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An Expedient Stereoselective Synthesis of Gluconolactam

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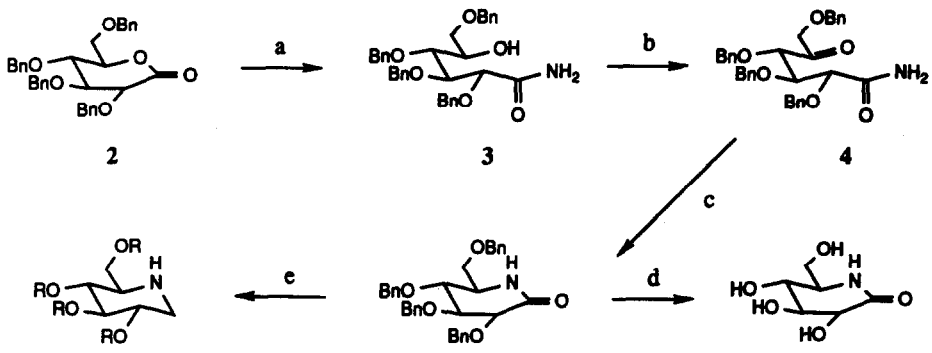
Abstract: An efficient synthesis of the title compound, starting from glucose, is described.

There is considerable interest in the synthesis of gluconolactam **1** both in view of its activity as a glycosidase inhibitor[2] and its structural relationship with the antibiotics nojirimycin and deoxynojirimycin[3], which have recently been shown to exhibit biological activity in a number of areas[4].

Comments on the syntheses of gluconolactam, reported thus far, are relevant to our work. The first reported synthesis of gluconolactam by Inouye and coworkers[5] employs the naturally occurring antibiotic nojirimycin, obtained from *Streptomyces* such as *Str. roseochromogenes* and *Str. lavedulae* as the starting material. A second synthesis, also presented by the Inouye group, makes use of an enzymatic step and yields a mixture of idonolactam (35%; major product) and gluconolactam (17 %; minor product), which requires a further separation step. A recently reported chemical preparation of gluconolactam and its derivatives[6] was later shown to be unfounded[7]. The first fully chemical synthesis of gluconolactam was described by Fleet et. al.[7]; however, the synthetic strategy employed by these workers suffers from several practical disadvantages. The synthesis starts with 3-O-Acetyl-6-O-benzoyl-5-O-(methylsulfonyl)-1,2-O-isopropylidene-α-D-glucofuranose and involves a sequence of nine steps with an overall yield of 15%.

In connection with a programme on the development of antibody catalysts, in our laboratory[8], we required a facile access to reasonable quantities of gluconolactam. In this communication, we present an expedient synthesis of gluconolactam, which, starting from glucose, allows the preparation of the target product, in simple steps, in a good overall yield.

The synthesis starts with the tetrabenzylgluconolactone **2** (Scheme), which is readily available in large amounts from glucose[9]. Amination of **2** with ammonia resulted in the expected hydroxy amide **3**, in high yields (86%). Oxidation of **3** gave the corresponding keto amide **4** which, upon treatment with formic acid and sodium cyanoborohydride, in a one-pot reaction, smoothly cyclized to tetrabenzyl-gluconolactam **5**[10]. The overall yield of **5** from **3** was 58%. Debenzylation of **5** via hydrogenation over palladium gave gluconolactam **1**[11], m.p. 197-199°C, $[\alpha]_D$=63 (lit[7] m.p. 204-205°C, $[\alpha]_D$=57, lit[5] m.p. 202-204°C, $[\alpha]_D$=60). Reduction of **5** with lithium aluminiumhydride yielded the tetrabenzyl derivative (**6a**[12]) of deoxynojirimycin **6b**[13] as a thick oil[14] (63% unoptimized) $[\alpha]_D$=29.5 (lit[12] $[\alpha]_D$=33.1 m.p. 46.5-47.5°C). Compound **6a** can, in turn, serve as a precursor for new, highly functionalized piperidines. The facile access to lactam **5** opens up new opportunities for the synthesis of piperidine antibiotics and related compounds. This work is being pursued in our laboratory.



a: NH_3; b: DMSO, Ac_2O; c: $NaCNBH_3$, HCO_2H; d: H_2, Pd/C; e: $LiAlH_4$

Scheme

Notes and References

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10. **5**: m.p. 100-102°C, $[\alpha]_D$=105.5, ν_{max} ($CHCl_3$): 3385 (NH), 1670 (C=O), ^1H NMR (C_6D_6, 300 MHz): δ 3.11 (dd, *J* 6.4, *J* 9.6, C^6H), 3.2-3.4 (m, C^5H, C^6H), 3.49 (dd, *J* 8.3, C^4H), 3.83 (dd, *J* 8.3, C^3H), 4.00 (d, *J* 8.0, C^2H), 4.12-5.38 (10xd, $PhCH_2$), 6.75 (br s, NH), 7.00-7.50 (m, PhH's).
11. **1**: ν_{max} (KBr): 3380 (NH), 1645 (C=O). ^1H NMR (D_2O, 400 MHz): 3.34-3.38 (m, 1H), 3.66-3.83 (m, 4H), 3.79-4.01 (m, 1H). ^{13}C NMR (D_2O, 50 MHz, APT): 175.65 (q, C=O), 75.61 (t), 72.94 (t), 69.83 (t), 62.64 (s), 59.25 (t). The NMR spectra were recorded using sodium3-(trimethylsilyl)-propionate 2,2,3,3-d_4 as reference.
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14. **6a**: ν_{max}: 3340 (NH), 3000, 2960, 2920, 2880, 1950, 1870, 1820, 1490, 1450, 690. ^1H NMR ($CDCl_3$, 200MHz): 2.06 (br s, NH), 2.49 (dd, *J* 10.00, *J* 12.00, C^1H_a), 2.74 (ddd, *J* 2.6, *J* 6.1, *J* 9.0, C^5H), 3.26 (dd, *J* 4.5, *J* 12.2, C^1H_e), 3.37 (dd, *J* 8.8, *J* 9.6, C^4H), 3.45-3.60 (m, 3H), 3.69 (dd, *J* 2.6, *J* 9.0, C^6H), 4.40-5.00 (m,$PhCH_2$), 7.20-7.35 (m, PhH's).

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