, 1H, H-4), 3.90 (m, 1H, H-3′), 3.56 (dd, *J* = 9.5, 6.1 Hz, 1H, C*H*HOBn), 3.54 (m, 1H, H-2), 3.47 (m, 1H, CH*H*OBn), 3.34 (s, 1H, H-5), 2.53 (dd, *J* = 9.5, 4.9 Hz, 1H, H-2′), 1.86 (m, 1H, H-3a), 1.80 (m, 1H, H-3b), 1.27 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.11 (d, *J* = 6.3 Hz, 3H, $CHCH_3$), 1.04 (s, 9H, Si *t*-Bu).

^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0, 138.5, 138.4, 136.0, 135.9, 134.8, 134.2, 133.7, 129.7, 129.6, 128.3, 128.3, 127.6, 127.6, 127.5, 127.4, 127.3, 79.1, 73.2, 71.3, 68.7, 68.6, 60.5, 60.2, 59.8, 54.3, 35.2, 26.9, 19.7, 19.2, 14.3.

HRMS calcd for $C_{41}H_{52}NO_5Si$ $[M+H]^+$ 666.3615, found 666.3617.

(2*S*,3*S*,5*R*,6*S*,1′*R*)-3-Benzyloxy-2-benzyloxymethyl-6-(1′-tert-butyldiphenylsilyloxyethyl)-1-azabicyclo[3.2.0]heptan-7-one (9)

Compound **8** (1.5 g, 2.30 mmol) was dissolved in dry THF (46 ml), cooled to − 20 °C, and treated with (1.1 eq. 1.3 ml) of *tert*-butyl magnesium chloride (2M in Et_2O). The reaction progress was monitored by TLC. After about 15 min, a saturated solution of Na_2CO_3 was added and the reaction mixture was extracted with AcOEt. The extract was dried (Na_2SO_4), evaporated, and purified on silica gel using hexane/AcOEt 7:3 v/v as the eluent to afford **9**, 1.35 g (95%).

Colorless syrup; $[\alpha]_D$ +100.6 (*c* 0.4, $CHCl_3$);
IR (film) $\nu = 1760\ cm^{-1}$;
^1H NMR (600 MHz, $CDCl_3$) δ 7.69–7.22 (m, 20H, Ar), 4.56, 4.50 (2d, *J* = 12.0 Hz, 2H, Bn), 4.53, 4.47 (2d, *J* = 11.8 Hz, 2H, Bn), 4.35 (td, *J* = 5.3, 3.2 Hz, 1H, H-3), 4.17 (quint. *J* = 6.5 Hz, 1H, H-1′), 4.05 (q, *J* = 6.3 Hz, 1H, H-2), 3.72 (ddd, *J* = 8.0, 6.1, 2.0 Hz, 1H, H-5), 3.64 (dd, *J* = 9.6, 6.3 Hz, 1H, C*H*HOBn), 3.55 (dd, *J* = 9.6, 6.3 Hz, 1H, CH*H*OBn), 2.85 (dd, *J* = 6.5, 2.0 Hz, 1H, H-6), 2.24 (ddd, *J* = 13.3, 6.1, 3.2 Hz, 1H, H-4a), 1.58 (ddd, *J* = 13.3, 8.0, 5.3 Hz, 1H, H-4b), 1.16 (d, *J* = 6.5 Hz, 3H, CHC*H*$_3$), 1.04 (s, 9H, *t*-Bu);
^{13}C NMR (150 MHz, $CDCl_3$) δ 176.7, 138.3, 138.0, 135.9, 135.8, 134.1, 133.6, 129.7, 129.6, 128.4, 128.3, 127.7, 127.6, 127.6, 127.5, 127.5, 127.4, 84.1, 73.2, 72.2, 68.0, 68.0, 64.5, 61.3, 54.7, 36.2, 26.9, 22.4, 19.3;
HRMS calcd for $C_{39}H_{45}NO_4SiNa$ $[M+Na]^+$ 642.3016, found 642.3018.

(2*S*,3*S*,5*R*,6*S*,1′*R*)-6-(1′-*tert*-Butyldiphenylsilyloxyethyl)-3-hydroxy-2-hydroxymethyl-1-azabicyclo[3.2.0]heptan-7-one (11)

Compound **9** (0.20 g, 0.33 mmol), was dissolved in dry DCM (5.5 ml) The solution was cooled to − 78 °C, and treated with (3 eq, 1.0. mmol 1.0 ml) of BCl_3 (1M in DCM). The reaction progress was monitored by TLC. After about 20 min a saturated solution of Na_2CO_3 (10 ml) was added and the mixture was allowed to reach room temperature. Subsequently, the mixture was extracted with AcOEt. The extract was dried (Na_2SO_4), evaporated and purified on silica gel using hexane/AcOEt 6:4v/v as the eluent to afford **11**, 0.13 g (93%). Colorless syrup; $[\alpha]_D$ +79.7 (*c* 2.0, $CHCl_3$);
IR (film) ν 3417; 1738 cm^{-1};
^1H NMR (600 MHz, $CDCl_3$) δ 7.71–7.35 (m, 10H, Ar), 4.78 (bt, 1H, H-3), 4.22 (quint., *J* = 6.1 Hz, 1H, H-1′), 3.89 (dt, *J* = 6.7, 4.7 Hz, 1H, C-2), 3.85 (m, 1H, H-5), 3.85 (dd, J = 11.1, 4.3 Hz, C*H*HOH), 3.78 (dd, *J* = 11.1, 6.7 Hz, 1H, CH*H*OH), 2.98 (s, 2H, O*H*), 2.86 (dd, *J* = 6.1, 1.9 Hz, 1H, H-6), 2.19 (ddd, *J* = 13.6, 5.6, 2.3 Hz, 1H, H-4), 1.65 (ddd, *J* = 13.6, 9.0, 5.2 Hz, 1H, H-4), 1.15 (d, *J* = 6.1 Hz, 3H, CHC*H*$_3$), 1.05 (s, 9H, *t*-Bu).
^{13}C NMR (150 MHz, $CDCl_3$) δ 177.1, 135.9, 135.8, 134.2, 133.4, 129.8, 129.7, 127.7, 127.5, 79.4, 67.5, 64.5, 62.5, 61.5, 54.9, 40.4, 26.9, 22.3, 19.3.
HRMS calcd for $C_{25}H_{33}NO_4SiNa$ $[M+Na]^+$ 462.2077, found 462.2072

(2*S*,3*S*,5*R*,6*S*,1′*R*)-3-Benzyloxy-6-(1′-*tert*-butyldiphenylsilyl-oxyethyl)-2-hydroxymethyl-1-azabicyclo[3.2.0]heptan-7-one (10)

Compound **9** (0.12 g, 0.20 mmol), was dissolved in dry DCM (5.5 ml), cooled to -78 °C, and treated with freshly prepared BCl_3•SMe_2 (5 eq, 1.0 mmol 1.0 ml) (BCl_3 (1 M in DCM) and SMe_2 (6 eq. 1.20 mmol 0.1 ml)). The reaction progress was monitored by TLC. The reaction starts at -20 °C and should be terminated when the temperature reaches − 15 °C. Subsequently, a saturated solution of Na_2CO_3 (10 ml) was added. When the reaction reached room temperature, the mixture was extracted with AcOEt. The extract was dried (Na_2SO_4), evaporated and purified on silica gel using hexane/AcOEt 6:4v/v as the eluent to afford **10** (70 mg, 66%), and **11**, 16 mg (18%).
Compound **10**, colorless syrup, $[\alpha]_D$ +98.7 (*c* 1.5, $CHCl_3$);
IR (film) $\nu = 3438$; 1757 cm^{-1};
^1H NMR (600 MHz, $CDCl_3$) δ 7.73–7.27 (m, 15H, Ar), 4.58, 4.44 (2d, *J* = 11.7 Hz, 2H, Bn), 4.43 (m, 1H, H-3), 4.22 (quint., *J* = 6.3 Hz, 1H, H-1′), 3.99 (q, *J* = 5.8 Hz, 1H, H-2), 3.75–3.69 (m, 3H, H-5, CH_2OH), 2.89 (dd, *J* = 6.3, 2.0 Hz, 1H, H-6), 2.27 (ddd, *J* = 13.6, 6.2, 3.1 Hz, 1H, H-4), 2.12 (s, 1H, O*H*), 1.65 (ddd, *J* = 13.6, 7.7, 5.8 Hz, 1H, H-4), 1.20 (d, *J* = 6.3 Hz, 3H, CHC*H*$_3$), 1.07 (s, 9H, *t*-Bu);
^{13}C NMR (150 MHz, $CDCl_3$) δ 176.7, 137.3, 135.8, 135.8, 134.0, 133.5, 129.7, 129.7, 128.6, 128.3, 127.6, 127.5, 127.5, 84.9, 72.1, 67.9, 65.0, 62.7, 61.1, 54.5, 35.8, 26.8, 22.3, 19.3.
HRMS calcd for $C_{32}H_{39}NO_4NaSi$ $[M+Na]^+$ 552.2546, found 552.2542.

(2*S*,5*R*,6*S*,1′*R*)-6-(1′-*tert*-Butyldiphenylsilyloxyethyl)-2-hydroxymethyl-1-azabicyclo[3.2.0] heptane-3,7-dione (12)

Compound **11** (140 mg, 0.33 mmol) was dissolved in dry DCM (6.6 ml) and treated with MnO_2 (30eq. 860 mg, 9.9 mmol). The reaction was carried out for 24 h at room temperature. The reaction progress was monitored by TLC. Subsequently, the mixture was filtered through a short pad of Celite, evaporated, and purified on a silica gel column using hexane/AcOEt 1:1 v/v as the eluent to afford **12**, 70 mg (48%).
Colorless syrup; $[\alpha]_D$ +114.3 (*c* 3.3, $CHCl_3$);
IR (film) $\nu = 3475$; 1757 cm^{-1};
^1H NMR (600 MHz, $CDCl_3$) δ 7.75–7.27 (m, 10H, Ar), 4.31 (quint., *J* = 6.2 Hz, 1H, H-1′), 3.97 (t, *J* = 3.6 Hz, 1H, H-2), 3.87 (dd, *J* = 11.3, 3.6 Hz, 1H, C*H*HOH), 3.80 (ddd, *J* = 7.9, 7.0, 2.0 Hz, 1H, H-5), 3.74 (dd, *J* = 11.3, 3.6 Hz, 1H, CH*H*OH), 3.15 (dd, *J* = 6.2, 2.0 Hz, 1H, H-6), 2.65 (dd, *J* = 18.7, 7.0 Hz, 1H, H-4), 2.33 (dd, *J* = 18.7, 7.9 Hz, 1H, H-4), 1.71 (s, 1H, O*H*), 1.23 (d, *J* = 6.2 Hz, 3H, CHC*H*$_3$), 1.06 (s, 9H, *t*-Bu).
^{13}C NMR (150 MHz, cdcl$_3$) δ 214.6, 174.1, 135.8, 135.8, 133.8, 133.3, 130.0, 129.8, 127.7, 127.6, 68.6, 67.5, 63.5, 62.4, 52.0, 41.9, 26.8, 22.4, 19.3.
HRMS calcd for $C_{25}H_{31}NO_4SiNa$ $[M+Na]^+$ 460.1920, found 460.1925.

(5*R*,6*S*,1′*R*)-6-(1′-*tert*-Butyldiphenylsilyloxyethyl)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carbaldehyde (13)

Oxalyl chloride (2 eq. 84 mg, 0.66 mmol) was dissolved in dry DCM (2.4 ml). The solution was cooled to − 78 °C and DMSO (4eq. 103 mg, 1.32 mmol) in dry DCM (5.5 ml) was added. After 30 min substrate **11** (145 mg, 0.33 mmol) in dry DCM (1.7 ml) was added and after another 30 min Et_3N (8eq. 267 mg, 2.64 mmol) was added and the reaction mixture was allowed to reach room temperature. The mixture was then extracted with AcOEt, dried (Na_2SO_4), evaporated and purified on a silica gel column using hexane/AcOEt 1:1 v/v as the eluent to afford **13**, 30 mg (22%).
Colorless syrup; $[\alpha]_D$ +47.5 (*c* 1.8, $CHCl_3$);
IR (film) $\nu = 1779$; 1691 cm^{-1};
^1H NMR (600 MHz, $CDCl_3$) δ 9.58 (s, 1H, C*H*O), 7.74–7.35 (m, 10H, Ar), 6.44 (t, *J* = 3.1 Hz, 1H, H-3), 4.19 (quint, *J* = 6.3 Hz, 1H, H-1′), 4.03 (ddd, *J* = 10.0, 7.9, 3.1 Hz, 1H, H-5), 3.22 (dd, *J* = 6.3, 3.1 Hz, 1H, H-6), 2.87 (ddd, *J* = 20.1, 10.0, 3.1 Hz, 1H, H-4a), 2.80 (ddd, *J* = 20.1, 7.9, 3.1 Hz, 1H, H-4b), 1.21 (d, *J* = 6.3 Hz, 3H, CHC*H*$_3$), 1.06 (s, 9H, *t*-Bu).
^{13}C NMR (150 MHz, $CDCl_3$) δ 182.5, 176.4, 144.1, 137.0, 135.8, 135.8, 133.7, 133.3, 129.9, 129.9, 127.7, 127.7, 68.0, 67.7, 55.1, 35.9, 26.9, 22.2, 19.3.
HRMS calcd for $C_{25}H_{29}NO_3NaSi$ $[M+Na]^+$ 442.1814, found 442.1818.

(2S,3S,5R,6S,1′R)-6-(1′-*tert*-Butyldiphenylsilyloxyethyl)-3-hydroxy-2-trityloxymethyl-1-azabicyclo[3.2.0]heptan-7-one (14)

Compound **11** (44 mg, 0.1 mmol), was dissolved in dry DCM (1.0 ml) and treated with Et_3N (2 eq. 20 mg, 0.2 mmol). The solution was cooled to 0 °C and treated with TrCl (1.3 eq. 36 mg, 0.13 mmol) in dry DCM (0.5 ml). The reaction mixture was left for 24 h at room temperature. Subsequently, the solvent was evaporated and the residue was purified on silica gel using hexane/AcOEt 7:3 v/v as the eluent to afford **14** (63 mg, 92%).
Colorless syrup, $[\alpha]_D$+78.3 (*c*, 0.55, $CHCl_3$);
IR (film) $\nu = 3478$; 1758 cm^{-1};
^1H NMR (500 MHz, $CDCl_3$) δ 7.68–7.24 (m, 25 H, Ar), 4.80 (t, *J* = 5.3 Hz, 1H, H-3), 4.14 (quint., *J* = 6.2 Hz, 1H, H-1′), 4.03 (dt, *J* = 8.1, 5.3 Hz, 1H, H-2), 3.86 (ddd, *J* = 8.3, 5.7, 1.9 Hz, 1H, H-5), 3.46 (dd, *J* = 9.4, 5.3 Hz, 1H, C*H*HOTr), 3.10 (dd, *J* = 9.4, 8.1 Hz, 1H, CH*H*OTr), 2.85 (dd, *J* = 6.2, 1.9 Hz, 1H, H-6), 2.20 (ddd, *J* = 13.6, 5.7, 2.1 Hz, 1H, H-4a), 1.70 (ddd, *J* = 13.6, 8.3, 5.3 Hz, 1H, H-4b), 1.13 (d, *J* = 6.2 Hz, 3H, CHC*H*$_3$), 0.99 (s, 9H, *t*-Bu);
^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 143.2, 135.8, 135.8, 134.1, 133.4, 129.7, 129.6, 128.3, 128.1, 127.6, 127.5, 127.3, 87.3, 78.8, 67.8, 64.6, 62.3, 61.0, 55.1, 39.5, 26.9, 22.3, 19.3;
HRMS calcd for $C_{44}H_{47}NO_4KSi$ $[M+K]^+$ 720.2911, found 720.2917.

(2S,3S,5R,6S,1′R)-6-(1′-*tert*-Butyldiphenylsilyloxyethyl)-3-methanesulfonyloxy-2-trityloxymethyl-1-azabicyclo[3.2.0]heptan-7-one (15)

Compound **14** (0.37 g, 0.55 mmol), was dissolved in dry DCM (5.5 ml), Et_3N (3 eq. 0.17 g, 1.65 mmol) was added and the solution was cooled to 0 °C. Next, MsCl (1.1 eq. 0.07 g, 0.60 mmol) was added. The reaction was allowed to reach room temperature. The reaction progress was monitored by TLC (DCM), after ca. 1 h TLC shows disappearance of substrate. The reaction mixture was

extracted with a saturated Na_2CO_3 solution, dried (Na_2SO_4), evaporated and purified on a silica gel column using hexane/AcOEt 1:1 v/v as an eluent to afford **15**, 410 mg (98%).

Colorless syrup, $[\alpha]_D$ +63.6 (*c* 0.76 $CHCl_3$);

IR (film) $\nu = 1765\ cm^{-1}$;

^1H NMR (500 MHz, $CDCl_3$) δ 7.67–7.21 (m, 25 H, Ar), 5.38 (td, *J* = 5.6, 3.4 Hz, 1H, H-3), 4.13 (m, 1H, H-1′), 4.10 (m, 1H, H-2), 3.80 (ddd, *J* = 7.5, 6.2, 2.2 Hz, 1H, H-5), 3.31 (dd, *J* = 9.6, 5.1 Hz, 1H, C*H*HOTr), 3.11 (dd, *J* = 9.6, 6.5 Hz, 1H, CH*H*OTr), 2.95 (dd, *J* = 6.8, 2.2 Hz, 1H, H-6), 2.73 (s, 3H, OMs), 2.56 (ddd, *J* = 13.8, 6.2, 3.4 Hz, 1H, H-4a), 1.93 (ddd, *J* = 13.8, 7.5, 5.6 Hz, 1H, H-4b), 1.18 (d, *J* = 6.2 Hz, 3H, CHC*H*$_3$), 1.02 (s, 9H, Si*t*-Bu);

^{13}C NMR (125 MHz, $CDCl_3$) δ 176.2, 143.5, 135.8, 135.7, 133.9, 133.4, 129.9, 129.7, 128.6, 127.9, 127.7, 127.6, 127.2, 87.4, 83.9, 68.0, 65.1, 61.6, 60.6, 54.6, 38.2, 38.0, 26.9, 22.3, 19.3.

HRMS calcd for $C_{45}H_{49}NO_6SSiNa$ $[M+Na]^+$ 782.2948, found 782.2926.

(2S,3S,5R,6S,1′R)-6-(1′-*tert*-Butyldiphenylsilyloxyethyl)-3-methanesulfonyloxy-2-hydroxymethyl-1-azabicyclo[3.2.0]heptan-7-one (16)

Compound **15** (0.20 g, 0.26 mmol), was dissolved in dry DCM (2.6 ml) The solution was cooled to − 78 °C, and treated with (3 eq. 0.78 mmol, 0.78 ml) of BCl_3 (1M in DCM). The reaction progress was monitored by TLC. When the reaction reached room temperature, TLC showed disappearance of the substrate. Next, a saturated solution of Na_2CO_3 (5 ml) was added and the mixture was extracted with AcOEt. The extract was dried (Na_2SO_4), evaporated and purified on silica gel using hexane/AcOEt 4:6 v/v as an eluent to afford **16**, 0.125 g (93%).

Colorless syrup, $[\alpha]_D$ +87.1 (*c* 1.23 $CHCl_3$);

IR (film) $\nu = 3449, 1760\ cm^{-1}$;

^1H NMR (600 MHz, $CDCl_3$) δ 7.71–7.37 (m, 10H, Ar), 5.49 (td, *J* = 4.7, 1.8 Hz, 1H, H-3), 4.21 (quint., *J* = 6.1 Hz, 1H, H-1′), 4.05 (ddd, *J* = 7.8, 6.3, 4.7 Hz, 1H, H-2), 3.81 (ddd, *J* = 9.0, 5.5, 2.0 Hz, 1H, H-5), 3.72 (dd, *J* = 11.3, 6.3 Hz, 1H, C*H*HOH), 3.67 (dd, *J* = 11.3, 7.8 Hz, 1H, CH*H*OH), 3.08 (s, 3H, OMs), 2.91 (dd, *J* = 6.1, 2.0 Hz, 1H, H-6), 2.47 (ddd, *J* = 14.1, 5.5, 1.8 Hz, 1H, H-4a), 1.81 (ddd, *J* = 14.1, 9.0, 4.7 Hz, 1H, H-4b), 1.16 (d, *J* = 6.1 Hz, 3H, C*H*$_3$), 1.04 (s, 9H, *tert*-Bu);

^{13}C NMR (150 MHz, $CDCl_3$) δ 176.6, 135.8, 135.8, 133.9, 133.3, 129.9, 129.8, 127.7, 127.6, 85.6, 67.3, 64.4, 62.8, 60.2, 54.3, 38.8, 38.3, 26.8, 22.3, 19.3.

HRMS calcd for $C_{26}H_{35}NO_6NaSiS$ $[M+Na]^+$ 540.1852, found 540.1847.

Methyl (5*R*,6*S*,1′*R*)-6-(1′-*tert*-butyldiphenylsilyloxyethyl)-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate (17)

Compound **16** (0.12 g, 0.23 mmol) was dissolved in acetone (2.3 ml) and cooled to 0 °C. Subsequently aqueous 5% v/v $NaHCO_3$ solution (0.57 ml) was added, followed with potassium bromide (2.7 mg, 0.023 mmol) and TEMPO (1.1 eq. 40 mg, 0.25 mmol). Under stirring, a 5% aqueous NaOCl solution (0.46 ml) was added dropwise. After 1 h, an additional portion of 5% NaOCl solution in water (0.46 ml) was added, and stirring was continued at 0 °C while the progress of the reaction was monitored by TLC. The reaction was terminated by the addition of a 5% $NaHCO_3$ solution. Acetone was then removed on a rotary evaporator and the residue was suspended in dichloromethane (5 ml), treated with a saturated solution of NH_4Cl (5 ml) and the mixture was extracted with dichloromethane. The combined organic extracts were dried, concentrated, dissolved in Et_2O (5 ml), and treated with an excess of diazomethane in ether, then evaporated. The residue was purified by column chromatography on silica gel, hexane/EtOAc (10/1, then 8/2) to give compound **17** as colorless oil, 95 mg (92%).

Colorless syrup, $[\alpha]_D$ +88.7 (*c* 1.49 $CHCl_3$);

IR (film) $\nu = 1784, 1733\ cm^{-1}$;

^1H NMR (600 MHz, $CDCl_3$): δ 7.70–7.36 (m, 10H, Ar), 6.42 (dd, *J* = 3.1, 2.6 Hz, 1H, H-3), 4.16 (dq, *J* = 7.4, 6.2 Hz, 1H, H-1′), 3.99 (ddd, *J* = 9.9, 8.3, 3.0 Hz, 1H, H-5), 3.81 (s, 3H, OC*H*$_3$), 3.21 (dd, *J* = 7.4, 3.0 Hz, 1H, H-6), 2.78 (ddd, *J* = 19.2, 9.9, 3.1 Hz, 1H, H-4a), 2.72 (ddd, *J* = 19.2, 8.3, 2.6 Hz, 1H, H-4b), 1.23 (d, *J* = 6.2 Hz, 3H, C*H*$_3$), 1.05 (s, 9H, *tert*-Bu);

^{13}C NMR (150 MHz, $CDCl_3$): δ 176.6, 161.0, 135.8, 135.8, 135.2, 133.7, 133.4, 131.4, 129.9, 129.8, 127.7, 127.7, 68.3, 67.5, 55.7, 52.3, 35.8, 26.9, 22.2, 19.2.

HRMS calcd for $C_{26}H_{31}NO_4NaSi$ $[M+Na]^+$ 472.1920, found 472.1919.

(2S,3S)-3-Benzyloxy-2-(p-methoxybenzyloxymethyl)-3,4-dihydro-2H-pyrrole-1-oxide (18)

Nitrone **18** was synthesized according to the standard procedure described in Supplementary Information.

Colorless syrup; $[\alpha]_D$ +21.2 (*c* 1.5, $CHCl_3$);

IR (film) $\nu = 3098\ cm^{-1}$;

^1H NMR (600 MHz, $CDCl_3$) δ 7.36–6.81 (m, 10H, Ar), 6.86 (m, 1H, H-2), 4.59, 4.56 (2d, *J* = 11.8 Hz, 2H, Bn), 4.52, 4.48 (2d, *J* = 11.6 Hz, 2H, OPMB), 4.46 (dt, *J* = 7.1, 4.8 Hz, 1H, H-3), 4.09 (m, 1H, H-2), 4.06 (dd, *J* = 9.6, 6.2 Hz, 1H, C*H*HOPMB), 4.99 (dd, *J* = 9.6, 2.7 Hz, 1H, CH*H*OPMB), 3.79 (s, 3H, OC*H*$_3$), 2.83 (dddd, *J* = 18.0, 7.1, 2.5, 1.3 Hz, 1H, H-4a), 2.75 (dddd, *J* = 18.0, 4.5, 2.7, 1.3 Hz, 1H, H-4b).

^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 137.4, 133.1, 130.0, 129.3, 128.5, 127.9, 127.5, 113.7, 74.3, 73.6, 73.3, 72.2, 64.5, 55.2, 35.0.

HRMS calcd for $C_{20}H_{23}NO_4Na$ $[M+Na]^+$ 364.1525, found 364.1535.

Ethyl (2*R*,3*S*,3a*R*,5*S*,6*S*)-5-(benzyloxy)-6-(*p*-methoxybenzyloxymethyl)-2-methylhexahydro-pyrrolo[1,2-b]isoxazole-3-carboxylate (19)

Nitrone **18** (2.0 g, 5.85 mmol) was dissolved in dry toluene (73 ml) in an argon atmosphere, and ethyl crotonate (3 eq. 2.0 g, 17.55 mmol) was added. The reaction was carried out for 24 h at 40 °C while its progress was monitored by TLC and independently by NMR (a sample of the crude reaction mixture was evaporated and examined). Subsequently, the solvent was evaporated and the residue was purified on a silica gel column using hexane:AcOEt 7:3 v/v as the eluent to afford **19**, 2.4 g (96%).

Colorless syrup; $[\alpha]_D$ +152.6 (*c* 0.64, $CHCl_3$);

IR (film) $\nu = 1729\ cm^{-1}$;

^1H NMR (600 MHz, $CDCl_3$) δ 7.31–6.73 (m, 9H, Ar), 4.54, 4.44 (2d, *J* = 12.2 Hz, 2H, OBn), 4.50, 4.44 (2d, *J* = 11.5 Hz, 2H, OPMB), 4.26 (m, 1H, H-3a), 4.21 (m, 2H, H-2, H-5), 4.30 (m, 2H, C*H*$_2$CH$_3$), 3.85 (t, *J* = 9.1 Hz, C*H*HOPMB), 3.77 (s, 3H, OCH$_3$), 3.70 (dd, *J* = 9.1, 5.0 Hz, 1H, CH*H*OPMB), 3.35 (m, 1H, H-6), 3.05 (bt, *J* = 9.1, 10.0 Hz, 1H, H-3), 2.06 (dd, *J* = 13.5, 7.0 Hz, 1H, H-4a), 1.68 (ddd, *J* = 13.5, 9.9, 4.3.0 Hz, 1H, H-4b), 1.31 (d, *J* = 5.8 Hz, 3H, CHC*H*$_3$), 1.25 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$).

^{13}C NMR (150 MHz, $CDCl_3$) δ: 169.9, 159.1, 138.3, 129.5, 128.3, 128.2, 127.4, 127.3, 113.7, 78.1, 73.2, 71.8, 71.6 70.9, 68.1, 64.2, 60.8, 57.0, 55.2, 33.2, 16.4, 14.2;

HRMS calcd for $C_{26}H_{34}NO_6$ $[M+H]^+$ 456.2386, found 456.2397.

Ethyl (2R,4S,5S,2′S,3′R)-2′-[4-benzyloxy-5-(*p*-methoxybenzyl-oxymethyl)-pyrrolidin-2-yl]-3′-hydroxy-butanoate (20)

Adduct **19** (0.18 g, 0.4 mmol) in acetonitrile (8 ml) was treated with 10% HCl (0.8 ml) and Zn powder (10 eq. 0.26 g, 4.0 mmol). The mixture was stirred for 1 h at room temperature. The reaction progress was monitored by TLC, and after 1 h an additional portion of acid and Zn powder was added to complete the reaction. Subsequently, the solution was filtered and the precipitate was washed with AcOEt. The mixture was then neutralized with sodium bicarbonate and extracted with AcOEt. The extract was dried (Na_2SO_4), evaporated to afford **20**, 0.18 g (99%), which was used in the next step without chromatographic purification.

Colorless syrup; $[\alpha]_D$ +24.1 (*c* 1.1, $CHCl_3$);

IR (film) $\nu = 3331;\ 1727\ cm^{-1}$;

^1H NMR (600 MHz, $CDCl_3$) δ 7.35–6.84 (m, 9H, Ar), 4.53, 4.43 (2d, *J* = 11.9 Hz, 2H, OBn), 4.47, 4.43 (2d, *J* = 11.3 Hz, 2H, OPMB), 4.21 (dq, *J* = 8.8, 6.1 Hz, 1H, C*H*CH$_3$), 4.17 (m, 1H, H-4), 4.12 (m, 2H, OC*H*$_2$CH$_3$), 3.86 (ddd, *J* = 9.1, 7.5, 4.4 Hz, 1H, H-2), 3.79 (s, 3H, OC*H*$_3$), 3.59 (dd, *J* = 8.6, 4.6 Hz, 1H, C*H*HOPMB), 3.56 (m, 1H, CH*H*OPMB), 3.51 (m, 1H, H-5), 2.58 (dd, *J* = 8.8, 4.4 Hz, 1H, C*H*COOEt), 2.10 (ddd, *J* = 13.7, 9.1, 5.9 Hz, 1H, H-3a), 1.98 (ddd, *J* = 13.7, 7.5, 3.4 Hz, 1H, H-3b), 1.24 (t, *J* = 7.1 Hz, 3H, OCH$_2$C*H*$_3$), 1.17 (d, *J* = 6.1 Hz, 3H, CHC*H*$_3$).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.3, 159.2, 138.2, 130.1, 129.3, 128.3, 127.6, 127.3, 113.8, 78.9, 72.8, 71.5, 67.7, 66.3, 60.4, 59.8, 55.6, 55.2, 54.6, 32.6, 21.8, 14.1.

HRMS calcd for $C_{26}H_{36}NO_6$ $[M+H]^+$ 458.2543, found 458.2557.

Ethyl (2*R*,4*S*,5*S*,2′*S*,3′*R*)-2′-[4-benzyloxy-5-(*p*-methoxybenzyloxymethyl)-pyrrolidin-2-yl]-3′-*tert*-butyldimethylsilyloxybutanoate (21)

Compound **20** (2.0 g, 4.35 mmol) was dissolved in dichloromethane (43 ml), cooled to 0 °C, treated with imidazole (2 eq. 0.59 g, 8.70 mmol), and *tert*-butyldimethylchlorosilane (1.2 eq. 0.79 g 5.22 mmol) in dichloromethane (5 ml). The reaction mixture was stirred overnight, then it was filtered, dried, evaporated and purified on silica gel using hexane/AcOEt 7:3 v/v as the eluent to afford **21**, 2.4 g (98%).

Colorless syrup; $[\alpha]_D$ +14.1 (*c* 0.61, $CHCl_3$);

IR (film) $\nu = 1725\ cm^{-1}$;

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35–6.81 (m, 9H, Ar), 4.52, 4.44, (2d, *J* = 12.0 Hz, 1H, OBn), 4.44 (s, 2H, OPMB), 4.13 (m, 2H, OCH_2CH_3), 4.08 (m, 1H, H-4), 4.00 (quint., *J* = 6.3 Hz, 1H, H-3′), 3.78 (s, 3H, OCH_3), 3.67 (bq, *J* = 8.2 Hz, 1H, H-2), 3.59 (dd, *J* = 9.3, 5.5 Hz, 1H, C*H*HOPMB), 3.49 (dd, *J* = 9.3, 7.3 Hz, 1H, CH*H*OPMB), 3.43 (m, 1H, H-5), 2.46 (dd, *J* = 8.2, 6.3 Hz, 1H, H-2′), 2.09 (ddd, *J* = 13.5, 7.2, 3.0 Hz, 1H, H-3a), 1.65 (ddd, *J* = 13.5, 8.6, 5.5 Hz, 1H, H-3b), 1.24 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 1.16 (d, *J* = 6.3 Hz, 3H, $CHCH_3$), 0.88 (s, 9H, Si*t*-Bu), 0.06 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$);

^{13}C NMR (150 MHz, $CDCl_3$) δ 173.1, 159.1, 138.6, 130.6, 129.3, 128.3, 127.4, 127.3, 113.7, 79.3, 72.9, 71.4, 68.5, 68.1, 60.5, 60.2, 60.1, 55.2, 54.5, 36.3, 25.8, 21.2, 18.0, 14.3, −4.5, −4.8;

HRMS calcd for $C_{32}H_{50}NO_6Si$ $[M+H]^+$ 572.3407, found 572.3414.

(2*S*,3*S*,5*R*,6*S*,1′*R*)-3-Benzyloxy-6-(1′-*tert*-butyldimethylsilyloxyethyl)-2-(*p*-methoxybenzyloxy-methyl)-1-azabicyclo[3.2.0]heptan-7-one (23)

Compound **21** (2.34 g, 4.10 mmol), was dissolved in dry THF (82 ml), cooled to −20 °C, and treated with (1.1 eq 2.30 ml) of *tert*-butyl magnesium chloride (2 M in Et_2O). The reaction progress was monitored by TLC. After ca. 15 min a saturated solution of Na_2CO_3 was added and the reaction mixture was extracted with AcOEt. The extract was dried (Na_2SO_4), evaporated and purified on silica gel using hexane/AcOEt 7:3 v/v as the eluent to afford **23**, 1.68 g (78%).

Colorless syrup; $[\alpha]_D$ +82.6 (*c* 1.7, $CHCl_3$);

IR (film) $\nu = 1760\ cm^{-1}$;

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35–6.81 (m, 9H, Ar), 4.55, 4.50 (2d, *J* = 12.0 Hz, 2H, OBn), 4.51, 4.45 (2d, *J* = 11.5 Hz, 2H, OPMB), 4.36 (td, *J* = 5.2, 3.1 Hz, 1H, H-3), 4.16 (quint. *J* = 6.2 Hz, 1H, H-1′), 4.04 (q, *J* = 5.2 Hz, 1H, H-2), 3.84 (ddd, *J* = 8.1, 6.0, 2.0 Hz, 1H, H-5), 3.79 (s, 3H, OCH_3), 3.65 (dd, *J* = 9.7, 6.8 Hz, 1H, CH_2OPMB), 3.56 (dd, *J* = 9.7, 6.0 Hz, 1H, CH_2OPMB), 2.77 (dd, *J* = 6.2, 2.0 Hz, 1H, H-6), 2.30 (ddd, *J* = 13.3, 6.0, 3.1 Hz, 1H, H-4a), 1.59 (ddd, *J* = 13.3, 8.0, 5.2 Hz, 1H, H-4b), 1.22 (d, *J* = 6.2 Hz, 3H, $CHCH_3$), 0.87 (s, 9H, Si*t*-Bu), 0.06 (s, 6H Si $(CH_3)_2$);

^{13}C NMR (150 MHz, $CDCl_3$) δ 177.1, 159.1, 138.0, 130.4, 129.3, 128.4, 127.7, 127.4, 113.7, 84.2, 72.9, 72.3, 67.7, 66.3, 64.4, 61.3, 55.2, 54.0, 36.3, 25.7, 22.7, 18.0, −4.2, −4.9.

HRMS calcd for $C_{30}H_{43}NO_5NaSi$ $[M+H]^+$ 548.2808, found 548.2818.

(2*S*,3*S*,5*R*,6*S*,1′*R*)-3-Benzyloxy-6-(1′-tert-butyldimethylsilyloxyethyl)-2-hydroxymethyl-1-azabicyclo[3.2.0]heptan-7-one (5)

Compound **23** (0.2 g, 0.37 mmol) was dissolved in dichloromethane (3.7 ml) and water (0.015 ml) was added. Subsequently, the solution was cooled to 0 °C and treated with DDQ (2 eq. 0.17 g, 0.74 mmol). The reaction mixture was stirred for about 30 min, After TLC showed the disappearance of the substrate, the reaction mixture was extracted with AcOEt, and the extracts were evaporated and purified on silica gel using hexane/AcOEt 6:4v/v as the eluent to afford **5**, 0.11 g (77%).

Colorless syrup; $[\alpha]_D$ +62.1 (*c* 1.0, $CHCl_3$);

IR (film) $\nu = 3452$; $1758\ cm^{-1}$;

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39–7.27 (m, 5H, Ar), 4.61, 4.47 (2d, *J* = 11.8 Hz, 2H, OBn), 4.44 (dt, *J* = 3.2, 5.8 Hz, 1H, H-3), 4.18 (quint., *J* = 6.2 Hz, 1H, H-1′), 3.99 (q, *J* = 5.8 Hz, 1H, H-2), 3.87 (ddd, *J* = 7.8, 6.4, 2.1 Hz, 1H, H-5), 3.72 (bd, *J* = 5.8 Hz, 2H, CH_2OH), 2.79 (dd, *J* = 6.2, 2.1 Hz, 1H, H-6), 2.32 (ddd, *J* = 13.6, 6.4, 3.2 Hz, 1H, H-4a), 1.69 (ddd, *J* = 13.6, 7.8, 5.8 Hz, 1H, H-4b), 1.22 (d, *J* = 6.2 Hz, 3H, $CHCH_3$), 0.88 (s, 9H, Si*t*-Bu), 0.07 (s, 6H, $Si(CH_3)_2$);

^{13}C NMR (150 MHz, $CDCl_3$) δ 177.1, 137.3, 128.6, 128.0, 127.5, 84.9, 72.3, 66.1, 65.1, 62.7, 61.1, 53.8, 35.9, 25.6, 22.6, 17.9, −4.3, −5.0;

HRMS calcd for $C_{22}H_{35}N_4NaSi$ $[M+Na]^+$ 428.2233, found 428.2234.

Methyl (2R,3S,5R,6S,1′R)-3-(benzoyloxy)-6-(1′-(*tert*-butyldimethylsilyloxyethyl)-7-oxo-1-azabicyclo[3.2.0]heptane-2-carboxylate (25)

Compound **5** (0.10 g, 0.25 mmol) was dissolved in acetone (2.5 ml) and cooled to 0 °C. Subsequently, an aqueous saturated sodium bicarbonate solution (0.75 ml) was added, followed by potassium bromide (0.1 eq. 3 mg, 0.025 mmol) and TEMPO (1.1 eq. 43 mg, 0.27 mmol). Under stirring, a 5% aqueous NaOCl solution (0.6 ml) was added dropwise. After 1 h, additional portion of NaOCl 5% solution in water (0.6 ml) was added, and stirring was continued at 0 °C while the progress of the reaction was monitored by TLC. The reaction was terminated by the addition of a 5% $NaHCO_3$ solution. Acetone was then removed on a rotary evaporator and the residue was suspended in dichloromethane (5 ml), treated with a saturated solution of NH_4Cl (5 ml) and the mixture was extracted with dichloromethane. The combined organic extracts were dried, concentrated, dissolved in Et_2O (5 ml), and treated with excess of diazomethane in ether, then evaporated. The residue was purified by column chromatography on silica gel, hexane/EtOAc (10/1 then 7/3) to give compound **25** as a colorless oil, 47 mg (84%). The spectral and analytical data were identical with those reported by us recently.[10]

Colorless syrup, $[\alpha]_D$ +80.6 (*c* 1.0, $CHCl_3$);

IR (film) $\nu = 1766\ cm^{-1}$;

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37–7.24 (m, 5H, Ar), 4.61 (d, *J* = 5.6 Hz, 1H, H-2), 4.59 (td, *J* = 5.6, 3.1 Hz, 1H, H-3), 4.55, 4.54 (2d, *J* = 12.1 Hz, 2H, Bn), 4.22 (quit., *J* = 6.3 Hz, 1H, H-1′), 4.06 (ddd, *J* = 7.8, 6.2, 2.1 Hz, 1H, H-5), 3.70 (s, 3H, OCH_3), 2.82 (dd, *J* = 6.3, 2.1 Hz, 1H, H-6), 2.35 (ddd, *J* = 13.4, 6.2, 3.1 Hz, 1H, H-4a), 1.66 (ddd, *J* = 13.4, 7.8, 5.6 Hz, 1H, H-4b), 1.24 (d, *J* = 6.3 Hz, 3H, $CHCH_3$), 0.89 (s, 9H, *t*-Bu), 0.08 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$);

^{13}C NMR (150 MHz, $CDCl_3$) δ 175.8, 168.5, 137.3, 128.4, 127.8, 127.5, 85.4, 72.5, 66.2, 65.3, 63.6, 55.2, 52.0, 36.0, 25.6, 22.6, 17.9, −4.3, −5.0.

HRMS calcd for $C_{23}H_{35}NO_5NaSi$ $[M+H]^+$ 456.2182, found 456.2184.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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