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AN IMPROVED SYNTHESIS OF METHYL N-TRIFLUOROACETYL-6-HYDROXY-α-L-DAUNOSAMINIDE

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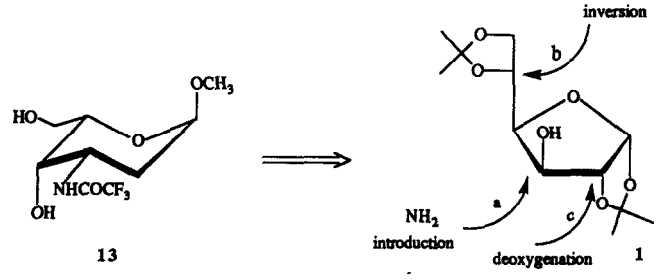
Abstract: *2,3-dideoxy-3-trifluoroacetamido-L-lyxo-hexose (or N-trifluoroacetyl-6-hydroxy-L-daunosamine) 13 has been synthesized from diacetone-D-glucose 1 in 13 steps and approximately 10% overall yield.*

Although there are a large number of syntheses of L-daunosamine[1], the sugar constituent of the antitumor antibiotics, daunorubicin and doxorubicin[2], relatively few publications have appeared concerning the synthesis of 6-hydroxy-L-daunosamine or related diastereoisomers having the L-configuration[3].

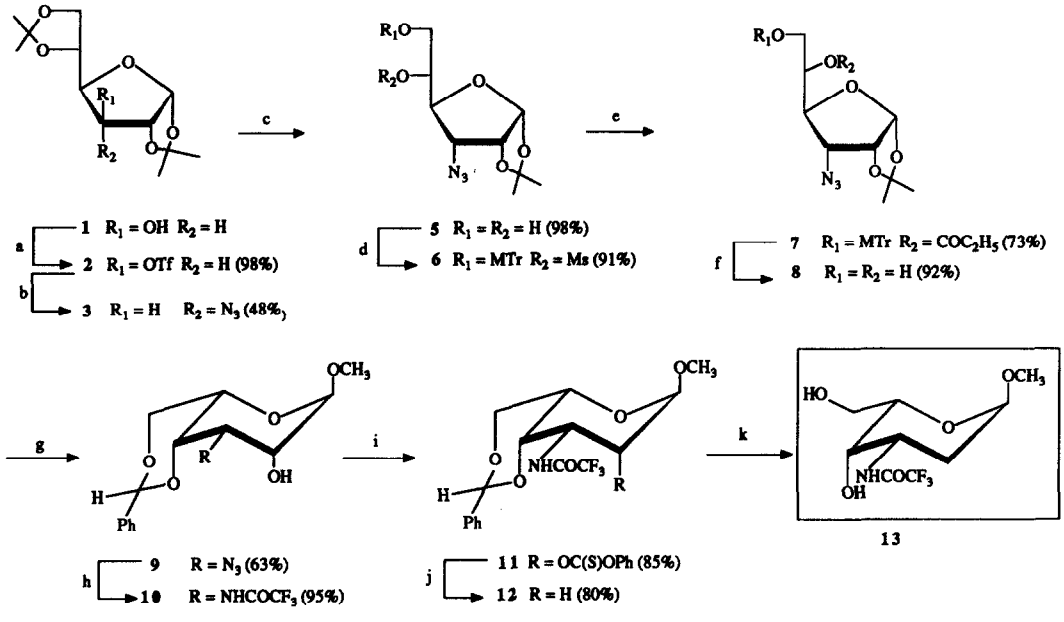
In connection with our general program aimed at the discovery of new anthracyclines including syntheses of 3-amino-2,3,6-trideoxy-L-hexoses[4] or 3-amino-2,3-dideoxy-L-hexoses, we report herein a synthesis of the title compound **13**, starting from diacetone-D-glucose **1**. As indicated on scheme 1, conversion of **1** to the 6-hydroxy-L-hexose derivative **13** requires introduction of nitrogen at C-3 (step a), inversion of configuration at C-5 (step b), and deoxygenation at C-2 (step c).



Scheme 1

It has been shown that displacement of the p-toluenesulfonyl group in 1,2:5,6-diisopropylidene-3-*O*-tosyl-D-glucofuranose is difficult to achieve with anionic nucleophiles in HMPT[5] or in DMF[6], even under drastic conditions. In contrast, inversion of configuration at C-3 to give allofuranose derivatives occurs more readily with ammonia[7] and hydrazine[8]. However, as the corresponding triflate derivative **2** is now available[9], and as marked enhanced reactivity of secondary triflates *versus* secondary tosylates has been underlined by several recent reports in the literature[10], our first objective was to introduce the nitrogen function at C-3 *via* this intermediate.

Thus, azidolysis of compound **2** to give **3** was studied under various conditions (NaN_3 or LiN_3, DMF or HMPT, 20°C to 80°C). However, considerable amounts of 3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-*erythro*-hex-3-enofuranose **4** were also formed (1:1) as a by-product in these reactions resulting from a base-induced elimination. In our hands, the best conditions involved reaction of **2** with NaN_3 (2 equiv.) in DMF at 50°C for 3.5h (48% yield of isolated azido-sugar **3**[6b,11] by flash chromatography[12] with hexane-EtOAc 6:1, then 4:1 and 1:1). During completion of this work[13], Baer and Gan[14] showed than and improved yield (62%) could still be obtained using tetramethylguanidinium azide in DMF at 25°C for 6h with less formation (but no yield was given) of unsaturated compound **4**.



(a) 1.2 eq.Tf_2O, CH_2Cl_2, Py, -10°C, 1.5 h (b) 2 eq.NaN_3, DMF, 50°C, 3.5h. (c) AcOH, MeOH, H_2O, 50°C, 17h. (d) 1.2 eq. p-anisyl chloride, Py, 20°C, 6h. then 1.5 eq. MsCl, 20°C,16h. (e) $CsCOOC_2H_5$ DMF, 120°C, 72h. (f) TsOH 2% in CH_2Cl_2-MeOH, 20°C, 1.5h.then MeONa, MeOH, 20°C, 1h. (g) 2% HCl in MeOH, 70°C, 20h. then PhCHO, $ZnCl_2$, 20°C, 9.5h. (h) Pd/C 10%, H_2, EtOH, 20°C, 3h then $(CF_3CO)_2O$, CH_2Cl_2, 0°C, 25 min. (i) PhOC(S)Cl, Py, O°--> 20°C, 19h. (j) Bu_3SnH, AIBN, toluene, 60°C, 1.5h. (k) AcCl, MeOH, R.T., 6h.

Scheme 2

After selective hydrolysis of the 5,6-O-isopropylidene acetal in AcOH:MeOH:H_2O (40:50:60, 50°C, 17h, 98% yield) , "one-pot" treatment of monoacetonide **5**[15] with p-anisyl chloride in pyridine (1.2 eq., 6h, 20°C) followed by addition of methanesulfonyl chloride (1.5 eq., 16h, 20°C) led to compound **6**[16] (m.p. 64°C, $(\alpha)_D$ + 44; 91% overall yield).

The C-5 configurational inversion (step b) was achieved at this stage using cesium propionate[17] in DMF (72h, 120°C) to cleanly afford (73% yield) L-talofuranose derivative **7** (m.p. 68°C, $(\alpha)_D$ + 32). Subsequent successive removal of the p-anisyl group with p-TsOH 2% in CH_2Cl_2-MeOH (7:3, 20°C, 1.5h) and of the propionic ester with MeONa-MeOH (20°C, 1h) led to **8** (m.p. 92°C, $(\alpha)_D$ + 114; 92% overall yield).

The benzylidene derivative of the α-L-methyl pyranoside **9** (m.p. 58-60°C, $(\alpha)_D$ - 68°) was obtained in 63% overall yield by hydrolysis of **8** with 2% HCl in methanol under thermodynamic conditions (70°C, 20h), treatment of the resultant product mixture with benzaldehyde in the presence of $ZnCl_2$ as catalyst (20°C, 9.5h), and purification by flash chromatography (hexane-EtOH, 10:1 then 2:1). Catalytic hydrogenation of the azido-group (Pd/C 10%, H_2, EtOH, 20°C, 3h) in **9** and subsequent trifluoroacetylation ($(CF_3CO_2)O$, CH_2Cl_2, 0°C, 25 min.) led to **10**. In order to achieve 2'-deoxygenation (step c) compound **10** was converted to its *O*-phenylthiocarbonate[18] **11** which was reacted[19] with Bu_3SnH to afford **12** (syrup, $(\alpha)_D$ - 137; 80% yield). Finally the methyl glycoside of N-trifluoroacetyl-6-hydroxy-L-daunosamine **13**[3a] was obtained (m.p. 189°; $(\alpha)_D$ - 180° in MeOH) by acidic hydrolysis (MeOH, HCl) of **12.**

To date this approach represents the best route to prepare 6-hydroxy-L-daunosamine in that previous syntheses[3a] started from the less available sugars, 2-deoxy-L-*arabino*-hexose or L-glucose, and afforded **13** in 10.5 % (12 steps) and 4% yields (14 steps), respectively..

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References and Notes.

1 Pelyvas, I.F.; Monneret, C.; Herczegh, P. *Synthetic Aspects of Aminodeoxysugars of Antibiotics* Springer-Verlag, Berlin-Heidelberg, 1989

2 Arcamone, F. *Doxorubicin Anticancer Antibiotics*, Academic Press, New York, 1981.

3 a) Bargiotti, A.; Cassinelli, G.; Franchi, G.; Gioia, B.; Lazzari, E.; Redaelli, S.; Vigevani, A.; Arcamone, F. *Carbohydr. Res.*, **58** (1977) 353; b) Mukaiyama, T.; Yamada, T.; Suzuki, K. *Chem. Letters* (1985) 5.

4 Abbaci, B.; Florent, J.- C.; Monneret, C. *Bull. Soc. Chim. Fr.* (1989) 667.

5 Nayak, U.G.; Whistler, R.L. *J. Org. Chem.* **34** (1969) 3819.

6 a) Ali, Y.; Richardson, A.C. *J. chem. Soc.* (1968) 1764; b) Whistler, R.L.; Donner, L.W. *Methods in Carbohydr. Chem.*, Ed. by Whistler, R.L., BeMiller, J.N., vol.VI, Academic Press, New-York,

7 a) Freudenberg, K.; Brauns, F. Ber. **55** (1922) 3233; b) Freudenberg, K.; Burkhart,O.; Brauns, G. *Ibid.* **59** (1926) 714; c) Lemieux R.U.; Chu, P. *J. Amer. Chem. Soc.* **80** (1958) 4745; d) Coxon, B.; Hough, L. *J. Chem. Soc.* (1961) 1643.

8 Wolfrom, M.L.; Shafizadeh, F.; Armstrong, R.K. *J. Amer. Chem. Soc.* **80** (1958), 4885; Wolfrom, M.L.; Shafizadeh, F.; Armstrong, R.K.; Shen Han T.M., *Ibid.* **81** (1959) 3716; Wolfrom,M.L.; Bernsmann, J.; Horton, D. *J. Org. Chem.*, **27** (1962) 4505.

9 Hall, L.D.; Miller, D.C. *Carbohydr. Res.*, **40** (1975) C1-C2 and **47** (1976) 299; Binkley, R.W.; Hehemann, D.G. *J. Org. Chem.* **43** (1978) 3244; Binkley, R.W.; Ambrose, M.G.; Hehemann, D.G., *Ibid.* **45** (1980) 4387.

10 Doboszewski, B.; Hay, G.W.; Szarek, W.A. *Can. J. Chem.*, **65** (1987) 412; Austin, G.W.; Baird, P.D.; Fleet, G.W.J.; Peach, J.M.; Smith, P.W.; Watkin, D.J., *Tetrahedron*, **43** (1987) 3095; Fleet, G.W.J.; Witty, D.R. *Tetrahedron Assymetry*, **1** (1990) 119.

11 All new compounds gave satisfactory spectral [IR , ^1H NMR ($CDCl_3$) , Mass spectra (DCI/NH_3)] and elemental analyses. $(\alpha)_D$ were measured in chloroform , c = 1.

12 Still, W.C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **43** (1978) 2923.

13 This result was presented at the VIth European Symposium on Carbohydrate Chemistry (Eurocarb VI) Edinburg 8-13 September 1991, *Abstract* **I6**.

14 Baer H.H.; Gan, Y. *Carbohydr. Res.* **210** (1991) 233.

15 Anisuzzaman, A.K.M.; Whistler, R.L. *J. Org. Chem.* **37** (1972) 3187; Elliott, R.P.; Fleet, G.W.J.; Vogt, K.; Wilson, F.X.; Wang, Y.; Witty, D.R.; Storer, R.; Myers, P.L.; Wallis, C.J. *Tetrahedron Asymmetry*, **1** (1990) 715.

16 Selected IR and NMR data: Compound **6**: δ 7.46-7.26 (15H,m, Ar), 5.74 (1H, d, J = *4*, 1-H), 5.01 (1H, m, 5-H), 4.70 (1H, dd, J=J'= *4*, 2-H), 4.31 (1H, dd, J=*9*, J' = *5*, 4-H), 3.79 and 3.00 (2 x 3H, s, 2 OMe), 3.52-3.35 (3H, m, 3-H, 6-CH_2), 3.03 (3H, s, OMs), 1.56 and 1.36 (2 x 3H, 2s, 2 Me). *Compound* **7**: δ 5.74 (1H, d, 1-H), 5.27 (1H, m, 5-H), 4.69 (1H, dd, 2-H), 4.32 (1H, dd, 4-H), 3.79 (3H, s, OMe), 3.37-3.27 (2H, d, 6-CH_2), 3.30 (1H, dd, 3-H), 2.42 (2H, q, CH_2), 1.55 and 1.35 (2 x 3H, 2s, 2 Me), 1.17 (3H, t, CH_3). *Compound* **8**: ; NMR: δ 5.82 (1H, d, J = *4*, 1-H), 4.75 (1H, dd, J = J' = *4*, 2-H), 4.08 (1H, dd, J = *10*, J' = *2*, 4-H), 3.87-3.78 (3H, m, 5-H and 6-CH_2), 3.71 (1H, dd, 3-H), 2.25 (2H, OH).*Compound* **9**: NMR: δ 7.29–7.19 (5H, m, Ph), 5.57 (1H, s, H-Ph.), 4.79 (1H, d, J = *2*, 1-H), 4.30 (1H, dd, J = J' = *2*, 4-H), 4.23 and 4.04 (2 x 1H, 2dd, J = *12*, J' = *2*, 6-H and 6'-H), 3.90-3.80 (1H, m, 2-H), 3.60 (1H, dd, J =J' = *2*, 3-H), 3.44 (1H, m, 5-H), 3.36 (3H,s, OMe). *Compound* **10**: IR: 3517, 3422 (OH and NH), 1725 cm^{-1} ($NHCOCF_3$); NMR: δ 7.41-7.30 (5H, m, Ph), 6.93 (1H, d, NH), 5.35 (1H, s, H-Ph), 4.81 (1H, d, J =*2*, 1-H), 4.36 (m, 1H, 5-H), 4.28 (1H, dd, 6-H),4.28 (1H, dd, 4-H), 4.04 (1H, dd, 6'-H), 3.72 (1H, d, J = J' = *2*, 3-H), 3.57 (1H, ddd, 2-H) 3.37 (3H, s, OMe), 3.17 (1H, d, OH).*Compound* **12**: IR: 1726 ($NHCOCF_3$); NMR: δ 7.55-7.35 (5H, m), 6.61 (1H, d), 5.57 (1H, s), 4.95 (1H, bs), 4.65 (1H, m), 4.30 (1H, dd), 4.12 (1H, bd), 4.08 (1H, dd), 3.72 (1H, d), 3.37 (3H, s), 2.04 (1H, ddd), 1.90 (1H, ddd).

17 Djikstra, G.; Kruizinga, W.H.; Kellog, R.M. *J. Org. Chem.* **52** (1987) 4230.

18 Robins, M.J.; Wilson, J.S.; Hansske, F. *J. Am. Chem. Soc.* **105** (1983) 4059.

19 Barton, D.H.R.; McCombie, S.W. *J. Chem. Soc.*, Perkin Trans *1* (1975) 1574.

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