Synthesis of Mycinose from 1,2:5,6-Di-*O*-Isopropylidene-α-D-glucofuranose

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Abstract: A facile synthesis of mycinose from commercially available 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose was developed. A selective and direct reductive debromination of α-hydroxy bromides in a simple $NaBH_4/EtOH/H_2O$ system was found.

Keywords: 1,2:5,6-Di-*O*-Isopropylidene-α-D-glucofuranose, debromination, mycinose, synthesis.

INTRODUCTION

Mycinose (6-deoxy-2,3-di-*O*-methyl-D-allose) is a structural component of many macrolide antibiotics such as tylosin, chalcomycin, and angolamycin [1-3]. In the past few decades, a number of macrolides from both natural and synthetic sources were found to contain mycinose [4-6]. However, there have only been a few synthetic approaches established for the preparation of mycinose after its structure determination [7,8]. In addition, a number of drawbacks of these methods were revealed, such as the unsatisfactory overall yields and not readily available starting material. 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose is a commercially available and versatile synthon in carbohydrate chemistry. It has been used in a variety of applications in the construction of many bioactive substances. As part of our study of the structure activity relationships and chemistry of new antibiotics agents, we sought to develop a reliable and efficient synthetic route from cheap, commercial sources that would allow ready access to mycinose. In this letter, we describe a new and efficient synthesis of mycinose from 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofuranose, which could be a useful addition to the synthesis of mycinose and its analogs.

RESULTS AND DISCUSSION

The synthetic route to mycinose is outlined in Scheme **1**. Our synthesis started with oxidation of 1,2:5,6-Di-*O*-isopropylidene-α-D-glucofura- nose **1**, in the presence of chromium trioxide to give the corresponding keton , which was reduced to furnish **2** in 78% yield. *O*-Methylation of **2** was achieved by treating with sodium hydride and methyl iodide in THF. Microwave assisted deprotection of the 5,6-diol of **3** with aqueous acetic acid at 40°C afforded **4** in 87% yield**.** Compared with the conventional hydrolysis at room temperature, microwave irradiation could accelerate the reaction rate significantly (3h:20h).

In the course of the synthesis of the C6 bromo derivative **5**, CBr_4/PPh_3 and N-bromosuccinimide/PPh_3 bromination systems at room temperature were tested [9,10], and the latter was found to be a more efficient agent. Furthermore, the influences of stoichiometry and solvent on the yields were also examined (Table **1**). Thus the selective bromination of the primary hydroxyl group in **4** was achieved by using NBS and PPh_3 in pyridine to give **5** in 91% yield (entry 6).

Since $LiAlH_4$ and H_2/Pd systems had been proved to be efficient and convenient methods for the reduction of organic bromine compounds [8,11], we treated **5** under the above mentioned conditions, respectively. However, the rates of reaction and yields of **6** were not satisfied (less than 60%). To our surprise, **5** was reduced smoothly to give **6** in 88% yield by the use of sodium borohydride (3.0 equiv) in $EtOH/H_2O$ at room temperature.

Then the secondary hydroxy function of **6** was protected with a benzyl group and the resulting benzyl ether **7** was treated with trifluoroacetic acid to give **8** in a 1.5:1 ratio of α:β anomers, respectively. Conversion of **8** into the corresponding benzyl ether by the treatment of benzyl alcohol and *p*-toluene sulfonic acid under reflux yielded **9** in 79% yield [12]. The β-stereochemistry at the anomeric position was determined by ^{1}H NMR (5.06 ppm, J = 0.9 Hz). Treatment of **9** with sodium hydride and methyl iodide in THF afforded compound **10**. Deprotection of the benzyl protecting groups *via* hydrogenolysis under ultrasound irradiation afforded an

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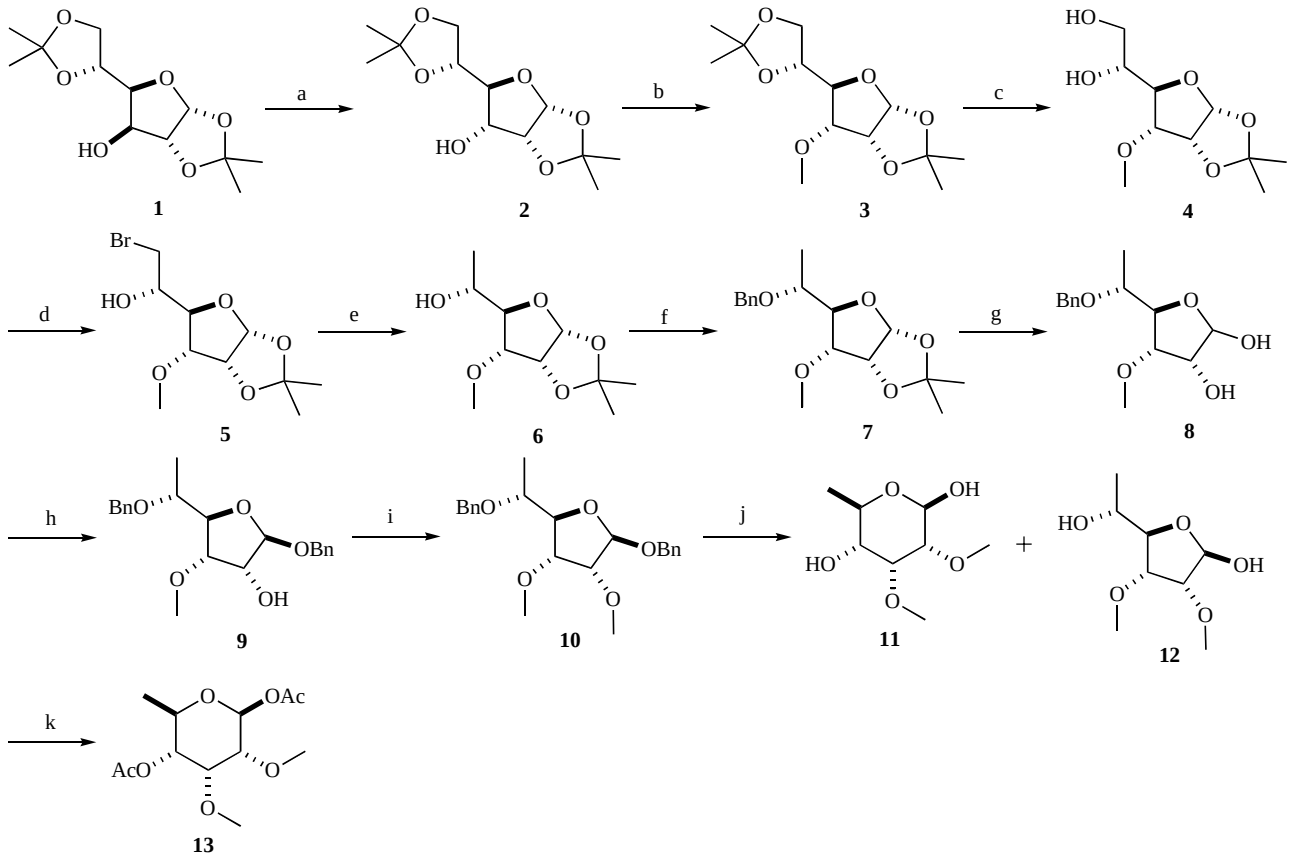


Scheme 1. Synthesis of mycinose. Reagents and conditions: (a) i) CrO_3, Ac_2O, py, CH_2Cl_2, r.t.; ii) $NaBH_4$, EtOH/H_2O (2.5:1), 0°C to r.t., 78%; (b) NaH, CH_3I, THF, r.t., 82%; (c) AcOH/H_2O (2:1), MW, 800W, 40°C, 87%; (d) NBS, PPh_3, py, r.t., 91%; (e) $NaBH_4$, EtOH/H_2O (2.5:1), r.t., 88%; (f) NaH, BnBr, THF, r.t., 76%; (g) TFA, H_2O, r.t., 83%; (h) TsOH, Benzyl alcohol, CH_2Cl_2, reflux, 79%; (i) NaH, CH_3I, THF, r.t., 84%; (j) Pd/C, H_2, AcOH, ultrasound, r.t., 91%; (k) Ac_2O, py, r.t., 80%.

Table 1. Selective Bromination of 4

Entry	Bromination Systems	Molar Ratio [a]	Solvent	Yield(%)
1	CBr_4, PPh_3	1:2:2	THF	40
2			DMF	25
3			Py	35
4	NBS, PPh_3	1:2:2	THF	28
5			DMF	31
6			Py	91
7		1:1:2	Py	74

[a]The molar ratio of **4** to CBr_4/NBS to PPh_3.

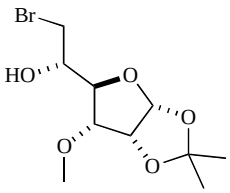
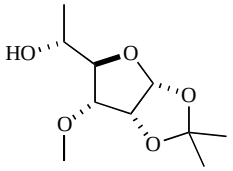
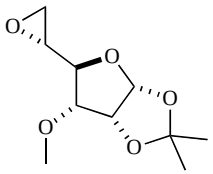
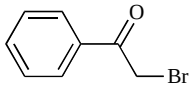
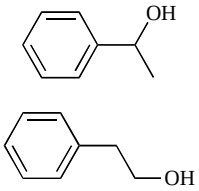
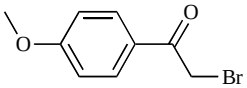
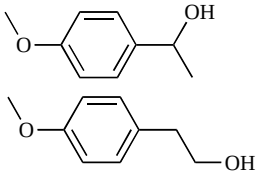
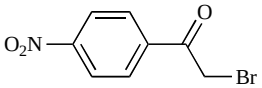
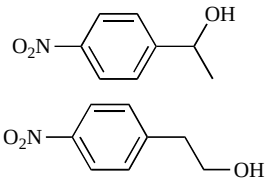
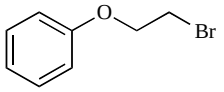
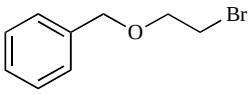
equilibrium mixture of pyranose **11** (75%) and furanose **12** (25**%**) in 91% yield.

Acetylation of compound **11** and **12**, with acetic anhydride in pyridine, gave diacetate **13** as the major product (80% yield), which was assigned to the β-configuration at C1 on the basis of NMR spectroscopy. In addition, 7% of furanose diacetate was yielded in this reaction. Synthetic **13** (11 steps in 14% overall yield) was identical in all respects (^{1}H NMR, ^{13}C NMR, MS) to synthetic product reported previously [8].

During the process from **5** to **6**, an uncommon reductive debromination of **5** using 3.0 equiv $NaBH_4$ in EtOH/H_2O (volume ratio 2.5:1) at room temperature was found. It is known that reduction of organic bromine compounds could be achieved by using $NaBH_4$ in dimethyl sulfoxide [13,14]. To the best our knowledge, however, direct reductive debromination of α-hydroxy bromides only using $NaBH_4$ in alcohol, has never been documented to date.

We believed that the α-hydroxyl group of **5** played a key role in the reduction and an epoxy intermediate might be involved. To test our speculation, we designed the following

Table 2. Reductive Debromination of Bromine Compounds Under $NaBH_4$, $EtOH/H_2O$ Conditions

Entry	Substrate	$NaBH_4$ (eqiuv)	Product	Yield (%)
1		1:3		88
2		1:1		65
3		1:3		62 17
4		1:3		39 46
5		1:3		50 41
6		1:3	--	--
7		1:3	--	--

reactions. As indicated in Table **2** (entry 1 and 2), the use of 3.0 equiv $NaBH_4$ in this reaction could generate **6** in 88% yield; by decreasing the quantity of $NaBH_4$ from 3.0 to 1.0 equiv, 65% of **5** was converted to the epoxy product.

We further investigated the reactions of several α-bromoketones (entry 3-5) under the standard conditions. It is known that the treatment of α-bromoketones with $NaBH_4$ resulted in reduction of the carbonyl bond [15,16]. Thus the resulting α-hydroxy bromides were epoxidized and then reduced by the residual $NaBH_4$ to give the expected mixture of primary and secondary alcohols, respectively. Attempts to reduce 2-bromoethyl benzyl ether and 2-bromoethyl phenyl ether under certain condition were failed, and only the unreacted starting materials were recovered. These results clearly indicated that the α-hydroxyl was necessary and an epoxy intermediate was generated during the reduction. Thus, the simple reduction system reported here ($NaBH_4$ in $EtOH/H_2O$), afforded a selective and direct reductive debromination of α-hydroxy bromides under mild conditions.

CONCLUSION

In conclusion, we have developed a new and efficient synthesis of mycinose using commercially available 1,2:5,6-diisopropyl-idene-α-D-glucose as the starting material under mild conditions. Furthermore, a selective and direct reductive debromination of α-hydroxy bromides in a simple $NaBH_4/EtOH/H_2O$ system was found. Mechanism research revealed that the α-hydroxyl was necessary and an epoxy intermediate was generated during the reduction.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

REFERENCES

[1] Hamill, R. H.; Haney, M. E. Jr.; Stamper, M. C.; Wiley, P. F. Tylosin, a new antibiotic. II. Isolation, properties, and preparation of desmycosin, a microbiologically active degradation product. *Antibiot Chemother*., **1961**, *11*, 328-334.

[2] Woo, P. W. K.; Rubin, J. R. Chalcomycin: Single-crystal X-ray crystallographic analysis; Biosynthetic and stereochemical correlations with other polyoxo macrolide antibiotics. *Tetrahedron*, **1996**, *52*(11), 3857-3872.

[3] Kadar-Pauncz, J.; Podanyi, B.; Horvath, G. Isolation and structure elucidation of new antibiotics related to angolamycin. *J. Antibiot.*, **1992**, *45*(8), 1231-1238.

[4] Park, J. S.; Yang, H. O.; Kwon, H. C. Aldgamycin I, an antibacterial 16-membered macrolide from the abandoned mine bacterium, *Streptomyces* sp. KMA-001. *J. Antibiot*., **2009**, *62*(3), 171-175.

[5] Blatter, F.; Brenner, M.; Hu, G. X.; Rager, T.; Warrass, R. Macrolide solid-state forms. PCT Int. Appl. WO 2009013351, January 29, 2009.

[6] Qiu, Y. L.; Liu, T. Z.; Or, Y. S.; Phan, L. T. 3, 6-Bridged tylosin derivatives. PCT Int. Appl. WO 2008019240, February 14, 2008.

[7] Brimacombe, J. S.; Ching, O. A.; Stacey, M. A New Synthesis of Mycinose (6-Deoxy-2,3-di-*O*-methyl- D-allose). *J. Chem. Soc.C*., **1969**, *2*, 197-198.

[8] Poss, J.; Smyth, M. S. The total synthesis of D-mycinose. *Tetrahedron Lett*., **1988**, *29*(45), 5723-5724.

[9] Chaveriat, L.; Stasik, I.; Demailly, G.; Beaupère, D. Improved synthesis of 6-amino-6-deoxy-D- galactono-1,6-lactam and D-mannono-1,6-lactam from corresponding unprotected D-hexono-1,4-l actones. *Tetrahedron*, **2004**, *60*(9), 2079-2081.

[10] Barradas, J. S.; Errea, M. I.; D'Accorso, N. B.; Sepúlveda, C. S.; Talarico, L. B.; Damonte, E. B. Synthesis and antiviral activity of azoles obtained from carbohydrates. *Carbohydr. Res*., **2008**, *343*(14), 2468-2474.

[11] Compernolle, F.; Mao, H.; Tahri, A.; Kozlecki, T.; Eycken, E. Van der; Medaer, B.; Hoornaert, G. J. Stereoselective synthesis of trans-fused tetrahydrofuran derivatives of 5H-dibenzo[*a*,*d*] cycloheptene. *Tetrahedron Lett*., **2002**, *43*(16), 3011-3015.

[12] Clive, D. L. J.; Ardelean, E.-S. Synthesis of (+)-Juruenolide C: Use of Sequential 5-*Exo-Digonal* Radical Cyclization, 1,5-Intramolecular Hydrogen Transfer, and 5-*Endo-Trigonal* Cyclization. *J. Org. Chem*., **2001**, *66*(14), 4841-4844.

[13] Bell, H. M.; Vanderslice, C. W.; Spehar, A. Reduction of organic halogen compounds by sodium borohydride. *J. Org. Chem*., **1969**, *34*(12), 3923-3926.

[14] Gu, Z. H.; Wang, X. K.; Shu, W.; Ma, Shengming. Palladium Acetate-Catalyzed Cyclization Reaction of 2,3-Allenoic Acids in the Presence of Simple Allenes: An Efficient Synthesis of 4-(1'-Bromoalk- 2'(Z)-en-2'-yl)furan-2(5H)-one Derivatives and the Synthetic Application. *J. Am. Chem. Soc*., **2007**, *129*(35), 10948-10956.

[15] Wierenga, W.; Harrison, A. W.; Evans, B. R.; Chidester, C. G. Antibacterial benzisoxazolones. An unusual rearrangement product from o-nitrostyrene oxide en route to the photolabile carbonyl protecting group, (o-nitrophenyl)ethylene glycol. *J. Org. Chem*., **1984**, *49*(3), 438-442.

[16] Perrone, R.; Berardi, F.; Leopoldo, M.; Tortorella, V. Lograno, M. D.; Daniele, E.; Govoni, S. Oxygen isosteric derivatives of 3-(3-hydroxyphenyl)-N-n- propylpiperidine *J. Med. Chem*., **1992**, *35*(16), 3045-3049.