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Article

A novel method for deoxygenation of sugar lactones: a practical route to synthesis of the key intermediates of the "Statins"

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ABSTRACT

A novel and alternate deoxygenation method for selective removal of a hydroxyl group in carbohydrates is described. The method could be used as a synthetic tool to transform complex carbohydrates into desirable synthetic targets, particularly targets having 1,3-dihydroxy dispositions. The usefulness of this methodology is demonstrated in the preparation of a (2R, 5S)-dihydroxy hexanoic acid ester which served as the precursor for generating the side chain of rosuvastatin calcium, a cholesterol lowering drug.

Key words: Carbohydrates, Deoxy sugars, Statins, Rosuvastatin calcium.

1. INTRODUCTION

Carbohydrates have been known for decades as structural components not just in plants but also in animals. Carbohydrates are essential in the cell recognition process. They interact with a variety of receptors and control a variety of processes. Deoxy sugars are a kind of carbohydrate that may be found in a variety of bioactive compounds and natural products and are involved in a variety of biological activities (Figure 1) [1-3]. For example, 6-deoxy-L-galactose **1**, also known as L-fucose, works as a recognition molecule (SLeX) [4]. 2-deoxy-D-ribose **2**, which is found in DNA as a carbohydrate backbone, is a well-known example of a deoxy sugar [5]. During the COVID pandemic, Defence Research and Development Organisation (DRDO) in collaboration with Dr. Reddy's Laboratories (DRL) in India developed 2-deoxy-D-glucose (2-DG) **3** for the treatment of anti-COVID therapy [6-8].

Deoxy sugars are an important chiral pool for the synthesis of biologically active molecules. The deoxygenation of alcohols is an important and rather broad area of research in modern organic chemistry [9]. Deoxy sugars may be synthesized by deoxyhalo sugars [10,11], sulfonates [12], radical-mediated deoxygenation [13,14] or even by direct reduction of hydroxyl groups. Reductive decarbonylation is also employed as a tactic in removing hydroxyl groups in sugars (Wolff–Kishner and Clemmensen reductions, conversion into dithioacetals, and subsequent reduction), although these methods often use drastic conditions. Here, we developed a novel mild deoxygenation strategy and utilized it for the synthesis of the top-selling drug rosuvastatin calcium.

2. EXPERIMENTAL

All reactions were performed in oven or flame-dried glassware's in a moisture-free environment. N, N-diisopropylethylamine, and triethylamine were distilled before use. All other reagents were used as supplied. Unless otherwise noted, reactions were mechanically stirred and monitored by thin layer chromatography (TLC) using Merck aluminium coated silica gel 60 F_{254} plates. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO at 300 or 400 MHz as indicated. Chemical shifts are reported in parts per million relative to $CDCl_3$ (^{1}H, δ7.26; ^{13}C, δ77.16), and DMSO-d_6 (^{1}H, δ2.50; ^{13}C, δ39.52). Specific optical rotations were recorded on a Rodolph Autopol V Polarimeter. SRS Optimelt MPA 100 melting point apparatus was used to record melting points. Infrared spectra were recorded on a FT-IR Bruker Alpha T spectrometer. Mass spectra were obtained from the Agilent 6400 Series Triple Quad LC/MS system.

2.1. Potassium D-arabinonate (5)

Oxygen gas was bubbled into a stirred solution of potassium hydroxide (600 g, 10.69 mol) in water (1.2 L) and MeOH (5.0 L) at room temperature. Simultaneously, D-Glucose **4** (600 g, 3.33 mol) dissolved in a mixture of MeOH and H_2O (1:1) (1.0 L) was added slowly drop-wise over a period of 13 h at room temperature. After the completion of the addition, air was bubbled at the same temperature for 48 h. The precipitated solid was filtered and dried to afford potassium D-arabinonate **5** (480 g, 71%) as a white solid.

$[\alpha]_D^{25}$ = +11.2 (c 0.5, H_2O); IR (KBr): 3182, 2912, 1596, 1432, 1266, 1194, 1076, 998 cm^{-1}; ^{1}H NMR (400 MHz, D_2O): δ 4.06 (d, J = 1.2 Hz, 1H), 3.70-3.66 (m, 2H), 3.57-3.47 (m, 2H); ^{13}C NMR (100 MHz, D_2O): δ 179.2, 72.0, 71.4, 71.0, 62.9; MS (ESI): 165 [Acid, M-H]$^-$.

2.2. (3S,4S,5R)-3,4-dihydroxy-5 (hydroxymethyl) dihydrofuran-2(3H)-one (6)

To a stirred solution of potassium D-arabinonate **5** (400 g, 1.96 mol) in isopropyl alcohol (2.5 L) was added a HCl solution (70 g of HCl in 300 mL of IPA, 19.6 mol) added slowly drop-wise over a period

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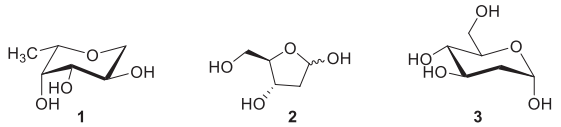


Figure 1: Some of the frequent deoxy sugars.

of 30 min. The reaction mixture was heated to reflux and stirred for 2 h at reflux. The reaction mixture was cooled to room temperature and filtered to remove the solid. It was washed with IPA (50 mL). The filtrate was evaporated completely under reduced pressure at 50°C to give a gummy compound. The gummy compound was dried under a high vacuum pump for 1 h to remove all traces of IPA. Then, 600 mL of 2-butanone was added to the gummy compound. The reaction mixture was stirred for 2 h at 70°C. The solvent was evaporated completely under reduced pressure to afford arabino lactone **6 (**262 g, 90%) as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ 6.06 (brs, 1H), 5.83 (brs, 1H), 5.05 (brs, 1H), 4.23 (d, J = 8.8 Hz, 1H), 4.02-3.93 (m, 2H), 3.72-3.68 (m, 1H), 3.50-3.43 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.2, 81.7, 74.3, 72.8, 59.6; MS (ESI): 149 $[M+H]^+$.

2.3. (3S,4S,5R)-3,4-dihydroxy-5 (hydroxymethyl)di hydrofuran-2(3H)-one (7)

To a stirred solution of arabino lactone **6 (**250 g, 1.69 mol) in pyridine (750 mL) was added trityl chloride (495 g, 1.77 mol) at −10°C. The reaction mixture was slowly warmed to room temperature and stirred for 16 h at this temperature. The reaction mixture was poured into ice water (2.5 L). The aqueous layer was decanted from the gummy compound. The gummy compound was dissolved in EtOAc (2.5 L) and washed with 10% citric acid solution (2 × 1.5 L), water (2 × 2 L), brine (2 L), dried over Na_2SO_4, filtered, and evaporated solvent completely under reduced pressure to get the gummy compound. The gummy compound was triturated with n-pentane (500 mL) to afford trityl lactone compound **7 (**650 g, 99%) as an off-white solid. The compound was carried to the next step without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.22 (m, 15H), 4.44 (d, J = 8.4 Hz, 1H), 4.37–4.33 (m, 1H), 4.25 (dd, J = 4.4, 8.0 Hz, 1H), 3.54 (dd, J = 4.4, 10.8 Hz, 1H), 3.38 (dd, J = 4.4, 10.8 Hz, 1H); MS (ESI): 389 $[M-H]^-$.

2.4. 5-O-(Triphenylmethyl)-3-deoxy-2-O-(Acetyl)-D-glycero-pent-2-enono-1,4-lactone (8)

To a stirred solution of the tritylated lactone **7 (**600 g, 1.53 mol) in dichloromethane (3 L) was added N, N-diisopropylethylamine (Hünig's base) (994 g, 7.69 mol) under nitrogen at -10°C. After 10 min, acetyl chloride (304 g, 3.84 mol) was added drop by drop to the mixture over a period of 1 h at −10°C. The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 16 h. The reaction mixture was washed with a 10% aqueous citric acid solution (2 × 1.5 L), water (2 × 1.0 L), and brine solution (1.0 L). The organic layer was dried over sodium sulfate and evaporated under reduced pressure to furnish α, β-unsaturated lactone **8 (**490 g, 77%) as an off-white solid.

m. p. 162°C; $[\alpha]_D^{25}$ = +1.59 (c 0.5, $CHCl_3$); IR (KBr): 3133, 2934, 2877, 1771, 1593, 1400, 1330, 1202, 1110, 1027 cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.43 (m, 6H), 7.35-7.31 (m, 6H), 7.29-7.25 (m, 3H), 7.20 (d, J = 1.65 Hz, 1H), 5.10-5.07 (m, 1H), 3.46-3.38 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDC1_3$): δ 166.9, 166.6, 143.2, 138.2, 131.4, 128.5, 127.9, 127.2, 87.1, 78.1, 63.8, 20.8; MS (ESI): 437 $[M+Na]^+$.

2.5. 5-O-(Triphenylmethyl)-3-deoxy-2-O-(acetyl)-D-threo-pentono-1, 4-lactone (9):

Raney nickel (16.5 g) was added to a solution of α, β- unsaturated lactone **8 (**110 g, 265.4 mmol) in ethyl acetate (1.1 L) under a nitrogen atmosphere. The reaction mixture was hydrogenated at a hydrogen pressure of 100 psi at room temperature. After the completion of the reaction, the reaction mixture was filtered through a celite pad. The pad was washed with EtOAc (100 mL). The filtrate was concentrated under reduced pressure to obtain the saturated lactone **9 (**101.6 g, 92%) as a white solid.

m. p. 126°C; $[\alpha]_D^{25}$ = +6.57 (c 0.5, $CHCl_3$); IR (KBr): 3135, 2876, 2361, 1965, 1789, 1744, 1593, 1489, 1400, 1257, 1172 cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.47 (m, 6H), 7.36-7.29 (m, 6H), 7.27-7.26 (m, 3H), 5.52 (t, J = 10.0 Hz, 1H), 4.60-4.57 (m, 1H), 3.41 (dd, J = 3.2, 10.4 Hz, 1H), 3.27 (dd, J = 5.6, 10.8 Hz, 1H), 2.71-2.64 (m, 1H), 2.15 (s, 3H), 2.21-2.15 (m, 1H); ^{13}C NMR (100 MHz, $CDC1_3$): δ172.2, 169.6, 143.3, 128.6, 128.1, 128.0, 127.1, 86.9, 75.8, 68.3, 64.3, 30.9, 20.6; MS (ESI): 439 $[M+Na]^+$; HPLC purity: 97.5%.

2.6. 5-O-(Triphenylmethyl)-3-deoxy-2-O-(hydroxy)-D-threo-pentono-1,4-lactone (10)

Sodium methoxide (5.19 g, 96.1 mmoles) was added to a solution of the saturated lactone **9 (**400 g, 961.5 mmoles) in methanol (3.2 L) at 0°C under a nitrogen atmosphere. The reaction mixture was stirred for 4 h at this temperature. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to give the gummy compound. The gummy compound obtained was dissolved in ethyl acetate (2.5 L). The organic layer was washed with water (2 × 2.0 L), brine (2 × 2.0 L), dried over sodium sulfate, and concentrated under reduced pressure to give hydroxy lactone compound **10 (**323 g, 90%) as a gummy compound. The crude material was carried to the next step without any further purification.

MS (ESI)**:** 375 $[M+H]^+$.

2.7. 5-O-(Triphenylmethyl)-3-deoxy-2-O-(methane sulfonyl)-D-threo-pentono-1,4-lactone (11)

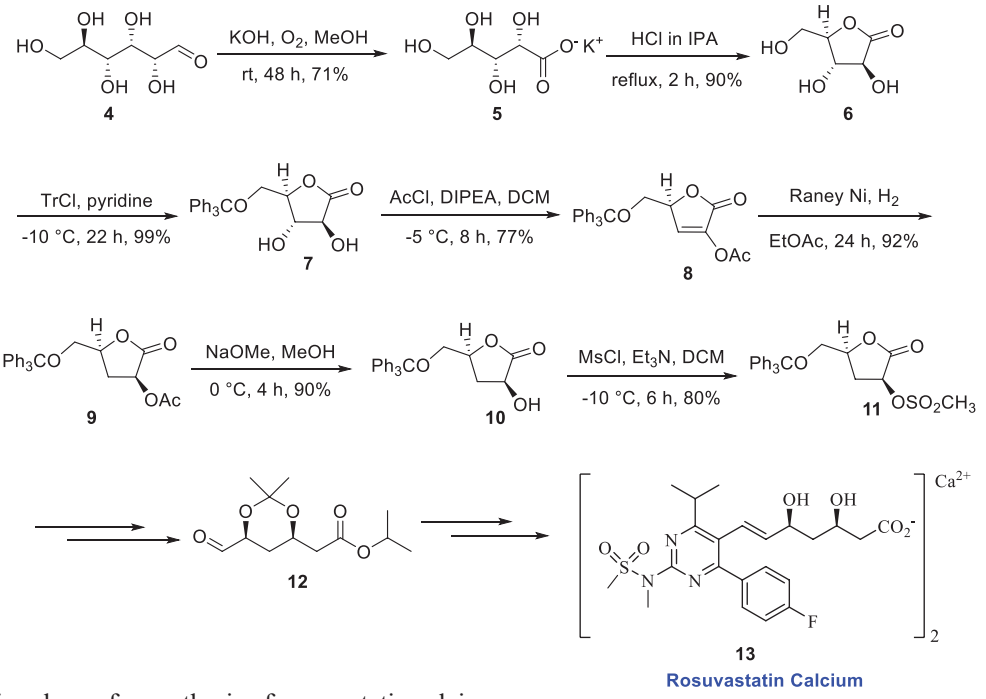
Triethylamine (405 g, 4.01 mol) was added to a solution of the hydroxy lactone compound **10 (**300 g, 0.80 mol) in dichloromethane (1.1 L) at −10°C under a nitrogen atmosphere. After 10 min, methanesulfonyl chloride (78.7 mL, 0.962 mol) was added drop-wise over a period of 30 min. The reaction mixture was stirred at this temperature for 6 h. The reaction mixture was allowed to warm to room temperature, washed with water (3 × 1000 mL), 10% aqueous citric acid solution (2 × 1000 mL), water (2 × 1000 mL), and brine (1000 mL). The organic layer was dried over sodium sulfate and evaporated solvent completely under reduced pressure to give the mesylated lactone **11 (**290 g, 80%) as an off-white solid.

m. p. 130°C; $[\alpha]_D^{25}$= -7.9 (c 0.5, $CHCl_3$); IR (KBr)**:** 3135, 2933, 1782, 1594, 1489, 1400, 1257, 1215, 1172 cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$):δ 7.45-7.4 (m, 6H), 7.37-7.28 (m, 6H), 7.28-7.22 (m, 3H), 5.4-5.35 (dd, J = 9.2, 10 Hz, 1H), 4.6-4.5 (m, 1 H), 3.44 (dd, J = 3.6, 10.8 Hz, 1H), 3.28 (s, 3H), 3.26 (dd, J = 5.2, 10.8 Hz, 1H), 2.8-2.6 (m, 1H), 2.5-2.3 (m, 1H);

^{13}C NMR (100 MHz, $CDC1_3$)**:** δ 170.9, 143, 128.49, 128.04, 127, 86.9, 76, 73.8, 63.99, 39.6, 31.0; MS (ESI)**:** 451 $[M-H]^-$.

3. RESULTS AND DISCUSSION

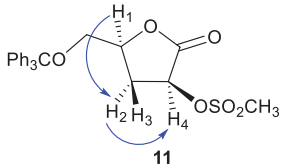
Our synthetic approach commenced with the preparation of an arabino lactone **6**. The lactone **6,** which was prepared in two steps from D-glucose, was converted to the rosuvastatin calcium as illustrated in Scheme 1.



Scheme 1: Synthetic scheme for synthesis of rosuvastatin calcium.

D-Glucose **4** was treated with oxygen in the presence of KOH solution to give potassium D-arabinonate **5** [15]. The resulting potassium D-arabinonate **5** was converted into lactone **6** by the reaction with HCl in isopropyl alcohol in a 90% yield [16]. The lactone **6** was treated with triphenylmethyl chloride and pyridine to furnish a tritylated lactone **7** in quantitative yield. The lactone **7** was then treated with acetyl chloride and Hunig's base. The treatment triggered β-elimination of the hydroxyl group [17], generating a double bond in the molecule to afford α, β-unsaturated lactone **8**. The α, β-unsaturated lactone **8** was reduced by hydrogenation in ethyl acetate at 100 psi using Raney nickel (10% w/w) as the catalyst. The saturated lactone **9** was obtained in 92% yield. The steric hindrance of the trityl group effectively dictates the facial selectivity of hydrogenation, forcing hydrogen to approach preferentially the surface of the double bond from the less hindered side.

The saturated lactone **9** thus obtained was subjected to Zemplén's saponification [18] with methanol and a catalytic amount of sodium methoxide to furnish an hydroxy lactone **10**. The hydroxy lactone **10** was then treated with mesyl chloride and triethyamine to furnish the mesyl lactone **11**. The relative stereochemistry of the chiral centre bearing the methanesulfonyl group was determined unequivocally by 2D NOESY NMR spectroscopy. In the 2D NOESY spectrum, H_1 correlated with H_2 and H_2 correlated with H_4. This indicates that H_1, H_2, and H_4 are in the same plane.



11

The mesyl lactone **11** was subsequently converted to the 1,3-syn dihydroxy ester **12** following a sequence of steps developed by our group [19,20]. This 1,3 syn dihydroxy ester **12** served as the key intermediate for generating the side-chain of rosuvastatin calcium **13**.

4. CONCLUSION

The Barton-McCombie deoxygenation has been studied and developed extensively over more than 35 years. It is the method to which most chemists fall back when faced with the removal of a hydroxyl group. We have developed an alternative deoxygenation approach for the removal of a hydroxyl group from a carbohydrate lactone in a selective manner.

5. CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest in relation to the publication of this article.

6. REFERENCES

1. K. A. Kline, S. Fälker, S. Dahlberg, S. Normark, B. Henriques-Normark, (2009) Bacterial adhesins in host-microbe interactions, ***Cell Host Microbe***, **5(6)**: 580-592.
2. R. Raman, K. Tharakaraman, V. Sasisekharan, R. Sasisekharan, (2016) Glycan-protein interactions in viral pathogenesis, ***Current Opinion in Structural Biology***, **40:** 153-162.
3. A. Varki, (2017) Biological roles of glycans, ***Glycobiology***, **27(1)**: 3-49.
4. A. Varki, (1994) Selectin ligands, ***Proceedings of the National Academy of Sciences of the United States of America***, **91(16)**: 7390-7394.
5. J. Thiem, W. Klaffke, (1990) Syntheses of deoxy oligosaccharides. In: ***Carbohydrate Chemistry***, Berlin, Heidelberg: Springer.
6. C. H. Marzabadi, R. W. Franck, (2000) The synthesis of 2-deoxyglycosides: 1988-1999, ***Tetrahedron***, **56:** 8385-8417.
7. J. S. Thorson, S. F. Lo, O. Ploux, X. He, H. W. J. Liu, (1994) Studies of the biosynthesis of 3,6-dideoxyhexoses: Molecular cloning and characterization of the asc (ascarylose) region from Yersinia pseudotuberculosis serogroup VA, ***Journal of Bacteriology***, **176(17)**: 5483-5493.
8. K. K. Sahu, R. Kumar, (2021) Role of 2-Deoxy-D-Glucose (2-DG) in COVID-19 disease: A potential game-changer, ***Journal of Family Medicine and Primary Care***, **10(10)**: 3548-3552.
9. R. M. D. Lederkremer, C. Marino, (2007) Deoxy sugars: Occurrence and synthesis, ***Advances in Carbohydrate Chemistry and Biochemistry***, **61:** 143-216.

10. W. A. Szarek, X. Kong, (1997) Direct halogenation of carbohydrate derivatives. In: S. Hanessian (Ed.), ***Preparative Carbohydrate Chemistry***, New York: Marcel Dekker, Inc., p105-126.
11. A. Hitoshi, U. Nobuhiko, M. Yoshio, (1972) The reduction of chlorodeoxy sugars by tributyltin hydride, ***Bulletin of the Chemical Society of Japan***, **45(2)**: 567-569.
12. H. H. Baer, H. R. Hanna, (1982) Desulfonyloxylations of some secondary *p*-toluene sulfonates of glycosides by lithium triethylborohydride; A high-yielding route to 2-and 3-deoxy sugars, ***Carbohydrate Research***, **110(1)**: 19-41.
13. D. H. R. Barton, S. W. McCombie, (1974) A new method for the deoxygenation of secondary alcohols, ***Journal of The Chemical Society Perkin Transactions 1***, **6(16)**: 1574-1585.
14. D. H. R. Barton, D. O. Jang, J. C. Jaszberenyi, (1990) On the mechanism of deoxygenation of secondary alcohols by tin hydride reduction of methyl xanthates and other thiocarbonyl derivatives, ***Tetrahedron Letters***, **31(28)**: 3991-3994.
15. W. J. Humphlett, (1967) Synthesis of some esters and lactones of aldonic acids, ***Carbohydrate Research***, **4(2)**: 157-164.
16. H. S. Isbell, (1963) Reactions of Carbohydrates, ***Methods Carbohydr. Chem***, **2:** 13.
17. O. J. Varela, A. F. Cireli, R. M. De. Lederkremer, (1979) Synthesis of 3,6-dideoxy L-*arabino*-hexose, ***Carbohydrate Research***, **70:** 27-35.
18. G. Zemplén, A. Kuntz, (1924) Studien über Amygdalin, IV: Synthese des natürlichen l-Amygdalins, ***Berichte der deutschen chemischen Gesellschaft (A and B Series)***: **57(8);**1357-1359.
19. N. Vempala, S. V. Rao, A. J. Shree, B. S. Pradhan, (2016) An asymmetric synthesis of rosuvastatin calcium, ***Synthesis***, **48:** 4167-4174.
20. N. Vempala, B. Matta, S. V. Rao, S. J. Maddirala, A. J. Shree, (2022) An efficient, cyanide free total synthesis of rosuvastatin calcium, ***Tetrahedron***, **111:** 132717.

***Bibliographical Sketch**

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