Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of 3,5-O-Benzylidene-2-deoxy-L-riboaldose from 5,5-Dihydroxy-2-phenyl-1,3-dioxane

Trond Ulven [a] & Per H. J. Carlsen [a]
[a] Department of Organic Chemistry , Norwegian University of Science and Technology , N-7034, Trondheim, Norway
Published online: 04 Dec 2007.

To cite this article: Trond Ulven & Per H. J. Carlsen (2000) Synthesis of 3,5-O-Benzylidene-2-deoxy-L-riboaldose from 5,5-Dihydroxy-2-phenyl-1,3-dioxane, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 30:13, 2275-2280, DOI: 10.1080/00397910008086866

To link to this article: http://dx.doi.org/10.1080/00397910008086866

SYNTHETIC COMMUNICATIONS, 30(13), 2275–2280 (2000)

Synthesis of 3,5-*O*-Benzylidene-2-deoxy-L-riboaldose from 5,5-Dihydroxy-2-phenyl-1,3-dioxane.

Trond Ulven and Per H. J. Carlsen*

Department of Organic Chemistry, Norwegian University of Science and Technology, N-7034 Trondheim, Norway.

Abstract. The asymmetric alkylation of 2-phenyl-1,3-dioxan-5-one was achieved *via* the RAMP-hydrazone. Regeneration of the ketone followed by setreoselective reduction and ozonolysis, gave the protected 2-deoxy-L-ribose, 3,5-*O*-benzyldiene-2-deoxy-L-*erythro*-pentoaldose with 98 % e.e. Removal of the benzylidene yielded the unnatural 2-deoxy-L-ribose.

Introduction

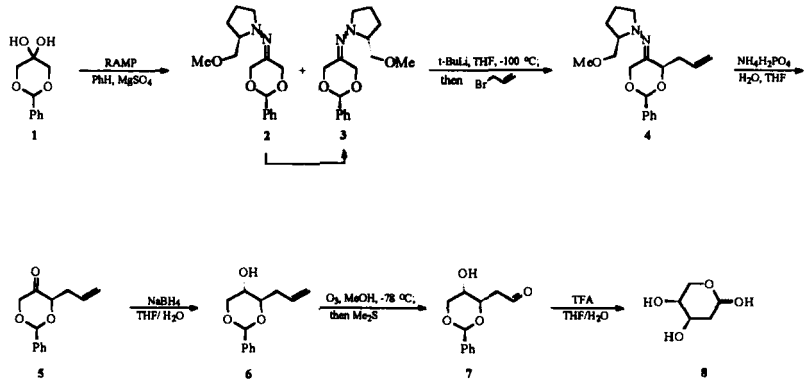
With the pursuit of demonstrating the synthetic utility of the benzylidene-protected 1,3-dihydroxyacetone (BDHA), we recently reported the synthesis of the racemic 3,5-*O*-benzylidene-protected 2-deoxyribose and 2-deoxyxylose. [1]

Enders *et al.* have demonstrated the asymmetric alkylation of the (*R*)- or (*S*)-1-amino-2-(methoxymethyl)pyrrolidine-hydrazone (SAMP- or RAMP-hydrazone) of the related compound 2,2-dimethyl-1,3-dioxan-5-one with excellent stereoselectivity.[2] Condensation of BDHA, or its hydrate-form, **1**, with the RAMP-auxiliary gives two diastereomeric hydrazones, **2** and **3**. Because of this, high stereoselectivity was not expected to be obtained in the alkylation of **1** by this method. Nevertheless, because of the successful employment of the dimethylhydrazone, and because of very limited success with alternative methods of asymmetric alkylation, the RAMP/SAMP-method was investigated.

* To whom correspondence should be addressed.

Results and discussion

Upon condensation of **1** with RAMP, the hydrazones **2** and **3** was obtained quantitatively in a 1 : 3 ratio. After storing of the crystalline product in at 4 °C for several weeks, the ratio had unexpectedly changed to > 25 : 1 in favor of **3**. The identity of **3** was determined by X-ray crystallography. The alkylation of **3** with allyl bromide yielded the substituted product, which after *N*-isomerization at room temperature gave **4** of 90 % d.e.



Removal of the RAMP-auxiliary by the usual methods was not possible, as ozonolysis is incompatible with the olefinic substituent, and the "salt-method" was expected to result in concomitant hydrolysis the acetal.[3] The hydrazone was, however, selectively hydrolyzed by a weakly acidic ammonium dihydrogen phosphate buffer, yielding the ketone **5** in 97 % yield. The RAMP-auxiliary could be recovered from the buffer-solution by addition of sodium hydroxide until pH > 12, followed by continuous extraction with diethyl ether. Reduction of the ketone with sodium borohydride in THF/water gave the equatorial alcohol, **6**, with a selectivity of 28 : 1 with respect to the axial alcohol.

All reactions in this sequence proceeds cleanly and in good yield, and the reactions can in general be performed on the crude product from the previous step. Because the hydrazones are somewhat unstable on silica, and because the ketone **5** has a tendency towards hydrate-formation, it was found that the overall yield was significantly improved by delaying purifications until after the reduction.

After chromatographic purification, **6** was subjected to ozonolysis, which gave the 3,5-protected aldose **7** in 97 % yield. Analysis by chiral GC determined the product to be of 98

% e.e. The absolute configuration was confirmed by removal of the benzylidene group, upon which the unnatural 2-deoxy-L-ribose, **8**, was formed. The optical rotation of an equilibrated aqueous solution of this product was $[\alpha]_D^{20} = +52^\circ$ (c = 0.6, H_2O). (Natural 2-deoxy-D-ribose: $[\alpha]_D^{20} = -56\pm1^\circ$ (c = 0.6, H_2O).[4])

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 300 or DPX 400. IR spectra were obtained from a Nicolet 200-SXC FT-IR spectrometer or a Perkin-Elmer 1420 IR spectrometer. Mass spectra were recorded on an AEI MS-902 spectrometer at 70 eV (IP) and 180 °C. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. GC analyses were performed on a Chrompack CP 9000 gas chromatograph equipped with a 12.5 m CP-Sil 5CB column. Chiral GC analysis were performed on a Carlo-Erba GC 8000 equipped with a CP Chirasil-dex CB fused silca WCOT column (25 m x 0.25 mm). THF was distilled from sodium metal and benzophenone.

(2R,2'S)-(-)-1-(2-Phenyl-1,3-dioxan-5-ylideneamino)-2-(methoxymethyl)pyrrolidine, **3**. A mixture of **1** (1.15 g, 5.9 mmol), (*R*)-1-amino-2-(methoxymethyl)pyrrolidine (0.78 ml, 5.9 mmol), and $MgSO_4$ (560 mg) in benzene (7.5 ml) under an inert atmosphere, was heated to reflux. After 40 min the reaction mixture was cooled and added Et_2O (20 ml). The organic phase was washed with pH 7-buffer (2 ml) and brine (2 x 2 ml), dried ($MgSO_4$), and concentrated under vacuum to give 1.70 mg (100 %) of the crude product as a white solid. The crude product consisted of a mixture of the diastereomers **2** and **3** in 1:3 ratio, with a purity of 98 % (determined by GC and NMR). Upon standing, the diastereomeric ratio in the crude product shifted to >25:1 in favor of **3**. Recrystallization from Et_2O and pentane provided crystals of **3** for structural determination by X-ray crystallography. All spectra and physical data were obtained from recrystalized **3**.

m.p. 82-84 °C. $[\alpha]_D^{20} = -247^\circ$ (c = 1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63-1.73 (1H, m; *H-3*), 1.80-1.89 (2H, m; *2H-4*), 1.98-2.07 (1H, m; *H-3*), 2.42 (1H, dt, *J* = 8.8, 7.1 Hz; *H-5*), 3.07-3.13 (1H, m; *H-5*), 3.29 (1H, dd, *J* = 9.3, 7.2 Hz; *H-1''*), 3.37 (3H, s; *MeO*), 3.35-3.45 (1H, m; *H-2*), 3.50 (1H, dd, *J* = 9.3, 4.1 Hz; *H-1''*), 4.39 (1H, d, *J* = 14.7 Hz; *H-4'*), 4.54 (1H, d, *J* = 14.1 Hz; *H-6'*), 4.62 (1H, d, *J* = 14.1 Hz; *H-6'*), 5.08 (1H, d, *J* = 14.7 Hz; *H-4'*), 5.71 (1H, s; *H-2'*), 7.34-7.40 (3H, m; *Ph*), 7.48-7.51 (2H, m; *Ph*). ^{13}C-NMR (400 MHz, $CDCl_3$): δ 23.1 (*C-4*), 27.0 (*C-3*), 56.1 (*C-5*), 59.3,

65.8, 66.8, 69.9, 75.6 (*C-2''*), 100.5 (*C-2'*), 126.1 (*Ph*), 128.3 (*Ph*), 129.1 (*Ph*), 137.6 (*Ph*), 151.5 (*C-5*). IR (KBr, cm^{-1}): 2967, 2876, 2822, 1450, 1384, 1253, 1118, 1097, 1089, 1032, 972, 752, 700. MS [*m/z* (% relative intensity)]: 291 (1.6), 290 (8, M^+), 246 (18), 243 (100), 147 (10), 146 (87), 139 (43), 106 (35), 105 (65), 77 (34). Found M^+: 290.1624. Calcd. for $C_{16}H_{22}N_2O_3$: 290.1630. Elem. anal. Calcd. C, 66.18; H, 7.64; N, 9.65. Found C, 66.28; H, 7.61; N, 9.38.

(2R,2'S,4'R)-(-)-E-1-(4-allyl-2-phenyl-1,3-dioxan-5-ylideneamnio)-2-(methoxymethyl)pyrrolidine, 4. A stirred solution of **3** (349 mg, 1.20 mmol) in THF (5 ml) at -100 °C under N_2, was added *t*-BuLi (885 µl, 1.5 M in pentane, 1.1 eq) dropwise, and the temperature was maintained between -100 and -78 °C for 3 h. The temperature was lowered to -100 °C and allyl bromide (125 µl, 1.2 eq) was added. The temperature was kept below -90 °C for 70 min, and then slowly allowed to reach r.t. (about 15 h). Diethyl ether (30 ml) was added to the reaction mixture. The organic phase was washed with pH 7-buffer (2 x 3.5 ml) and brine (2 x 3.5 ml), dried ($MgSO_4$), and concentrated under vacuum to give 381 mg (98 %) of **4** as a yellow oil (96 % pure by GC and about 92 % d.e. estimated by ^{13}C NMR). The product was subjected to flash chromatography (SiO_2, Et_2O / cyclohexane, 1:2) prior to characterization. $[\alpha]^{20}_D$ = -188 ° (c = 3.25, $CHCl_3$).

^1H-NMR (300 MHz, $CDCl_3$): δ 1.59-1.72 (1H, m; *H-3*), 1.85 (2H, m; *2H-4*), 2.01 (1H, m; *H-3*), 2.50-2.64 (2H, m; *H-5*, *H-1''*), 2.77 (1H, m; *H-1''*), 3.10 (1H, dt, *J* = 9.4, 6.4 Hz; *H-5*), 3.27-3.42 (2H, m; *H-1'''*, *H-2*), 3.37 (3H, s; *MeO*), 3.46 (1H, dd, *J* = 8.3, 3.5 Hz; *H-1'''*), 4.62 (1H, d, *J* = 15.4 Hz; *H-6'$_{ax}$*), 4.63 (1H, ddd, *J* = 7.3, 4.8, 1.1 Hz; *H-4'*), 4.75 (1H, dd, *J* = 15.4, 1.1 Hz; *H-6'$_{eq}$*), 5.10 (1H, dm, *J* = 10.2 Hz; *H-E-3''*), 5.16 (1H, dm, *J* = 17.2; *H-Z-3''*), 5.76 (1H, s, *H-2'*), 6.00 (1H, ddt, *J* = 17.2, 10.2, 7.0 Hz; *H-2''*), 7.33-7.41 (3H, m; *Ph*), 7.48-7.53 (2H, m; *Ph*). ^{13}C-NMR (300 MHz, $CDCl_3$): δ 22.9 (*C-4*), 26.8 (*C-3*), 38.3 (*C-1''*), 56.0 (*C-5*), 59.2, 64.8 (*C-6'*), 66.7, 75.4 (*C-2''*), 78.0 (*C-4'*), 98.8 (*C-2'*), 117.2 (*C-3''*), 126.2 (*Ph*), 128.3 (*Ph*), 128.9 (*Ph*), 134.4 (*C-2''*), 138.1 (*Ph*), 156.4 (*C-5'*). IR (neat, cm^{-1}): 2974, 2922, 2873, 2830, 1453, 1395, 1116, 1073, 1029, 915, 748, 698. MS [*m/z* (% rel. int.)]: 331 (0.7), 330 (3.4, M^+), 287 (2), 286 (13), 285 (69), 224 (3), 184 (11), 183 (82), 179 (39), 147 (11), 146 (100), 114 (15), 107 (13), 106 (46), 105 (70), 82 (12), 80 (15), 78 (10), 77 (45). Found M^+ 330.1939. Calcd. for $C_{19}H_{26}N_2O_3$: 330.1943.

(2S,4R)-(+)-4-Allyl-2-phenyl-1,3-dioxan-5-one, 5. A solution of **4** (397 mg, 1.20 mmol) in THF (7 ml) was added 1.6 M aq. $NH_4H_2PO_4$ (34 ml). After stirring vigorously at r.t. for 7 h,

the reaction mixture was extracted with CH_2Cl_2 (3 x 10 ml). The extract was dried ($MgSO_4$) and concentrated under vacuum to give a yellow oil (268 mg), still containing 10 % of **4**. The product was again dissolved in THF (5 ml), and 1.6 M aq. $NH_4H_2PO_4$ (25 ml) was added. The mixture was stirred for 1 hour at r.t., and work-up was performed as described above, to give 254 mg (97%) of a yellow solid consisting of a mixture of **5** and the corresponding axially substituted ketone in 10:1 ratio. Prior the characterization, **5** was subject to flash-chromatography (SiO_2, Et_2O/cyclohexane, 1:4), yielding a light yellow solid.

m.p. slightly above r.t. $[\alpha]_D^{20} = +31$ (c = 1.5, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$) δ 2.59 (1H, m; *H-1'*), 2.76 (1H, m; *H-1'*), 4.45 (2H, "s + s"; *2H-6*), 4.52 (1H, dd, *J* = 7.2, 4.2 Hz; *H-4*), 5.14 (1H, dm, *J* = 10.2 Hz; *H-E-3'*), 5.20 (1H, dm, *J* = 17.2, Hz; *H-Z-3'*), 5.93 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz; *H-2'*), 5.96 (1H, s; *H-2*), 7.38-7.44 (3H, m; *Ph*), 7.51-7.56 (2H, m; *Ph*) ppm. ^{13}C-NMR (300 MHz, $CDCl_3$) δ 34.2 (*C-1'*), 72.2 (*C-6*), 82.4 (*C-4*), 99.3 (*C-2*), 118 (*C-3'*), 126.1 (*Ph*), 128.4 (*Ph*), 129.3 (*Ph*), 132.9, 137.0, 205.3 (*C-5*). IR (neat, cm^{-1}): 3074, 2867, 2832, 1738, 1396, 1125, 1029, 991, 920, 759, 699. MS [*m/z* (%rel.int.)]: 219 (0.58), 218 (2.62, M^+), 178 (3), 177 (30), 149 (10), 148 (91), 120 (50), 119 (44), 107 (24), 106 (44), 105 (100), 92 (37), 91 (44), 90 (45), 89 (24), 82 (12), 79 (15), 78 (10), 77 (47).

(2S,4R,5S)-(+)-4-Allyl-5-hydroxy-2-phenyl-1,3-dioxane, ***6*** The crude product **5** (219 mg, 1.00 mmol) in THF/water (1:4, 35 ml) at 0 °C was added $NaBH_4$ (35 mg, 1.0 mmol). After 1 h, the reaction mixture was extracted with CH_2Cl_2 (3 x 10 ml). The organic phase was dried ($MgSO_4$), and concentrated. Purification by flash-chromatography (SiO_2, Et_2O/cyclohexane, 2:3) yielded **5** as white crystals (187 mg, 85 %).

mp. 90 °C. $[\alpha]_D^{20} = +41$ ° (c = 1, $CHCl_3$).

Spectroscopic data obtained for **6** were in perfect accordance with the previously the data obtained for the racemic material.[1]

*(+)-3,5-*O*-Benzylidene-2-deoxy-*L*-riboaldose,* ***7***, was prepared from **6** (138 mg, 0.63 mmol) by ozonolysis.[1] The crude product was subject to chromatographic purification (SiO_2, Et_2O/cyclohexane, 1:1; then ethyl acetate), yielding **7** as a colorless oil in 97 % yield, with 98 % e.e. (determined by chiral GC).

$[\alpha]_D^{20} = +34$ ° (c = 0.7, $CHCl_3$).

Spectroscopic data obtained for **7** were in perfect accordance with the previously the data obtained for the racemic material.[1]

(+)-2-deoxy-L-ribofuranose, **8**. A solution of **7** (71 mg, 0.32 mmol) in THF (0.5 ml) was added 0.01 M aq. trifluoroacetic acid (TFA) (1.5 ml), and the mixture was stirred at r.t. for 24 h. The mixture was concentrated in vacuo. The addition of more aq. TFA and THF, follwed by concentration, was repeated until no more residues of **7** was detected (TLC). Water (2.0 ml) and THF (0.5 ml) was added and evaporated off *in vacuo*, and the procedure was repeated until no more benzaldehyde or TFA was detected (TLC, pH-paper). Drying over P_2O_5 *in vacuo* gave 35 mg (81 %) of **8** as a yellow syrup. After equilibration in water for 14 days, the optical rotation was stable at $[\alpha]_D^{20} = +52^\circ$ (c = 0.6, H_2O). ^1H and ^{13}C NMR spectra were in perfect accordance with published data.[5]

References

1. Ulven, T., Sørbye, K. A., Carlsen, P. H., *Acta Chem. Scand.* **1997** (51) 1041.
2. Enders, D., Bockstigel, B., *Synthesis* **1989** 493.
3. Enders, D., Eichenauer, H., Baus, U. Shubert, H., Kremer, K. A. M., *Tetrahedron*, **1984** (40) 1345.
4. *The Merck Index*, 9th Ed. No. 2869.
5. Wong, M. Y. H., Gray, G. R., *J. Am. Chem. Soc.* **1978** (100) 3548.

Accepted 9/30/99