Synthesis of *N*-Trifluoroacetyl-L-acosamine and -L-daunosamine

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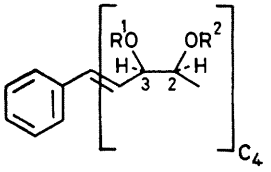
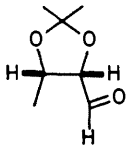
Summary *N*-Trifluoroacetyl-L-acosamine (**18**) has been chirally synthesised from the chiral educt (**1**) obtained from cinnamaldehyde and bakers' yeast, whereas *N*-trifluoroacetyl-L-daunosamine (**17**) was obtained by inverting the configuration at C-4 of the intermediate δ-lactone (**11**); compounds (**18**) and (**17**) have also been prepared from L-threonine *via* the δ- and γ-lactones (**14**) and (**9**), by inverting the configuration at position 5 of (**9**).

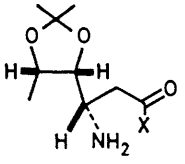
CURRENTLY there is considerable interest in efficient syntheses of the amino sugars L-daunosamine (2,3,6-trideoxy-3-amino-L-*lyxo*-hexose) (**15**) and L-acosamine (2,3,6-trideoxy-3-amino-L-*arabino*-hexose) (**16**), the components of the antitumour glycosides daunomycin[1] and adriamycin,[2] and of their 4′-epimers,[3] respectively. The known chiral syntheses of compounds (**15**) and (**16**) are all carbohydrate-based[4] and proceed either from readily available sugars of the D-series through multistep sequences or from the rare deoxy sugar L-rhamnose. We now report two syntheses of *N*-trifluoroacetyl-L-acosamine (**18**) and *N*-trifluoroacetyl-L-daunosamine (**17**), which are key intermediates in the synthesis of the above mentioned glycosides, using as optically active starting materials, (i) the (2*S*,3*R*), C_6–C_5 methyl diol (**1**), obtained from cinnamaldehyde and fermenting bakers' yeast,[5] and (ii) the readily accessible[6] amino acid L-threonine.



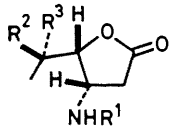
(1) $R^1 = R^2 = H$
(2) $R^1 = R^2 = CMe_2$



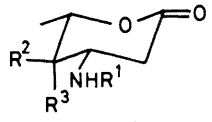
(3) X = O
(4) $X = CHCO_2Et$



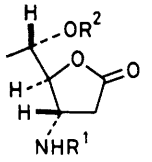
(5) X = OMe
(6) $X = NH_2$



(7) $R^1 = H.HCl$; $R^2 = H$; $R^3 = OH$
(8) $R^1 = COCF_3$; $R^2 = H$; $R^3 = OCOCF_3$
(9) $R^1 = COPh$; $R^2 = OH$; $R^3 = H$
(10) $R^1 = COPh$; $R^2 = H$; $R^3 = OH$

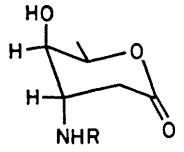


(11) $R^1 = COPh$; $R^2 = OH$; $R^3 = H$
(12) $R^1 = COPh$; $R^2 = H$; $R^3 = OH$

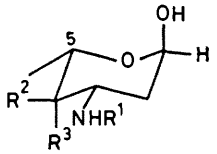


(13) $R^1 = R^2 = COCF_3$

(i) This procedure is based on the use of the C_4 chiral fragment [see structures (**1**) and (**2**)] with the (2*S*,3*R*) absolute configuration[7] matching that of positions 5 and 4 of L-acosamine (**16**), present in (**1**), and extruded from (**2**) as (**3**), to construct the chiral C_6, $\alpha\beta$-unsaturated ester (**4**). The latter material, as already shown in the racemic series,[8] stereoselectively adds ammonia to give (**5**), which is easily converted into the desired amino sugar derivative (**18**). Thus, the diol (**1**), prepared in 25—30% yield from cinnamaldehyde, acetaldehyde, and commercial bakers' yeast, was converted with 2,2-dimethoxypropane and toluene-*p*-sulphonic acid into the isopropylidene derivative (**2**), a distillable oil, $[\alpha]_D^{20}$ −2·45° (neat), in 90% yield. The latter compound, upon sequential treatment, in the same pot, with (i) O_3 in CH_2Cl_2, at −50 °C; (ii) *ca.* 1·5 mol equiv. of triphenylphosphine, and (iii) 1·5—1·8 mol equiv. of $Ph_3P{=}CHCO_2Et$, at −50 °C followed by refluxing for 2 h, gave rise to the ester (**4**) {the *E*-isomer collected by preparative g.l.c. showed $[\alpha]_D^{20}$ −2·4° (*c* 1·1, EtOH)}, in *ca.* 65% overall yield from (**2**), and ethylcinnamate, which were separated by column chromatography. In a modification of the above procedure designed to eliminate the formation of benzaldehyde which accompanies that of the aldehyde (**3**) in the ozonolysis of (**2**), O_3 was passed through a solution of (**2**) in dry ethyl acetate at −50 °C. The crude reaction mixture was hydrogenated (4 atm H_2) in the presence of 10% Pd–C at room temperature. Subsequent addition of $Ph_3P{=}CHCO_2Et$ led to (**4**), but in only 25–30% yield, and the g.l.c. analysis showed the absence of ethylcinnamate. The ester (**4**) was treated[8] with dry ammonia in methanol at room temperature for 5 days. The crude, evaporated mixture was partitioned between 2N HCl and Et_2O, which extracted *ca.* 15% of unreacted (**4**). The aqueous acidic solution, containing (**5**) and some (**6**), after refluxing for 4 h and taken to dryness, gave the lactone hydrochloride (**7**), $[\alpha]_D^{20}$ −23° (*c* 1, water), ν_{CO} (KBr) 1780 cm^{-1}, in *ca.* 70% yield from (**4**). This material, converted in 80% yield into the *ON*-ditrifluoroacetyl derivative (**8**), and reduced, in turn, with 3 mol equiv. of di-isobutyl aluminium hydride (DIBAH) in tetrahydrofuran (THF) at −50 °C for 3 h, gave rise to *N*-trifluoroacetyl-L-acosamine (**18**), m.p. 208—209 °C, $[\alpha]_D^{20}$ −36→−29° (*c* 1, dioxan), identical in every respect with an authentic sample,† in *ca.* 70% yield from (**8**).



(14) R = COPh



(15) $R^1 = R^2 = H$; $R^3 = OH$
(16) $R^1 = R^3 = H$; $R^2 = OH$
(17) $R^1 = COCF_3$; $R^2 = H$; $R^3 = OH$
(18) $R^1 = COCF_3$; $R^2 = OH$; $R^3 = H$

The amino lactone (**7**) with the *arabino* configuration served as starting material for the synthesis of *N*-trifluoroacetyl-L-daunosamine (**17**). Compound (**7**), in an excess of 5% NaOH, was benzoylated with 1·2 mol equiv. of PhCOCl. Rapid extraction of the acidified reaction mixture led to the *N*-benzoyl lactone (**11**), m.p. 190 °C, ν_{CO} (Nujol) 1720 and 1640 cm^{-1}, $[\alpha]_D^{20}$ 11·5° (*c* 1·1, EtOH). The six-membered ring structure of (**11**) is further supported by the n.m.r. data: there is a coupling constant of 5·7 Hz between H-4 and the OH group in the ^1H spectrum. In the ^{13}C spectrum the chemical shift of the lactone carbonyl group appears at 169·7 p.p.m., in $(CD_3)_2SO$. Furthermore, all the substituents have an equatorial orientation as shown by the values of $J_{3,4}$ 8·2 and $J_{4,5}$ 9·1 Hz. Compound (**11**) was converted into the mesyl derivative, which yielded, upon treatment with aqueous sodium acetate, the *N*-benzoyl-L-*lyxo* lactone (**12**), m.p. 125—127 °C, ν_{CO} (Nujol) 1740 and 1635 cm^{-1}, $[\alpha]_D^{20}$ −15·8° (*c* 1, EtOH). In Me_2SO compound (**12**) appears to be in the γ-lactone form, as indicated by the following n.m.r. data [$(CD_3)_2SO$]; ^1H: δ 1·18 (Me, $J_{5,6}$ 6·5 Hz) 2·58 (H-2, $J_{2,2'}$ 18·0 and $J_{2,3}$ 4·0 Hz); 2·98 (H-2′, $J_{2',3}$ 9·1 Hz); 4·32 (H-4, $J_{3,4}$ 3·2 Hz); 4·65 (H-3); 3·93 (H-5, $J_{4,5}$ 2·8 Hz); and 5·09 (OH, $J_{5,OH}$ 5·2 Hz). In the ^{13}C spectrum the lactone carbonyl group appears at 175·7 p.p.m. The overall yield of the conversion of the L-*arabino* (**11**) into the L-*lyxo* (**12**) was *ca.* 65%. Compound (**12**) was converted into the trifluoroacetyl derivative (**13**), m.p. 102 °C, $[\alpha]_D^{20}$ − 11·9° (*c* 1,05, EtOH), reduced with DIBAH, as above, in 75% yield, to *N*-trifluoroacetyl-L-daunosamine (**17**), m.p. 149—150 °C, $[\alpha]_D^{20}$ − 136°, (equilibrium *c* 1, dioxan), identical with an authentic sample.†

(ii) As a second starting material for the synthesis of compound (**18**), through the intermediacy of the amino lactone (**7**), which affords (**17**), we used the *N*-benzoyl-D-*xylo* lactone (**14**), already prepared[9] from L-threonine *via* the (4*S*,5*R*)-isomer of the C_6 ester (**4**). The lactone (**14**) on treatment with methanolic HCl isomerises to the γ-lactone (**9**), m.p. 166—168 °C, $[\alpha]_D^{20}$ −54° (*c* 1·1, EtOH), in nearly quantitative yield. The n.m.r. data of (**9**) in $(CD_3)SO$ are

† This was kindly provided by Drs G. Cassinelli and S. Penco, Farmitalia-Carlo Erba, Milano.

^{1}H δ 1·12 (Me, $J_{5,6}$ 6·5 Hz), 2·70 (H-2, $J_{2,2'}$ 17·2 and $J_{2,3}$ 9·0 Hz), 2·86 (H-2′, $J_{2',3}$ 7·0 Hz), 4·48 (H-4, $J_{3,4}$ 6·8 Hz), 4·90 (H-3), 3·84 (H-5, $J_{4,5}$ 3·8 Hz), 5·0 (OH, $J_{5,OH}$ 4·5 Hz) In the ^{13}C spectrum the carbonyl group of the γ-lactone appears at 175·1 p p m The D-*xylo* lactone (**9**), *via* mesylate and acetate displacement gave the L-*arabino* lactone (**10**), m p 155 °C, ν_{CO} (Nujol) 1780 and 1635 cm^{-1}, $[\alpha]_D^{20}$ − 43·2° (*c* 1·1, EtOH) Indeed, the lactone (**10**) upon acid hydrolysis gave (**7**), from which compounds (**18**) and (**17**) were obtained The overall yield of the conversion (**14**)→(**7**) was *ca* 55%.

Procedure (i) is a further example of the significance of transformations mediated by bakers' yeast of non-conventional substrates as sources of chiral educts [10] Moreover, since the ester (**4**) has been prepared, although *via* a much longer sequence than from (**1**), starting from L-*allo*-threonine and since the L-isomer of (**14**), which should allow the D-enantiomeric forms of daunosamine and acosamine to be obtained according to procedure (ii), has been prepared from natural tartaric acid,[9] the present results represent another example of the versatility of C_4 chiral molecules in the synthesis of the optically active forms of natural products [11]

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