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Synthesis of 1-oxacephems from D-arabinal and L-rhamnal

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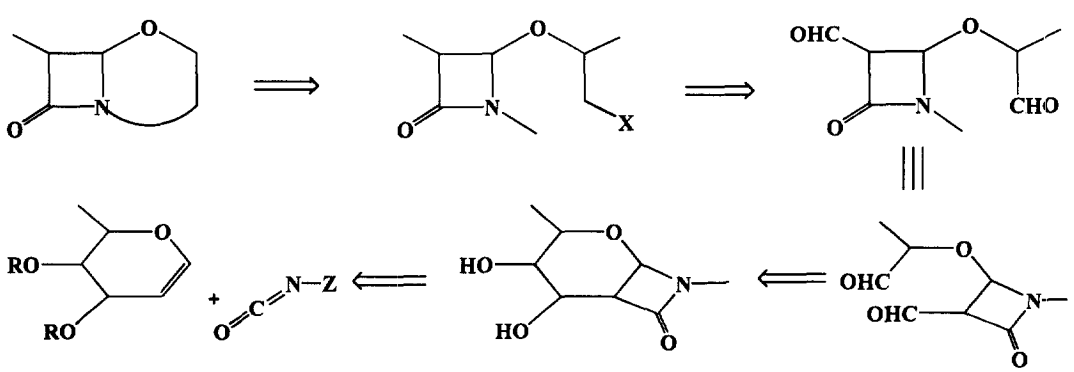
Abstract: Readily available from D-arabinal and L-rhamnal 2-C:1-N-carbonyl-2-deoxy-β-D-arabino- and -α-L-gluco-pyranosylamines **5**, **25** and **26** were transformed into cephems **45** and **49** via a sequence of reactions consisting of alkylation of the β-lactam nitrogen atom, deprotection of pyranoid hydroxy groups, glycolic cleavage of the *vic* diol grouping, discrimination of carbon atoms which were separated by periodate oxidation, and formation of the 1,3-oxazine six-membered ring fused to the β-lactam fragment. Discrimination of two aldehyde groups obtained during the glycolic cleavage step was achieved after their reduction and protection of one of the hydroxymethyl group by a bulky silyl substituent or by lactonization. © 1997 Elsevier Science Ltd.

INTRODUCTION

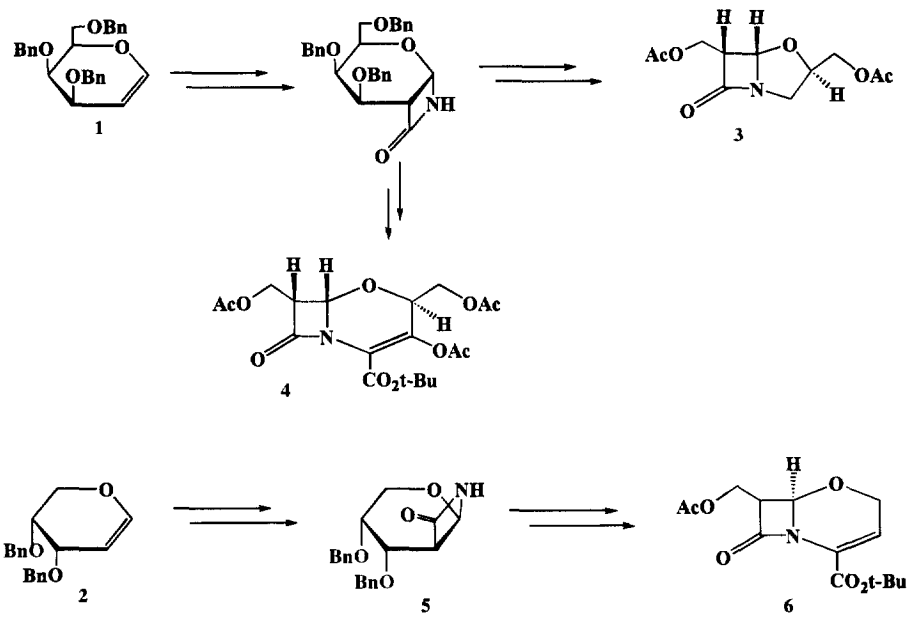
Several years ago, we have initiated a synthetic project leading from glycals and isocyanates to 1-oxabicyclic β-lactams (**Scheme 1**)[1]. We have exemplified the general idea of the project showing an entry to clavams[2] and 1-oxacephems[3,4].

Scheme 1

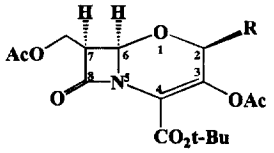


The stereochemical control of the synthetic strategy depicted in **Scheme 1** is a consequence of the high stereoselectivity of the [2+2]cycloaddiction step which proceeds exclusively *anti* to the substituent at the C-3 carbon atom of the sugar ring. The first two syntheses[2,3], which started from tri-*O*-benzyl-D-galactal **1** have not discriminated carbon atoms which were split during the glycolic cleavage step. The suitable protection of the terminal hydroxymethyl group allowed for retention of chirality at the carbon atom stemming from C-5 of the glycol molecule. The third synthesis[4], which used di-*O*-benzyl-D-arabinal **2** as a substrate, has employed an intramolecular Wittig reaction to trap one of the aldehyde groups formed during the glycolic cleavage step. Owing to the stereochemical pathway of the [2+2]cycloaddition, syntheses beginning from D-galactal **1** produced 1-oxabicyclic β-lactams **3** and **4** having (S) configuration, whereas that beginning from D-arabinal **2** afforded β-lactam **6** having (R) configuration at the bridge - head carbon atom, C-5 of the clavam skeleton or C-6 of the 1-oxacepham skeleton (**Scheme 2**).

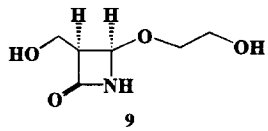
Scheme 2



In this paper we present the synthesis of cephems **7** and **8** from D-arabinal and L-rhamnal, respectively. Both products have the (6R, 7R) configuration of the 1-oxacephem skeleton.



7: R = H
8: R = Me



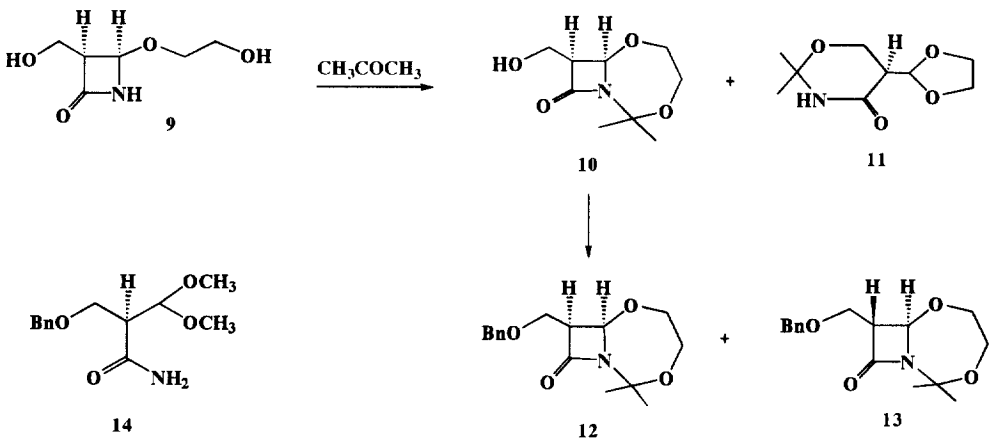
9

RESULTS AND DISCUSSION

Synthesis of compounds **7** and **8** employed a glycolic cleavage for opening of the sugar ring. This required discrimination between carbon atoms which were split during the glycolic cleavage step.

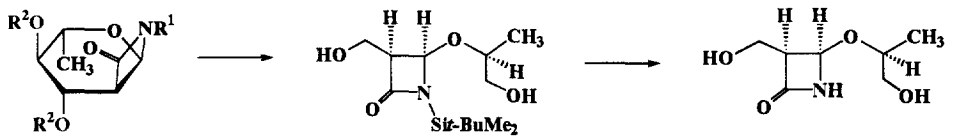
For the first attempt we selected 3,4-disubstituted azetidin-2-one **9** readily available from D-arabinal[5]. We expected that the condensation of **9** with acetone should provide the *N,O*-acetal which after protection of the hydroxymethyl group at C-3 followed by hydrolysis of the isopropylidene group should provide monosubstituted **9**, suitable for 1-oxacephem formation. An analogous strategy has been employed in the past for the syntheses of a variety of β-lactams[6]. Reaction of **9** with acetone provided a mixture of two isopropylidene derivatives **10** and **11** in a ratio about 7:1, respectively (**Scheme 3**). The structures of **10** and **11** were easily proved by the IR - carbonyl absorption and ^{1}H NMR spectroscopy. The hydroxyl group in **10** was benzylated using a standard *PTC* procedure to afford a mixture of ethers **12** and **13**; during benzylation a partial epimerization at C-3 carbon atom of the azetidinone ring occurred (**Scheme 3**). Numerous experiments of hydrolysis of the *N,O*-acetal in **12** and **13** failed. Trifluoroacetic acid gave debenzylation, whereas mineral acids yielded either decomposition of the substrate or, in methanol solution, opening of the β-lactam ring and formation of the acetal **14**.

Scheme 3



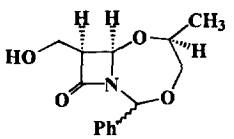
Compound **19**, prepared *via* standard transformations from 3,4-di-*O*-benzyl-L-rhamnal **15**[7] (**Scheme 4**), was employed for benzylidenation which offered an alternative, to the acetonide formation, strategy for discrimination between the carbon atoms separated during the glycolic cleavage step.

Scheme 4



15: R^1 = H, R^2 = Bn
16: R = $SiMe_2t$-Bu, R^2 = Bn
17: R^1 = Si*t*-$BuMe_2$, R^2 = H

18 **19**



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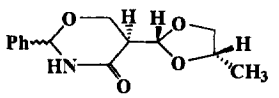


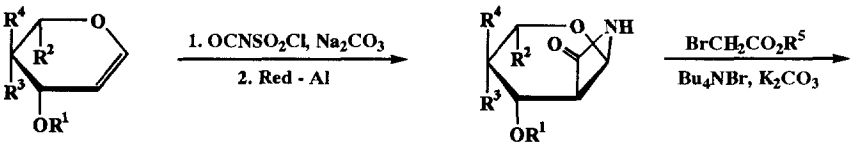
21

Compound **19** was treated with benzaldehyde in the presence of p-TsOH to give mixtures of diastereomers **20** and **21** in a ratio of about 1:3, respectively. The structure **21** was assumed by analogy to compound **11**.

Signals due to desired compound **20** were found in the ^{1}H NMR spectrum of the post-reaction mixture. Formation of **21** precluded the use of the benzylidene acetal formation as a tool for discrimination of hydroxymethyl groups present in **9** or **19**.

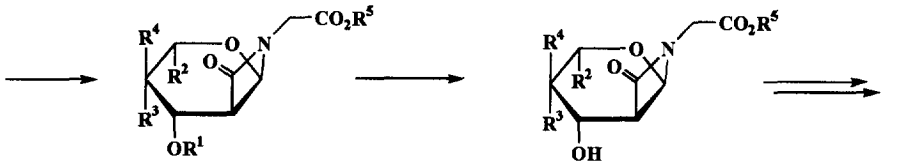
Other attempts at discrimination of hydroxymethyl groups in question were performed after preparation of *N*-alkylated azetidinones **33-35**. Compounds **33-35** were obtained from **5** and **15** respectively, using standard transformations shown in **Scheme 5**.

Scheme 5



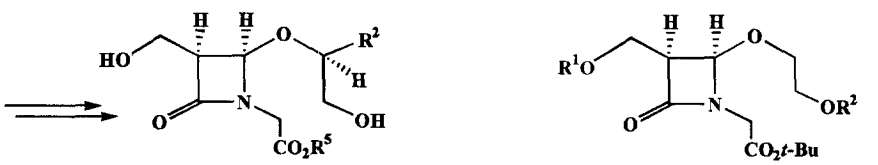
22: R^1 = Bn, R^2 = R^4 = H, R^3 = OBn
23: R^1 = TMS, R^2 = CH_3, R^3 = H, R^4 =OTMS
24: R^1 = TMS, R^2 = R^4 = H, R^3 = OTMS

5: R^1 = Bn, R^2 = R^4 = H, R^3 = OBn
25: R^1 = TMS, R^2 = CH_3, R^3 = H, R^4 = OTMS
26: R^1 = TMS, R^2 = R^4 = H, R^3 = OTMs



27: R^1 = Bn, R^2 = R^4 = H, R^3 = OBn, R^5 = *t*-Bu
28: R^1 = TMS, R^2 = CH_3, R^3 = H, R^4 = OTMS, R^5= Bn
29: R^1 = TMS, R^2 = R^4 = H, R^3 = OTMS, R^5 = Bn

30: R^2 = R^4 = H, R^3 = OH, R^5 = *t*-Bu
31: R^2 = CH_3, R^3 = H, R^4 = OH, R^5 = Bn
32: R^2 = R^4 = H, R^3 = OH, R^5 = Bn



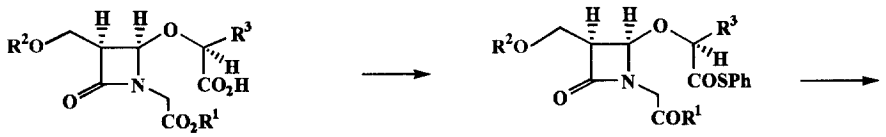
33: R^2 = H, R^5 = *t*-Bu
34: R^2 = CH_3, R^5 = Bn
35: R^2 = H, R^5 = Bn
40: R^2 = CH_3, R^5 = H
41: R^2 = R^5= H

36: R^1 = H, R^2 = Si*t*-$BuPh_2$
37: R^1 = Ac, R^2 = Si*t*-$BuPh_2$
38: R^1 = R^2 = Si*t*-$BuPh_2$
39: R^1 = Ac, R^2 = H

Due to the steric hindrance at the C-3 carbon atom of the azetidin-2-one ring, silylation of compound **33** with *t*-butyldiphenylsilyl chloride led to protection of the OH group located at C-2' carbon atom of the hydroxyethyl side chain. Compound **36** thus obtained was accompanied by trace of disilyl derivative **38** which was separated by chromatography. Hydroxyl group in **36** was in turn acetylated and the silyl protection was removed with hydrogen fluoride in pyridine to afford **39**. The hydroxymethyl group in **39** was oxidized to the

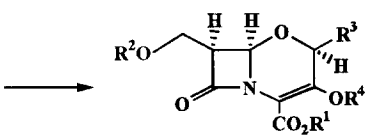
carboxyl function using a mixture of ruthenium trichloride and sodium metaperiodate[8]. The carboxylic acid **42** was treated with thiophenol in the presence of DCC and DMAP yielding thioester **43** which was subsequently subjected to cyclization in the presence of lithium di-TMS-amide to afford cephem **44**[9]. Acetylation of the enol hydroxy group provided the more stable diacetate **45** (**Scheme 6**).

Scheme 6



42: R^1 = *t*-Bu, R^2 = Ac, R^3 = H
46: $R^1 = R^3 = CH_3$, R^2 = Si*t*-BuPh$_2$

43: R^1 = *t*-Bu, R^2 = Ac, R^3 = H
47: $R^1 = R^3 = CH_3$, R^2 = Si*t*-BuPh$_2$



44: R^1 = *t*-Bu, R^2 = Ac, $R^3 = R^4$ = H
45: R^1 = *t*-Bu, $R^2 = R^4$ = Ac, R^3 = H
48: $R^1 = R^3 = CH_3$, R^2 = Si*t*-BuPh$_2$, R^4 = H
49: $R^1 = R^3 = CH_3$, R^2 = Si*t*-BuPh$_2$, R^4 = Ac

In the case of azetidinones **34** and **35**, primary hydroxymethyl groups could be discriminated by formation of eight-membered ring lactones **50** and **51**, respectively. This required hydrogenolysis of benzyl esters **34** and **35** to free acids **40** and **41**, respectively, which were subsequently treated with DCC and a catalytic amount of DMAP in acetonitrile[10] to afford respective lactones **50** and **51** in a good yield. It is worth noting that eight-membered ring lactones are particularly difficult to obtain[11]. In our case the β-lactam fragment introduces preorganization which helps to form the ring. The structure of crystalline lactone **50** was proved by X-ray (see Experimental, **Fig. 1**., **Tables 1**, **2**, **3**). Selected geometrical parameters presented in **Table 3** show that the molecule is characterized by long N-1 - C-10 and short C-10 - O-13 bond lengths. Such geometry is characteristic for β-lactam ring in the biologically active oxacepham and penicillin molecules. However, contrary to the latter, the β-lactam nitrogen atom is planar, as evidenced by the sum of its three valence angles - 359.9(2)°. As can be seen in **Fig. 1**, hydrogen atoms on the C-8 - C-9 bond are both located on the α-side of the β-lactam ring. The hydroxymethyl group located at the C-9 atom is wrapped around the β-lactam ring due to its engagement in intramolecular hydrogen bond with atom O-7 [O-15 ... O-7 = 2.960(2) Å, H-15 ... O-7 =

2.44(2) Å, O-15 - H-15 ... O-7 angle = 114.2(2)°]. Crystal lattice is constructed due to Van der Waals contacts and intermolecular hydrogen bond between the above hydroxyl and the β-lactam carbonyl oxygen atom O-13 transformed by symmetry 1-x ,y-1/2, 3/2-z: O-15 ... O-13 = 2.820 Å, H-15 ... O-13 = 1.97(2) Å, O-15 - H-15 ... O-13 = 147.8(2)°.

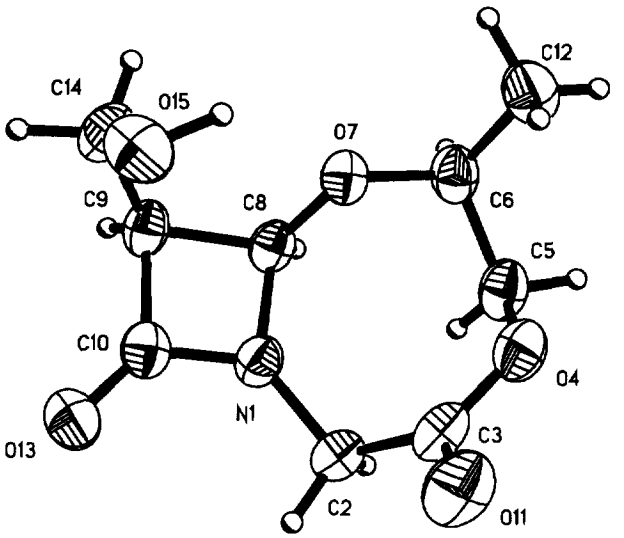
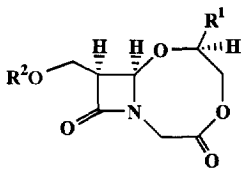
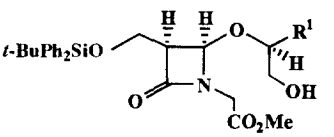


Fig.1. ORTEP diagram of compound **50**

The hydroxyl groups in **50** and **51** were silylated with *t*-butyldiphenylsilyl chloride and the lactone rings were subsequently opened with methanol in the presence of triethylamine[12] to furnish methyl esters **54** and **55**, respectively.



50: $R^1 = CH_3$, $R^2 = H$
51: $R^1 = R^2 = H$
52: $R^1 = CH_3$, $R^2 = Si$*t*-$BuPh_2$
53: $R^1 = H$, $R^2 = Si$*t*-$BuPh_2$



54: $R^1 = CH_3$
55: $R^1 = H$

Methyl ester **54** was transformed into cephem **49** *via* the sequence of reactions described for **45**.

We presented the stereocontrolled construction of cephems **45** and **49** having (R) configuration at the bridge-head carbon atom (C-6) and *cis* protons at C-6 and C-7 carbon atoms. The configuration of all stereogenic centers present in compounds **45** and **49** is a consequence of the stereochemical course of [2+2]cycloaddition to D-arabinal and L-rhamnal, respectively. The selection of L-rhamnal as the sugar substrate allowed the introduction of a methyl substituent to the C-2 carbon atom of the cephem skeleton. Methyl group in this position was found by Merck to be essential for pronounced biological activity[13].

EXPERIMENTAL

Optical rotations were measured with a JASCO DIP-360 digital polarimeter. ^{1}H NMR spectra were recorded with a Bruker AM 500 spectrometer. Signals for aromatic protons (phenyls) were not characteristic and therefore they were not included to spectral data. IR spectra were taken with a FT-IR-1600 Perkin Elmer spectrophotometer. Mass spectra were obtained with an AMD 604 spectrometer. Column chromatography was performed on Merck silica gel 230-400 mesh.

Known compounds **5**, **15**, **25** and compound **26** were synthesized according to the procedure described in Ref. 14; 3,4-disubstituted azetidinones **9** and **19** were synthesized from the respective precursors **5** and **15** according to known procedures[5].

(7R,8S) 1-Aza-2,2-dimethyl-3,6-dioxa-8-hydroxymethyl-9-oxo-bicyclo[5.2.0]nonane (**10**) *and (5S) 5-(1',3'-dioxolanyl-2')-2,2-dimethyl-4-oxo-1,3-oxazine* (**11**). Compound **9** (0.074 g, 0.37 mmol) in acetone (25 mL) was cooled to -5 °C, treated with 2,2-dimethoxypropane (3 mL) and *p*-TsOH (0.005 g), and left overnight at -5 °C. Subsequently, the mixture was neutralized with pyridine and evaporated. The residue was separated by chromatography using dichloromethane - acetone 3:1 $^v/_v$ as an eluent to give **10** (0.055 g, 62%) and **11** (0.005 g, 5.4 %).

10: syrup, $[\alpha]_D$ +70.6° (*c* 1.2, CH_2Cl_2); IR ($CHCl_3$): 3440, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$); δ 1.48, 1.66 (2s, 6H, $2CH_3$), 3.34 (ddd, 1H, *J* 3.9, 4.2, 6.7 Hz, H-8), 3.72-4.10 (m, 4H, H-4, 4', 5, 5'), 3.93 (dd, 1H, *J* 3.9, 11.7 Hz, C**H**$_A$H$_B$OH), 4.03 (dd, 1H, *J* 6.7, 11.7 Hz, CH$_A$**H**$_B$OH), 5.23 (d, 1H, *J* 4.2 Hz, H-7). *Anal.* Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 54.1; H, 7.5; N, 7.1.

11: syrup; $[\alpha]_D$ -27.4° (*c* 1, CH_2Cl_2); IR (CH_2Cl_2): 3393, 1669 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.46, 1.50 (2s, 6H, $2CH_3$), 2.86 (ddd, H, *J* 3.1, 3.4, 10.8 Hz, H-5), 4.00 (m, 6H, H-6, 6a, 4', 4'a, 5', 5'a), 5.4 (d, 1H, *J* 3.4 Hz, H-2'), 6.40 (bs, 1H, NH). *Anal.* Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.7; H, 7.5; N, 6.9.

(7R,8S) and (7R,8R) 1-Aza-8-benzyloxymethyl-2,2-dimethyl-3,6-dioxa-9-oxo-bicyclo[5.2.0]nonane (**12** and **13**). Compound **10** (0.16 g, 0.78 mmol) in toluene (2 mL) was treated with benzyl chloride (0.2 g, 1.6 mmol), pulverized KOH (0.15) g and tetrabutylammonium bromide (0.025 g, 0.08 mmol). The mixture was stirred for 1.5 h, filtered and concentrated. The crude product was purified by chromatography to afford **12** (0.14 g, 63%), syrup; $[\alpha]_D$ +60.1° (*c* 1.4, CH_2Cl_2); IR ($CHCl_3$): 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.46, 1.63 (2s, 6H, $2CH_3$), 3.42 (ddd, 1H, *J* 4.2, 4.4, 8.8 Hz, H-8), 3.73, 3.98 (2m, 4H, H-4, 4', 5, 5'), 3.75 (dd, 1H, *J* 4.4, 10.3 Hz, C**H**$_A$H$_B$OBn), 3.90 (dd, 1H, *J* 8.8, 10.3 Hz, CH$_A$**H**$_B$OBn), 4.56 (s, 2H, OBn), 5.19 (d, 1H, *J* 4.2 Hz, H-7). *Anal.* Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.9; H, 7.3; N, 5.1.

Signals due to the isomer **13** which appears after prolongation of the benzylation time: 1.43, 1.66 (2s, 6H, $2CH_3$), 3.10 (m, 1H, *J* 1.0, 3.4, 4.8 Hz), 3.71, 3.87 (2m, 4H, H-4, 4', 5, 5'), 3.77 (dd, 1H, *J* 3.4, 10.3 Hz, C**H**$_A$H$_B$OBn), 4.04 (dd, 1H, *J* 4.8, 10.3 Hz, CH$_A$**H**$_B$OBn), 4.55 (s, 2H, Bn), 5.14 (d, 1H, *J* 1.0 Hz, H-7).

(S) 3-Benzyloxy-2-dimethoxymethyl-propionamide (**14**). Compound **10** (0.05 g, 0.17 mmol) in methanol (5 mL) was treated with Amberlite IR 120 (0.2 g) and stirred for 2 h. Subsequently, the mixture was filtered, concentrated and purified by chromatography to afford **14** (0.042 g, 95%), ^{1}H NMR ($CDCl_3$): δ 2.86 (m, 1H, H-2), 3.42, 3.45 (2s, 6H, $2OCH_3$), 3.75 (m, 2H, H-3, 3'), 4.55 (s, 2H, Bn), 4.68 (d, 1H, *J* 5.7 Hz, $CH(OCH_3)_2$), 5.35, 6.40 (2bs, 2H, NH_2); MS (LSIMS) *m/z* $(M+H)^+$ 254.

3,4-Di-O-benzyl-N-t-butyldimethylsilyl-1-N,2-C-carbonyl-2,6-dideoxy-α-L-glucopyranosylamine (**16**). Compound **15** (3.53 g, 10 mmol) in dichloromethane (20 mL) was cooled to -5 °C, treated with a solution of *t*-

butyldimethylsilyl chloride (1.81 g, 12 mmol) in dichloromethane (7 mL) and with ethyldiisopropylamine (2.62 ml, 15 mmol). The mixture was left overnight, evaporated carefully and purified by chromatography using hexane-ethyl acetate 8 : 1 $^{v}/_{v}$ as an eluent to afford **16** (4.43 g, 95%); $[\alpha]_D$ -67.0° (*c* 1, $CHCl_3$); IR ($CHCl_3$): 1748 cm^{-1}, ^1H NMR ($CDCl_3$): δ 0.24, 0.26, 0.96 (3s, 15H, *t*-$BuMe_2Si$), 1.28 (d, 1H, *J* 6.2 Hz, CH_3), 3.28 (dd, 1H, *J* 7.2, 9.5 Hz, H-4), 3.59 (dd, 1H, *J* 2.9, 4.7 Hz, H-2), 3.83 (dq, 1H, J 6.2, 9.5 Hz, H-5), 4.06 (dd, 1H, *J* 2.3, 7.4 Hz, H-3), 4.54, 4.69 (2d, 2H, *J* 11.4 Hz, Bn), 4.59, 4.81 (2d, 2H, *J* 11.6 Hz, Bn), 5.35 (d, 1H, *J* 4.7 Hz, H-1); *Anal.* Calcd for $C_{27}H_{37}NO_4Si$: C, 69.34; H, 7.97; N, 2.99. Found: C, 69.4; H, 7.9; N, 3.0.

N-*t-Butyldimethylsilyl-1*-N:*2*-C-*carbonyl-2,6-dideoxy*-α-L-*glucopyranosylamine* (**17**). Compound **16** (4.68 g, 10 mmol) in methanol (120 mL) was hydrogenated over 10% Pd/C (Degussa). The crude product was purified by chromatography using hexane - ethyl acetate 5:1 $^{v}/_{v}$ as an eluent to give 17 (2.55 g, 89%); m.p. 89-90 °C; $[\alpha]_D$ -78.2° (*c* 1, $CHCl_3$); IR ($CHCl_3$): 3393, 1730 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.24, 0.25, 0.95 (3s, 15H, *t*-$BuMe_2Si$); 1.29 (d, 1H, *J* 6.2 Hz, CH_3), 3.28 (ddd, 1H, *J* 3.6, 8.4, 9.3 Hz, H-4), 3.39 (dd, 1H, *J* 3.2, 4.7 Hz, H-2), 3.71 (dq, 1H, *J* 6.2, 9.3 Hz, H-5), 4.03 (ddd, *J* 2.7, 3.2, 8.4 Hz, H-3), 5.32 (d, 1H, *J* 4.7 Hz, H-1). *Anal.* Calcd for $C_{13}H_{25}NO_4Si$: C, 54.32; H, 8.77; N, 4.87. Found: C, 54.5; H, 8.8; N, 4.8.

(3S,4R,1'S) N-*t-Butyldimethylsilyl-3-hydroxymethyl-4-(1'-hydroxymethyl)ethoxyazetidin-2-one* (**18**). Compound **17** (1.15 g, 4 mmol) in 50% aqueous methanol (60 mL) was cooled to 0 °C and treated with a solution of sodium periodate (1.71 g, 8 mmol) and ammonium sulfate (1.6 g) in water (15 mL). The stirring and cooling were continued for 2 h. Subsequently, sodium borohydride (0.30 g, 8 mmol) in water (5 mL) was added after 15 min. The mixture was filtered and methanol evaporated. The aqueous solution was extracted with ethyl acetate. The extract was dried, evaporated and the crude product was purified by chromatography using hexane - ethyl acetate 2 : 1 $^{v}/_{v}$ as an eluent to afford **18** (0.88 g, 76%); $[\alpha]_D$ -27.8 ° (*c* 1, $CHCl_3$); IR (film): 3406, 1732 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.24, 0.28, 0.97 (3s, 15H, *t*-$BuMe_2Si$), 1.23 (d, 3H, *J* 6.4 Hz, CH_3), 3.46 (ddd, 1H, *J* 3.7, 4.0, 5.0 Hz, H-3), 3.57 (dd, 1H, *J* 5.0 Hz, 11.7 Hz, CH_AH_BOH), 3.66 (dd, 1H, *J* 3.7, 11.7 Hz, CH_AH_BOH), 3.84 (dd, 1H, *J* 5.0, 12.2 Hz, CH_AH_BOH), 5.17 (d, 1H, *J* 4.0 Hz, H-4). *Anal.* Calcd for $C_{13}H_{27}NO_4Si$: C, 53.95; H, 9.40; N, 4.84. Found: C, 53.9; H, 9.5; N, 4.8.

(3S,4R,1'S) 3-Hydroxymethyl-4-(1'-hydroxymethyl)ethoxy-azetidin-2-one (**19**). Compound **18** (0.59 g, 2 mmol) in anhydrous ethyl ether (50 mL) cooled to 0°C was treated with 70% hydrogen fluoride-pyridine complex (0.2 mL) and left overnight. Crystals were separated and washed with ethyl ether to afford **19** (0.35 g, 93%); m.p. 91-92 °C; $[\alpha]_D$ +73.4° (*c* 1, MeOH); IR (KBr): 3355, 3221, 1751 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.19 (d, 3H, *J* 6.4 Hz, CH_3), 3.4-4.10 (m, 6H, H-3, CH_2, CH_2CHMe), 5.29 (d, 1H, *J* 4.2 Hz, H-4). *Anal.* Calcd for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 8.00. Found: C,47.89; H, 7.35; N, 7.95.

(5S,7R,8S) 1-Aza-3,6-dioxa-8-hydroxymethyl-5-methyl-9-oxo-bicyclo[5.2.0]nonane (**20**) and *(4S, 2'R,4'S) 5-(4'-methyl-1',3'-dioxolanyl-2')-4-oxo-2-phenyl-1,3-oxazine* (**21**). Compound **19** (0.35 g, 2.0 mmol) was dissolved in benzaldehyde (2 mL) and treated with *p*-TsOH (10 mg). The mixture was left overnight. Subsequently, it was diluted with hexane (2 mL) and purified by chromatography to afford diastereomeric mixtures of compounds **20** and **21** (0.40 g, 77%) in proportion 1 : 3, respectively. The mixture was purified by chromatography using hexane-ethyl acethate 4 : 1 $^{v}/_{v}$ as an eluent to give **21** (0.09 g) and mixture of **20** and **21** (0.30 g). The mixture of **20** and **21** was acetylated with acetic anhydride - pyridine mixture. After standard work up the mixture was separated to give unchanged **21** (0.18 g) and *O*-acetyl derivative of **20** (0.1 g).

21: 10:1 mixture of C-2 stereoisomers, m.p. 173-174 °C; IR (film): 3434, 1658 cm^{-1}; ^1H NMR ($CDCl_3$) signals due to the major isomer: 1.32 (d, 3H, *J* 6.0 Hz, CH_3), 2.84 (ddd, *J* 3.2, 3.3, 5.5 Hz, H-5), 3.09 (dd, 1H, *J* 5.5, 12.0 Hz, H-6), 3.47 (t, 1H, *J* 7.4 Hz, H-5'), 4.01 (dd, 1H, *J* 6.4, 7.4 Hz, H-5'a), 4.25 (m, 1H, $CHCH_3$), 4.36 (dd, 1H, 3.3, *J* 12.0 Hz, H-6a), 5.49 (d, 1H, *J* 3.2 Hz, H-2'), 5.76 (s, 1H, H-2). *Anal.* Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.7; H, 6.4; N, 5.2.

The acetate of **20**: 10:1 mixture of C-2 stereoisomers, IR (film): 1765 cm^{-1}; ^1H NMR ($CDCl_3$) signals due to the major isomer: 1.19 (d, 3H, *J* 6.5 Hz, CH_3), 2.07 (s, 3H, Ac), 3.31 (ddd, 1H, *J* 4.1, 6.0, 7.5 Hz, H-8), 3.70 (dd, 1H, *J* 9.0, 13.2 Hz, H-4), 3.95-4.15 (m, 2H, H-4', 5), 4.41 (dd, 1H, *J* 6.0, 11.8 Hz, CH_AH_BOAc), 4.47 (dd, 1H, *J* 7.5, 11.8 Hz, CH_AH_BOAc), 5.45 (d, 1H, *J* 4.1 Hz, H-7), 5.85 (s, 1H, H-2). *Anal.* Calcd. For $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.8; H, 6.3; N, 4.6.

1-N:*2*-C-*Carbonyl-2,6-dideoxy-3,4-di*-O-*trimethylsilyl*-α-L-*glucopyranosylamine* (**25**). Compound **25** was obtained from rhamnal **23** according to the known procedure[14] (62%); m.p. 60-61 °C; $[\alpha]_D$ -81.2° (*c* 1, $CHCl_3$); IR (KBr): 3332, 1761 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.15, 0.23 (2s, 6H, 2TMS), 1.22 (d, 2H, *J* 6.4 Hz,

CH_3), 3.23 (ddd, 1H, *J* 2.9, 3.0, 4.6 Hz, H-2), 3.30 (dd, 1H, *J* 7.2, 9.0 Hz, H-4), 3.81 (dq, 1H, *J* 6.4, 9.0 Hz, H-5), 4.01 (dd, 1H, *J* 3.0, 7.2 Hz, H-3), 5.41 (d, 1H, *J* 4.6 Hz, H-1). *Anal.* Calcd for $C_{13}H_{27}NO_4Si_2$: C, 49.18; H, 8.57; N, 4.41. Found: C, 49.1; H, 8.5; N, 4.5.

3,4-Di-O-*benzyl*-N-*(t-butoxycarbonyl)methyl-2*-C:*1*-N-*carbonyl-2-deoxy*-β-D-*arabinopyranosylamine* (**27**). Compound **27** was obtained from arabinal **22** according to the known procedure (87%); $[\alpha]_D$ -71.3° (*c* 2.2, CH_2Cl_2); IR (film): 1769, 1738 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.45 (s, 9H, *t*-Bu), 3.48 (dd, 1H, *J* 4.5, 5.4 Hz, H-2), 3.72-3.93 (m, 6H, H-3, 4, 5, 5', NCH_2), 4.64, 4.78 (2d, 2H, *J* 12.2 Hz, Bn), 5.47 (d, 1H, *J* 4.5 Hz, H-1). *Anal.* Calcd for $C_{26}H_{31}NO_6$: C, 68.86; H, 6.89; N, 3.09. Found: C, 68.6; H, 6.7; N, 2.9.

N-*(Benzyloxycarbonyl)methyl-2*-C:*1*-N-*carbonyl-2,6-dideoxy-3,4-di*-O-*trimethylsilyl*-α-L-*glucopyranosylamine* (**28**). The mixture of compound **25** (7.79 g, 24.4 mmol), benzyl bromoacetate (6.79 g, 29.2 mmol), tetrabutylammonium bromide (1.6 g, 10 mmol) and fine grounded anhydrous potassium carbonate in anhydrous benzene was refluxed for 6 h. After cooling, the mixture was filtered, evaporated and the remaining oil was purified by chromatography using hexane-ethyl acetate 4:1 $^v/_v$ as an eluent to give **28** (8.62 g, 76%); $[\alpha]_D$ -85.1° (*c* 1, $CHCl_3$); IR (film): 1773, 1752 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.17 (d, 3H, *J* 6.2 Hz, CH_3), 3.28 (dd, 1H, *J* 3.1, 4.7 Hz, H-2), 3.29 (dd, 1H, *J* 7.8, 9.1 Hz, H-4), 3.75 (dq, 1H, *J* 6.3, 9.1 Hz, H-5), 3.83, 4.02 (dd, 2H, *J* 18.1 Hz, CH_3CO), 3.98 (dd, 1H, *J* 3.1, 7.8, Hz, H-3), 5.16 (s, 2H, OBn), 5.41 (d, 1H, *J* 4.7 Hz, H-1). *Anal.* Calcd for $C_{22}H_{35}NO_6Si_2$: C, 56.74; H, 7.58; N, 3.01. Found: C, 56.6; H, 7.6; N, 3.0.

N-*(Benzyloxycarbonyl)methyl-3,4-di*-O-*trimethylsilyl-2*-C:*1*-N-*carbonyl-2-deoxy*-β-D-*arabinopyranosylamine* (**29**). Compound **29** was obtained from known **26** by the procedure described above in 65% yield; m.p. 86-87 °C; $[\alpha]_D$ -63.3° (*c* 2, CH_2Cl_2); IR ($CHCl_3$): 1780, 1760 cm^{-1}; ^1H NMR ($CDCl_3$): 3.32 (t, 1H, *J* 4.3 Hz, H-2); 3.68 - 3.80 (m, 2H, H-5, 5'), 3.95 - 4.02 (m, 3H, H-4, NCH_2), 4.11 (dd, 1H, *J* 2.7, 4.3 Hz, H-3), 5.17 (s, 2H, Bn), 5.39 (d, 1H, *J* 4.3 Hz, H-1). *Anal.* Calcd for $C_{21}H_{33}NO_6Si_2$: C, 55.85; H, 7.36; N, 3.10. Found: C, 55.8; H, 7.4; N, 3.1.

N-*(Butoxycarbonyl)methyl-2*-C:*1*-N-*carbonyl-2-deoxy*-α-D-*arabinopyranosylamine* (**30**). Compound **27** (41.5 g, 0.092 mol) in anhydrous methanol (500 mL) was hydrogenated in the presence of 10% Pd/C. After 2 h the mixture was filtered through Celite and evaporated to afford **30** (23.7 g, 95%); $[\alpha]_D$ -96.5° (*c* 2.7, CH_2Cl_2); IR (film): 1753, 1723 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.46 (s, 9H, t-Bu), 3.33 (dd, 1H, *J* 4.1, 4.4 Hz, H-2), 3.77, 3.91 (2d, 2H, *J* 17.8 Hz, NCH_2), 3.86 (dd, 1H, *J* 4.2, 12.2 Hz, H-5), 3.89 (dd, 1H, *J* 2.1, 12.2 Hz, H-5') 3.94 (bs, 1H, H-4), 4.18 (bt, 1H, H-3), 5.46 (d, 1H, *J* 4.4 Hz, H-1). *Anal.* Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.9; H, 7.3; N, 5.0.

N-*(Benzyloxycarbonyl)methyl-2*-C:*1*-N-*carbonyl-2,6-dideoxy*-α-L-glucopyranosylamine (**31**). Compound **28** (4.66 g, 10 mmol) dissolved in dichloromethane (60 mL) and pyridine (10 mL) was desilylated using 70% hydrogen fluoride-pyridine complex (1.5 g). After 2 h the solution was poured into saturated solution of sodium hydrogen carbonate (200 ml) and extracted with dichloromethane. The extract was washed, dried and evaporated. The residue was purified by chromatography using hexane-ethyl acetate 4 : 1 $^v/_v$ as an eluent to afford **31** (3.0 g, 93%); m.p. 88.5-89 °C; $[\alpha]_D$ -99.8° (*c* 1, $CHCl_3$); IR ($CHCl_3$): 3415, 1747 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.26 (d, 1H, *J* 6.2 Hz, CH_3), 3.26 (ddd, 1H, *J* 4.0, 8.5, 9.4 Hz, H-4), 3.38 (dd, 1H, *J* 3.5, 4.4 Hz, H-2), 3.77 (dq, 1H, *J* 6.2, 9.4 Hz, H-5), 3.88, 4.07 (2d, 2H, *J* 18.0 Hz, NCH_2), 4.04 (m, 1H, H-3), 5.44 (d, 1H, *J* 4.4 Hz, H-1). *Anal.* Calcd for $C_{16}H_{19}NO_6$: C, 59.80; H, 5.96; N, 4.36. Found: C, 59.6; H, 6.1; N, 4.4.

N-*(Benzyloxycarbonyl)methyl-2*-C:*1*-N-*carbonyl-2-deoxy*-β-D-*arabinopyranosylamine* (**32**). Compound **29** (0.10 g, 0.22 mmol) in methanol (10 mL) was treated with Amberlite IR 120 (0.05 g) and stirrred for 30 min. Subsequently, the resin was filtered and the solvent was evaporated. The residue was crystallized from hexane-ethyl acetate to give **32** (0.055 g, 80%), m.p. 107-109 °C; $[\alpha]_D$ -83.7° (*c* 1.4, CH_2Cl_2); IR ($CHCl_3$): 1766, 1747 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.31 (dd, 1H, *J* 3.8, 4.4 Hz, H-2), 3.81 (dd, 1H, *J* 4.3, 12.4 Hz, H-5), 3.87 (dd, 1H, *J* 1.8, 12.4 Hz, H-5'), 3.91 (m, 1H, H-4), 3.95, 4.04 (2d, 2H, *J* 18.0 Hz, CH_2CO_2Bn), 4.16 (m, 1H, H-3), 5.15, 5.19 (2d, 2H, *J* 12.2 Hz, Bn), 5.45 (d, 1H, *J* 4.4 Hz, H-1). *Anal.* Calcd for $C_{15}H_{17}NO_6$: C, 59.63; H, 5.58; N, 4.56. Found: C, 58.5; H, 5.6; N, 4.5.

(3S,4R) N-*(t-Butoxycarbonyl)methyl-3-hydroxymethyl-4-(2'-hydroxy)ethoxy-azetidin-2-one* (**33**). Compound **33** was obtained from **30** according to the procedure described for **18** (88%); $[\alpha]_D$ -9.85° (*c* 1.7, CH_2Cl_2); IR (film): 3406, 1757, 1736 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.48 (s, 9H, *t*-Bu), 3.55 (ddd, 1H, *J* 3.7, 3.9, 8.2 Hz, H-3), 3.75-3.90 (m, 4H, CH_2CH_2), 3.71, 4.13 (2d, 2H, *J* 17.7 Hz, NCH_2), 3.93 (dd, 1H, *J* 3.7, 12.0

Hz, CH_AH_BOH), 4.05 (m, 1H, CH_AH_BOH), 5.35 (d, 1H, *J* 3.9 Hz, H-4); MS (LSIMS, HR) *m/z*: $M^{+\cdot}$ calcd for $C_{12}H_{22}NO_6$: 276.14471. Found: 276.14472.

Anal. Calcd for $C_{12}H_{21}NO_6$: C, 52.35; H, 7.69; N, 5.09; Found: C, 52.5, H, 7.7; N, 4.8.

(3S,4R,1'S) N-*(Benzyloxycarbonyl)methyl-3-hydroxymethyl-4-(1'-hydroxymethyl)ethoxy-azetidin-2-one* (**34**). Compound **34** was obtained from **31** according to the procedure described for **18** (78%); m.p. 63.5-64.0 °C; $[\alpha]_D$ +8.5° (*c* 1, $CHCl_3$); IR ($CHCl_3$): 3405, 1747 cm^{-1}; ^1H NMR ($CHCl_3$): δ 1.13 (d, 3H, *J* 6.4 Hz, CH_3), 3.40-3.60 (m, 3H, H-3, CH_2OH), 3.77 (m, 1H, H-1'), 3.91 (dd, 1H, *J* 3.4, 12.3 Hz, CH_AH_BOH), 4.01 (dd, 1H, *J* 5.6, 12.3 Hz, CH_AH_BOH), 4.00, 4.29 (2d, 2H, *J* 18.1 Hz, NCH_2), 5.17 (s, 2H, OBn), 5.45 (d, 1H, *J* 4.20 Hz, H-4). *Anal.* Calcd for $C_{16}H_{21}NO_6$: C, 59.43; H, 6.55; N, 4.33. Found: C, 59.2; H, 6.6; N, 4.2.

(3S,4R) N-*(Benzyloxycarbonyl)methyl-3-hydroxymethyl-4-(2'-hydroxyethoxy)azetidin-2-one* (**35**). Compound **35** was obtained from **32** according to the procedure described for **18** (62%); $[\alpha]_D$ -14.4° (*c* 1.2, CH_2Cl_2); IR (film): 3393, 1766, 1746 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.35 (dt, 1H, *J* 3.7, 3.9, 8.2 Hz, H-3), 3.64-3.83 (m, 4H, CH_2CH_2), 3.86, 4.28 (2d, 2H, *J* 18.0 Hz, NCH_2), 3.92 (bd, 1H, *J* 12.2 Hz, CH_AH_B), 4.03 (bt, 1H, CH_AH_B), 5.17, 5.19 (2d, 2H, *J* 12.2 Hz, Bn), 5.32 (d, 1H, *J* 3.9 Hz, H-4). *Anal.* Calcd for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19; N, 4.53. Found: C, 58.0; H, 6.3; N, 4.8.

(3S,4R) N-*(t-Butoxycarbonyl)methyl-4-(2'-t-butyldiphenylsiloxyethoxy)-3-hydroxymethyl-azetidin-2-one* (**36**) and *(3S,4R)* N-*(t-butoxycarbonyl)methyl-4-(2'-t-butyldiphenylsiloxyethoxy)-3-(t-butyldiphenylsiloxy)-methyl-azetidin-2-one* (**38**). Compound **33** (0.19 g, 0.7 mmol) in dichloromethane (2 mL) and pyridine (2 mL) was treated with DMPA (0.09 g, 0.7 mmol). The mixture was cooled to -5 °C and *t*-butyldiphenylsilyl chloride (0.22 g, 0.8 mmol) was added in portions. After 6 h methanol (1 mL) was added to quench the reaction progress. Subsequently, the mixture was concentrated and separated on a silica gel column using hexane-ethyl acetate 1 : 1 $^v/_v$ as an eluent to give **36** (0.092 g, 26%) and **38** (0.01 g, 2%).

36: syrup; $[\alpha]_D$ -6.5° (*c* 1, CH_2Cl_2); IR (film): 3458, 1770, 1738 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.06 (s, 9H, Si*t*-Bu), 1.46 (s, 9H, *t*-Bu), 3.55 (ddd, 1H, *J* 3.8, 4.0, 7.0 Hz, H-3), 3.65, 4.18 (2d, 2H, *J* 17.9 Hz, NCH_2), 3.67-3.85 (m, 4H, CH_2CH_2), 3.90-4.07 (m, 2H, CH_2OH), 5.38 (d, 1H, *J* 4.05 Hz, H-1).

Anal. Calcd for $C_{28}H_{39}NO_6$: C, 65.47; H, 7.65; N, 2.73. Found: C, 65.55; H, 7.71; N, 2.88.

38: syrup, $[\alpha]_D$ -6.7° (*c* 1, CH_2Cl_2); IR ($CHCl_3$): 1737, 1762 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.03, 1.06, (2s, 18H, 2*t*-Bu), 1.43 (s, 9H, CO_2*t*-Bu), 3.53 (m, 1H, *J* 3.7, 4.1, 9.3 Hz, H-3), 3.56, 4.10 (2d, 2H, *J* 18.0 Hz, NCH_2), 3.67, 3.79 (2m, 4H, OCH_2CH_2O), 3.91, 4.05 (2d, 2H, *J* 10.9 Hz, CH_2OSi), 5.35 (d, 1H, *J* 3.7 Hz, H-4). MS (HR, LSIMS) *m/z* $(M+Na)^+$ calcd for $C_{44}H_{57}NO_6Si_2Na$: 774.36221. Found: 774.36144.

(3S,4R) 3-*Acetoxymethyl*-N-*(t-butoxycarbonyl)methyl-4-(2'-t-butyldiphenylsiloxy)ethoxy-azetidin-2-one* (**37**). Compound **37** was obtained from **36** by standard acetylation procedure; $[\alpha]_D$ -13.5° (*c* 1.4, CH_2Cl_2), IR (film): 1776, 1741 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu), 2.00 (s, 3H, Ac), 3.61 (ddd, 1H, *J* 3.9, 5.5, 8.2 Hz, H-3), 3.62, 4.15 (2d, 2H, *J* 17.9 Hz, NCH_2), 3.69, 3.80 (m, 4H, CH_2CH_2) 4.34 (dd, 1H, *J* 8.2, 11.7 Hz, CH_AH_BOH), 4.43 (dd, 1H, *J* 5.5, 11.7 Hz, CH_AH_BOH), 5.35 (d, 1H, *J* 3.9 Hz, H-4); MS (LSIMS, HR) *m/z* $(MNa)^+$ calcd for $C_{30}H_{41}NO_7SiNa$: 578.25499. Found: 578.25486. Anal. Calcd for $C_{30}H_{41}NO_7Si$: C, 64.84; H, 7.44; N, 2.52. Found: C, 64.5; H, 7.6; N, 2.5.

(3S,4R) 3-*Acetoxymethyl*-N-t-*butoxycarbonyl)methyl-4-(2'-hydroxy)ethoxy-azetidin-2-one* (**39**). Compound **37** was desilated in pyridine using 1 equiv. HF. After evaporation of the solvent the crude product was purified on a silica gel column using hexane - ethyl acetate 1:3 $^v/_v$ as an eluent (62%); $[\alpha]_D$ -11.2° (*c* 1.4, CH_2Cl); IR (film): 3460, 1776, 1739 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.46 (s, 9H, *t*-Bu), 2.07 (s,3H, Ac), 3.62 (ddd, 1H, *J* 4.0, 4.5, 8.3 Hz, H-3), 3.68, 4.14 (2d, 2H, *J* 17.9 Hz, NCH_2), 3.68-3.78 (m, 4H, CH_2CH_2), 4.42 (dd, 1H, *J* 8.3, 11.8 Hz, CH_AH_BOAc), 4.48 (dd, 1H, *J* 4.5, 11.8 Hz, CH_AH_BOAc), 5.33 (d, 1H, *J* 4.0 Hz, H-4), MS (LSIMS, HR) *m/z* $(M+Na)^+$ calcd for $C_{14}H_{23}NO_7Na$: 340.13722. Found: 340.13714.

(3S,4R,1'S) N-*Carboxymethyl-3-hydroxymethyl-4-(1'-hydroxymethyl)ethoxy-azetidin-2-one* (**40**). Compound **34** (3.23 g, 10 mmol) in methanol (200 ml) was hydrogenated over 10% Pd/C (Degussa) for 1 h. The mixture was filtered and evaporated to afford **40** (2.21 g, 95%). The crude acid was used for the next step; m.p. 120-121 °C (from ethyl acetate); $[\alpha]_D$ -75.3° (*c* 1, MeOH); IR (KBr): 3380, 3283, 1758, 1740 cm^{-1}; ^1H NMR; MS (LSIMS) *m/z*, $(M+H)^+$ 234. *Anal.* Calcd for $C_9H_{15}NO_6$: C, 46.35; H, 6.48; N, 6.01. Found: C, 45.4; H, 6.6; N, 6.1.

(3S,4R) N-*Carboxymethyl-3-hydroxymethyl-4-(2'-hydroxyethoxy)-azetidin-2-one* (**41**). Compound **41** was obtained from **35** according to the procedure described above (95%).

(6S,8R,9S) 1-Aza-4,7-dioxo-9-hydroxymethyl-6-methyl-10-oxa-bicyclo-[2.6.0]-decane (**50**). To dihydroxy acid **40** (2.33 g, 10 mmol), upon stirring at room temperature, DCC (2.08 g, 10 mmol) and DMAP (0.1 g) were added in one portion. Stirring was continued for 1 h. Subsequently, the precipitate was filtered off. The filtrate was evaporated, treated with acetonitrile (10 ml), filtered and evaporated again. The crude crystalline product was recrystallized from hexane-ethyl acetate. The mother liquor was evaporated and purified by chromatography using hexane - ethyl acetate 2:1 as an eluent. Total yield of **50** 1.82 g, (85%); m.p. 116-117 °C; $[\alpha]_D$ -35.4° (*c* CH_2Cl_2); IR (KBr): 3423, 1769, 1750, 1721 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.25 (d, 1H, *J* 6.4 Hz, CH_3), 3.50 (m, 1H, H-9), 3.75 (dd, 1H, *J* 1.7, 12.4 Hz, H-2), 3.91 (dd, 1H, *J* 3.9, 12.3 Hz, CH_AH_BOH), 3.98 (dd, 1H, *J* 6.3, 12.3 Hz, CH_AH_BOH), 4.02-4.12 (m, 2H, H-5, 6), 4.26 (d, 1H, *J* 12.4 Hz, H-2'), 4.52 (m, 1H, H-5'), 5.35 (d, 1H, *J* 4.3 Hz, H-8). *Anal.* Calcd for $C_{19}H_{13}NO_5$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.36; H, 6.13; N, 6.47.

Crystal data, details of data collection and refinement for compound (**50**). The crystals suitable for X-ray structure analysis of compound **50** were obtained by slow evaporation of the hexane - ethyl acetate solution. The intensities were collected on an Enraf-Nonius Mach3 diffractometer with graphite monochromatized CuK_α radiation. Lorentz and polarization corrections were applied to the 1114 independent reflections.

Structure was solved by direct methods with the use of SHELXS86 (Sheldrick, 1986)[15] and refined against F^2 using SHELXL93 (Sheldrick, 1993)[16]. Non-hydrogen atoms were refined anisotropically, whereas the H-atoms were placed in the calculated positions and refined with the riding model and refined isotropic displacement parameters.

Table 1. Crystal data and structure refinement for **50**.

Formula weight	215.20
Temperature (K)	293(2)
Wavelength (Å)	1.54178
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions (Å):	a = 5.4230(3)
	b = 10.2473(4).
	c = 18.4224(8).
Volume ($Å^3$)	1023.75(8)
Z	4
D_{calc} ($Mg \cdot m^{-3}$)	1.396
Absorption coefficient (mm^{-1})	0.981
F(000)	456
Crystal size (mm)	0.49 x 0.175 x 0.07
θ-range for data collection(°)	4.80 to 73.86
Reflections collected / indep.	1114 / 1114
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1114 / 0 / 189
Goodness-of-fit on F^2	0.932
Final R indices [$I>\sigma(I)$]	R_1 = 0.0328, wR_2 = 0.0905
R indices (all data)	R_1 = 0.0331, wR_2 = 0.0911
Absolute structure parameter	-0.2(3)
Extinction coefficient	0.0076(13)
Largest diff. peak and hole (e $Å^{-3}$)	0.215 and -0.150

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for **50**. U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
N(1)	1711(4)	6780(2)	8246(1)	37(1)
C(2)	2450(5)	7464(2)	8898(1)	39(1)
C(3)	4479(4)	6743(2)	9307(1)	41(1)
O(4)	4009(3)	5614(2)	9639(1)	48(1)
C(5)	1593(5)	5017(3)	9612(1)	45(1)
C(6)	1516(5)	3944(2)	9040(1)	42(1)
O(7)	2083(3)	4459(1)	8332(1)	38(1)
C(8)	587(4)	5492(2)	8120(1)	35(1)
C(9)	736(4)	5808(2)	7298(1)	38(1)
C(10)	1920(4)	7091(2)	7531(1)	37(1)
C(12)	3319(7)	2851(3)	9177(2)	56(1)
O(11)	6531(3)	7175(2)	9348(1)	59(1)
O(13)	2724(4)	8051(2)	7229(1)	49(1)
C(14)	2304(5)	4948(3)	6818(1)	48(1)
O(15)	4848(3)	5031(2)	6984(1)	53(1)

Table 3. Selected bond lengths [Å] and angles [°] for **50**.

N(1)-C(10)	1.360(2)	C(6)-C(12)	1.508(4)
N(1)-C(2)	1.447(2)	C(6)-H(12)	1.05(4)
N(1)-C(8)	1.472(3)	O(7)-C(8)	1.390(3)
C(2)-C(3)	1.524(3)	C(8)-C(9)	1.552(3)
C(3)-O(11)	1.200(3)	C(9)-C(14)	1.510(3)
C(3)-O(4)	1.333(3)	C(9)-C(10)	1.525(3)
O(4)-C(5)	1.447(3)	C(10)-O(13)	1.211(3)
C(5)-C(6)	1.524(3)	C(14)-O(15)	1.415(3)
C(6)-O(7)	1.440(2)	O(15)-HO15	0.95(4)
C(10)-N(1)-C(2)	131.9(2)	C(8)-O(7)-C(6)	114.2(2)
C(10)-N(1)-C(8)	95.3(2)	O(7)-C(8)-N(1)	113.4(2)
C(2)-N(1)-C(8)	132.8(2)	O(7)-C(8)-C(9)	113.8(2)
N(1)-C(2)-C(3)	112.1(2)	N(1)-C(8)-C(9)	86.9(2)
O(11)-C(3)-O(4)	117.9(2)	C(14)-C(9)-C(10)	115.6(2)
O(11)-C(3)-C(2)	121.5(2)	C(14)-C(9)-C(8)	118.6(2)
O(4)-C(3)-C(2)	120.6(2)	C(10)-C(9)-C(8)	85.8(2)
C(3)-O(4)-C(5)	121.6(2)	O(13)-C(10)-N(1)	131.7(2)
O(4)-C(5)-C(6)	110.7(2)	O(13)-C(10)-C(9)	136.2(2)
O(7)-C(6)-C(12)	106.5(2)	N(1)-C(10)-C(9)	92.1(2)
O(7)-C(6)-C(5)	110.8(2)	O(15)-C(14)-C(9)	112.8(2)
C(12)-C(6)-C(5)	113.8(2)	C(14)-O(15)-HO15	105(3)

(8R,9S) 1-Aza-4,7-dioxa-3,10-dioxo-9-hydroxymethyl-bicyclo[2.6.0]decane (**51**). Compound **51** was obtained according to the procedure described above, 60%. Crude compound **51** was used for the next step.

(6S,8R,9S) 1-Aza-9-t-butyldiphenylsiloxymethyl-4,7-dioxa-3,10-dioxo-6-methyl-bicyclo-[2.6.0]decane (**52**). Compound **50** was silylated with *t*-butyldiphenylsilyl chloride in the presence of imidazole and DMAP under standard conditions (89%); m.p. 82-83 °C; $[\alpha]_D$ -18.6° (*c* 1, CH_2Cl_2); IR ($CHCl_3$): 1772, 1757, 1718 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.03 (s, 9H, t-Bu), 1.17 (d, 3H, *J* 6.4 Hz, CH_3); 3.52 (m, 1H, H-9), 3.74 (dd, 1H, *J* 1.7, 12.5 Hz, H-2), 3.90 (dd, 1H, *J* 3.6, 10.8 Hz, C**H**$_A$H$_B$OSi), 4.02 (m, 1H, H-6), 4.07 (dd, 1H, 7.9, 10.8 Hz, CH$_A$**H**$_B$OSi), 4.09 (dd, 1H, *J* 3.1, 11.8 Hz, H-5), 4.13 (d, 1H, *J* 12.5 Hz, H-2'), 4.48 (dd, 1H, *J* 9.2, 11.8 Hz, H-5'), 5.30 (d, 1H, *J* 4.3 Hz, H-8). *Anal.* Calcd for $C_{25}H_{31}NO_5Si$: C, 66.20; H, 6.88; N, 3.09. Found: C, 66.3; H, 6.8; N, 3.2.

(8R,9S) 1-Aza-9-t-butyldiphenylsiloxymethyl-4,7-dioxa-3,10-dioxo-bicyclo[2.6.0]decane (**53**). Compound **53** was obtained according to the procedure described above, 70%; m.p. 104-105 °C; $[\alpha]_D$ -12.1° (*c* 1.4, CH_2Cl_2); IR ($CHCl_3$): 1774, 1758 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.04, 0.05, 0.88 (3s, 15H, Si*t*-BuMe$_2$), 3.50 (dddd, 1H, *J* 1.6, 4.2, 4.2, 8.6 Hz, H-9), 3.81 (dd, 1H, *J* 1.6, 12.4 Hz, H-2), 4.25 (d, 1H, *J* 12.4 Hz, H-2'), 3.87 (dd, 1H, *J* 8.6, 10.7 Hz, C**H**$_A$H$_B$OSi), 3.88, 4.14, 4.21, 4.76 (4m, 4H, H-5, 5', 6, 6'), 4.00 (dd, 1H, *J* 4.2, 10.7 Hz, CH$_A$**H**$_B$OSi), 5.20 (d, 1H, *J* 4.2 Hz, H-8); MS (HR-LSIMS) *m/z* $(M+Na)^+$ calcd for $C_{14}H_{25}NO_5SiNa$: 338.139966. Found: 338.139001.

(3S,4R,1'S) 3-t-Butyldiphenylsiloxymethyl)ethoxy-N-(methoxycarbonyl)methyl (**54**). Compound **52** (0.9 g, 2.0 mmol), triethylamine (0.4 mL) and acetic acid (0.13 mL) in anhydrous methanol (8 mL) was kept at room temperature for 2 h. Subsequently the mixture was evaporated and the residue was purified by chromatography using hexane ethyl acetate 3:1 $^v/_v$ as an eluent to give **54** (0.9 g, 93%); $[\alpha]_D$ -11.3° (*c* 1, CH_2Cl_2); IR ($CHCl_3$): 3504, 1764, 1746 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.04 (s, 9H, *t*-Bu), 1.12 (d, 3H, *J* 6.2 Hz, CH_3), 3.32-3.64 (m, 3H, H-3), 3.32-3.64 (m, 3H, H-3, CH_2OSi) 3.74 (s, 3H, OCH_3), 3.81 (m, 1H, C**H**Me), 3.90, 4.20 (2d, 2H, *J* 17.9 Hz, CH_2CO), 3.23 (dd, 1H, *J* 3.7, 10.8 Hz, C**H**$_A$H$_B$OH), 4.11 (dd, 1H, *J* 8.4, 10.8 Hz, CH$_A$**H**$_B$OH), 5.47 (d, 1H, *J* 4.1 Hz, H-4). *Anal.* Calcd for $C_{26}H_{35}NO_6Si$: C, 64.31; H, 7.26; N, 2.88. Found: C, 64.4, H, 7.3; N, 2.8.

(3S,4R) 3-t-Butyldimethylsiloxymethyl-4-(2'-hydroxyethoxy)-N-(methoxycarbonyl)methyl (**55**). Compound **55** was obtained according to the procedure described above, 75%; syrup, $[\alpha]_D$ -11.3° (*c* 0.6, CH_2Cl_2); IR ($CHCl_3$): 3424, 1766, 1748 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.11, 0.12, 0.91 (3s, 15H, Si*t*-BuMe$_2$), 3.53 (ddd, 1H, *J* 3.4, 3.7, 10.5 Hz, H-3), 3.65-3.91 (2m, 4H, OCH_2CH_2O), 3.76 (s, 3H, OCH_3), 3.76, 4.20 (2d, 2H, *J* 18.0 Hz, CH_2CO_2Me), 3.94 (dd, 1H, *J* 3.4, 10.9 Hz, C**H**$_A$H$_B$OSi), 4.12 (dd, 1H, 10.5, 10.9 Hz, CH$_A$**H**$_B$OSi), 5.36 (d, 1H, *J* 3.7 Hz, H-4); MS (HR-LSIMS) *m/z* $(M+H)^+$ calcd for $C_{15}H_{30}NO_6Si$: 348.1842. Found: 348.1840.

(3S,4R,1'S) 3-t-Butyldiphenylsiloxymethyl-4-(1'-carboxy)ethoxy-N-methoxycarbonylmethyl-azetidin-2-one (**46**). To compound **54** (0.49 g, 1 mmol) in 70% acetone - water (15 mL) sodium periodate (0.86 g, 4 mmol) and 3% aqueous solution of ruthenium trichloride (5 mL) were added. Stirring was continued overnight at room temperature. Subsequently ethanol (5 ml) was added and stirring was continued for additional 1 h. The mixture was diluted with acetone (10 mL), then filtered and acetone was evaporated. The crude product was purified by chromatography using hexane - ethyl acetate 4:1 $^v/_v$ as an eluent to give **46** (0.46 g, 92%); $[\alpha]_D$ -35.3° (*c* 1, MeOH); IR ($CHCl_3$): δ 3500, 1765, 1749 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.06 (s, 9H, *t*-Bu), 1.45 (d, 1H, *J* 7.0 Hz, CH_3), 3.59 (ddd, 1H, *J* 3.6, 3.9, 10.0 Hz, H-3), 3.72 (s, 3H, OCH_3), 3.92, 4.22 (2d, 2H, *J* 18.0 Hz, NCH_2CO_2Me), 3.93 (dd, 1H, *J* 3.9, 10.9 Hz, C**H**$_A$H$_B$OSi), 4.12 (dd, 1H, *J* 10.0, 10.9 Hz, CH$_A$**H**$_B$OSi), 4.34 (q, 1H, *J* 7.0 Hz, C**H**CH_3), 5.27 (d, 1H, *J* 3.6 Hz, H-4). *Anal.* Calcd for $C_{26}H_{33}NO_7Si$: C, 62.51; H, 6.65; N, 2.80. Found: C, 62.40; H, 6.58; N, 2.73.

(3S,4R) 3-Acetoxymethyl-4-(carboxymethyl)-N-t-butoxycarbonylmethyl-azetidin-2-one (**42**). Compound **42** was obtained from **39** according to the procedure described for **46**, 94%; ^1H NMR ($CDCl_3$): δ 1.47 (s, 9H, *t*-Bu), 2.08 (s, 3H, Ac), 3.66 (m, 1H, H-3), 3.80, 4.16 (2d, 2H, *J* 17.9 Hz, NCH_2), 4.22, 4.32 (2d, 2H, *J* 17.0 Hz, CH_2CO_2H), 4.37-4.53 (m, 2H, CH_2OAc), 5.31 (d, 1H, *J* 3.8 Hz, H-4). Crude acid **42** was used for the next step.

(3S,4R) 3-Acetoxymethyl-N-(t-butoxycarbonyl)-methyl-4-(thiophenoxycarbonyl)methoxy-azetidin-2-one (**43**). To a solution of compound **42** (0.20 g, 0.6 mmol) in anhydrous acetonitrile (3 mL), thiophenol (0 1 g,

0.9 mmol), DCC (0.12 g, 0.6 mmol) and DMAP (0.074 g, 0.6 mmol) were added. The mixture was stirred for 3 h at room temperature. Subsequently, the mixture was diluted with dichloromethane (10 mL), filtered, washed with 5% sodium hydrogen carbonate and water, dried, and concentrated. The crude product was purified by chromatography to give **43** (0.11 g, 43%), syrup; $[\alpha]_D$ -30.5° (*c* 0.7, CH_2Cl_2); IR (film): 1780, 1742, 1708 cm^{-1} ; ^1H NMR ($CDCl_3$): δ 1.44 (s, 3H, *t*-Bu), 2.08 (s, 3H, OAc), 3.71 (ddd, 1H, *J* 3.8, 4.9, 8.8 Hz, H-3), 3.82, 4.24 (2d, 2H, *J* 18.1 Hz, NCH_2CO_2), 4.35, 4.43 2d, 2H, *J* 16.3 Hz, OCH_2COSPh), 4.40 (dd, 1H, *J* 8.8, 11.8 Hz, CH_AH_BOAc), 4.51 (dd, 1H, *J* 4.3, 11.8 Hz, CH_AH_BOAc), 5.42 (d, 1H, *J* 3.8 Hz, H-4); MS (HR-LSIMS) *m/z* $(M+H)^+$ calcd for $C_{20}H_{26}NO_7S$: 424.14299. Found: 424.14303.

(3S,4R,1'S) 3-t-Butyldiphenylsiloxymethyl-N-methoxycarbonylmethyl-4-(1'-thiophenoxycarbonyl)ethoxy-azetidin-2-one (**47**). Compound **47** was obtained from **46** according to the procedure described above, 78%; m.p. 103-104 °C; $[\alpha]_D$ -41.4° (*c* 1, CH_2Cl_2); IR ($CHCl_3$): 1770, 1749, 1705 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.07 (s, 9H, *t*-Bu), 1.46(d, 1H, *J* 6.8 Hz, CH_3), 3.60 (ddd, 1H, *J* 3.6, 3.8, 10.0 Hz, H-3), 3.69 (s, 3H, OCH_3), 3.96 (dd, 1H, *J* 3.8, 11.0 Hz. CH_AH_BOSi), 3.97, 4.33 (dd, 2H, *J* 18.1 Hz, NCH_2CO_2Me), 4.15 (dd, 1H *J* 10.0, 11.0 Hz, CH_AH_BOSi), 4.45 (q, 1H, *J* 6.8 Hz, $CHCH_3$), 5.43 (d, 1H, *J* 3.6 Hz, H-4). *Anal.* Calcd for $C_{23}H_{37}NO_6SSi$: C, 64.35; H, 6.30; N, 2.37. Found: C, 64.8; H, 6.3; N, 2.3.

(3S,4R) t-Butyl 7-deamino-3-acetoxy-7-acetoxymethyl-1-oxa-1-dethia-ceph-3-em-4-carboxylate (**45**). A solution of compound **43** (0.04 g, 0.09 mmol) in anhydrous THF (2 mL) was cooled -78 °C and treated with 1M solution of lithium bis-trimethylsilylamide in hexane (0.4 mL, 0.38 mmol). After 10 min. acetic acid (0.022 mL) was added and after additional 10 min acetic anhydride (0.5 mL) and pyridine (1.0 mL) were added. The temperature of reaction was allowed to rise to room temperature. The mixture was poured to into ice-water and extracted with toluene. The extract was washed, dried and concentrated. The crude product was purified by chromatography to give **45** (0.2 g, 50%), $[\alpha]_D$ +39.0° (*c* 0.8, CH_2Cl_2); IR (film): 1787, 1743, 1721 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.51 (s, 9H, *t*-Bu), 2.08, 2.23 (2s, 6H, 2OAc), 3.80 (ddd, 1H, *J* 4.0, 5.6, 8.6 Hz, H-7), 4.32, 4.36 (2d, 2H, *J* 17.4 Hz, H-2, 2'), 4.42 (dd, 1H, *J* 5.6, 11.8 Hz, CH_AH_BOAc), 4.45 (ddd, 1H, *J* 8.6, 11.8 Hz, CH_AH_BOAc), 5.13 (d, 1H, *J* 4.0 Hz, H-6). MS (HR-LSIMS) *m/z* $(M+Na)^-$ calcd for $C_{16}H_{21}NO_8Na$: 378.11648. Found: 378.11648.

(2S,6R,7S) Methyl 3-acetoxy-7-t-butyldiphenylsiloxymethyl-7-deamino-2-methyl-1-oxa-1-dethia-ceph-3-em-4-carboxylate (**49**). Compound **49** was obtained according to the procedure described above, 68%; oil, $[\alpha]_D$ +24.1° (*c* 1, CH_2Cl_2); IR ($CHCl_3$): 1786, 1727, 1644 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.04 (s, 9H, t-Bu), 1.37 (d, 1H, *J* 6.7 Hz, CH_3), 2.24 (s, 3H, OAc), 3.79 (m, 1H, H-7), 3.90 (s, 3H, OCH_3), 3.93 (dd, 1H, *J* 4.4, 10.7 Hz, CH_AH_BOSi), 4.18 (dd, 1H, *J* 9.5, 10.7 Hz, CH_AH_BOSi), 4.56 (q, 1H, *J* 6.7 Hz, H-2), 5.18 (d, 1H, *J* 4.0 Hz, H-6). *Anal.* Calcd for $C_{28}H_{33}NO_7Si$: C, 64.22; H, 6.35; N, 2.67. Found: C, 64.2; H, 6.5; N, 2.6.

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