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SYNTHESIS OF (6R) 4-*t*-BUTOXYCARBONYL-7-HYDROXYMETHYL-1-OXA-3-CEPHEM FROM D-ARABINAL

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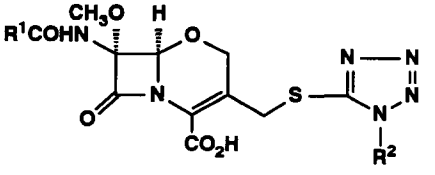
Abstract: Readily available from 3,4-di-*O*-trimethylsilyl-D-arabinal (**13**) bicyclic β-lactam **14** was converted into ylide **17** which was subsequently desilylated and subjected to glycolic cleavage of the *vic*-diol grouping. Dialdehyde **19** spontaneously cyclizied to a 1-oxacephem skeleton **16** which was subsequently reduced to *t*-butyl 7-hydroxymethyl-1-oxa-3-cephem-4-carboxylate (**21**).

The discovery by the Merck group[1] that 1-oxacephems display a higher antibacterial activity than that of the 1-thia congeners has prompted many laboratories[2] to develop new stereocontrolled and efficient entries to this class of antibiotics. Structure - activity relationship studies have led to the introduction by Shionogi on market of two 1-oxacephamycins: latamoxef **1**[3] in 1979 and flomoxef **2**[4] in 1985.



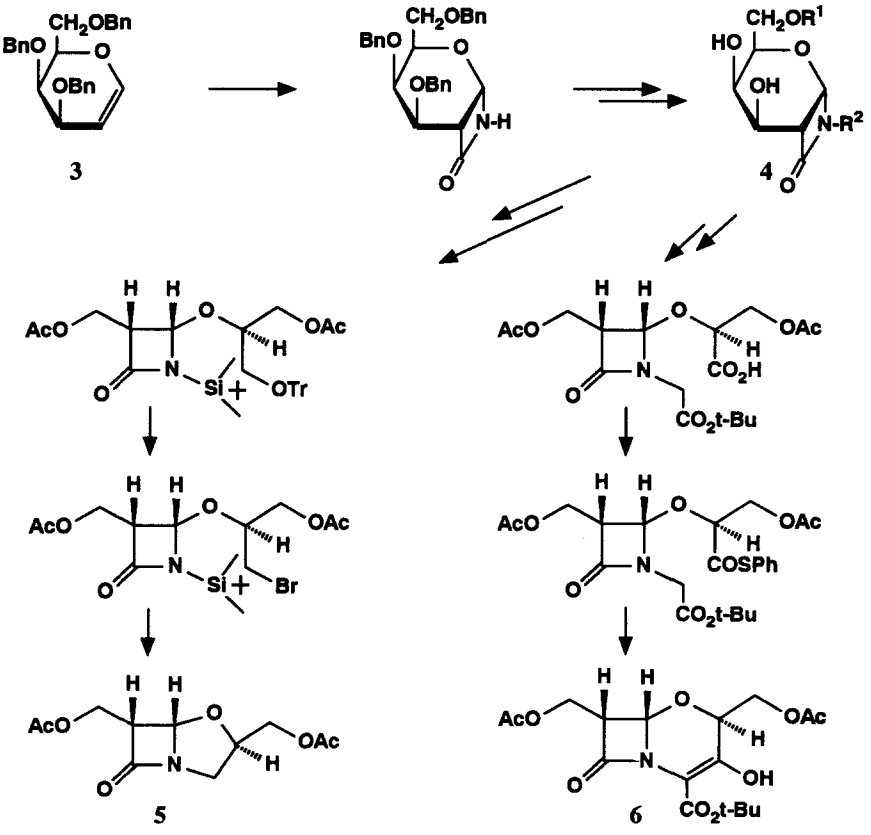
1: R^1= $HOC_6H_4\underset{|}{C}HCO_2H$, R^2= CH_3
2: R^1= $F_2CHSCH_2^-$, R^2= CH_2CH_2OH

Several years ago we have initiated a synthetic project leading from glycals and isocyanates to 1-oxabicyclic β-lactams.[5] Recently we have exemplified the general idea of the project, showing an entry to clavams[6] and 1-oxacephems[7] from tri-*O*-benzyl-D-galactal **3** (Scheme 1).

Stereocontrolled transformations of compound **4** into **5** and **6** have been a consequence of the specificity of [2+2]cycloaddition and suitable protection of the terminal hydroxymethyl group. This protection

allowed for retainment of chirality at the carbon atom stemming from C-5 of the glycal molecule. In both syntheses shown in Scheme 1 we have not discriminated carbon atoms which were split during the glycolic cleavage step. Our attempts to discriminate them *via* oxidation of dialdehyde **8** to the respective dicarboxylic acid **9**, and then decarboxylation of the group being in a malonyl array with the β-lactam carbonyl group failed, due to the β-elimination reaction[8] (Scheme 2).

Scheme 1

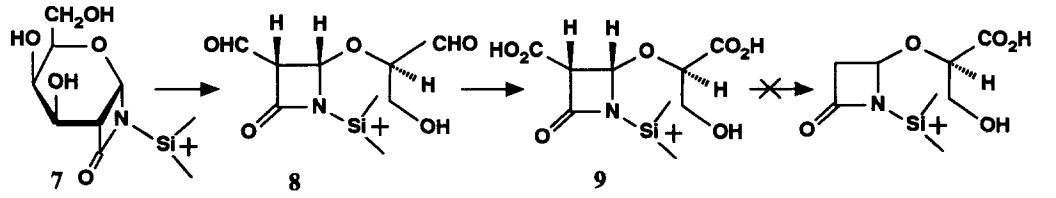


The discrimination of aldehyde groups obtained during a glycolic cleavage step could be achieved *via* trapping of one group by a nucleophilic center located next to the nitrogen atom to form simultaneously the 1-oxacephem skeleton. The simplest strategy of that kind required introduction to the nitrogen atom a malonyl fragment; the same approach had been accomplished by Merck group.[9]

In our case one aldehyde group formed during glycolic cleavage should simultaneously undergo the intramolecular aldol reaction with carbanion generated in the presence of a base. It should be, however,

pointed out that the intermediate contains two such nucleophilic centers. One located next to the nitrogen atom and the second one at C-3 of the azetidinone ring. Intramolecular aldol reaction involving C-3 carbon atom is a known process accompanying the glycolic cleavage reaction.[10]

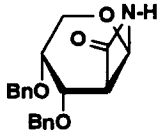
Scheme 2



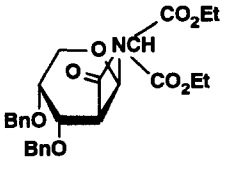
Alkylation of known β-lactam **10** was carried out with diethyl bromomalonate in a typical two-phase system according to the procedure described by Kałuża et al.[10,11] for alkylation of **10** with benzyl bromoacetate or benzyl chloride. The target molecule **11** was obtained, however, in 20%, yield only. Main products incorporated two or more malonyl molecules and were not investigated further.

Low yield of alkylation of **10** with bromomalonate prompted us to apply the glyoxylate method commonly used in β-lactam synthesis.[12,13] Alkylation of **10** with diethyl ketomalonate afforded hydroxyester **12** in a good yield. The next step, however, consisting in replacement of hydroxyl with a chlorine atom followed by reduction with tributylphosphine of the halogen gave **11** in 10% yield only. Due to the low yield of alkylation of **10** we resolved not to investigate further the aldol - reaction approach to 1-oxacephem skeleton.

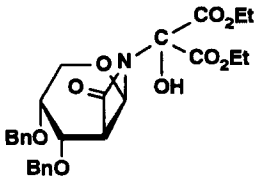
Discrimination of both carbon atoms in question can be achieved, however, directly after a glycolic cleavage step *via* trapping of one aldehyde group in intramolecular Wittig cyclization.



10



11

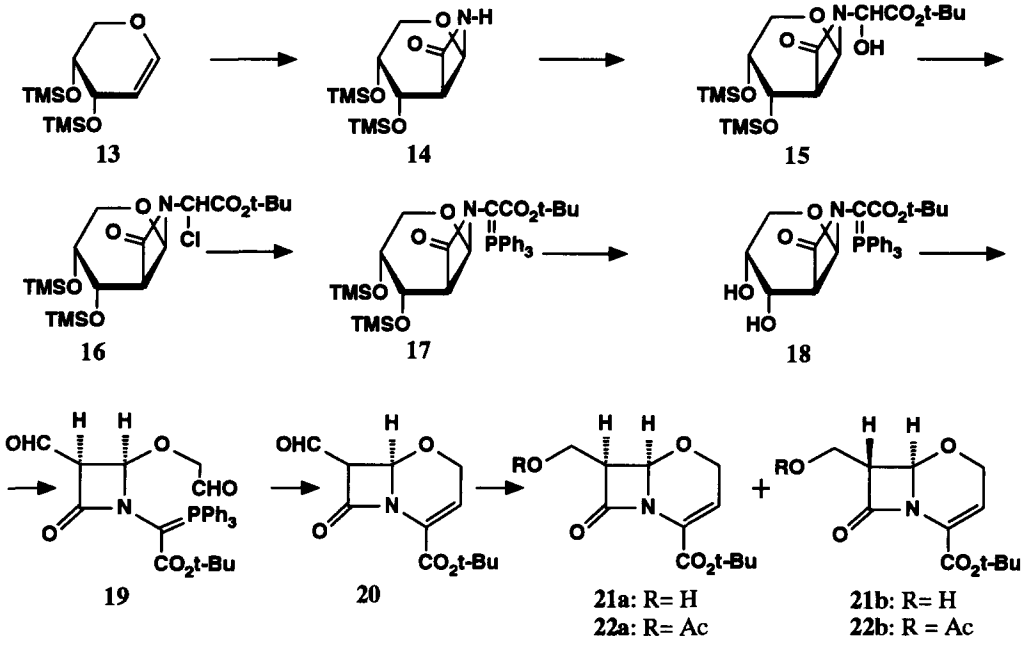


12

For our studies we selected 3,4-di-*O*-trimethylsilyl-D-arabinal **13**[10,14]; other protections of D-arabinal hydroxy groups, such as *O*-benzyl or *O*-isopropylidene, could not be removed at the later step of the synthesis. Compound **13** was subjected to [2+2]cycloaddition with chlorosulfonyl isocyanate in the presence of sodium carbonate;[15] the adduct was reduced with Red-Al[16] in order to remove the substituent from the nitrogen atom to afford known β-lactam **14**.[14] Bicyclic β-lactam **14** was converted into phosphorane **17** by

application of the well known Woodward[12] process as shown in Scheme 3. Silyl protections were subsequently removed with a hydrogen fluoride - pyridine complex to give diol **18**. Glycolic cleavage of the *vic* diol grouping with sodium metaperiodate proceeded smoothly to provide dialdehyde **19** which at pH 7-8 spontaneously cyclized to epimeric oxacephems **20**.

Scheme 3



Aldehydes **20** were subsequently reduced to the alcohols **21**, acetylated and characterized as a mixture of acetates (6R, 7S) **22a** and (6R, 7R) **22b** in a 3:2 ratio, respectively. Attempts to separate the mixture **22** into pure diastereomers by HPLC failed. The basic conditions of the intramolecular Wittig reaction caused epimerization at the carbon atom being the center of the malonyl fragment present in **19** and **20**. The sensitivity of that center to epimerization has been noticed earlier.[10]

Intramolecular Wittig cyclization and its variants have found much attention in penem and carbapenem synthesis[13] but has not so far been used for discrimination of two aldehyde functions during formation of a bicyclic skeleton.

The present synthesis of the 1-oxacephem system, is simple and the resulting product has R configuration of the C-6 carbon atom, which should be promising with regard to the potential biological activity of compounds **21**.[17]

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 using Varian Gemini 200 and Brucker AM 500 spectrometers. Mass spectra were obtained with an AMD 604 spectrometer. UV spectra were recorded with a Sonopan type ASP-87 spectrometer. Column chromatography was performed on Merck Kieselgel (230-400 mesh).

Compounds **10** and **14** were obtained according to the procedure described earlier.[15]

3,4-Di-*O*-benzyl-*N*-(di-ethoxycarbonyl)methyl-2-*C*:1-*N*-carbonyl-2-deoxy-β-D-arabino-pyranosylamine (11). To a solution of compound **10** (0.68 g, 2 mmol) in dry benzene (18 mL), anh. pulverized K_2CO_3 (8 g) and tetrabutylammonium bromide were added. Upon stirring and heating to 70°C for 1 h a solution of diethyl bromomolonate (0.3 mL, 3 mmol) in dry benzene (2 mL) was added dropwise. Stirring was continued for an additional 3 h. Subsequently the mixture was filtered, washed, dried, and evaporated. The crude syrup was purified on a silica gel and then separated on HPLC using dichloromethane - hexane - isopropanol 10:70:1 $^v/_v$ as an eluent to afford **11** (17 mg, 18%); $[\alpha]_D$ -82.0° (*c* 0.65, CH_2Cl_2); IR ($CHCl_3$): 1760, 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) selected absorptions: 1.28, 1.30 (dt, 6H, 2 CH_3), 3.56 (dd, 1H, *J* 5.3, 4.6 Hz, H-2), 5.00 (s, 1H, NCH), 5.77 (d, 1H, *J* 4.6 Hz, H-1); MS m/z: $M^{+\cdot}$ +1 498.

3,4-Di-*O*-benzyl-*N*-(di-ethoxycarbonyl)hydroxymethyl-2-*C*:1-*N*-carbonyl-2-deoxy-β-D-arabino-pyranosylamine (12). Compound **10** (0.68 g, 2 mmol) was dissolved in dry toluene (16 mL) and dry DMF (4 mL) and treated under dry nitrogen with molecular sieves 3Å (5 g) and diethyl ketomalonate (0.92 mL, 6 mmol). The mixture was stirred for 20 h at 40°C. Subsequently it was filtered through Celite, and evaporated. The crude product was purified on a silica gel column using hexane - ethyl acetate 2:1 $^v/_v$ as an eluent to give **12** (0.87 g, 85%); mp. 53-55°C; $[\alpha]_D$ -72.8° (*c* 1.0, CH_2Cl_2); IR ($CHCl_3$): 3400, 1760 cm^{-1}; ^{1}H NMR ($CDCl_3$) selected absorption: 1.29, 1.30 (2 t, 6H, 2 CH_3), 3.46 (t, 1H, *J* 4.6 Hz, H-2), 5.80 (d, 1H, *J* 4.6 Hz, H-1). Anal. calcd for $C_{27}H_{31}NO_4$: C, 63.15; H, 6.08; N, 2.73. Found: C, 62.75; H, 6.10; N, 3.00.

3,4-Di-*O*-benzyl-*N*-(di-ethoxycarbonyl)methyl-2-*C*:1-*N*-carbonyl-2-deoxy-β-D-arabino-pyranosylamine (11) from **12**. Compound **12** (0.51 g, 1 mmol) in dry THF (15 mL) and dry pyridine (0.1 mL, 12 mmol) was cooled under dry argon to -20°C and treated with thionyl chloride (0.08 mL, 1.1 mmol) in dry THF (1 mL). After 5 min temperature was raised to 0°C and the mixture was stirred for an additional 20 min. Subsequently it was filtered under dry argon, concentrated, and treated with tributylphosphine (0.55 mL, 2.2 mmol) dissolved in DMF - water 9:1 $^v/_v$ mixture (22 mL) and with KH_2PO_4 (1.1 molar equiv.). After 40 min the mixture was poured into brine (20 mL) and extracted with ethyl acetate. The solution was

washed, dry and evaporated. The crude product was purified on a silica gel column using hexane - ethyl acetate 6:1 $^{v}/_{v}$ as an eluent to give **11** (10%).

***N*-(*t*-butyloxycarbonyl)hydroxymethyl-3,4-di-*O*-trimethylsilyl-2-*C*:1-*N*-carbonyl-2-deoxy-β-D-arabino-pyranosylamine (15).** A mixture of **14** (0.9 g, 3.1 mmol), *t*-butyl glyoxylate (1.0 g, 7.8 mmol), activated molecular sieves 3Å (6 g), dry toluene (20 mL) and dry dimethylformamide (5 mL) was stirred overnight under argon atmosphere at 40°C. The sieves were filtered off, washed with toluene and the combined filtrates were concentrated in *vacuo*. The crude residue contained two stereoisomers **15** (1.4 g); IR ($CHCl_3$): 3320, 1770, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) selected absorption: major isomer (70%) 1.51 (s, 9H, *t*-Bu), 3.21 (t, 1H, *J* 4.7 Hz, H-2), 4.05 (dd, 1H, *J* 3.0, 4.7 Hz, H-3), 5.27 (s, 1H, NCH), 5.47 (d, 1H, *J* 4.7 Hz, H-1); minor isomer (30%) 1.53 (s, 9H, *t*-Bu), 3.23 (t, 1H, *J* 4.5 Hz, H-2), 4.08 (dd, 1H, *J* 2.9, 4.5 Hz, H-3), 5.11 (s, 1H, NCH), 5.37 (d, 1H, *J* 4.5 Hz, H-1).

***N*-(*t*-Butoxycarbonyl)chlorometyl-3,4-di-*O*-trimethylsilyl-2-*C*:1-*N*-carbonyl-2-deoxy-β-D-arabinopyranosylamine (16).** To a cold solution of the crude hydroxy derivative **15** (1.4 g) in THF (30 mL) and pyridine (0.8 mL), a solution of thionyl chloride (0.28 mL, 3.8 mmol) in THF (2 mL) was added at -20°C under argon. After being stirred for 30 min at about -20°C, the reaction mixture was diluted with toluene, washed with cold water, dried, and evaporated under reduced pressure to give crude chloride **16** (1.6 g); IR ($CHCl_3$): 1790, 1780, 1760, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) selected absorptions: major isomer (70%) 1.51 (s, 9H, *t*-Bu), 3.26 (t, 1H, *J* 4.9, H-2), 4.05 (dd, 1H, *J* 2.9, 4.9 Hz, H-3), 5.57 (d, 1H, *J* 4.9 Hz, H-1), 5.90 (s, 1H, NCH); minor isomer (30%) 1.52 (s, 3H, *t*-Bu), 3.33 (t, 1H, *J* 4.4 Hz, H-2), 4.10 (dd, 1H, *J* 2.6, 4.4 Hz, H-3), 5.75 (d, 1H, *J* 4.40 Hz, H-1), 5.85 (s, 1H, NCH).

***N*-(*t*-Butyloxycarbonyl)triphenylphosphoranylidenemethyl-3,4-di-*O*-trimethylsilyl-2-*C*:1-*N*-carbonyl-2-deoxy-β-D-arabinopyranosylamine (17).** To a solution of crude chloride **16** (1.6 g) in dry THF (40 mL), 2,6-lutidine (0.6 mL, 5.2 mmol) and triphenylphosphine (1.3 g, 5 mmol) were added, and the mixture was stirred under argon for 16 h at 40°C. The reaction mixture was diluted with toluene, washed with brine, dried, and concentrated. The residue was purified on a silica gel column, using *t*-butyl methyl ether - hexane as an eluent to obtain ylide **17** (~1.1 g, 53%); mp (with decomp.) 171-174°C; $[\alpha]_D$ -92.2° (*c* 1, CH_2Cl_2); IR (KBr): 1745, 1637, 1625 cm^{-1}; Anal. calcd for $C_{36}H_{48}NO_6PSi_2$: C, 63.78; H, 7.14; N, 2.07. Found: C, 63.59; H, 7.22; N, 2.32; MS (EI) m/z: $M^{+\cdot}$ calcd for $C_{36}H_{48}NO_6PSi_2$: 677.27578. Found: 677.27595.

***N*-(*t*-Butyloxycarbonyl)triphenylphosphoranylidenemethyl-2-*C*:1-*N*-carbonyl-2-deoxy-β-D-arabino-pyranosylamine (18).** To the ylide **17** (1.1 g, 1.6 mmol) in dry Et_2O (50 mL) at -70°C, the hydrogen

fluoride-pyridine complex in dry THF (0.5:4.5 $^{v}/_{v}$; 1 mL) was added. When the addition was complete, the solution was slowly warmed to -20°C and left in deep-freezing compartment for two days. The crystalline product was separated by filtration (0.52 g); additionally, 0.15 g of **18** was obtained from the filtrate by chromatography on silica gel (hexane/ethyl acetate/methanol 25:20:7 as an eluent) (85%); mp (with decomp.) 148-152°C; $[\alpha]_D$ -88.2° (*c* 0.8, MeOH); IR (KBr): 3433, 1738, 1616 cm^{-1}; MS (CI) m/z: 534 (M^++ H). Anal. calcd for $C_{30}H_{32}NO_6P$: C, 67.53; H, 6.05; N, 2.63. Found: C, 67.37; H, 6.19; N, 2.75.

(6R, 7S) and (6R, 7R) *t*-Butyl 7-acetoxymethyl-1-oxa-3-cephem-4-carboxylate (22a and **22b)**. Compound **18** (0.51 g, 0.95 mmol) was dissolved in methanol (14 mL) and 3% aqueous ammonium sulfate (14 mL), cooled to -4°C, and treated with $NaIO_4$ (0.23 g, 1.1 mmol) in water (1.5 mL). After 15 min saturated aqueous sodium hydrogen carbonate (4 mL) was added, and the temperature was allowed to rise to 10°C. Stirring and cooling (below 10°C) were maintained for an additional 30 min. Subsequently sodium borohydride (3 eq, 0.12 g) in water (1 mL) was added. Methanol was evaporated, the solution was salted out with ammonium sulfate, and extracted with ethyl acetate. The extract was dried, evaporated, and the residue was acetylated; the acetate was purified on a silica gel column using hexane-*t*-butyl methyl ether - CH_2Cl_2 (9:1:0.5 $^{v}/_{v}$, respectively) as an eluent to give **22a** and **22b** in a 3:2 ratio (43 mg, 16% from **18**). IR (film): 1787, 1744 cm^{-1}; UV (EtOH): 257.4 nm (ε = 7300); ^1H NMR (C_6D_6): **22a** (60%) 1.50 (s, 9H, *t*-Bu), 1.55 (s, 3H, OAc), 3,27 (m, 1H, H-7), 3.46 (dd, 1H, *J* 2.0, *J* 18.5 Hz, H-2), 3.65 (dd, 1H, *J* 3.9, 8.5 Hz, H-2'), 4.15 (d, 1H, *J* 4.1 Hz, H-6), 4.38, 4.45 (2 x dd, 2H, CH_2OAc), 5.81 (dd, 1H, H-3); **22b** (40%) 1.51 (s, 9H, *t*-Bu), 1.59 (s, 3H, OAc), 3.07 (m, 1H, H-7), 3.55 (dd, 1H, *J* 2.0, 18.5 Hz, H-2), 3.73 (dd, 1H, *J* 4.0, 18.5 Hz, H-2'), 4.03, 4.06 (2 dd, 2H, CH_2OAc), 4.35 (bs, 1H, H-6), 5.84 (dd, 1H, H-3). Anal. calcd for $C_{14}H_{19}NO_6$: C, 56.56; H, 6.44; N, 4.71. Found: C, 55.98; H, 6.68; N, 4.30; MS (EI) m/z: $M^{+\cdot}$ calcd for $C_{14}H_{19}NO_6$: 297.12123. Found: 297.12246.

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