Total Synthesis of Acarbose and Adiposin-2

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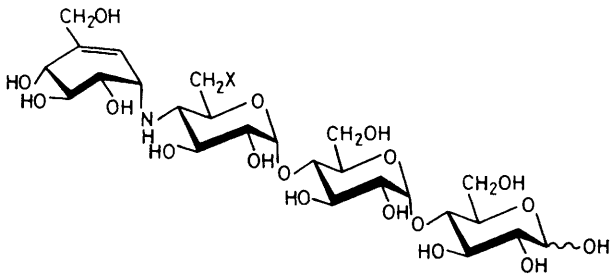
The first complete synthesis of acarbose (**1a**), the pseudotetrasaccharidic α-amylase inhibitor, is reported: coupling of the protected (+)-valienamine (**16**) and the epoxide (**9**) derived from 1″,6″-anhydromaltotriose (**3**), followed by deprotection; likewise, adiposin-2 (**2a**), the 6′-hydroxy analogue of (**1a**), has also been synthesised.

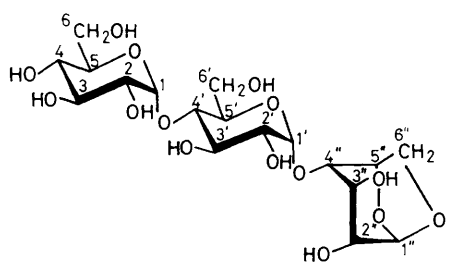
The pseudotetrasaccharide acarbose (**1a**),[1] produced by *Actinomycetales* strains, is a potent inhibitor of intestinal α-D-glucosidases and saccharases *in vitro*,[2] and may now be used clinically as an effective oral antidiabetic agent. Considerable interest has therefore been stimulated in the biochemistry of this class of inhibitors,[3] and extensive synthetic studies have been carried out by several research groups[4—7]

We describe herein the first total synthesis of (**1a**) and its 6′-hydroxy analogue adiposin-2 (**2a**)[8,9] by coupling the protected anhydro derivatives (**9**) and (**11**) of the trisaccharide with the optically pure di-*O*-isopropylidene-(+)-valienamine (**16**), respectively, followed by deprotection.

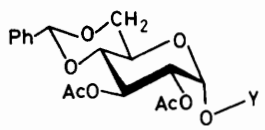
Monobenzylidenation of 1″,6″-anhydromaltotriose (**3**)[10] was carried out by treatment with α,α-dimethoxytoluene in *N*,*N*-dimethylformamide (DMF) in the presence of *p*-toluenesulphonic acid (PTSA) at 60 °C to give, after acetylation (Ac_2O, pyridine), the 4,6-*O*-benzylidene derivative (**4**) {58%, $[\alpha]_D^{25}$ +57° ($CHCl_3$)}. The diol (**5**), obtained in 75% yield by treatment of (**4**) with aqueous 20% acetic acid, was treated with methanesulphonyl chloride in pyridine, and the resulting bis(methanesulphonate) was refluxed with sodium iodide in acetonitrile to give the 6-iodide, which was then hydrogenolysed (Raney nickel T-4[11]) to afford the crystalline 6-deoxy derivative (**6**) {m.p. 205 °C, $[\alpha]_D^{25}$ +73° ($CHCl_3$)} in 95% overall yield. Treatment of (**6**) with excess methanolic sodium methoxide in CH_2Cl_2–MeOH at 50 °C produced, after acetylation, 65% of the 3,4-epoxide (**8**) contaminated with the



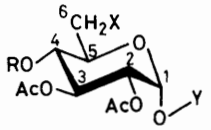
(**1a**) Acarbose ; X = H
(**1b**) Acarbose trideca—Ac
(**2a**) Adiposin—2 ; X = OH
(**2b**) Adiposin—2 tetradeca—Ac



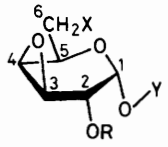
(**3**)



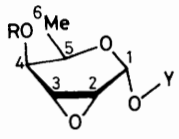
(4)



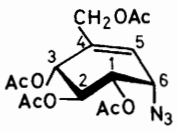
(5) R = H, X = OH
(6) R = $MeSO_3$, X = H
(7) R = $MeSO_3$, X = OBz



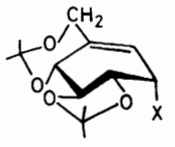
(8) R = Ac, X = H
(9) R = X = H
(10) R = Ac, X = OAc
(11) R = H, X = OH



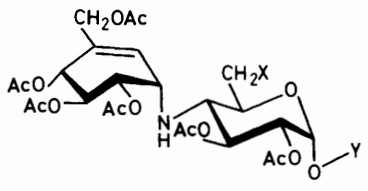
(12) R = Ac
(13) R = H



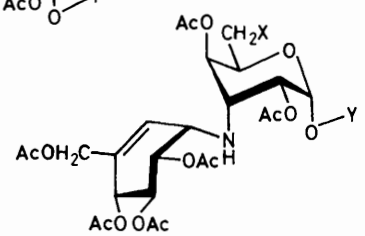
(14)



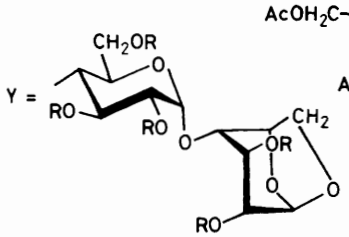
(15) X = N_3
(16) X = NH_2



(17) X = H
(19) X = OAc



(18) X = H
(20) X = OAc



(5)-(8), (10), (12), (17)-(20) R = Ac
(9), (11), (13) R = H

2,3-epoxide (**12**) (<10%) formed *via* migration of the epoxide group. The mixture of products was *O*-deacetylated with methanolic sodium methoxide in CH_2Cl_2 at 0 °C to give a 10 : 1 mixture of the epoxides (**9**) and (**13**), which was used directly in the coupling reaction.

4,7:5,6-Di-*O*-isopropylidene-(+)-valienamine (**16**) {$[\alpha]_D^{22}$ +65° ($CHCl_3$)} was prepared in 65% overall yield from (1*S*)-(1,3,6/2)-1,2,3-triacetoxy-4-acetoxymethyl-6-azido-cyclohex-4-ene (**14**)[12] by the following sequence: *O*-deacetylation, isopropylidentation with 2,2-dimethoxypropane in DMF–PTSA [(**14**)→(**15**)], and reduction of the azido group with H_2S in aqueous pyridine [(**15**)→(**16**)]. Coupling of crude epoxide (**9**) with a slight excess of the amine (**16**) in propan-2-ol–DMF (1 : 1, v/v) at 120 °C for 70 h gave a mixture of the condensates, which was *O*-deisopropylidenated with aqueous 30% acetic acid and then acetylated. The products were separated on a silica gel column [EtOH–toluene (1 : 1, v/v)] to give the protected acarbose (**17**){19%, $[\alpha]_D^{24}$ +65° ($CHCl_3$)} and its isomer (**18**) {30%, $[\alpha]_D^{20}$ +58° ($CHCl_3$)}. Acetolysis of (**17**) was readily carried out by using acetic acid–acetic anhydride–conc. sulphuric acid (30 : 70 : 1) at room temperature to give acarbose trideca-acetate (**1b**), the α-anomer, {$[\alpha]_D^{21}$ +87° ($CHCl_3$)}, quantitatively. The structure was evidenced by the ^1H n.m.r. data (400 MHz, $CDCl_3$). *O*-Deacetylation of (**1b**) gave acarbose (**1a**) {59%, $[\alpha]_D^{18}$ +165° (H_2O); lit.,[1] +171°}, the ^1H n.m.r. data of which coincided with those of an authentic sample.[1,13]

On the other hand, the primary hydroxy group of (**5**) was selectively benzoylated with benzoyl chloride in pyridine and then converted to the 4-methanesulphonate (**7**), 95%. Epoxidation of (**7**) with methanolic sodium methoxide in CH_2Cl_2 at room temperature, followed by acetylation, gave selectively the desired epoxide (**10**) {76%, $[\alpha]_D^{22}$ +28° ($CHCl_3$)}.

Likewise, coupling of (**16**) with the epoxide (**11**), derived from (**10**), followed by deprotection and acetylation, gave two pseudotetrasaccharides, which were separarable on a silica gel column to afford the protected adiposin-2 (**19**) {33%, $[\alpha]_D^{24}$ +70° ($CHCl_3$)} and its isomer (**20**) {21%, $[\alpha]_D^{21}$ +39° ($CHCl_3$)}. Acetolysis of (**19**) provided adiposin-2 tetradeca-acetate (**2b**) {78%, $[\alpha]_D^{21}$ +102° ($CHCl_3$)}, the ^1H n.m.r. spectrum could be almost interpreted as first-order. Deprotection of (**2b**) afforded adiposin-2 (**2a**) {78%, $[\alpha]_D^{18}$ +154° (H_2O); lit.,[6] +163°}, identified by comparison with an authentic sample on the basis of the 400 MHz ^1H n.m.r. data.[6]

Received, 21st December 1987; Com. 1827

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