Tetrahedron Letters,Vol.30,No.32,pp 4287-4290,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

A MILD GENERAL METHOD FOR THE SYNTHESIS OF α-2-DEOXY-DISACCHARIDES: SYNTHESIS OF L-OLEANDROSYL-L-OLEANDROSE FROM D-GLUCOSE

D.Ravi, Vinayak R. Kulkarni and Hari Babu Mereyala*
National Chemical Laboratory, Pune 411 008, India

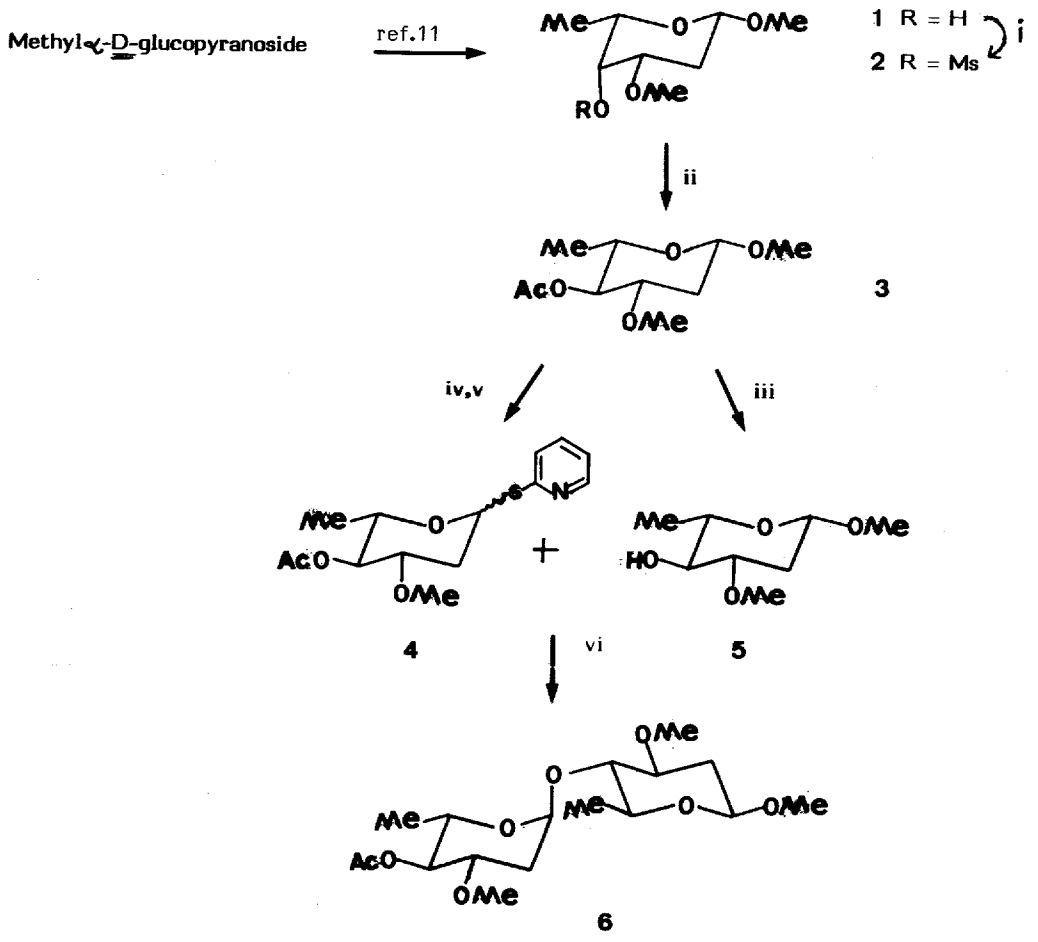
A mild, general method for the stereoselective synthesis of α-2-deoxy disaccharides is described using 2-deoxy-2-pyridyl 1-thioglycosides **4**, **7**, **8** as glycosyl donors and methyl iodide as an activator. Thus, a disaccharide **6** component of avermectin family is synthesized starting from D-glucose.

α-2-Deoxy-glycosides have been identified as constituents of many biologically important structural units, specially in the field of anthracycline and avermectin family of antibiotics[1,2]. Although in the past various methods for the synthesis of such α-glycosides have been investigated, most of them do not lead exclusively to the α-glycosides[3]. In recent years glycosyl fluorides have also been used, however, they involve use of toxic reagents and generality of this method with respect to the stability of common protecting groups is yet to be demonstrated[4]. Current methods of choice however, involves either glycosyloxyhalogenation[5a,b] or selenium based addition[5c](seleno-glycosylation) to glycals and a reduction step. Problems still appearing in the synthesis of complex disaccharides necessitates invention of newer methods.

We report here that by the methyl iodide activated 2-pyridylthio methodology developed by us[6], it is possible to achieve high axial fidelity in the synthesis of α-2-deoxyglycosides. Thus, very stable substrates **4**, **7** and **8**, that are easily available[6,7] as their anomeric mixture (α/β, 2/3) as such can be utilized for performing glycosylations. Metal and proton mediated glycosylations of 2-deoxy pyridylthioglycosides have earlier been known to result in the formation of anomeric mixtures[7b,8].

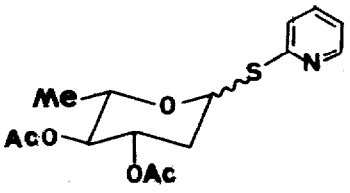
Thus, methyl 4-O-(4-O-acetyl-α-L-oleandrosyl)-β-L-oleandroside **6** (78%), m.p. 100-101°C, $[\alpha]^{25}$ -37.2° (c 1.0, $CHCl_3$), a disaccharide fragment[4a] of avermectin family, was smoothly synthesized essentially as a single α-anomer[9] (Scheme 1) starting from D-glucose by partnering pyridyl thio-oleandroside **4**[7] (ca 2/3, α/β) (1.2 mmol) (CH_2Cl_2, 10 ml, containing 3% methyl iodide, 4-Å molecular sieves, 20 h at 50°C) with methyl β-L-oleandroside **5** (1.0 mmol), m.p. 69-70°C, $[\alpha]^{25}$ + 39.7° (c 0.51, $CHCl_3$). A minor (8%) amount of 3-O-methyl-4-O-acetyl-L-rhamnal[10] was obtained as a by-product, which can be recycled. Synthesis of **4**[7] and **5** was done in a straightforward manner starting from **1** which is easily accessible from methyl α-D-glucopyranoside[11]. **1** was converted to its crystalline mesylate **2**, m.p. 93°C, $[\alpha]^{25}$ +9.9° (c, 0.53, $CHCl_3$) which on further reaction with CsOAc[12] gave the desired S_N2 bimolecular inversion product **3** (syrup) in good yield,

$[\alpha]^{25}$ +79° (c 1.0, $CHCl_3$). **4**[7] (syrup) and **5** (syrup) $[\alpha]^{25}$ +39.7° (c 0.5, $CHCl_3$) were obtained from **3** by known methods[7].



Scheme 1: (i) MsCl-Py, RT 10 h (98%); (ii) CsOAc-DMF, 100°C, 26 h (72%); (iii) NaOMe Cat.-MeOH, 45°C, 1h (98%); (iv) AcOH-H_2O (5:1), 60°C, 1h (82%); (v) $(2\text{-Py-S})_2/P(n\text{-Bu})_3/CH_2Cl_2$/ RT/30 min. (89%), α : β anomers 2:3 ratio); (vi) CH_2Cl_2 (3% MeI). 10 ml, 4-Å, 50°C 20 h, (78%).

Similarly, a reaction of **7** with methyl-α-2,3-O-isopropylidene-L-rhamnoside **9** (18 h) yielded **11** (81%, syrup) $[\alpha]^{25}$ -121° (c 1.02, $CHCl_3$) the α-anomer[9] and 3,4-di-O-acetyl-L-rhamnal[10] (5%). A reaction of **7** (16 h) and **8** (18 h) with more reactive primary alcohol 2,3:4,6-di-O-isopropylidene galactose **10**, yielded **12** (86%, syrup) $[\alpha]^{25}$ - 103.9° (c 1.26, $CHCl_3$) and **13** (88%, syrup) $[\alpha]^{25}$ + 10.4° (c 1.0, MeOH) respectively, primarily as α-anomers (α : β anomers, 85:15 ratio by ^{1}H-n.m.r. and ^{13}C-n.m.r.)[9,13].



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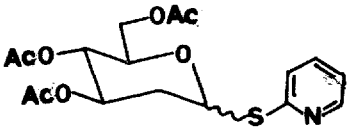

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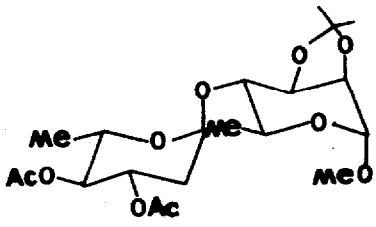

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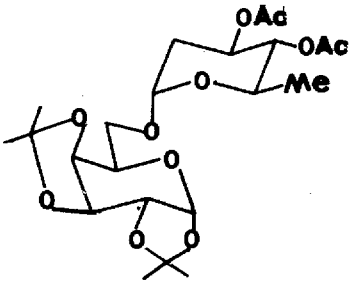

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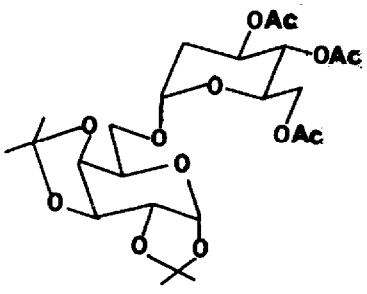

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The unusual efficiency and simplicity of this pyridyl thioglycosidation methodology is thus demonstrated. Refinement and further applications are in progress in our laboratory.

Acknowledgement:

D.R. thanks the Council of Scientific & Industrial Research, New Delhi for financial support.

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9. ^{1}H-n.m.r. data (300 MHz) ^{13}C-n.m.r. (22.63 MHz) ($CDCl_3$, TMS, δ, J in Hz) **3:** 1.13 (3H, d, J 6.3, C-5'Me), 1.34 (3H, d, J 6.1, C-5Me), 1.44 (1H, ddd, J 11.47, 9.78, 1.98, H-2ax), 1.66 (1H, ddd, J 11.6, 9.76, 2.8, H-2'ax), 2.11 (3H, s, 4'-OAc), 2.24-2.37 (2H, m, H-2,2'eq), 3.2 (1H, t, J 9,48, H-4), 3.25-3.33 (2H, m, H-3,3'), 3.35 (6H, s, C-3,3'OMe), 3.49 (3H, s, C-10Me), 3.56 (1H, dq, J 9.48, H-5), 3.84 (1H, dq, J 9.77, H-5'), 4.34 (1H, dd, H-1), 4.66 (1H, t, J 9.77, H-4'), 5.40 (1H, d, H-1'). ^{13}C-n.m.r: 100.8 (C-1), 98.46 (C-1'). **11:** 1.17, 1.31 (d, 6H, J, 6.28, 6.24, C-5,5'),, 1.33, 1.54 (s, 6H: CMe_2), 1.80 (1H, ddd, J 16.6, 12.9, 3.15, H-2'ax), 2.01, 2.05 (6H, s, C-3', 4'OAc), 2.22 (1H, dd, J 6.36, H-2'eq), 3.38 (3H, s, C-10Me), 3.47 (1H, dd, J 9.9, 7.26, H-4), 3.67 (1H, ddd, H-5), 3.85 (1H, ddd, J 9.72, H-5'), 4.07 (1H, dd, J 5.57, 0.58, H-2), 4.17 (1H, dd, H-3), 4.74 (t, 1H, H-4'), 4.85 (1H, brs, H-1), 5.18 (1H, ddd, H-3'), 5.49 (1H, d, H-1'). ^{13}C-n.m.r: 95.34, 98.33 (C-1,1'). Selected ^{1}H-n.m.r. data, **12:** (α/β, 85/15) 1.16 (2.55H, d, J 6.2, C-5'Me), 1.21 (0.45H, d, C-5'Me), 1.34 (6H, s, :CMe_2), 1.44, 1.56 (6H, s, : CMe_2), 2.00, 2.05 (6H, s, 2-OAc), 5.51 (0.85H, d, J 3.3, H-1'), 5.54 (1H, J 5.1, H-1). ^{13}C-n.m.r: 96.45, 96.90 (α, C-1, 1'), 100.02 (β, C-1'). ^{1}H-n.m.r.: **13:** (α/β, 85/15), 1.26, 1.62 (12H, s, 2CMe_2), 1.71, 1.85 (1H, m, H-2'ax), 1.92-2.05 (9H, m, 3-OAc), 2.10-2.33 (1H, m, H-2'eq), 5.33-5.56 (1.85H, m, H-1, 1'). ^{13}C-n.m.r.: 96.38, 97.03 (α, C-1, 1'), 100.02 (β, C-1', 15%).

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13. All new compounds were characterised by ^{1}H (300 MHz) and ^{13}C-(22.63 MHz)-n.m.r. spectra and satisfactory analytical data.

(Received in UK 26 June 1989)

+ NCL Communication No.4688.