FORMATION OF AN UNEXPECTED PRODUCT, A FUNCTIONALIZED DIOXANE, UNDER APROTIC ACETALIZATION CONDITIONS

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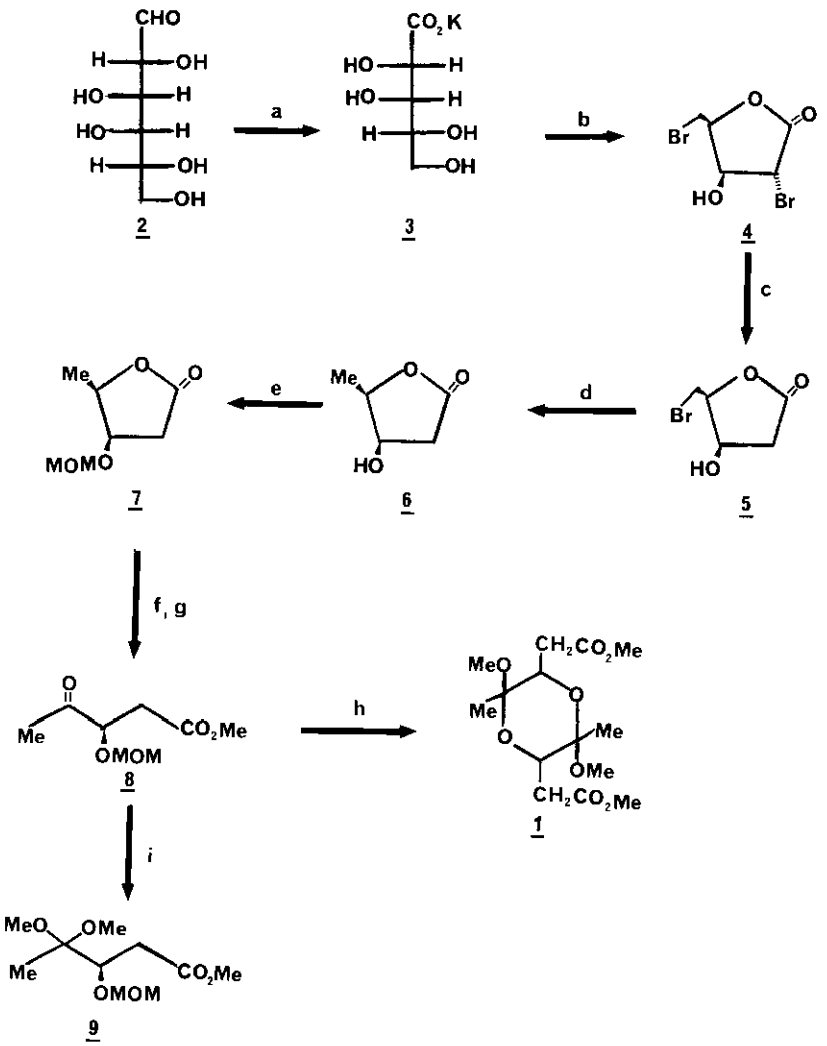
Abstract — *The formation of a substituted dioxane under aprotic acetalization conditions is observed.*

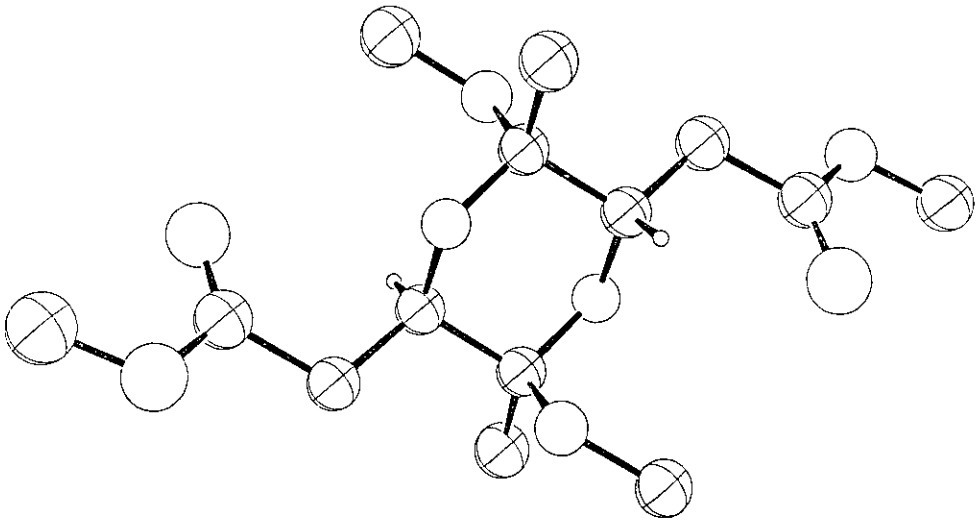
The protection of a carbonyl group as an acetal is sometimes necessary in the manipulation of multifunctional organic molecules. Most practical methods for acetalization employ alcoholic media containing an acid catalyst.[1] In 1980, Noyori and co-workers[2] described a mild, facile procedure for acetalization under aprotic conditions using alkoxytrimethylsilane as the acetalizing agent and trimethylsilyl triflate as the catalyst. In connection with our studies dealing with the synthesis of the antibiotic (+) R-avellaneol[3,4] we have encountered the formation of a highly substituted 1,4 dioxane derivative (1) under these conditions.

D-Galactose (2) was oxidized to potassium D-lyxonate (3) in 55% yield by potassium hydroxide and oxygen.[5] Treatment of 3 with a 35% solution of hydrogen bromide in acetic acid, followed by deacetylation with methanol, a procedure developed by Bock,[6] gave 4 in 70% yield. Selective hydrogenation[6] of dibromide 4 afforded 5 in 90% yield. Debromination of monobromide 5 with tri-n-butyltin hydride gave 6[7] in 93% yield. The hydroxyl group in 6 was protected as the methoxymethyl (MOM) ether by reaction with dimethoxymethane and phosphorus pentoxide, an improved method[8] involving an acid catalyzed acetal exchange reaction. Reaction of 7 with triethylamine and methanol, followed by Collins oxidation afforded 8 in 65% yield for the two steps. Treatment of 8 with methoxytrimethylsilane and trimethylsilyl triflate in methylene chloride, under an argon atmosphere, gave an unexpected product in 63% yield as the only isolable product. The structure of this unusual product was established as 1 on the basis of spectroscopic data and X-ray crystallographic analysis. This compound was stable to a catalytic amount of p-toluenesulfonic acid in acetone at room temperature, and to dilute HCl in THF. The formation of this substituted dioxane can be visualized as resulting from a bimolecular loss of methanol from the initially formed dimethyl acetal under acid catalysis as described recently by Moriarty and Hou[9]. However, the desired dimethoxy acetal 9 was obtained in 63% yield by reacting the ketone 8 with trimethyl orthoformate, methanol and ammonium nitrate. Further functionalization of 9 is currently underway.

SCHEME



[a] 1. O_2, KOH, 2. MeOH, H_2O; [b] 1. HBr (35%) in HOAc, 2. MeOH; [c] H_2, Pd/C, EtOAc, NEt_3; [d] n-Bu_3SnH, AIBN, Tol, Δ; [e] $CH_2(OCH_3)_2$, P_2O_5; [f] NEt_3, MeOH; [g] CrO_3, Py; [h] $(Me)_3Si\text{-}OCH_3$; $Me_3Si\text{-}OTf$, CH_2Cl_2; [i] $CH(OMe)_3$, MeOH, NH_4NO_3.



ORTEP Drawing of compound 1.

EXPERIMENTAL

General Methods. ^{1}H nmr spectra were obtained in $CDCl_3$ on a Bruker WM (250MHz) Fourier transform spectrometer. High-resolution mass spectra were obtained on a Hitachi-Perkin Elmer RMH-2 high resolution, double focusing, electron impact spectrometer or a vacuum Generator's V.G. 707H spectrometer interfaced with a Kratos DS-50-S data system. Infrared spectra (ir) were obtained on a Perkin-Elmer infrared spectrophotometer model 281B as a thin film (neat) on sodium chloride plates.

Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Elemental microanalyses were performed at Mic Anal Organic Microanalysis, P.O. Box 41838, Tucson, Arizona. Analytical thin layer chromatography (TLC) was performed on pre-coated silica gel plates (250 μm) with a fluorescent indicator, supplied by E. Merck. Visualization was effected with ultraviolet light (uv), or 7% w/v ethanolic 12-phosphomolybdic acid (PMA). Flash column chromatography was performed on Merck SG-60 (230-400 mesh) silica gel. All solvents used were reagent grade; methylene chloride was distilled from calcium hydride.

2,5-Dideoxy-D-threo-pentono-γ-lactone (6). To a solution of 5 (3.04 g; 15.60 mM) in dry toluene (75 ml) was added tri-n-butyltin hydride (8.2 ml; 31.17 mM) and α,α-azobisisobutyronitrile (20 mg) under a nitrogen atmosphere. The reaction mixture was heated for 20 h at 90°C. The residue obtained by evaporation of volatile materials under reduced pressure was dissolved in acetonitrile (50 ml) and washed with hexane (4 x 15 ml). Evaporation of the solvent afforded a crude product that was purified by column chromatography using ethyl acetate as eluant to give 6 (1.68 g, 93%

yield) as a colorless liquid; $[\alpha]_D^{18}$ + 77.4° (c 1.75, H_2O), lit[7] + 57° (C 0.98, H_2O); ir (neat): 3620, 3020, 2940, 1780, 1410, 1390, 1340, 1195, 1165, 1135, 1100, 1060, 990, 940, 880, 700, 660 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.42 (3H, d, J = 6.5 Hz), 2.54 (1H, dd, J = 0.9 and 17.7 Hz), 2.82 (1H, d, J = 5.5 Hz), 3.74 (1H, s), 4.44 (1H, s), 4.59 (1H, d, J = 3.7 Hz).

2,5-Dideoxy-D-threo-pentono-γ-lactone Methoxymethyl Ether (7). To a stirred solution of compound 6 (0.45 g; 3.87 mM) in methylene chloride (15 ml), dimethoxymethane (22.2 g; 290 mM) and phosphorus pentoxide (5 g; 36 mM) were added. The reaction mixture was stirred at ambient temperature for 15-30 min (TLC). It was then diluted with ether (50 ml) and filtered. The precipitate was washed with additional amount (3 x 10 ml) of ether. The combined organic layers were washed with 10% aq. Na_2CO_3 solution, brine and dried (Na_2SO_4). Concentration of the solvent followed by purification by chromatography using ether as eluant afforded product 7 (0.58 g; 93% yield). R_f 0.4 (ether); ir (neat) 2960, 2910,2850, 1785, 1450, 1410, 1390, 1345, 1308, 1250, 1220, 1210, 1170, 1140, 1090, 1040, 970, 950, 920, 900 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.44 (3H, d, J = 6.5 Hz), 2.64 (1H, dd, J = 2.4 and 17.7 Hz), 2.75 (1H, dd, J = 5.2 and 17.7 Hz), 4.34 (1H, m), 4.65 (1H, m), 3.38 (3H, s), 4.68 (2H, dd, J = 7.1 and 11.3 Hz). High resolution mass spectrum (CI) M^++1, Calcd. for $C_7H_{12}O_4$: 161.0821. Found: 161.0826.

Methyl (R)-3-O-Methoxymethoxy-4-oxopentanoate (8). Compound 7 (2.1 g; 13 mM) was stirred at room temperature with dry methanol (50 ml) and triethylamine (1.32 g; 13 mM) for 4-5 h. Solvents were removed and the residue was extracted with ether. The ether layer was washed with brine, dried (Na_2SO_4) and concentrated. The crude product without further purification was added to a stirred solution of chromium trioxide (3.74 g; 37.45 mM), pyridine (5.91 g; 74.88 mM) in dry methylene chloride (100 ml). The reaction mixture was stirred at room temperature for 20 min and then diluted with ether. It was then filtered and the black precipitate was washed with ether (3 x 10 ml). The combined organic layer was filtered through Florasil and azeotroped with toluene to remove pyridine. Removal of the solvent followed by purification of the residue by chromatography, using ether as eluant, afforded product 8 (0.7226 g; 65% yield for two steps; corrected for starting material recovered 1.1154 g). R_f 0.63 (ether); ir (neat) 3000, 2970, 2810, 1730, 1440, 1360, 1150 cm^{-1}; ^1H nmr ($CDCl_3$) δ 2.3 (3H, s), 2.79 (2H, d, J = 5.8 Hz), 3.39 (3H, s), 3.7 (3H, s), 4.34 (1H, t, J = 5.8 Hz), 4.74 (2H, dd, J = 6.9 and 12.5 Hz). High resolution mass spectrum (CI) M^++1, Calcd. for $C_8H_{14}O_5$: 191.0919. Found: 191.0893.

3,6-Carboxymethyl-2,5-dimethoxy-2,5-dimethyl-1,4-dioxane (1). To a solution of trimethylsilyl triflate (1.2 mg) in dry methylene chloride (2 ml), at -78°C under an atmosphere of argon, methoxytrimethylsilane (0.11 g; 1.052 mM) and compound 8 (0.1 g; 0.526 mM) were added. The reaction mixture was stirred at -20°C overnight. Dry pyridine (0.2 ml) and aq. $NaHCO_3$ (0.5 ml) were then added and the aqueous layer was extracted with ether (3 x 20 ml). The combined organic

layers were dried (Na_2SO_4) and concentrated. Purification by column chromatography using petroleum ether: ether (2:1) as eluant afforded 1 (0.053 g; 63% yield). R_f 0.77 (ether); ir (neat) 2810, 1710, 1410, 1350, 1270, 1140 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.24 (3H, s), 2.45 (1H, dd, J = 16.1 and 3.1 Hz), 2.63 (1H, dd, J = 16.1 and 10 Hz), 3.29 (3H, s), 3.69 (3H, s), 4.18 (1H, dd, J = 3.1 and 10 Hz). Anal. Calcd. for $C_{14}H_{24}O_8$: C, 52.48; H, 7.55. Found: C, 52.72; H, 7.66.

Methyl 4-Dimethylacetal 3-(R)Methoxymethoxypentanoate (9). A mixture of compound 8 (0.4 g; 2.104 mM), methanol (40 ml), trimethyl orthoformate (0.848 g; 8 mM) and ammonium nitrate (0.01 g) was refluxed for 12 h. An additional amount (0.848 g) of trimethyl orthoformate was added and the reaction mixture further refluxed for 9 h. Methanol was removed in vacuo and the residue was taken up in ether. Filtration to remove the ammonium nitrate, concentration of the solvent and purification of the residue by chromatography using petroleum ether: ether (2:1) as eluant yielded pure 9 (0.313 g; 63% yield). R_f 0.74 (ether); ir (neat) 3000, 2970, 2910, 2850, 1740, 1440, 1380, 1290, 1260 cm^{-1}; ^1H nmr ($CDCl_3$) δ 1.22 (3H, s), 2.42 (1H, dd, J = 9 and 15.6 Hz), 2.63 (1H, dd, J = 3.2 and 15.6 Hz), 3.15 (3H, s), 3.19 (3H, s), 3.3 (3H, s), 3.66 (3H, s), 4.18 (1H, dd, J = 9 and 3.2 Hz), 4.67 (2H, dd, J = 6.6 and 23.1 Hz). Anal. Calcd. for $C_{10}H_{20}O_6$: C, 50.83; H, 8.53. Found: C, 51.15; H, 8.78.

REFERENCES

1. T. W. Green, "Protective Groups in Organic Synthesis", John Wiley & Sons, New York, 1981, p. 116.
2. T. Tsunoda, M. Suzuki and R. Noyori, Tetrahedron Lett., 21, 1357 (1980).
3. S. T. Carey and C. T. Rogerson, Brittonia, 28, 381 (1976).
4. L. Ananthasubramanian, S. T. Carey and M. S. R. Nair, Tetrahedron Lett., 3527 (1978).
5. W. J. Humphlett, Carbohyd. Res., 4, 157 (1967).
6. K. Bock, I. Lundt and C. Pederson, Carbohyd. Res., 90, 17 (1981).
7. G. Nakaminami, S. Shioi, Y. Sugiyama, S. Isemura, M. Shibuga, and M. Nakagawa, Bull. Chem. Soc. Jpn., 45, 2624 (1972).
8. K. Fuji, S. Nakano and E. Fujita, Synthesis, 276 (1975).
9. R. M. Moriarty and K.-C. Hou, J. Org. Chem., 69, 4581 (1984).

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