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ELECTROPHILIC ADDITIONS CONTROLLED BY REMOTE SUBSTITUENTS. TOTAL SYNTHESIS OF DAUNOSAMINE.

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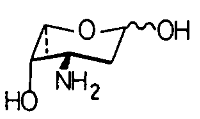
Summary. A new route to daunosamine based on the stereospecific electrophilic addition to 2-acetoxy-7-oxabicyclo[2.2.1]hept-5-ene-2-carbonitrile is presented.

Several syntheses of the important amino-sugar, daunosamine (1)[1] have been reported, starting from both carbohydrate[2] and non-sugar substrates[2,3]. We present a short, stereospecific methodology which transforms the readily obtained 7-oxanorbornene 2[4] to (±)-daunosamine.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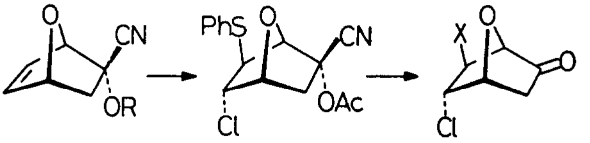
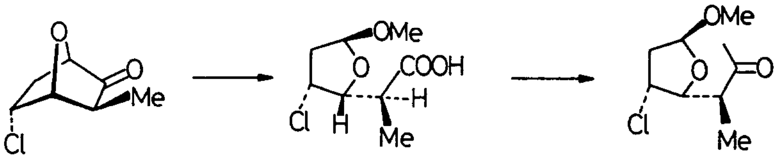

2 : R = Ac
3 : R = camphanyl
4
5 : X = PhS
6 : X = H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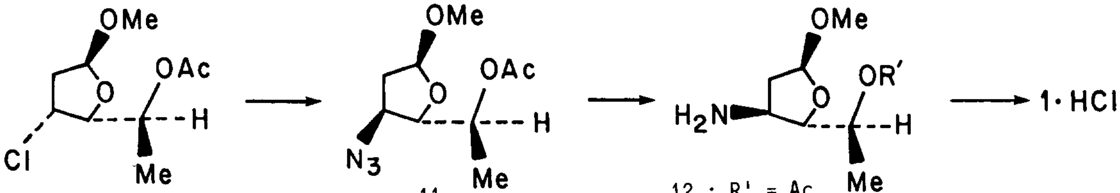
10
11
12 : R' = Ac
13 : R' = H

Electrophilic additions to bicyclo[2.2.1]hept-5-enes of arenesulfenyl and areneselenyl halides are highly stereoselective; their regioselectivity can be controlled by the substituents at C(2).[5] This is also true for 7-oxabicyclo[2.2.1]hept-5-ene-2-one and its precursor 2.[6] With benzenesulfenyl chloride (CH_2Cl_2, -78°C) 2 gave adduct 4 quantitatively. Transesterification (MeOH, MeONa, 20°C, 2 h) followed by treatment with formaline (37% aqueous solution of H_2CO, 20°C, 15 min) furnished ketone 5 (95%). Desulfurization with excess of Raney nickel (benzene, 15°C) or Bu_3SnH with AIBN (1 mol%) as initiator (toluene, 80°C) gave the chloroketone 6 (40-50%)[7] which was monomethylated stereoselectively (tBuOK in THF was added dropwise to a 1:5 mixture of 6 and CH_3I in THF stirred at 0°C for 15 min, then at 20°C for 2 h) to 7 (m.p. 46°C, 67%). Less than 8% of the corresponding gem-dimethylated derivative was formed competitively. Baeyer-Villiger oxidation (mCPBA, $NaHCO_3$, $CHCl_3$, 8°C, 3 h) followed by work-up with anhydrous methanol containing a trace of methanesulfonic acid (-15°C, 15 min) led to the acid 8 (m.p. 118-120°C, 67%).[8] Treatment with 2 equiv. of MeLi (Et_2O, 0°C, 1 h, then dissolution of the lithium carboxylate with THF, 0°C, 2 h) gave 9 (60%) which was oxidized to 10 (85%) with CF_3CO_3H (NaH_2PO_4, CH_2Cl_2, 20°C, 5 h). Heating of 10 with NaN_3 in DMF (120°C, 12 h) afforded the azide 11 (b.p. 180°C, 760 Torr, 80%) which was reduced (H_2/Pd/C, EtOH, 4 h) to 12 (90%).[9] Ammonolysis (NH_3, MeOH, 20°C, 100 h) gave 13 (92%) which was transformed (HCl 0.1 N, 50°C, 15 h) into the (±)-daunosamine hydrochloride whose spectral data were identical with those of an authentic sample of 1•HCl.[10] The structures of products 4-13 were established by their physical and spectral data and by their mode of formation. The optically pure camphanate 3 can be prepared readily.[11] The synthetic route presented here can thus be adapted to produce L-daunosamine and other related derivatives in an optically pure form.

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7. This compound was isolated by column chromatography on silica gel. It is part of a mixture containing varying amounts of 7-oxa-2-bicyclo[2.2.1]heptanone, 7-oxa-2-bicyclo-[2.2.1]heptanols and 5-chloro-7-oxa-2-bicyclo[2.2.1]heptanols.
8. The α-anomer 8 is the major isomer. The corresponding β-anomer is also present as an impurity (ca. 5%).
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