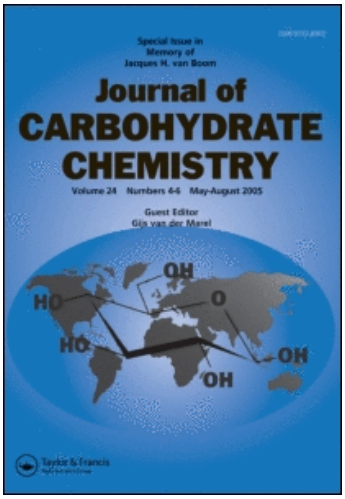


Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Synthesis of (3*R*,5*S*,6*R*) 2,6-Diacetoxymethylclavam from D-Galactal

Marek Chmielewski[a]; Jacek Grodner[a]
[a] Institute of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland

To cite this Article Chmielewski, Marek and Grodner, Jacek(1992) '(3*R*,5*S*,6*R*) 2,6-Diacetoxymethylclavam from D-Galactal', Journal of Carbohydrate Chemistry, 11: 6, 691 — 698
To link to this Article: DOI: 10.1080/07328309208020086
URL: http://dx.doi.org/10.1080/07328309208020086

J. CARBOHYDRATE CHEMISTRY, 11(6), 691-698 (1992)

SYNTHESIS OF (3*R*,5*S*,6*R*) 2,6-DIACETOXYMETHYLCLAVAM FROM D-GALACTAL

Marek Chmielewski* and Jacek Grodner

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

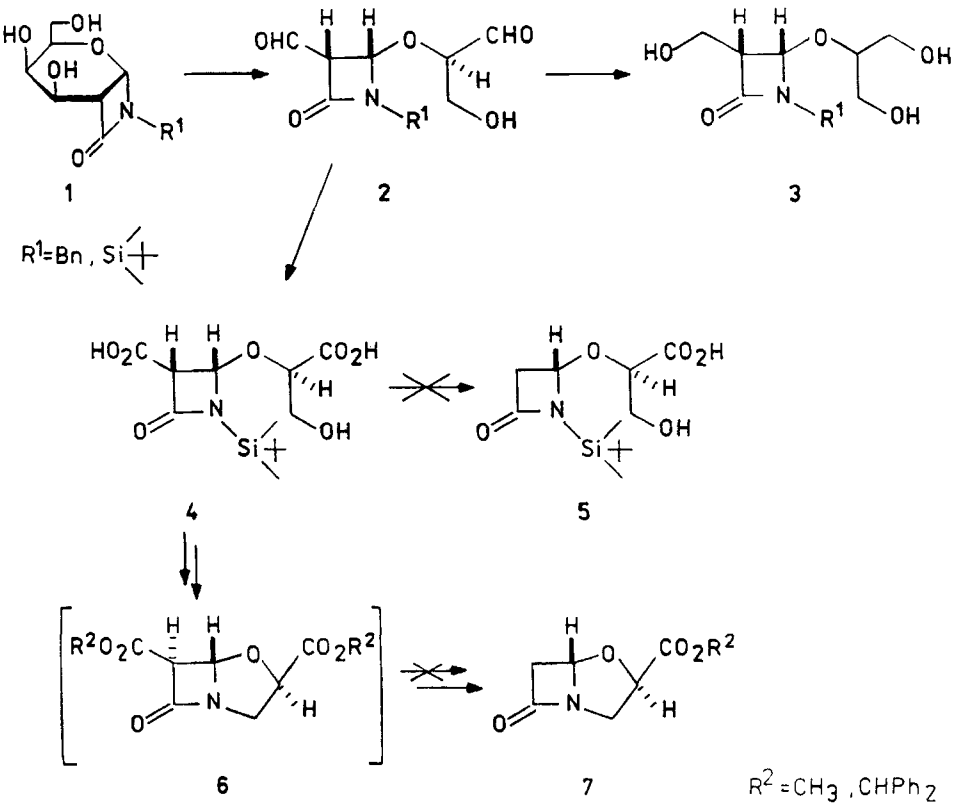
Received January 7, 1992 - Final form May 26, 1992

ABSTRACT

N-(*t*-Butyl)dimethylsilyl-2-*C*:1-*N*-carbonyl-2-deoxy-α-D-galactopyranosylamine (1) was tritylated and the product was subjected to a glycolic cleavage to give dialdehyde 10. Subsequently, compound 10 was transformed into bromide 14 using standard procedures. The fluoride anion induced cyclization in 14 afforded clavam 15.

INTRODUCTION

Recently we have reported that the readily available *N*-benzylated or *N*-silylated 2-*C*:1-*N*-carbonyl-2-deoxy-α-D-galactopyranosylamines (1) could be oxidized to reactive dialdehydes 2[1,2,3] which had to be stabilized either by reduction to triols 3[1,2] or by oxidation to dicarboxylic acids 4.[3] Compounds 3 and 4 open a stereocontrolled access to 1-oxabicyclic β-lactams. However, attempts to transform the dicarboxylic acid 4 into the clavam skeleton 7 either *via* decarboxylation-cyclization, or by a reversed sequence (Scheme 1) have failed. This could be attributed to the low stability of the 3-alkoxycarbonyl-4-alkoxyazetidinone-2 system, which promoted decomposition *via* β-elimination pathways.[3]

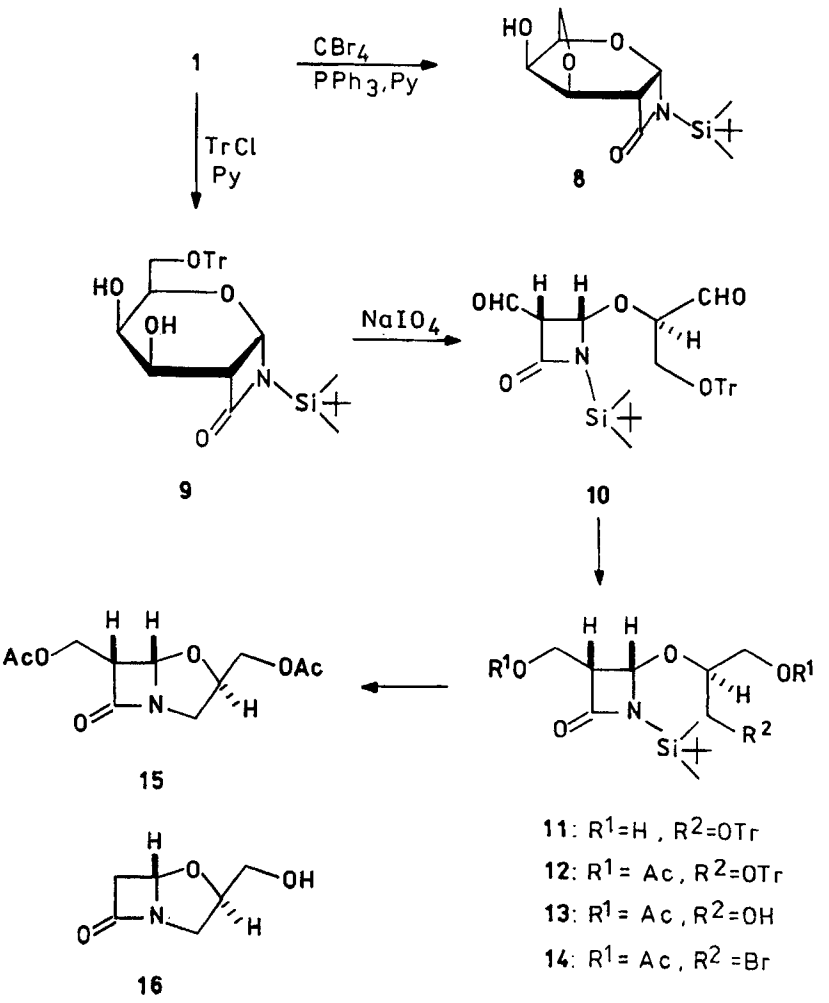


Scheme 1

RESULTS AND DISCUSSION

The negative results mentioned above prompted us to investigate the construction of the clavam skeleton by an alternative route, utilizing derivatives of the triol 3. Since there is a loss of chirality at the carbon atom stemming from C-5 of the sugar 1 after the reduction of 2, such approach requires selective protection of the 6-OH group, or its tran sformation into a substituent, for example a leaving group, which can be useful at the later step of the clavam synthesis.

Treatment of the sugar 1[3] with the carbon tetrabromide - triphenyl phosphine system led to formation of the 3,6-anhydro compound 8 (Scheme 2). This undesirable intramolecular displacement, which is opposed to the literature data,[4] did not encourage further studies in that way.



Scheme 2

The 6-OH group was tritylated using the standard procedure to afford 9. Glycolic cleavage of the *vic*-diol grouping in 9 with sodium metaperiodate proceeded satisfactorily to give dialdehyde 10 which was immediately reduced, and the resulting hydroxyl groups were acetylated; the *cis* configuration of the azetidinone ring was preserved. The trityl group in 12 was removed by hydrogenolysis;[5] the *N*-TBDMS protecting group remained untouched. Displacement of the OH group by a bromine atom using the carbon tetrabromide - triphenylphosphine reagent,[4] produced compound 14. The fluoride anion induced intramolecular cyclization[6] led to

formation of the clavam skeleton 15 being the 6-substituted derivative of the β-lactam metabolite 16 discovered by Brown, Evans, and Fletton.[7] Removal of the 6-hydroxymethyl group from 15 remains the unsolved problem of the above presented approach to clavams, a particularly important problem because natural clavams do not have any substituent at the C-6 carbon atom.[7,8]

EXPERIMENTAL

Melting points are reported uncorrected. Optical rotations were measured with a JASCO Dip-360 digital polarimeter. IR spectra were taken with a Beckman 4240 spectrophotometer. ^{1}H NMR spectra were recorded with Varian Gemini 200 and Bruker AM 500 spectrometers. Column chromatography was performed on Merck Kieselgel 60 (230-400 mesh).

Compound 1 was obtained by the reaction sequence described earlier.[1,3,9]

3,6-Anhydro-*N*-*t*-butyldimethylsilyl-2-*C*:1-*N*-carbonyl-2-deoxy-α-D-galactopyranosylamine (8). Compound 1 (0.61 g, 2 mmol) was dissolved in anhydr. pyridine (20 mL) and treated with triphenylphosphine (1.6 g, 6 mmol). The solution was cooled to 0 °C and treated with carbon tetrabromide (1.02 g, 3 mmol). The mixture was stored at room temp. for 6 h, whereupon it was poured into cold water and extracted with chloroform. The extract was washed, dried and concentrated. The residue was purified on a silica gel column using hexane-ethyl acetate (4 : 1 v/v) as an eluent to give 8 (0.42 g, 72%) mp 134-136 °C; $[\alpha]_D$ +58.9° (*c* 1, CH_2Cl_2); IR (KBr) 1710 cm^{-1} (β-lactam); ^{1}H NMR ($CDCl_3$) δ 0.23, 0.26, 0.97 (3s, 15H, *t*-BuMe_2Si), 3.74 (t, 1H, $J_{1,2}$ = 4.2, $J_{2,3}$ = 3.6 Hz, H-2), 3.90 (d, 1H, $J_{6,6'}$ = 10.1 Hz, H-6), 4.16 (dd, 1H, $J_{5,6'}$ = 3.6 Hz, H-6'), 4.38 (bd, 1H, H-5), 4.50 (d, 1H, H-3), 4.55 (d, 1H, $J_{4,5}$ = 1.3 Hz, H-4), 5.19 (d, 1H, H-1).

Anal. Calcd for $C_{13}H_{23}NO_4Si$: C, 54.70; H, 8.14; N, 4.91. Found: C, 54.84; H, 8.40; N, 5.11.

Acetate: mp 114-115 °C; $[\alpha]_D$ +35.5° (*c* 1, CH_2Cl_2); IR (KBr) 1730 cm^{-1} (β-lactam, acetate); ^{1}H NMR ($CDCl_3$) δ 0.25, 0.28, 1.00 (3s, 15H, *t*-BuMe_2Si), 2.09 (s, 3H, OAc), 3.78 (t, 1H, $J_{1,2}$ = 4.2, $J_{2,3}$ = 3.6 Hz, H-2), 3.96 (d, 1H, $J_{6,6'}$ = 10.2 Hz, H-6), 4.03 (dd, 1H, $J_{5,6'}$ = 3.5 Hz,

H-6'), 4.46 (m, 1H, H-5), 4.61 (d, 1H, H-3), 5.23 (d, 1H, H-1), 5.52 (d, 1H, $J_{4,5}$ = 1.2 Hz, H-4).

Anal. Calcd for $C_{15}H_{25}NO_5Si$: C, 55.01; H, 7.70; N, 4.28. Found: C, 54.84; H, 7.82; N,4.09.

***N*-*t*-Butyldimethylsilyl-6-*O*-trityl-2-*C*:1-*N*-carbonyl-2-deoxy-α-D-galactopyranosylamine** (9). To a solution of compound 1 (0.61 g, 2 mmol) in anhydr. pyridine (20 mL), 4-*N*,*N*-dimethylaminopyridine (10 mg) and triphenylmethyl chloride (0.67 g, 2.4 mmol) were added. The mixture was stored at room temp. for several days, until disappearance of the substrate (TLC: hexane acetate 1:1 v/v hexane-ethyl acetate 1:1 v/v). The mixture was then poured into ice-water and extracted with toluene (2 x 100 mL). The extract was washed, dried and concentrated. The residue was purified on silica gel using hexane-ethyl acetate (2:1 v/v) as an eluent to give **9** (0.76 g, 70%); mp 81-84 °C; $[\alpha]_D$ +41.8° (*c* 1, CH_2Cl_2); IR (film) 1760 cm^{-1}(β-lactam); ^1H NMR ($CDCl_3$) δ 0.24, 0.26, 0.94 (3s, 15H, *t*-BuMe_2Si), 3.27 (t, 1H, $J_{1,2}$ = 4.8, $J_{2,3}$ = 3.9 Hz, H-2), 3.32 (dd, 1H, $J_{5,6}$ = 4.8, $J_{6,6'}$ = 9.8 Hz, H-6), 3.43 (dd, 1H, $J_{5,6'}$ = 5.4 Hz, H-6'), 3.78 (t, 1H, H-5), 3.94 (d, 1H, $J_{3,4}$ = 4.2 Hz, H-4), 4.05 (t, 1H, H-3), 5.44 (d, 1H, H-1);

Anal. Calcd for $C_{32}H_{39}NO_5Si$: C, 70.43; H, 7.20; N,2.57. Found: C, 70.33; H, 7.25; N,2.80.

Diacetate: mp 63-65 °C; $[\alpha]_D$ +60.4° (*c* 1, CH_2Cl_2); IR (film) 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.24, 0.25, 0.95 (3s, 15H, *t*-BuMe_2Si), 1.91, 1.99 (2s, 6H, 2 OAc), 3.02 (dd, 1H, $J_{5,6}$ = 7.5, $J_{6,6'}$ =9.3 Hz, H-6), 3.26 (dd, 1H, $J_{5,6'}$ = 5.5 Hz, H-6'), 3.29 (t, 1H, $J_{1,2}$ = 4.8, $J_{2,3}$ = 4.9 Hz, H-2), 4.02 (dd, 1H, H-5), 5.35 (dd, 1H, $J_{3,4}$ = 4.3 Hz, H-3), 5.38 (d, 1H, H-1), 5.50 (dd, 1H, $J_{4,5}$ = 0.6 Hz, H-4);

Anal. Calcd for $C_{36}H_{43}NO_7Si$: C, 68.65; H, 6.88; N, 2.22. Found: C, 68.80; H, 7.07; N, 2.31

(3*R*,4*S*,1'*R*) 3-Acetoxymethyl-*N*-*t*-butyldimethylsilyl-4-(1'-acetoxymethyl-2'-triphenylmethoxy)-ethoxyazetidinone-2 (12). Compound **9** (0.21 g, 0.38 mmol) was dissolved in a mixture of *t*-butyl alcohol (6 mL) and a 4% aqueous solution of $(NH_4)_2SO_4$ (6 mL). Subsequently the mixture was cooled to 0 °C and treated with sodium metaperiodate (88 mg, 0.41 mmol) in water (0.5 mL) and *t*-butyl alcohol (0.5 mL). After 30 min at 0°C sodium borohydride (32 mg) in water (0.4 mL) was added. The reaction mixture was saturated with ammonium sulfate and extracted with chloroform. The

extract was dried, concentrated, and acetylated with an acetic anhydride-pyridine mixture to give after a standard work up **12** (98 mg; 41%), $[\alpha]_D$ +16.1° (*c* 0.8, CH_2Cl_2); IR (film) 1775 cm^{-1}(β-lactam, acetate); ^1H NMR ($CDCl_3$) δ 0.20, 0.26, 0.95 (3s, 15H, *t*-$BuMe_2Si$), 1.87. 2.01 (2s, 6H, 2 OAc), 3.19 (dd, 1H, J = 5.4, 10.5 Hz, H-2a'), 3.37 (dd, 1H, J = 4.9 Hz, H-2b'), 3.43 (m, 1H, H-3), 3.65 (m, 1H, H-1'), 4.05 (dd, 1H, J = 7.1, 11.8 Hz, C-3 CH_aH_bOAc), 4.16 (dd, 1H, J = 5.8, 11.7 Hz, C-1' CH_aH_bOAc), 4.20 (dd, 1H, J = 4.5 Hz, C-1' CH_aH_bOAc), 4.35 (dd, 1H, J = 4.7 Hz, C-3, CH_aH_bOAc), 5.04 (d, 1H, $J_{3,4}$ = 3.8 Hz, H-4);

Anal. Calcd for $C_{36}H_{45}NO_7Si$: C, 68.43; H, 7.18; N, 2.22. Found: C, 67.95; H, 7.53; N, 1.98.

(3*R*,4*S*,1'*R*) 3-Acetoxymethyl-*N*-*t*-butyldimethylsilyl-4-(1'-acetoxymethyl-2'-hydroxy)ethoxyazetidinone-2 (13). Compound 12 (88 mg, 0.14 mmol) in ethanol (5 mL) was shaken under hydrogen in the presence of 5% Pd/C, for 16 h. Subsequently the catalyst was filtered off and the solvent was evaporated. The residue was purified on a silica gel column to afford **13** using hexane-ethyl acetate (2:1 v/v) as an eluent (41 mg, 74%), $[\alpha]_D$ +20.6° (*c* 0.9, CH_2Cl_2); IR (film) 3440 (hydroxyl), 1760 cm^{-1}(β-lactam, acetate); ^1H NMR ($CDCl_3$) δ 0.24, 0.28, 0.96 (3s, 15H, *t*-$BuMe_2Si$), 2.08, 2.09 (2s, 6H, 2 OAc), 3.55 (m, 4H, H-3,1' CH_2OH), 4.20 (m, 2H, C-1' CH_2OAc), 4.34 (dd, 1H, J = 8.3, 11.9 Hz, C-3 CH_aH_bOAc), 4.60 (dd, 1H, J = 4.0 Hz, C-3 CH_aH_bOAc), 5.23 (d, 1H, $J_{3,4}$ = 3.8 Hz, H-4);

Anal. Calcd for $C_{17}H_{31}NO_7Si$: C, 52.42; H, 8.02; N, 3.60. Found: C, 52.17; H, 7.76; N, 3.49.

(3*R*,4*S*,1'*R*) 3-Acetoxymethyl-*N*-*t*-butyldimethylsilyl-4-(1'-acetoxymethyl-2'-bromo)ethoxyazetidinone-2 (14). To the compound **13** (38 mg, 0.11 mmol) and triphenylphosphine (79 mg, 0.3 mmol), dissolved in anhydr. pyridine (1.5 mL), carbon tetrabromide (50 mg, 0.15 mmol) in pyridine (0.5 mL), was added dropwise. The mixture was stirred for 2 h at room temp. Subsequently toluene (10 mL) was added. The solution was washedwith water, dried, and concentrated. The crude residue was purified on a silica gel column using hexane-ethyl acetate (9:1 v/v) as an eluent to give **14** (27 mg, 65%); $[\alpha]_D$ +22.9° (*c* 0.75, CH_2Cl_2); IR (film) 1760 cm^{-1}(β-lactam, acetate); ^1H NMR ($CDCl_3$) δ 0.22, 0.28, 0.96 (3s,15H, *t*-$BuMe_2Si$), 2.08, 2.10 (2s, 6H, 2 OAc), 3.43 (m, 2H, CH_2Br), 3.64 (m, 1H, H-3), 3.92 (m, 1H, H-1'), 4.29 (m, 3H, C-1'CH_2OAc, C-3 CH_aH_bOAc), 4.58

(dd, 1H, J = 3.8, 11.9 Hz, C-3 CH_aH_bOAc), 5.23 (d, 1H, $J_{3,4}$ = 3.7 Hz, H-4).

Anal. Calcd for $C_{17}H_{30}NO_6BrSi$: C, 45.13; H, 6.68; N, 3.10. Found: C, 45.63; H, 6.78; N,2.95.

(3*R*,5*S*,6*R*) 2,6-Diacetoxymethylclavam (15). Compound **14** 27 mg (0,06 mmol) in THF (1 mL), at -60 °C, under argon, was treated with 0.22 mL of the solution of anhydr. tetrabutylammonium fluoride[10] (0.3 mmol) in THF (1 mL). The mixture was stirred at -60 °C for 15 min, and then the temperature was allowed to rise to 0°C, while stirring was continued for an additional 30 min. Subsequently 8% solution of KH_2PO_4 (0.5 mL) was added, and the mixture was extracted with ethyl ether. The extract was washed, dried, and concentrated. The residue was purified on a silica gel column using hexane-ethyl acetate (4:1 v/v) as an eluent to give 15 (11 mg, 71%), $[\alpha]_D$ -97.1° (*c* 0.7, CH_2Cl_2); IR (film) 1795 (β-lactam), 1750 cm^{-1} (acetate); ^1H NMR ($CDCl_3$) δ 2.08, 2.16 (2s, 6H, 2OAc), 2.82 (dd, 1H, $J_{2,3}$ = 6.8, $J_{3,3'}$ = 11.7 Hz, H-3), 3.74 (dt, 1H, H-6), 3.99 (dd, 1H, $J_{2,3'}$ = 6.9 Hz, H-3'), 4.10-4.36 (m, 4H, $2CH_2OAc$), 4.50 (m, 1H, H-2), 5.41 (d, 1H, $J_{5,6}$ = 3.0 Hz, H-5).

Anal. Calcd for $C_{11}H_{15}NO_6$: C, 51.36; H, 5.85; N, 5.44. Found: C, 51.62; H, 6.07; N, 5.14.

REFERENCES

1. M. Chmielewski, Z. Kaluza, W. Abramski, J. Grodner, C. Belzecki, and P. Sedmera, *Tetrahedron*, **45**, 227 (1989).

2. Z. Kaluza and M. Chmielewski, *Tetrahedron*, **45**, 7195 (1989).

3. M. Chmielewski, J. Grodner, Wang Fudong, and Z. Urbańczyk-Lipkowska, submitted for publication.

4. A. K. M. Anisuzzman and R. L. Whistler, *Carbohydr. Res.*, **61**, 511 (1978).

5. R. N. Mirrington and K. J. Schmalzl, *J. Org. Chem.*, **37**, 2877 (1972).

6. G. G. Furin, O. A. Vyazankina, B. A. Gostevsky, and N. S. Vyazankin, *Tetrahedron*, **44**, 2675 (1988).

7. D. Brown, J. R. Evans, and R. A. Fletton, *J. Chem. Soc. Chem. Commun.*, 282 (1979); D. Hoppe and T. Hilpert, *Tetrahedron*, **43**, 2467 (1987).

8. D. L. Pruess and M. Kellett, *J. Antibiot.*, **36**, 208 (1983); M. Wannig, H. Zähner, B. Krone, and A. Zeeck, *Tetrahedron Lett.*, **22**, 2539 (1981); T. T. Howorth, A. G. Brown, and T. J. King, *J. Chem. Soc. Chem. Commun.*, 266 (1976); H. D. King, J. Langharing, and J.J. Sanglier, *J. Antibiot*, 39, 510 (1986); H. V. Naegeli, H. R. Looshi, and A. Nussbaumer, ibid, 39, 516 (1986).

9. J. Grodner, R. Urbanski, C. Belzecki, and M. Chmielewski, *Polish J. Chem.*, 66, 813 (1992).

10. D. P. Cox, J. Terpinski, and W. Lawrynowicz, *J. Org. Chem.*, 49, 3216 (1984).