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Stereospecific route for the Synthesis of 1,5-Lactams : Synthesis of (2S,3S,4R,5R)-Methyl-3,4,5-triphenyl-methylenoxy-6-oxo-piperidine-2-carboxylate

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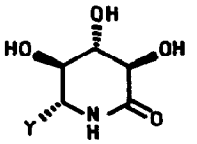
Abstract : Synthesis of derivative **4**, an oxidation product of nojirimycin, from D-glucose is described, involving, ozonolysis of **8** as key step.

D-Glucaro-1,5-lactam derivatives have been shown to act as therapeutic and or prophylactic agents for viral infections particularly human immunodeficiency virus (HIV) infection[1]. They have been ascribed to inhibition of β-glucuronidase an enzyme which is located in renal lyposomes[2]. Thus renal failure or congestive edema caused by amino glycoside antibiotics such as vancomycin, gentamycin, tobramycin, amphotericin B are prevented by glucaro-1,5-lactam derivatives and its salts[2]. They have also been shown to inhibit carragenan induced paw edema of rats[3]. Lactams derived from oxidation of nojirimycin were shown to be more potent inhibitors of β-glucuronidase than D-glucaro-1,4-lactone[4]. Patented literature describes the synthesis of such lactams **1**, **2** and **3** from oxidation of nojirimycin by bromine at 0°C[4].



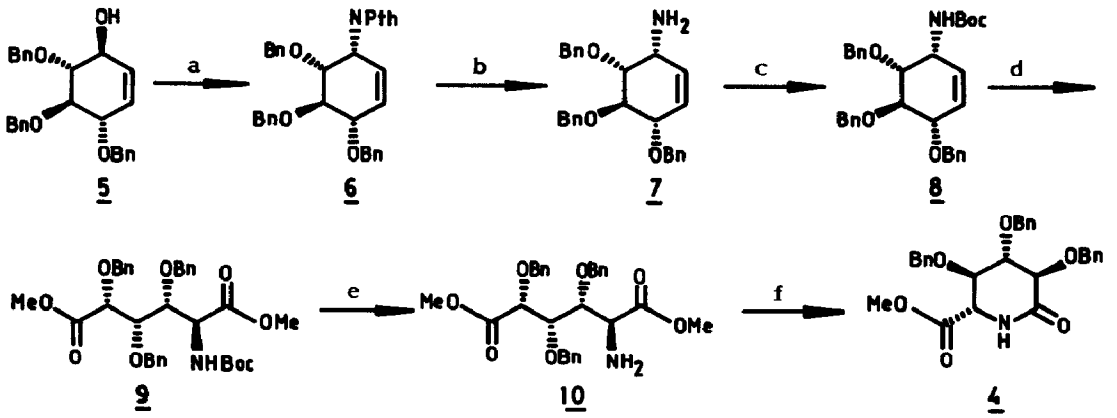
1 Y = CH_2OH

2 Y = COOH

3 Y = COOR (R = $C_1 - C_8$ alkyl)

Herein, we describe an elegant route to obtain one such lactam derivative, (2S,3S,4R,5R) methyl-3,4,5-triphenylmethylenoxy-6-oxo-piperidine-2-carboxylate (**4**) via cyclohexene alcohol **5** (scheme), prepared from D-Glucose by known methods[5,6]. Mitsunobu reaction[7] of **5** (DEAD/ Ph_3P/pthalimide) in THF at RT gave the pthalimidocyclohexene derivative **6** in 92% yield as a syrup {$[\alpha]_D$ -105° (c 1.0, $CHCl_3$)} **6** on reaction with hydrazine hydrate gave the amine **7**{$[\alpha]_D$ 9.4° (c 1.0, $CHCl_3$)} as a syrup in quantitative yield. Reaction of **7** with Boc-anhydride gave the protected amine **8** {$[\alpha]_D$ -23° (c 1.0, $CHCl_3$)}. Transformation of the aminocyclohexene derivative **8** to the diester **9** was the key step in this reaction sequence. Ozonolysis of **8** in dichloromethane/NaOH/MeOH at -78°C gave the diester **9**[8] {$[\alpha]_D$ 23.4° (c 1.0, $CHCl_3$)} in 71% yield as a syrup. Reaction of **9** with CF_3CO_2H in dichloromethane at RT provided the amine **10** {$[\alpha]_D$ 15.4° (c 1.0, $CHCl_3$)} which was briefly refluxed for 5 min in THF to obtain the required 1,5-lactam derivative **4** m.p. 86°C, {$[\alpha]_D$ 67.2° (c 1.0, $CHCl_3$)}.

In summary, a simple route to transform D-glucose through the cyclohexene alcohol **5** to the lactam ester **4** in 65% overall yield involving ozonolysis of **8** as key step has been developed. This simple protocol will provide an easy access to the synthesis of several other related lactams and further work in this direction is in progress.



Reagents and conditions : a) DEAD, PPh_3, phthalimide, THF, RT, 3h, 92%; b) NH_2NH_2-H_2O, EtOH, reflux, 2h, quantitative yield; c) Boc-anhydride, CH_2Cl_2, RT, 4h, quantitative yield; d) O_3, 2.5M NaOH/MeOH, CH_2Cl_2, -78°C, 4h, 71%; e) CF_3CO_2H 25% in CH_2Cl_2, RT, 1h, quantitative yield; f) THF, reflux, 5 min, quantitative yield.

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References and Notes:

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9. ^1H NMR data for compounds **4** and **9** : (200 MHz, $CDCl_3$, in ppm): **9** 7.5-7.2 (m, 15H, aromatic), 5.68 (d, J=8.1 Hz, NH), 4.83-4.4 (m, 7H, $PhCH_2Ox3$, H-2), 4.32 (d, 1H, $J_{4,5}$ = 2.9 Hz, H-5), 4.1-3.98 (m, 2H, H-3,4), 3.75, 3.56 (2s, 6H, OCH_3x2), 1.42 (s, 9H, tert. butyl). **4** 7.5-7.15 (m, 15H, aromatic), 6.37 (d, 1H, J=3.5 Hz, NH), 5.2-4.5 (m, 6H, $PhCH_2Ox3$), 4.27 (dd, 1H, $J_{2,3}$=4.3 Hz, H-2), 4.10-3.95 (m, 2H, H-4,5), 3.89 (dd, 1H, $J_{3,4}$ = 6.3 Hz, H-3), 3.65 (s, 3H, OCH_3). IR (KBR) cm^{-1} : 1747, 1685.
All the new compounds have shown satisfactory elemental analysis.

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