Tetrahedron Vol. 45, No. 22, pp. 7195 to 7200, 1989
Printed in Great Britain.

0040-4020/89 $3.00+.00

SYNTHESIS OF 1-OXABICYCLIC β-LACTAM PRECURSORS FROM 4,6-O-BENZYLIDENE-D-ALLAL

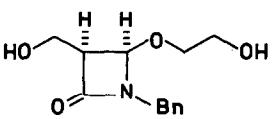
Zbigniew Kaluza and Marek Chmielewski*

Institute of Organic Chemistry Polish Academy of Sciences
01-224 Warsaw, POLAND

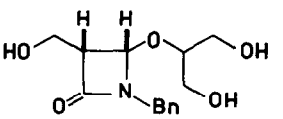
(*Received in UK 29 August* 1989)

Abstract: Cycloaddition of trichloroacetyl isocyanate to 4,6-O-benzylidene-D-allal **4** follwed by N-deprotection of the adduct produces β-lactam **9** with a good yield. Subsequent N-benzylation, 4,6-O-deprotection by hydrogenolysis, and a glycolic cleavage of the *vic* diol grouping in N-benzyl-2-carboxy-2-deoxy-β-D-altrohexo-pyranosylaminoalactam (**13**) affords 3,4-disubstituted azetidinone **5**, which is in enantiomeric relation to the previously reported compound **2**[1,2].

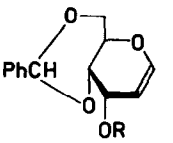
Recently, we reported on the synthesis of 3-hydroxymethyl-4-alkoxyazetidinones **1** and **2** from glycals[1,2]. Owing to stereospecificity of a crucial [2+2] cycloaddition step[3], the configuration at the C-3 carbon atom of the starting glycal determines the configuration at the carbon atom attached to the nitrogen and oxygen atoms[2]. The R configuration at that carbon atom determines biological activity of β-lactam antibiotics[4].



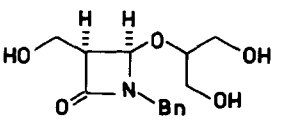
1



2



3: R=H
4: R=TMS



5

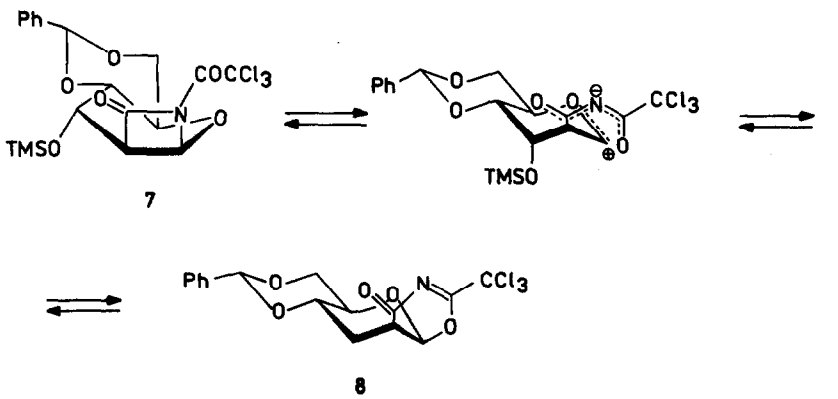
Scheme 1

R configuration at C-3 of a glycal, present for example in D-glucal or D-galactal, produces S configuration at C-4 of the azetidinone derivative 2, thus precluding the use of these glycals in the synthesis of biologically active 1-oxaphenams and 1-oxacephems having side chains at C-2.

1,5-Anhydro-4,6-O-benzylidene-2-deoxy-D-ribohexitol (4,6-O-benzylidene-D-allal, 3), readily available from methyl α-D-glucoside[5], has S configuration at C-3 and thus offers formation of 5 which is the enantiomeric form of 2 obtained previously from D-glucal or D-galactal.

Cycloaddition of trichloroacetyl isocyanate (6) to silylated allal 4 proceeds more slowly than is observed in reactions with monocyclic glycals. In $CDCl_3$ with two molar equiv. of the isocyanate, the reaction mixture contained after 7 days 72% of [2+2] cycloadduct 7, 15.7% of [4+2] cycloaduduct 8, and 12.3% of the substrate 4, whereas after 14 days, the respective proportions were 66.8% of 7, 27.5% of 8, and 5.7% of 4. In nitromethane with four molar equiv., after 3 days, 76.0% of 7, 8.7% of 8, and 15.0% of 4; after 4 days, 81.0% of 7, 12.9% of 8, and 6.1% of 4, and after 5 days, 80.3% of 7, 14.3% of 8, and 5.4% of 4 were found. The high yield of 7 found in this reaction should be noted, since in the previously performed reactions, the content of [2+2] cycloadducts exceeded 50% only in one case[2]. In this instance, 3,4,6-tri-O-benzyl-D-galactal with trichloroacetyl isocyanate in acetonitrile solution afforded a mixture of cycloadducts containing up to 75% of the [2+2] cycloadduct[2].

The dependence of [2+2] cycloadduct content on a glycal substitution and on configuration remains unclear. In all cases, [2+2] cycloadduct is a kinetic product which slowly rearranges to the [4+2] imidate *via* a zwitterion intermediate[3,6]. (Scheme 2).



Scheme 2

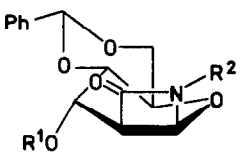
Surprisingly, in this case also, the content of 8 increases with reaction time, despite unfavorable stereoelectronic effects associated with substituents at the C-1 and C-2 carbon atoms in 8.

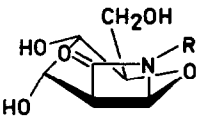
The mixture of cycloadducts 7 and 8 obtained in nitromethane solution was treated with ammonia to deprotect the β-lactam nitrogen atom and to bind unreacted isocyanate. After crystallization from methanol-water, 9 was obtained in 50% yield. According to ^{1}H NMR and X-ray data, the pyranoid rings in 9 and 10 exist as a regular half-chair form[7] in solution as well as in the crystalline state.

Hydrogenolysis of 9 in methanol over a palladium catalyst gave unprotected sugar β-lactam 11 with β-altro configuration. Examination of the ^{1}H NMR data of 11 (J_{45} = 7.8 Hz) verifies the substantial preference of $^4H_5$ conformation in the equillibrium.

Benzylation of the nitrogen atom in 9 in boiling benzene using potassium carbonate and tetrabytylammonium bromide as a catalyst afforded N-benzyl derivative 11 only.

Hydrogenolysis of 11 over a palladium catalyst led to deprotection of oxygen atoms affording 12.





9: R^1=R^2=H
10: R^1=Ac, R^2=H
11: R^1=H, R^2=Bn

12: R=H
13: R=Bn

Scheme 3

Glycolic cleavage of the *vic* diol grouping present in 12, with sodium metaperiodate under standard conditions, led to formation of a dialdehyde which, without isolation, was subsequently reduced to the diol 5. Compound 5 showed the same spectral data as its enantiomer 2[2].

EXPERIMENTAL

Melting points are uncorrected. Optical rotations were measured with a JASCO Dip-360 digital polarimeter. IR spectra were recorded with a Beckman

4240 spectrophotometer. ^{1}H NMR spectra were recorded with a Bruker AM 500 spectrometer. Column chromatography was performed on Merck Kieselgel 60 (230-400 mesh).

Compound 4 was obtained from 3 using a standard silylation method with trimethylchlorosilane and pyridine.

4,6-O-Benzylidene-3-carboxy-2-deoxy-β-D-altrohexopyranosylamino-lactam (9). Allal 4 (3.0 g, 10 mmol) was dissolved in dry niromethane (10 mL) after which trichloroacetyl isocyanate (4.75 mL, 40 mmol) was added at room temperature. The mixture remained for 4 days at room temperature to complete the cycloaddition, the time of reaction being determined by conducting a pilot experiment in a ^{1}H NMR tube[3]. Subsequently, the mixture was diluted with nitromethane (10 mL) and cooled to -30°C, after which ammonia in nitromethane solution (30 mL; 1 mL contained 1.4 mmol of ammonia) was added, and the tempereture was allowed to rise to room temperature. The solvent was then evaporated and the residue was treated with diethyl ether. The crystalline precipitate was removed by filtration and washed with hexane. This filtrate and washings were combined and evaporated. The oily residue was purified on a column of silica gel by flash chromatography to give 9 (1.4g, 50%); m.p. 137.0-138.0°C; $[\alpha]_D$ = -30.0° (*c* 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): 3.64 (m, 1H, H-2), 3.65 (t, 1H, J_{56} = 10.2, $J_{66'}$ = 10.5 Hz, H-6), 3.94 (dd, 1H, J_{34} = 2.9, J_{45} = 9.5 Hz, H-4), 4.13 (dt, 1H, $J_{56'}$ = 5.2 Hz, H-5), 4.33 (dd, 1H, H-6'), 4.50 (m, 1H, H-3), 5.40 (d, 1H, J_{12} = 4 Hz, H-1). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 58.42; H, 6.63; N, 4.01. Found: C, 58.7; H, 6.8; N, 4.1.

2-carboxy-2-deoxy-β-D-altrohexopyranosylaminolactam (12). Compound 9 (0.28 g, 1 mmol) in methanol (10 mL) was shaken at room temperature in the presence of 10% Pd/C under hydrogen (1 atm) for 6 h. Subsequently, the solvent was evaporated to afford 12 (0.17 g , 90%); m.p. 142-143°C; $[\alpha]_D$ = +28.5° (*c* 1, CH_3OH); ^{1}H NMR (D_2O): 3.59 (dd, 1H, J_{12} = 4.0, J_{23} = 4.6 Hz, H-2), 3.73 (dd, 1H, J_{56} = 6.2, $J_{66'}$ = 12.3 Hz, H-6), 3.79 (dd, 1H, $J_{56'}$ = 2.9 Hz, H-6'), 3.90 (dt, 1H, J_{45} = 7.8 Hz, H-5), 3.93 (dd, 1H, J_{34} = 2.6 Hz, H-3), 4.65 (dd, 1H, H-3), 3.95 (d, 1H, H-1). IR (nujol): 3440, 3320, 1755 cm^{-1}. Anal. Calcd for $C_7H_{11}NO_5$: C, 44.45; H, 5.86; N, 7.40. Found: C, 44.4; H, 5.9; N 7.6.

N-benzyl-4,6-O-benzylidene-2-carboxy-2-deoxy-β-D-altrohexopyranosylamino-lactam (11). To a solution of 9 (0.14 g, 0.5 mmol) in benzene (10 mL) were added pulverized K_2CO_3, tetrabutylammonium bromide (0.1 g), and benzyl bromide (0.08 mL). The mixture was stirred under reflux for 2 h, at which time 8 disappeared (TLC). The reaction mixture was then filtered, evaporated, purified on silica gel, and crystallized from ethyl acetate - hexane to give 11 (0.125 g, 68%); m.p. 154-155°C; $[\alpha]_D$ = -58.7° (*c* 1, CH_2Cl_2); IR ($CDCl_3$):

3600, 1775 cm^{-1}; ^1H NMR ($CDCl_3$): 3.45 (t, 1H, J_{56} = 20.2, $J_{66'}$ = 10.6 Hz, H-6), 3.64(bd, 1H, H-2), 3.91 (dd, 1H, J_{34} = 2.9, J_{45} = 9.6 Hz, H-4), 4.15 (dt, 1H, $J_{56'}$ = 5.2 Hz, H-5), 4.24, 4.51 (2d, 2H, CH_2Ph), 4.28 (dd, 1H, H-6'), 4.56 (m, 1H, H-3), 5.26 (d, 1H, J_{12} = 3.8 Hz, H-1). Anal. Calcd. for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81. Found: C, 68.8; H, 5.5; N, 3.80.

N-Benzyl-2-carboxy-2-deoxy-β-D-altrohexopyranosylaminolactam (13). Compound 11 (0.22 g, 0.6 mmol) in methanol (10 mL) was shaken at room temperature in the presence of 10% Pd/C under hydrogen (3 atm) for 4 h. Subsequently, the solvent was evaporated and crude 13 was recrystallized from methanol - ethyl acetate - hexane to give a 0.134 g (80%) yield; m.p. 141-142°C; $[\alpha]_D$ = +6.2° (*c* 1, CH_3OH); IR (nujol): 3420, 1755 cm^{-1}; ^1H NMR (D_2O): 3.43 (dd, 1H, J_{56} = 6.2, $J_{66'}$ = 12.2 Hz, H-6), 3.64 (t, 1H, J_{12} = 4.1, J_{23} = 3.9 Hz, H-2), 3.71 (dd, 1H, $J_{56'}$ = 2.6 Hz, H-6'), 3.91 (dd, 1H, J_{34} = 2.4, J_{45} = 8.4 Hz, H-4), 3.93 (dt, 1H, H-5), 4.30 (dd, 1H, H-3), 4.42, 4.54 (2d, 1H, CH_2Ph), 5.34 (d, 1H, H-1). Anal. Calcd. for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.13; N, 5.01. Found: C, 60.2; H, 6.1; N, 5.2.

(3S,4R)-N-Benzyl-3-hydroxymethyl-4-(1',3'-dihydroxyizopropoxy)-azetidinone (5) To a solution of 13 (0.084 g, 0.3 mmol) in methanol - water (1:3 v/v; 4 mL), ammonium sulfate (0.14 g) was added. The mixture was cooled to -5°C and sodium metaperiodate (0.071 g, 0.33 mmol) in water (1 mL) was added. The stirring and cooling were maintained for 5 min.. Subsequently, sodium borohydride (0.04 g) was added. The precipitate of sodium iodate was removed by filtration, methanol was evaporated, and ammonium sulfate (2 g) was added. The solution was extracted with ethyl acetate. The extract was dried, evaprated, and purified on a silica gel column to give 5 (0.075 g, 90%); m.p. 76-77°C; $[\alpha]_D$ = +28° (*c* 1, CH_3OH); spectral data were identical with those reported previously[2]. Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.9; H, 7.0; N, 4.7.

ACKNOWLEDGMENT

This work was supported by the Polish Academy of Sciences grant CPBP - 01.13.2.15.

REFERENCES

1. M. Chmielewski, Z. Kaluza, W. Abramski, and C. Belzecki, *Tetrahedron Lett.*, 28, 3035 (1987);

2. M. Chmielewski, Z. Kaluza, W. Abramski, J. Grodner, C. Belzecki, and P. Sedmera, *Terahedron*, **45**, 227 (1989).
3. M. Chmielewski and Z. Kaluza, *Carbohydr. Res.*, **167**, 143 (1987); M. Chmielewski, Z. Kaluza, W. Abramski, D. Mostowicz, B. Hintze, and C. Belzecki, *Bull. Pol. Acad. Sci. Chem.*, **35**, 245 (1987).
4. R.B. Morin and M. Gorman Ed., *Chemistry and Biology of β-Lactam Antibiotics*, Academic Press, 1982, New York.
5. M. Sharma, R.K. Brown, *Canad. J. Chem.*, **44**, 2825 (1966).
6. J.L. Chitwood, P.G. Gott, and J.C. Martin, *J. Org. Chem.*, **36**, 2228 (1971).
7. M. Chmielewski, Z. Kaluza, K. Suwińska, H. Dodziuk, D. Rosenbaum, H. Duddeck, P. Magnus, and J. C. Huffman, *Carbohydr. Res.*, to be published.