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Synthesis of a 1-Oxacephem Structurally Related to Clavulanic Acid from D-Glucuronolactone.

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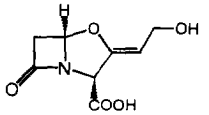
Abstract: [2+2]Cycloaddition of chlorosulfonyl isocyanate to 3-*O*-vinyl ethers derived from D-glucose and D-glucuronolactone proceeded with an excellent stereoselectivity to provide azetidin-2-ones with (R) configuration at C-4'. Intramolecular N-alkylation afforded 1-oxabicyclic-β-lactams having six- or seven-membered ring fused to the four-membered one. © 1997 Elsevier Science Ltd.

The [2+2]cycloaddition of chlorosulfonyl isocyanate (CSI) to vinyl esters or vinyl silyl ethers has become an attractive synthetic way for stereoselective construction of a variety of β-lactam compounds.[1] In contrast, there are only a few reports on similar application of cycloadditions between isocyanates and vinyl ethers, although successful examples such as syntheses of 1-β-methylcarbapenems [2], thienamycin [3,4], and the structural analog of clavulanic acid [5] have been noticed.

Recently, we have reported a simple and efficient synthesis of 1-oxacephams from readily available 1,2-*O*-isopropylidene-3-*O*-vinyl-α-D-xylofuranose. We have found that a large substituent at the C-4 carbon atom of the furanose ring blocks the isocyanate entry from the *re* side and affords the 4'-alkoxy-azetidin-2'-one ring having (R) configuration at the C-4' carbon atom with high stereoselectivity.[6]

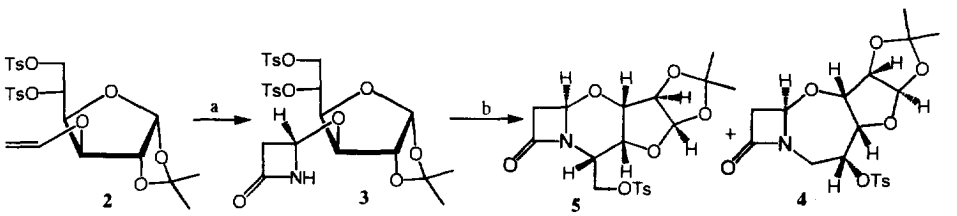
The present synthesis employs the above mentioned methodology for stereocontrolled formation of 1-oxacepham structurally related to clavulanic acid **1**. It should be noted that many of structural analogs of β-lactam antibiotics show interesting biological activity.[7,8]



1

We have noticed that the formation of the β-lactam *via* [2+2]cycloaddition of CSI to 1,2-*O*-isopropylidene-5,6-di-*O*-tosyl-3-*O*-vinyl-α-D-glucofuranose **2**[6] proceeded with an excellent stereoselectivity to afford 4'-alkoxy-azetidin-2'-one having (R) configuration at the C-4' carbon atom. Compound **3** has offered an entry to cephams having carboxyl group at the C-4 carbon atom by nucleophilic displacement at C-5 of the sugar chain. The presently performed intramolecular alkylation of the nitrogen atom in **3** using a two-phase system afforded compound **4** with seven-membered ring in a very good yield. Only a minute amount of **5** (<3 %) was found in the ^{1}H-NMR spectrum of **4** (Scheme 1).

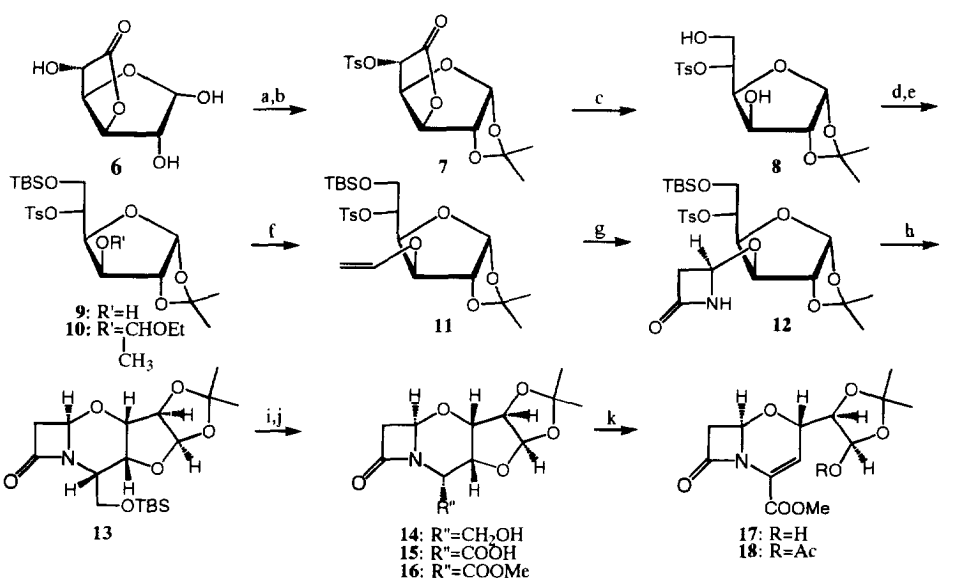
Scheme 1



Scheme 1. *Reagents and conditions*: a, CSI, Na_2CO_3, -70 °C, 2 h, then Red-Al; b, Bu_4NBr, Na_2CO_3, CH_3CN, Δ, 3 h.

The failure of the use of **2** in construction of the 1-oxacepham **5** prompted us to apply D-glucuronolactone for that purpose. The synthetic strategy employed is outlined in Scheme 2.

Scheme 2



Scheme 2. *Reagents and conditions*: a, ref.[9]; b, TsCl, C_5H_5N, CH_2Cl_2, rt, 12 h; c, $NaBH_4$, THF:H_2O (9:1), 0 °C; d, TBSCl, CH_3CN, imidazole; e, ethyl vinyl ether, CF_3COOH; f, TMSOTf, CH_2Cl_2, Et_3N, 5 °C, 2 h; g, CSI, Na_2CO_3, -78 °C, 3 h, then Red-Al; h, 2.2 equiv BuLi, 1.1 equiv Bu_4NHSO_4, THF, 0 °C to rt, 4 h; i, C_5H_5N·HF, C_5H_5N; j, $RuCl_3$, $NaIO_4$, CCl_4:CH_3CN:H_2O (2:2:3), then CH_2N_2; k, 2.0 equiv BuLi, THF, -70 °C to -40 °C, then AcOH and C_5H_5N, Ac_2O.

Tosylation of the readily available 1,2-*O*-isopropylidene-α-D-glucuronolactone (**6**), followed by the reduction of the tosylate **7** with sodium borohydride gave the diol **8** in 95 % yield, formation of the 4,5-epoxide was not observed. The primary hydroxy group in compound **8** was silylated and subsequently the secondary hydroxy group was reacted with ethyl vinyl ether in the presence of trifluoroacetic acid to afford a mixed acetal **10** in high yield. Elimination of ethanol by treatment of **10** with TMSOTf and Et_3N afforded vinyl ether **11** in 87 % yield. [2+2]Cycloaddition of acid-free CSI [10] to vinyl ether **11** in the presence of anhydrous sodium carbonate, followed by reduction of chlorosulfonyl group with Red-Al [4] gave the β-lactam **12** as a single diastereomer in 57 % yield. In the next step we found some unexpected difficulties. The method previously applied for intramolecular alkylation of the nitrogen atom consisting in a two-phase system (Bu_4NBr, Na_2CO_3, CH_3CN) gave **13** in 8 % yield only. The search for a more efficient method of cyclization led us to the use of a mixture of 1.1 equiv of Bu_4NHSO_4 and 2.2 equiv of BuLi in tetrahydrofuran solution. Intramolecular alkylation in the presence of this reagent gave 1-oxacepham **13** in 75 % yield. Deprotection of the silyl ether by hydrogen fluoride in pyridine gave alcohol **14** in quantitative yield. Subsequent oxidation of the hydroxymethyl group gave acid **15** which was used for the next step without purification. Treatment of the acid **15** with diazomethane in ethyl acetate yielded methyl ester of 1-oxacepham **16**. The 1-oxacepham **16** had two fused five-membered rings which contained two carbon atoms derived from C-1 and C-2 of the furanose ring. These two carbon atoms could play the role of the side chain clavulanic acid **1** or they could eventually be transformed into such a fragment. The possible way of doing that was demonstrated by the opening of the furanoid fragment in **16**. β-Elimination in the presence of butyllithium at -40 °C opened the furanoid ring and introduced a double bond to the six-membered ring affording unstable 1-oxacephem **17** which was characterized as its acetate **18**. Structures of all new compounds were assigned on the basis of analytical and spectroscopic data. The absolute configuration of the newly formed stereogenic center (C-6 of the cepham skeleton) in **15** was unequivocally determined by NOE experiments. It has been shown that H-2 and H-6 protons in cis arrangement display NOE absorption enhacement whereas those in trans arrangement do not.[6,11]

Cepham **16** displays low antibacterial activity against *E. coli* (MIC 800 μg/ml) and does not show any anti-penicillinase activity (contrary to clavulanic acid **1** and configurationally related clavams)[12], whereas it shows anti-cephalosporinase activity. In composition with cephotaxime: concentration of 1.2 mg/ml of **16** decreases MIC of the antibiotic against *E. coli* from 0.032 μg/ml to 0.024 μg/ml; concentration of 3.2 mg/ml of **16** decreases MIC of the antibiotic against *Klebsiella pneumonia* from 0.256 μg/ml to 0.064 μg/ml. These biological data create the possibility of finding interesting activity in the group of β-lactams derived from sugars.

In conclusion, the presented results show the usefulness of D-glucuronolactone as a chiral template in the synthesis of the 1-oxacepham system. High stereoselectivity of the [2+2]cycloaddition step, and good yield of other steps should be emphasized.

EXPERIMENTAL

Optical rotations were measured with a JASCO Dip-360 digital polarimeter. IR spectra were obtained with a FT-IR-1600 Perkin-Elmer spectrophotometer. ^{1}H-NMR spectra were recorded with Bruker AM 500 and Varian Gemini 200 spectrometers. Mass spectra were recorded with a AMD 604 mass spectrometer. Column chromatography was performed on Merck Kiesel gel (230-400 mesh).

(4'R) 6-Deoxy-6-*C*:3-*O*-(azetidin-2'-on-1',4'-diyl)-1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-glucofuranose (4) To a solution of **3** [6] (0.06 g, 0.10 mmol) in acetonitrile (5 mL) tetrabutylammonium bromide (0.04 g, 0.11 mmol) and potassium carbonate (0.17 g, 1.3 mmol) were added. The mixture was heated under reflux for 5 h, cooled, diluted with toluene (5 mL) and filtered. The colourless solution was washed with water (5 mL), dried over magnesium sulfate, filtered and concentrated to dryness. The residue was purified by column chromatography on silica gel using hexane-ethyl acetate 1:1 $^v/_v$ as eluent, to give **4** (0.034 g, 80 %) as a colourless oil. $[\alpha]_D$ +58.3° (*c* 0.3, CH_2Cl_2); IR (CH_2Cl_2) 1760 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.31, 1.45 (2s, 6H, isopr.), 2.46 (s, 3H, Ts), 2.76 (d, 1H, *J* 15.0Hz, H-3'a), 3.11 (ddd, 1H, *J* 1.9, 3.8 and 15.0Hz, H-3'b), 3.40 (bt, 1H, *J* 12.9Hz, H-6a), 3.79 (dd, 1H, *J* 4.7 and 12.9Hz, H-6b), 4.30 (d, 1H, *J* 4.1Hz, H-3), 4.58 (dd, 1H, *J* 4.1 and 9.8Hz, H-4), 4.60 (d, 1H, *J* 4.0Hz, H-2), 4.81 (d, 1H, *J* 3.8Hz, H-4'), 4.88 (dd, 1H, *J* 4.7 and 9.8Hz, H-5), 5.91 (d, 1H, *J* 4.0Hz, H-1); *Anal.* Calcd for $C_{19}H_{23}O_8NS$: C, 53.65; H, 5.41; N, 3.29; S, 7.53. Found: C, 53.62; H, 5.30; N, 3.08; S, 7.61.

1,2-*O*-Isopropylidene-α-D-glucuronolactone (6) was prepared by the method of Fleet at al.[9]

1,2-*O*-Isopropylidene-5-*O*-tosyl-α-D-glucuronolactone (7) Known compound 7 was obtained according to the general procedure described earlier (89 %).[13] $[\alpha]_D$ +49.3° (*c* 0.9, CH_2Cl_2); IR ($CHCl_3$): 1817cm^{-1}; ^{1}H-NMR($CDCl_3$): 1.33, 1.48 (2s, 6H, isopr.), 2.45 (s, 3H, Ts), 4.78 (d, 1H, *J* 3.6Hz, H-2), 4.83 (d, 1H, *J* 2.8Hz, H-5), 4.96 (dd, 1H, *J* 2.8 and 4.2Hz, H-4), 5.22 (d, 1H, *J* 4.2Hz, H-3), 5.97 (d, 1H, *J* 3.6Hz, H-1); *Anal.* Calcd for $C_{16}H_{18}O_8S$: C, 51.89; H, 4.86; S, 8.65. Found: C, 51.80; H, 5.08; S, 8.58.

1,2-*O*-Isopropylidene-5-*O*-tosyl-α-D-glucofuranose (8) To a well stirred solution of **7** (11.10 g, 30 mmol) in THF:H_2O (9:1, 450 mL), cooled to 0 °C, $NaBH_4$ (11.40 g, 300 mmol) was added in one portion. After 1h at 0 °C the reaction was completed. The solution was diluted with ethyl acetate (700 mL) and washed with 10 % AcOH (200 mL) and brine. The organic layers were dried over sodium sulfate, filtered and concetrated to dryness. Compound **8** (10.90 g, 97 %) was obtained as colourless crystals: m.p. 122-123 °C, $[\alpha]_D$ +11.7° (*c* 1.4, CH_2Cl_2); IR ($CHCl_3$): 3528 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.31, 1.47 (2s, 6H, isopr.), 2.27 (s, 3H, Ts), 3.75 (dd, 1H, *J* 5.7 and 12.9Hz, H-6a), 3.76 (dd, 1H, *J* 1.8 and 12.9Hz, H-6b), 4.27 (dd, 1H, *J* 2.3 and 9.4Hz, H-4), 4.35 (d, 1H, *J* 2.3Hz, H-3), 4.57 (d, 1H, *J* 3.6Hz, H-2), 4.83 (ddd, 1H, *J* 1.8, 5.7 and 9.4Hz, H-5), 5.90 (d, 1H, *J* 3.6Hz, H-1); *Anal.* Calcd for $C_{16}H_{22}O_8S$: C, 51.34; H, 5.88; S, 8.56. Found: C, 51.32; H, 5.79; S, 8.60.

6-*O*-*t*-Butyldimethylsilyl-1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-glucofuranose (9) A solution of compound **8**

(6.57 g, 17.6 mmol) in dry acetonitrile (70 mL) was cooled to 0 °C and treated with imidazole (1.29 g, 19.0 mmol) and t-butyldimethylsilyl chloride (2.85 g, 19.0 mmol). The temperature of reaction was allowed to rise to room temperature and the mixture was left for 3 h until of the substrate disappeared (TLC). Subsequently, the solution was diluted with t-butyl methyl ether (300 mL) and washed three times with water. Organic solution was dried and evaporated. The residual solid was recrystallized from ethyl ether-hexane (1:20 $^{v}/_{v}$) to give 7.65 g, of **9** (89 %) as colourless crystals: m.p. 143-144 °C, $[\alpha]_D$ -6.4° (*c* 0.4, CH_2Cl_2); IR ($CHCl_3$):1174,3524 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 0.83 (s, 9H, t-Bu), 1.31, 1.46 (2s, 6H, isopr.), 2.46 (s, 2H, Ts), 3.78 (m, 2H, H-6a,6b), 4.27 (dd, 1H, *J* 2.3 and 9.4Hz, H-4), 4.28 (d, 1H, *J* 2.3Hz, H-3), 4.52 (d, 1H, *J* 3.6Hz, H-2), 4.78 (ddd, 1H, *J* 2.0, 3.3 and 9.4Hz, H-5), 5.87 (d, 1H, *J* 3.6Hz, H-1). MS (LSIMS, HR) m/z, ($M-CH_3$) calcd for $C_{21}H_{33}O_8SSi$: 473.165845. Found: 473.16654. *Anal.* Calcd for $C_{22}H_{36}O_8SSi$: C, 54.09; H, 7.38. Found: C, 53.87; H, 7.47.

6-*O*-*t*-Butyldimethylsilyl-3-*O*-(1'-ethoxyethyl)-1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-glucofuranose (10) A solution of compound **9** (3.30 g, 6.75 mmol) in ethyl vinyl ether (40 mL) was cooled to 0 °C and treated with trifluoroacetic acid (10 μl). The mixture was left at room temperature till disappearance of the substrate (5 days). Subsequently, upon stirring, pulverized sodium carbonate (1 g) was added. After 1 h the mixture was filtered and the ether was evaporated. The crude product was purified on silica gel column using hexane-t-butyl methyl ether 9:1 $^{v}/_{v}$ as eluent to afford **10** as a 1:1 diastereomeric mixture (3.678 g, 97 %). ^{1}H-NMR ($CDCl_3$) selected signals of protons due to two diastereomers: 1.22, 1.24 (2t, 3H, CH_2CH_3), 1.37, 1.41 (2d, 3H, $CHCH_3$), 3.63, 3.72 (2q, 2H, CH_2CH_3), 4.84, 4.87 (2q, 1H, O-$CH(CH_3)$-O). MS (LSIMS, HR) m/z, $(M+Na)^+$ calcd for $C_{26}H_{44}O_9SSiNa$: 583.236937. Found: 583.237303. *Anal.* Calcd for $C_{26}H_{44}O_9SSi$: C, 55.71; H, 7.86. Found: C, 55.65; H, 8.07.

6-*O*-*t*-Butyldimethylsilyl-1,2-*O*-isopropylidene-5-*O*-tosyl-3-*O*-vinyl-α-D-glucofuranose (11) To a solution of the acetal **10** (3.92 g, 7.0 mmol) in CH_2Cl_2 (7 mL), triethylamine (1.46 mL, 10.5 mmol) was added at room temperature under argon. The mixture was then cooled to 0 °C and TMSOTf (1.76 mL, 9.1 mmol) was added dropwise, followed by further stirring for 2 h at 0 °C. The mixture was treated with 10 % NaOH (10 mL) and diluted with hexane (100 mL). After evaporation of the solvent, column chromatography of the residue afforded the enol ether **11** (3.13 g, 87 %). $[\alpha]_D$ -17.0° (*c* 0.5, CH_2Cl_2); IR (film): 1621 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 0.84 (s, 9H, t-Bu), 1.29, 1.46 (2s, 6H, isopr.), 2.42 (s, 3H, Ts), 3.81 (dd, 1H, *J* 3.2 and 12.0Hz, H-6b), 3.98 (dd, 1H, *J* 2.0 and 12.0Hz, H-6a), 4.12 (dd, 1H, *J* 2.4 and 6.8Hz, H-2'a), 4.28 (d, 1H, *J* 3.0Hz, H-3), 4.32 (dd, 1H, *J* 2.4 and 14.3Hz, H-2'b), 4.50 (dd, 1H, *J* 3.0 and 8.7Hz, H-4), 4.56 (d, 1H, *J* 3.8Hz, H-2), 4.88 (ddd, 1H, *J* 2.0, 3.2 and 8.7Hz, H-5), 5.83 (d, 1H, *J* 3.8Hz, H-1), 6.21 (dd, 1H, *J* 6.8 and 14.3Hz, H-1'); MS (LSIMS, HR) m/z, $(M+H)^+$ calcd for $C_{24}H_{39}O_8SSi$: 515.21349. Found: 515.212974. *Anal.* Calcd for $C_{24}H_{38}O_8SSi$: C, 56.03; H, 7.39. Found: C, 56.35; H, 7.32.

(4'R) 3-*O*-(Azetidin-2'-on-4'-yl)-6-*O*-*t*-butyldimethylsilyl-1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-glucofuranose (12) To a well stirred solution of sodium carbonate (0.83 g, 7.8 mmol) and chlorosulfonyl isocyanate

(1.03 g, 7.28 mmol) in dry toluene (5 mL) a solution of **11** (2.69 g, 5.2 mmol) in dry toluene (5 mL) was added under argon atmosphere at -70 °C within 5 min. The mixture was stirred at the same temperature for another 3h and then it was diluted with toluene (50 mL). Red-Al (10.4 mL of 1 M solution in toluene) was added slowly and the reaction mixture was stirred for 30 min. The cooling bath was removed and water (6 mL) was added at 0 °C. After additional 15 min of intensive stirring the suspension was filtered and washed with toluene. Organic solutions were combined and evaporated. The residue was purified by column chromatography on silica gel using hexane-ethyl acetate 3:2 $^{v}/_{v}$ as eluent, to give **12** (1.67 g, 57 %) as a colourless oil. $[\alpha]_D$ -32.5° (*c* 0.2, CH_2Cl_2); IR (film): 1776 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 0.78 (s, 9H, t-Bu), 1.31, 1.45 (2s, 6H, isopr.), 3.07 (dd, 1H, *J* 1.8 and 15.5Hz, H-3'a), 3.22 (ddd, 1H, *J* 3.3, 4.0 and 15.5Hz, H-3'b), 3.72 (m, 2H, H-6a, 6b), 4.25 (d, 1H, *J* 3.2Hz, H-3), 4.48 (dd, 1H, *J* 3.2 and 9.4Hz, H-4), 4.56 (d, 1H, *J* 3.6Hz, H-2), 4.93 (ddd, 1H, *J* 2.2, 2.3 and 9.4Hz, H-5), 5.40 (dd, 1H, *J* 1.8 and 4.0Hz, H-4'), 5.90 (d, 1H, *J* 3.6Hz, H-1); MS (LSIMS, HR) m/z, (M+H) calcd for $C_{25}H_{40}O_9NSSi$: 558.2193. Found: 558.218875. *Anal.* Calcd for $C_{25}H_{39}O_9NSSi$: C, 53.86; H, 7.00; N, 2.51. Found: C, 53.75; H, 7.21; N, 2.38.

(4'R) 6-*O*-*t*-Butyldimethylsilyl-5-deoxy-5-*C*:3-*O*-(azetidin-2'-on-1',4'-diyl)-1,2-*O*-isopropylidene-β-L-idofuranose (13) To a cold (-78 °C) stirred solution of **12** (0.57 g, 1.02 mmol) and Bu_4NHSO_4 (0.38 g, 1.12 mmol) in THF (20 mL) under argon atmosphere BuLi (2.5 M solution in hexane, 1.10 mL, 2.7 mmol) was added dropwise. The mixture was stirred at -78 °C for 30 min, then at room temperature for 4 h. Subsequently water (100 mL) was added. The mixture was extracted with t-butyl methyl ether (30 mL×2). The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography on silica gel (hexane-t-butyl methyl ether 1:1 $^{v}/_{v}$) to give (0.28 g, 75 %) of **13** as a colourless oil. $[\alpha]_D$ +124.3° (*c* 0.9, CH_2Cl_2); IR ($CHCl_3$): 1764 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 0.89 (s, 9H, t-Bu), 1.32, 1.47 (2s, 6H, isopr.), 2.70 (d, 1H, *J* 15.2Hz, H-3'a), 3.13 (ddd, 1H, *J* 0.7, 3.2 and 15.2Hz, H-3'b), 3.76-3.86 (m, 3H, H-5, 6a, 6b), 4.36 (d, 1H, *J* 3.4Hz, H-3), 4.53 (dd, 1H, *J* 2.6 and 3.4Hz, H-4), 4.61 (d, 1H, *J* 3.8Hz, H-2), 4.86 (dd, 1H, *J* 0.7 and 3.2Hz, H-4'), 5.92 (d, 1H, *J* 3.8Hz, H-1). MS (LSIMS, HR) m/z, ($M-CH_3$) calcd for $C_{17}H_{28}O_6NSi$: 370.169757. Found: 370.16977. *Anal.* Calcd for $C_{18}H_{31}O_6NSi$: C, 56.10; H, 8.05; N, 3.64. Found: C, 56.12; H, 8.30; N, 3.57.

(4'R) 5-Deoxy-5-*C*:3-*O*-(azetidin-2'-on-1',4'-diyl)-1,2-*O*-isopropylidene-β-L-idofuranose (14) Compound **13** (0.17 g, 0.45 mmol) was dissolved in dry pyridine (2 mL) to which was added hydrogen fluoride-pyridine complex (~ 70 % hydrogen fluoride, ~ 30 % pyridine 0.2 mL). The reaction mixture was stirred at room temperature until TLC indicated complete removal of the silyl protection. Evaporation of the solvent and column chromatography of the resulting residue afforded compound **14** (0.12 g, 98 %) as a syrup. $[\alpha]_D$ +107.2° (*c* 1.0, CH_2Cl_2); IR (film) 1766, 3455 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.33, 1.50 (2s, 6H, isopr.), 2.79 (d,1H, *J* 15.2Hz, H-3'a), 3.20 (ddd, 1H, *J* 0.7, 3.2 and 15.2Hz, H-3'b), 3.78-3.90 (m, 3H, H-5, 6a, 6b), 4.39 (d, 1H, *J* 3.4Hz, H-3), 4.50 (dd, 1H, *J* 3.4 and 3.2Hz, H-4), 4.63 (d, 1H, *J* 3.8Hz, H-2), 4.95 (dd, 1H, *J* 0.7 and 3.2Hz,

H-4'), 5.95 (d, 1H, *J* 3.8Hz, H-1); MS (LSIMS, HR) m/z, $(M+H)^+$ calcd for $C_{12}H_{18}O_6N$: 272.11341. Found: 272.11424. *Anal.* Calcd for $C_{12}H_{17}O_6N$: C, 53.14; H, 6.27; N, 5.17. Found: C, 53.04; H, 6.50; N, 4.90.

(4'R) Methyl 5-*C*:3-*O*-(azetidin-2'-on-1',4'-diyl)-1,2-*O*-isopropylidene-β-L-idofuranouronate (16) To a stirred solution of **14** (0.068 g, 0.25 mmol) in CH_3CN:CCl_4:H_2O (2:2:3) 10 mL, sodium periodate (0.214 g, 1.0 mmol) and catalytic amount of ruthenium(III) chloride hydrate (0.001 g, 0.005 mmol) were added. The two-phase reaction mixture was stirred at room temperature and the progress of the reaction was monitored by TLC. The reaction was completed within 20 h. Subsequently ethyl acetate (20 mL) was added and the organic phase was dried and filtered. The colorless solution was then cooled to 0 °C and treated with diazomethane in ether. After 0.5 h reaction was completed, and the crude product was purified by chromatography using hexane-t-butyl methyl ether 1:4 $^v/_v$ to afford 0.07 g of **16** (93 %) as colourless oil. $[\alpha]_D$ +147.7° (*c* 0.8, CH_2Cl_2); IR ($CHCl_3$): 1775cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.31, 1.51 (2s, 6H, isopr.), 2.78 (d, 1H, *J* 15.2Hz, H-3'a), 3.28 (ddd, 1H, *J* 0.7, 3.3 and 15.2Hz, H-3'b), 3.83 (s, 3H, CH_3), 4.41 (d, 1H, *J* 3.7Hz, H-5), 4.44 (d, 1H, *J* 3.4Hz, H-3), 4.63 (d, 1H, *J* 3.8Hz, H-2), 4.72 (dd, 1H, *J* 3.4 and 3.7Hz, H-4), 5.02 (dd, 1H, *J* 0.7 and 3.3Hz, H-4'), 5.94 (d, 1H, *J* 3.8Hz, H-1). MS (LSIMS, HR) m/z, (M+Na) calcd for $C_{13}H_{17}O_7NNa$: 322.090272. Found: 322.089291. *Anal.* Calcd for $C_{13}H_{17}O_7N$: C, 52.17; H, 5.68; N, 4.68. Found: C, 52.30; H, 5.96; N, 4.45.

(6R, 2S, 4'R, 5'S) Methyl 2-(5'-acetoxy-2',2'-dimethyl-1',3'-dioxolanyl-4')-7-deamino-1-dethia-1-oxa-ceph-3-em-4-carboxylate (18) To a cold (-78 °C) stirred solution of **16** (0.039 g, 0.125 mmol) in THF (2 mL) under argon atmosphere BuLi (2.5 M solution in hexan, 0.100 mL, 0.25 mmol) was added dropwise. The mixture was stirred at -78 °C for 10 min, then at -40 °C for 10 min. Subsequently, AcOH (0.3 mL) was added. The mixture was concentrated *in vacuo*. Crude product was dissolved in dry pyridine (3 mL) and $(CH_3CO)_2O$ (0.050 g, 0.50 mmol) was added slowly and the reaction mixture was stirred for 1 h. After evaporation of the solvent the residue was purified by column chromatography on silica gel (hexane-ethyl acetate 3:2 $^v/_v$) to give (0.031 g, 70 %). $[\alpha]_D$ +75.3° (*c* 0.5, CH_2Cl_2); IR (film): 1749, 1788 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 1.51 (s, 6H, isopr.), 2.11 (s, 3H, $COCH_3$), 2.99 (bd, 1H, *J* 15.2Hz, H-7a), 3.40 (dd, 1H, *J* 3.2 and 15.2Hz, H-7b), 3.77 (s, 3H, CH_3), 4.53 (m, 1H, H-4'), 4.76 (dd, 1H, *J* 1.4 and 3.7Hz, H-2), 5.28 (dd, 1H, *J* 0.8 and 3.7Hz, H-3), 5.29 (d, 1H, *J* 3.2Hz, H-6), 6.22 (d, 1H, *J* 2.3Hz, H-1). MS (LSIMS, HR) m/z: $(M-CH_3)$ calcd for $C_{14}H_{16}O_8N$: 326.087592. Found: 326.087372.

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