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Synthetic ventures in pseudo-sugar chemistry

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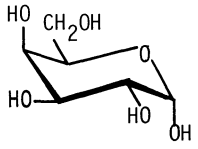
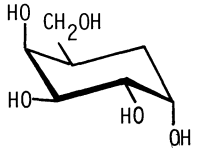
Abstract - Pseudo-sugar is a compound in which a ring-oxygen of a pyranoid sugar is replaced by a methylene group, and there are 32 theoretically possible stereoisomers in the pseudo-sugar family. All the predicted 16 DL-forms have been synthesized, as well as 9 enantiomers. The most accessible starting material for a synthesis of pseudo-sugars is endo-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid which is obtained by the Diels-Alder reaction of furan and acrylic acid. Recently, it has been found that some pseudo-sugars are almost equally sweet as their respective true sugars.

INTRODUCTION

In the last two decades, several biologically active branched-chain cyclitols and their erivatives have been found in Nature, such as (+)-(1,2,3/4,5)-tetrahydroxy-1-cyclohexanemethanol (1) (ref. 1), validamycin antibiotics (2) (ref. 2), glucosidase-inhibitors: acarbose (ref. 3), trestatins (ref. 4), adiposins (ref. 5) and oligostatins (refs. 6, 7). Since their common component, hydroxymethyl-cyclohexanetetrol or its amino derivative, is structurally closely related to a true sugar, this compound has been designated as a pseudo-sugar or a pseudo-amino sugar. Thus, the pseudo-sugar is a name of a class of compounds in which a ring-oxygen of a pyranoid sugar is replaced by a methylene group.



α-D-GALACTOPYRANOSE



PSEUDO-α-D-GALACTOPYRANOSE

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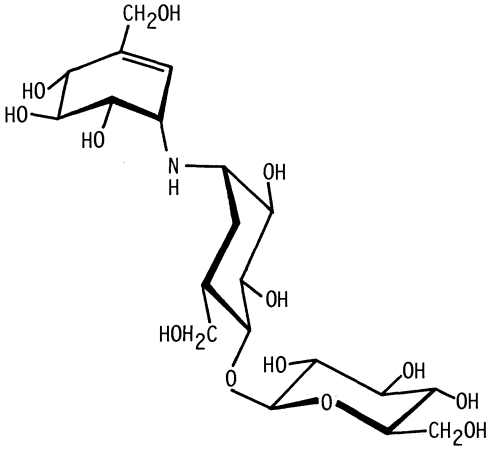

VALIDAMYCIN A

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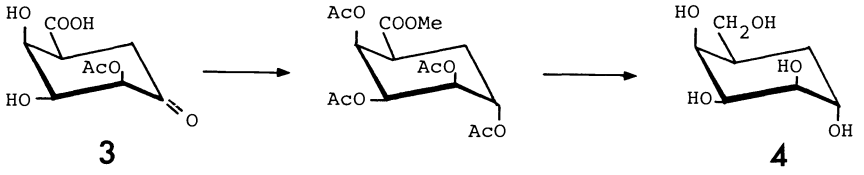
The term "pseudo-sugar" was first proposed by McCasland at the time when he synthesized the first pseudo-sugar, namely pseudo-α-DL-talopyranose in 1966 (ref. 8). He and his coworkers synthesized two more pseudo-sugars: pseudo-β-DL-gulopyranose (ref. 9) and pseudo-α-DL-galactopyranose (ref. 10). He suggested that pseudo-sugars may possess some biological activities, due to their structural resemblance to natural sugars. Hope has been expressed that in some cases, pseudo-sugars will be accepted by enzymes or biological systems in place of the corresponding true sugars, and thus may serve to inhibit a growth of malignant or pathogenic cells. In fact, seven years after his prediction, the first naturally occurring pseudo-α-D-galactopyranose (1) was discovered in a fermentation broth of Streptomyces sp. MA-4145 as an antibiotic active against Klebsiella pneumoniae MB-1264 (ref. 1). The racemic form of this pseudo-sugar had been synthesized by McCasland and his coworkers, five years prior to the discovery (ref. 10). In the pseudo-sugar family, there are 32 theoretically possible stereoisomers, including anomer-like compounds, and up to the present, all the predicted 16 racemic pseudo-sugars have been synthesized, as well as 9 enantiomers.

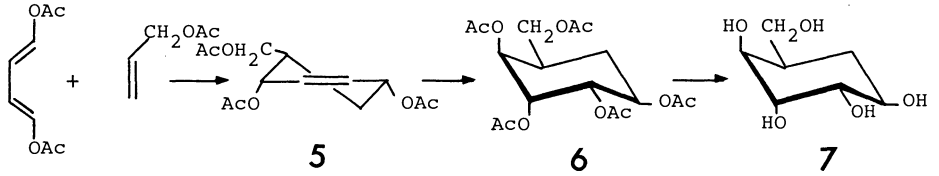
SYNTHESIS OF RACEMIC PSEUDO-SUGARS

The first pseudo-sugar, pseudo-α-DL-talopyranose (4) was synthesized from 4-acetoxy-2,3-dihydroxy-5-oxo-cyclohexanecarboxylic acid (3). Hydrogenation of (3) with sodium borohydride and successive esterification, followed by acetylation gave the tetraacetate, which was converted into the pseudo-sugar (4) by hydrogenation with lithium aluminium hydride and subsequent hydrolysis (ref. 8).



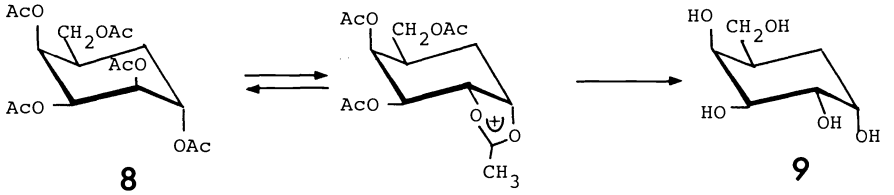
3 4

2,5-Dihydroxy-3-cyclohexene-1-methanol triacetate (5), which was prepared by cycloaddition of 1,4-diacetoxy-1,3-butadiene and allyl acetate, was converted into 2,3,4,5-tetrahydroxy-1-cyclohexanemethanol pentaacetate (6) by hydroxylation and successive acetylation. Hydrolysis of (6) gave pseudo-β-DL-gulopyranose (7) (ref. 9).



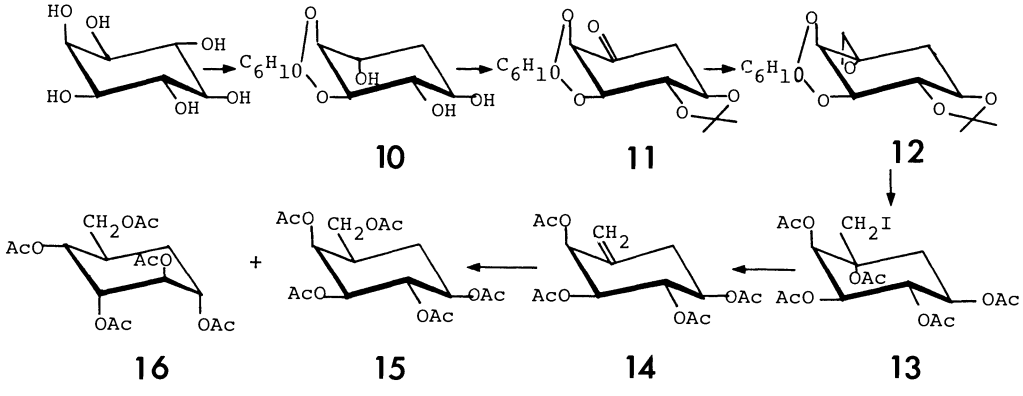
5 6 7

When pseudo-α-DL-talopyranose pentaacetate (8) was heated in acetic acid containing sulfuric acid, it underwent an epimerization on C-4 (C-2 in a true sugar numbering) and pseudo-α-DL-galactopyranose (9) was obtained, after deacetylation (ref. 10).



8 9

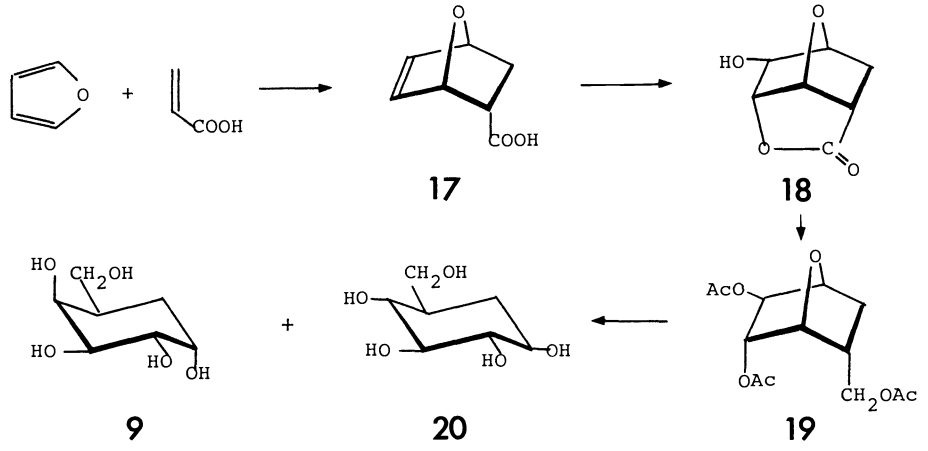
Two pseudo-sugars: pseudo-β-DL-galactopyranose and pseudo-α-DL-altropyranose were prepared from myo-inositol. At first, myo-inositol was converyed into 1,2-O-cyclohexylidene-5-deoxy-chiro-inositol (10) by a 4 steps reaction (ref. 11). O-Isopropylidenation of (10) with 2,2-dimethoxypropane, followed by Pfitzner-Moffatt oxidation yielded the 2-deoxy-chiro-inosose-1 derivative (11). Introduction of a side chain into (11) with diazomethane gave the spiro epoxide (12) in a yield of 82%. Opening of the oxirane ring of (12) with hydriodic



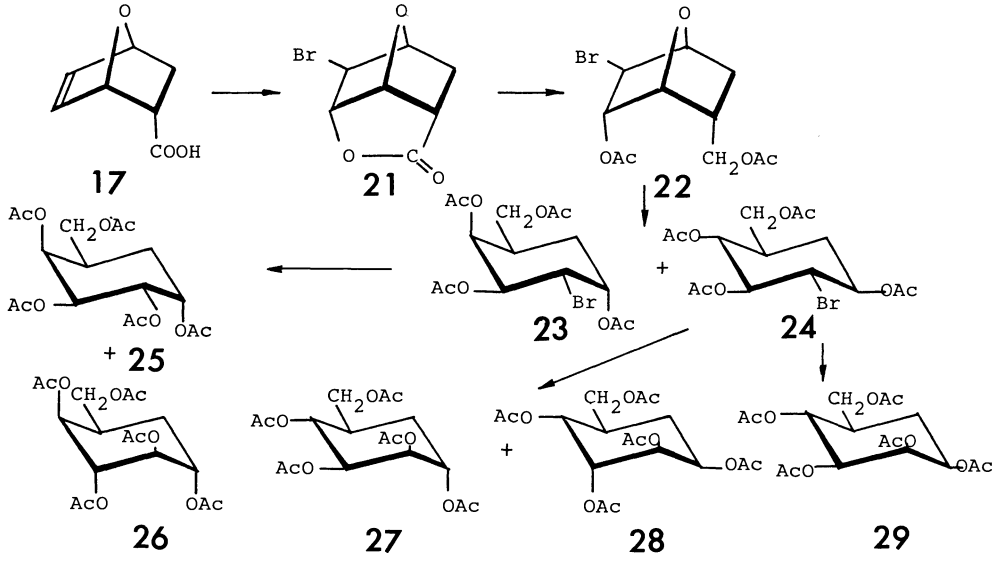
10 11 12 13 14 15 16

acid, followed by acetylation gave the pentaacetate (13), which was converted into the exocyclic olefin (14) by heating with zinc powder in glacial acetic acid. Hydroboration of (14) and successive oxidation with hydrogen peroxide, followed by acetylation gave pseudo-β-DL-galactopyranose pentaacetate (15) and pseudo-α-DL-altropyranose pentaacetate (16) in 13 and 17% yields, respectively. Hydrolysis of (15) and (16) yielded the corresponding pseudo-sugars (ref. 12).

As these reactions from myo-inositol were considerably laborious, a facile synthesis has been attempted. In order to obtain a more accessible starting material, a Diels-Alder reaction was extensively exploited. For example, the Diels-Alder addition of furan and acrylic acid gave known endo-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid (17), which was an ideal starting material for a forthcoming synthesis of various pseudo-sugars (ref. 13). Hydroxylation of (17) with hydrogen peroxide in formic acid resulted in a spontaneous lactonization to give exo-9-hydroxy-2,7-dioxatricyclo[4.2.1.$0^{1,8}$]nonan-3-one (18). Reduction of (18) with lithium aluminium hydride afforded exo-5-endo-6-dihydroxy-endo-2-hydroxymethyl-7-oxabicyclo[2.2.1]heptane, which was converted into the triacetate (19) by acetylation. Acetolysis of (19) in acetic anhydride - acetic acid containing a small volume of sulfuric acid gave rise to an opening of the 1,4-anhydro ring and an approximately 1:1 mixture of pseudo-α-DL-galactose pentaacetate and pseudo-β-DL-glucopyranose pentaacetate was obtained, which was hydrolyzed to the corresponding pseudo-sugars (9) and (20) (ref. 14).

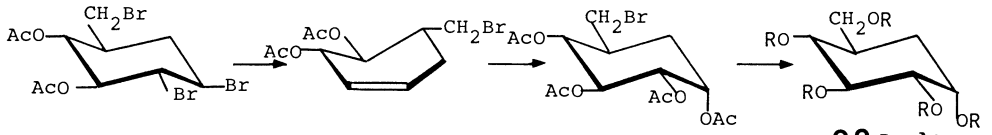


Four other pseudo-sugars having α-ido, α-manno, β-altro and β-manno configurations have been prepared from (17) by the following reaction. Acetolysis of endo-3-acetoxy-endo-5-acetoxymethyl-exo-2-bromo-7-oxabicyclo[2.2.1]heptane (22), which was prepared from (17) via the bromo lactone (21) (ref. 15), in a mixture of acetic anhydride, acetic acid and sulfuric acid afforded tetra-O-acetyl-(1,2/3,4,5)-2-bromo-5-hydroxymethyl-1,3,4-cyclohexanetriol (23) and



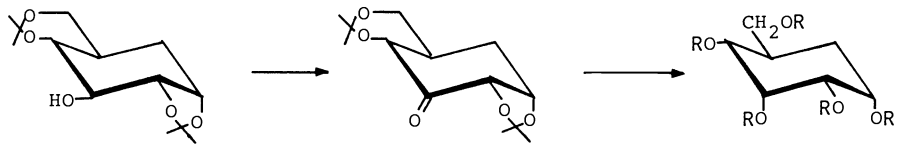
the corresponding (1,3,5/2,4)-isomer (24) in 31 and 13% yields, respectively. Nucleophilic displacement of (23) with an acetate anion, followed by acetylation gave pseudo-α-DL-galactopyranose pentaacetate (25) in 10% yield and pseudo-α-DL-idopyranose pentaacetate (26) in 31% yield. The displacement reaction of a bromine atom by an acetate anion proceeded via an intermediary 2,3-cyclic acetoxonium ion with an anchimeric assistance of a vicinal trans acetoxyl group (ref. 14). An analogous displacement reaction of (24) with an acetate anion gave pseudo-α-DL-mannopyranose pentaacetate (27) in 29% yield and pseudo-β-DL-altropyranose pentaacetate (28) in 27% yield, which were converted into the corresponding pseudo-sugars by hydrolysis. When (24) reacted with sodium benzoate, rather than sodium acetate, a direct S_N2 displacement occurred to give the pseudo-β-DL-mannopyranose derivative (29) in a yield of 49%. Hydrolysis of (29) gave pseudo-β-DL-mannopyranose (ref. 14).

While bromination of (22) in hydrobromic acid gave di-O-acetyl-(1,3/2,4,6)-3,4-dibromo-6-bromomethyl-1,2-cyclohexanediol (30) almost quantitatively (ref. 15). Debromination of (30) with zinc dust in glacial acetic acid gave the cyclohexene derivative (31). Hydroxylation of (31) with osmium tetroxide and subsequent acetylation gave the bromomethyl-cyclohexanetetrol (32). Displacement of a bromine atom with sodium acetate in (32), followed by acetylation gave pseudo-α-DL-glucopyranose pentaacetate (33). Hydrolysis of (33) gave pseudo-α-DL-glucopyranose (34) (refs. 16,18). Alternatively, the same compound (33) was obtained as a minor product by a reaction of tri-O-acetyl-(1,3/2,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol and sodium acetate (ref. 17).



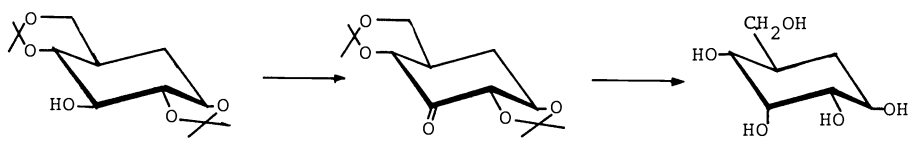
30 31 32 33 R: Ac 34 R: H

O-Isopropylidenation of (34) with 2,2-dimethoxypropane gave the 1,2:4,7-di-O-isopropylidene-derivative (35), which was oxidized by ruthenium tetroxide and sodium metaperiodate to the 3-oxo derivative (36) in 89% yield. Catalytic hydrogenation of (36) in the presence of Raney nickel and subsequent removal of the isopropylidene group, followed by acetylation yielded pseudo-α-DL-allopyranose pentaacetate (37). Deacetylation of (37) gave pseudo-α-DL-allopyranose (38) (ref. 18).



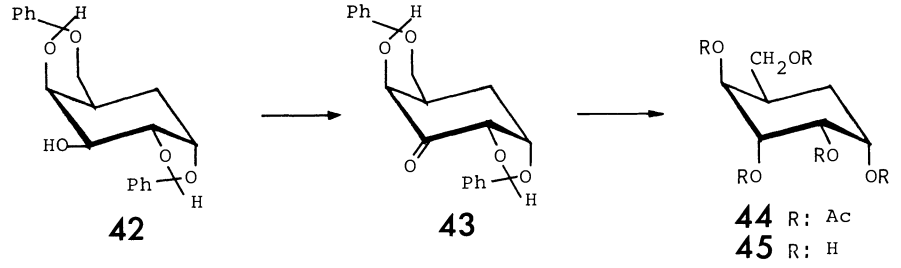
35 36 37 R: Ac 38 R: H

Analogous O-isopropylidenation of pseudo-β-DL-glucopyranose (21) (ref. 14) gave the 1,2:4,7-di-O-isopropylidene derivative (39) and a positional isomer in 26 and 39% yield, respectively. Oxidation of (39) with ruthenium tetroxide gave the 3-oxo derivative (40), which was converted into pseudo-β-DL-allopyranose (41) by the analogous reaction employed in the synthesis of (38) (ref. 18).

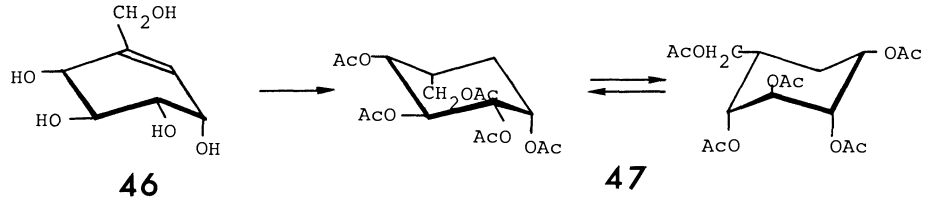


39 40 41

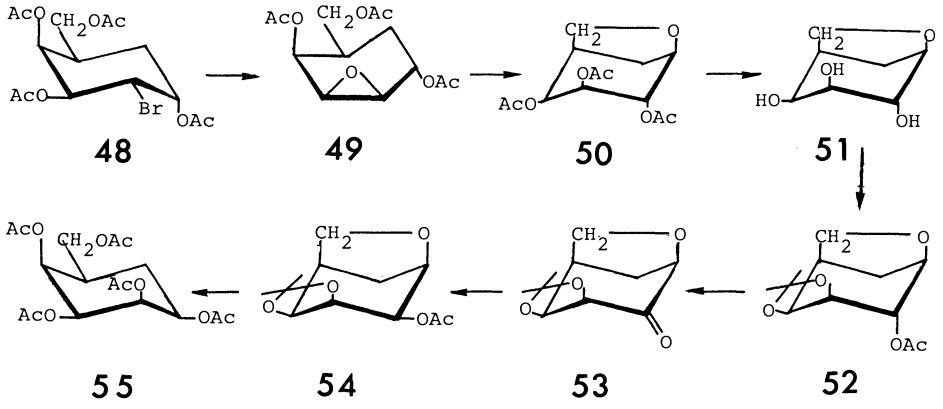
O-Benzylidenation of pseudo-α-DL-galactopyranose (9) (ref. 10) with α,α-dimethoxytoluene gave the 1,2:4,7-di-O-benzylidene derivative (42), which was transformed into the 3-oxo derivative (43) by oxidation with ruthenium tetroxide. Hydrogenation of (43) with sodium borohydride and subsequent removal of the benzylidene group, followed by acetylation, gave pseudo-α-DL-gulopyranose pentaacetate (44). Hydrolysis of (44) gave the corresponding pseudo-sugar (45) (ref. 18).



Pseudo-β-DL-idopyranose pentaacetate (47) was synthesized from (1,2,4/3)-5-hydroxymethyl-5-cyclohexene-1,2,3,4-tetrol (46) (ref. 19) by catalytic hydrogenation over a platinum catalyst (ref. 18).



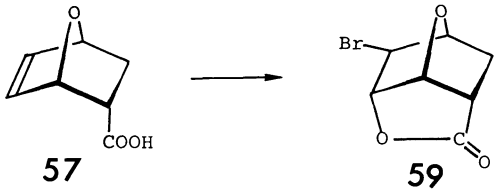
The last unknown racemic pseudo-β-DL-talopyranose pentaacetate (55) was synthesized from 1,3,4-tri-O-acetyl-5-acetoxymethyl-2-bromo-1,3,4-cyclohexanetriol (48) (ref. 14) as follows. Treatment of (48) with sodium methoxide resulted in a formation of the 5,7-anhydro derivative (50) through an intramolecular migration of the intitially formed 2,3-epoxide (49). Compound (50) was converted into pseudo-β-DL-talopyranose pentaacetate (55) by epimerization of the hydroxyl group on C-4 (C-2 in a true sugar numbering) (ref. 20).

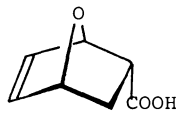


Now, all the theoretically possible 16 racemic pseudo-sugars have been prepared. Three pseudo-sugars having α-talo (4), β-gulo (7) and α-galacto configurations were synthesized by McCasland and his coworkers. Two other pseudo-sugars of β-galacto (15) and α-altro (16) configurations were synthesized from myo-inositol, and the rest 11 pseudo-sugars have been synthesized from the Diels-Alder adduct (17) of furan and acrylic acid. The Diels-Alder adduct (17) was the most accessible starting material for the synthesis of a variety of pseudo-sugars.

SYNTHESIS OF ENANTIOMERIC PSEUDO-SUGARS

The Diels-Alder adduct (17) is readily optically resolved by an optically active amine as follows. Treatment of (17) with (R)-(+)-α-methylbenzylamine (56), followed by fractional recrystallization gave the salt of (56) and the (-)-adduct (57) in 30% yield. Removal of the amine from the salt by an ion-exchange resin, Dowex 50W X2 gave the optically pure (-)-adduct (57), $[\alpha]_D$ -111.8° (ethanol). The analogous procedure with (S)-(-)-α-methylbenzylamine and (17) gave the optically pure (+)-adduct (58), $[\alpha]_D$ +110.7° (ethanol) (ref. 21). Moreover all the racemic pseudo-sugars are obtainable from the adduct (17) as a common starting material, and therefore, all enantiomeric pseudo-sugars will be accessible either in D or L forms, starting from the optical antipodes (57) or (58) by the same reaction employed in the synthesis of racemic pseudo-sugars. The reaction is exemplified in a following synthesis of pseudo-α-D-galactopyranose (1) and pseudo-β-D-glucopyranose (60). First of all, the absolute configuration of the (-)-adduct (57) must be determined. Bromolactonization of (57) with hypobromous acid gave the bromo-lactone (59), whose absolute configuration has been established by a X-ray crystal structure analysis as (3S)-(+)-2-exo-bromo-4,8-dioxatricyclo[4.2.1.$0^{3,7}$]nonan-5-one. Accordingly, it was revealed that the (-)-adduct (57) corresponded to a pseudo-sugar belonged to the D-series and the (+)-adduct (58) corresponded with that in the L-series (ref. 22).





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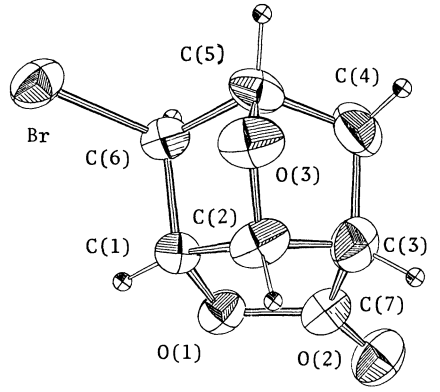
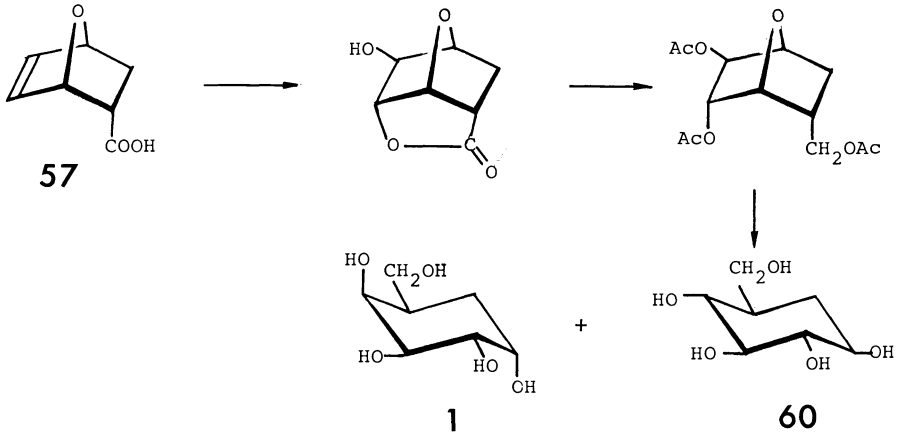


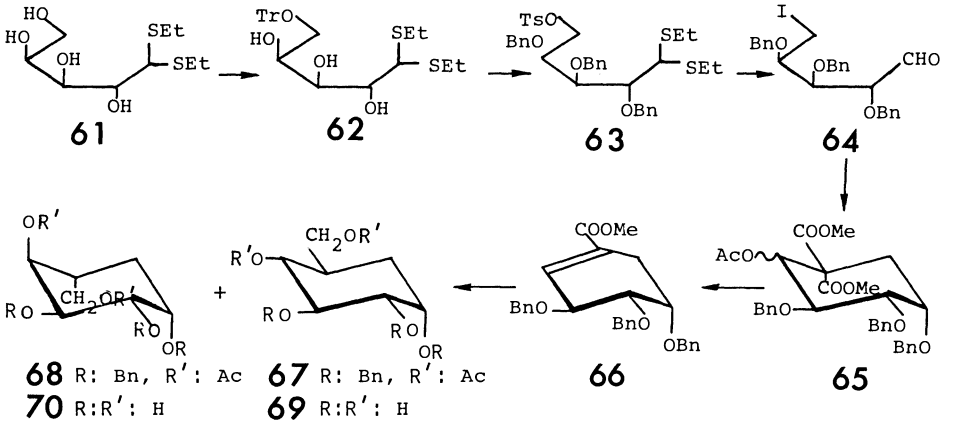
ORTEP drawing of (59) with 50% probability ellipsoids, indicating numbering of atoms.

Starting from the (-)-Diels-Alder adduct (57), the analogous reaction employed in the synthesis of racemic pseudo-sugars, (9) and (20), (ref. 14) gave pseudo-α-D-galactopyranose (1), m.p. 162.5°C, $[\alpha]_D$ +66.3° (water) and pseudo-β-D-glucopyranose (60), syrup, $[\alpha]_D$ +13.0° (water) (ref. 21).

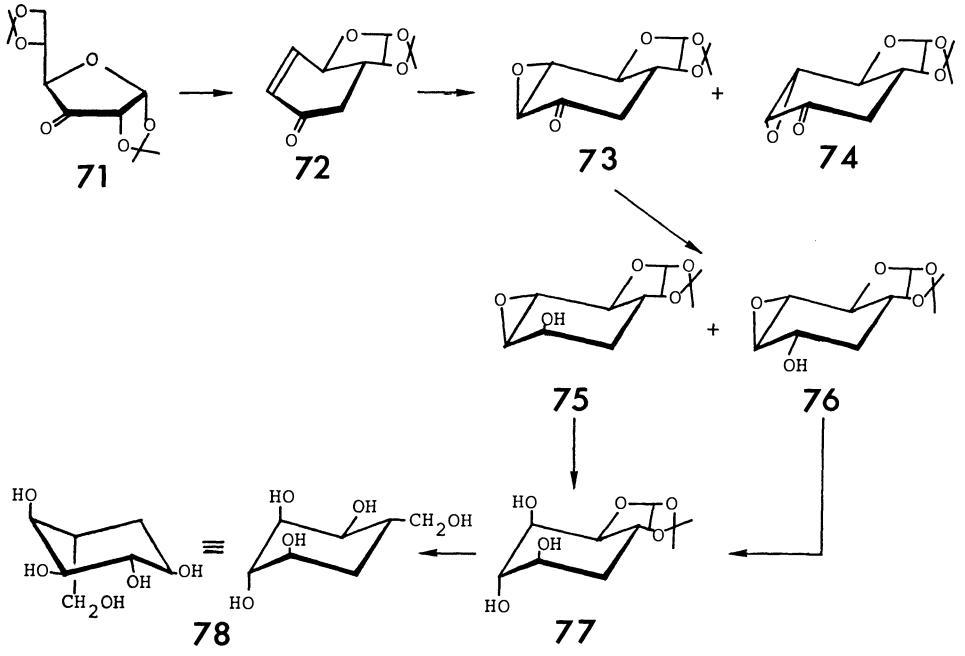


1 60

Seven optically pure enantiomers have been synthesized by a chiral synthesis. Tritylation of L-arabinose diethyl dithioacetal (61) (ref. 23) with trityl chloride gave the 5-O-trityl derivative (62). Benzylation of (62) with benzyl bromide and sodium hydride, followed by hydrolysis and successive tosylation gave 2,3,4-tri-O-benzyl-5-O-tosyl-L-arabinose diethyl dithioacetal (63). Dethioacetalization of (63), followed by displacement of the tosyloxy group by an iodide anion yielded the 5-iodo derivative (64). Cyclization of (64) with dimethyl malonate and sodium hydride, and subsequent acetylation resulted in a formation of the cyclohexane derivative (65) in 43% yield. Thermal decomposition of (65) gave the cyclohexene derivative (66) in 75% yield. Hydrogenation of (66) with lithium aluminium hydride and successive hydroboration, followed by oxidation and acetylation gave the pseudo-α-D-glucopyranose derivative (67) and the pseudo-β-L-altropyranose derivative (68) in 34 and 35% yields, respectively. Deprotection of (67) furnished pseudo-α-D-glucopyranose (69), $[\alpha]_D$ +30° (methanol), and that of (68) gave pseudo-β-L-altropyranose (70), $[\alpha]_D$ -49.5° (methanol) (ref. 24).

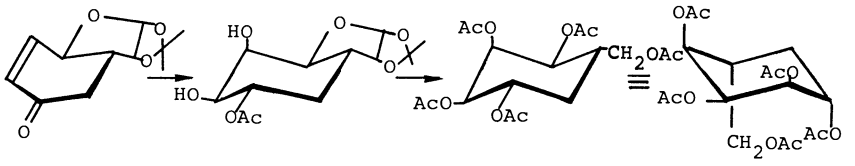


Pseudo-α-L-altropyranose (78) was synthesized from D-glucose. D-Glucose was converted into 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose (71) by a known method (ref. 25). Compound (71) was further convertible to 8,9-O-isopropylidene-3-oxo-7-oxabicyclo[4.3.0]non-4-ene-8,9-diol (72) by a 5-steps reaction. Epoxidation of (72) with hydrogen peroxide gave the β-epoxide (73) as a major product in 96% yield and the α-epoxide (74) as a minor product in 3% yield. Hydrogenation of (73) with sodium borohydride gave the two compounds (75) and (76) in a ratio of 4:1. Opening of the oxirane ring of (75) by a hydroxide anion proceeded



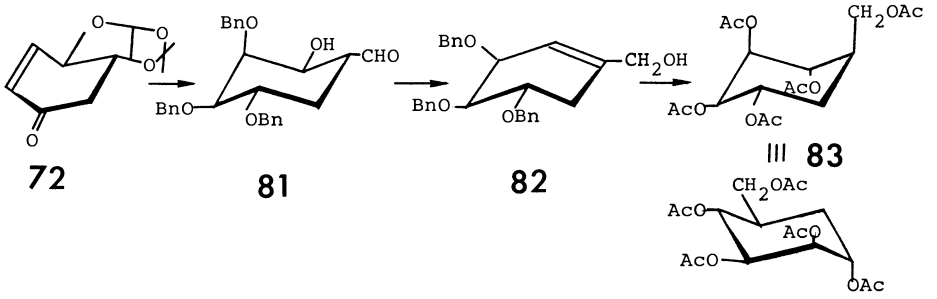
in a manner of trans diaxial opening to give 8,9-O-isopropylidene-7-oxabicyclo[4.3.0]nonane-3,4,5,8,9-pentol (77). Compound (77) was obtained from (76) by the analogous reaction, which involved an oxirane ring migration with an anchimeric assistance of the vicinal hydroxyl group on C-3. Compound (77) was converted into pseudo-α-L-altropyranose (78), $[\alpha]_D$ -43.6° (methanol), by removal of the protective group and shortening of the side chain (ref. 26).

Starting from (72), two other pseudo-sugars have been prepared. Reduction of (72) with diisobutyl aluminium hydride and subsequent acetylation, followed by hydroxylation with osmium tetroxide and hydrogen peroxide gave the glycol acetate (79). By the analogous reaction employed in the synthesis of (78), pseudo-β-L-allopyranose pentaacetate (80), m.p. 136°C, $[\alpha]_D$ +3.7° (chloroform), was obtained from (79) (ref. 27).



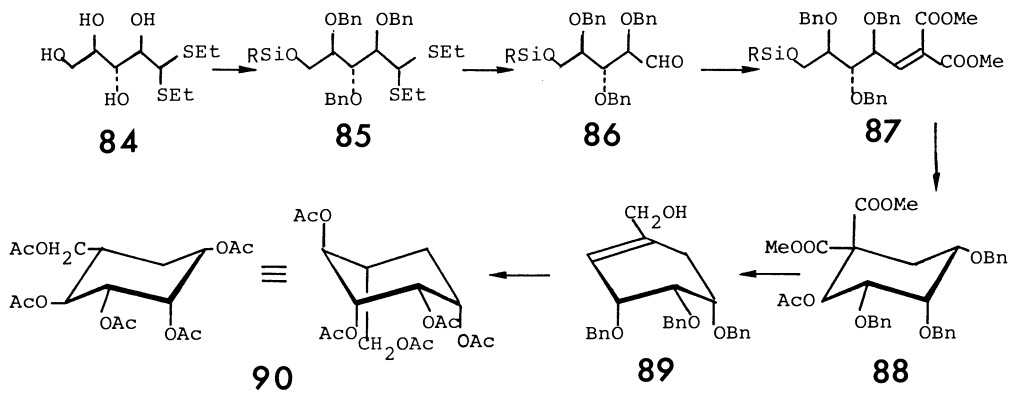
72 79 80

An aldehyde (81), which was prepared from (72) as an intermediary compound in the above synthesis, was converted into the cyclohexenol derivative (82). Hydroxylation of (82), followed by interchange of protective groups gave pseudo-α-D-mannopyranose pentaacetate (83), m.p. 81°C, $[\alpha]_D$ +27.8° (chloroform) (ref. 27).



72 81 82 ≡ 83

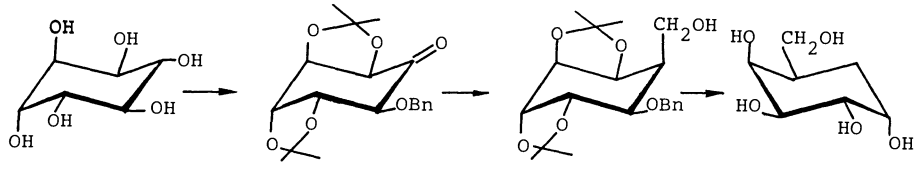
Pseudo-β-L-mannopyranose pentaacetate (90) was synthesized from D-ribose. D-Ribose diethyl dithioacetal (84) (ref. 28) was transformed to the 5-O-(tert-butyldiphenylsilyl) derivative (85). Dethioacetalization of (85) gave the aldehyde (86), which was converted into the unsaturated diester (87). Catalytic hydrogenation of (87) and successive partial deprotection, followed by cyclization yielded the cyclohexane derivative (88). Thermal decomposition of (88) and subsequent reduction with lithium aluminium hydride gave the compound (89). Hydroxylation of (89) and successive interchange of protective groups gave pseudo-β-L-mannopyranose pentaacetate (90), $[\alpha]_D$ -1.1° (chloroform) (ref. 29).



84 85 86 87 88 89 ≡ 90

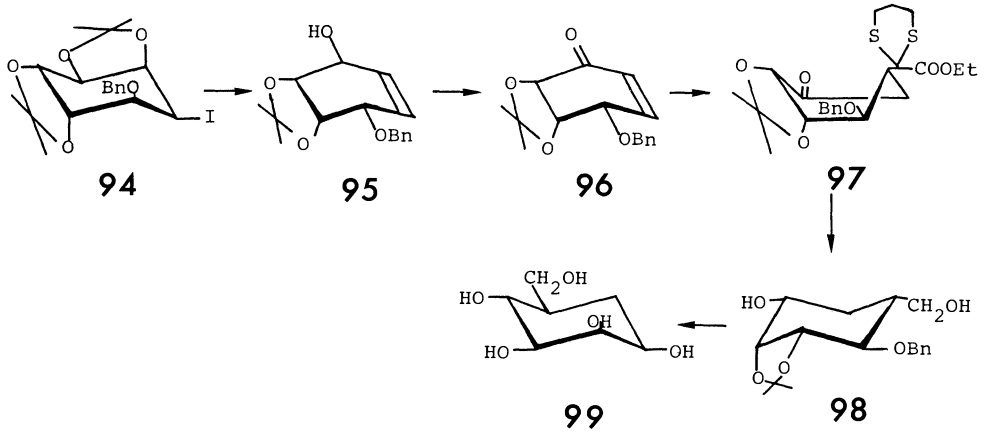
R: TBDP

Pseudo-α-D-galactopyranose (1) and pseudo-β-D-mannopyranose (99) have been synthesized by Paulsen and his coworkers. 1L-chiro-Inositol (91) was first converted into the inosose (92). Wittig reaction of (92) with methyl(triphenyl)phosphonium bromide, followed by hydroxylation gave the compound (93). Deoxygenation of (93) and successive deprotection afforded pseudo-α-D-galactopyranose (1), m.p. 161°C, $[\alpha]_D$ +47.9° (methanol) (ref. 30).



91 92 93 1

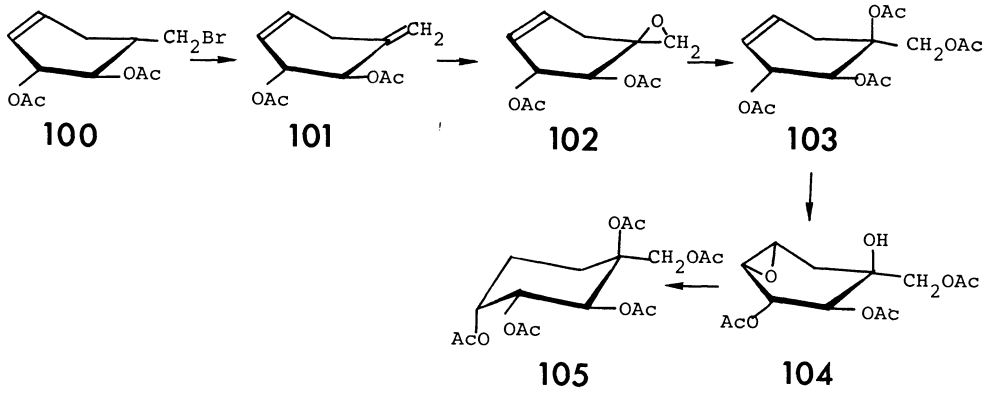
When 1L-4-O-benzyl-3-deoxy-3-iodo-1,2:5,6-di-O-isopropylidene-allo-inositol (94), which was prepared from (91), reacted with lithium aluminium hydride, the cyclohexene derivative (95) was obtained. Oxidation of (95) gave the enone (96), and addition of ethyl 2-lithio-1,3-dithiane-2-carboxylate to (96) yielded the compound (97). Reduction of (97), followed by shortening of the side chain gave the pseudo-sugar derivative (98), which was converted into pseudo-β-D-mannopyranose (99), m.p. 217°C, $[\alpha]_D$ +11.9° (methanol) (ref. 30).

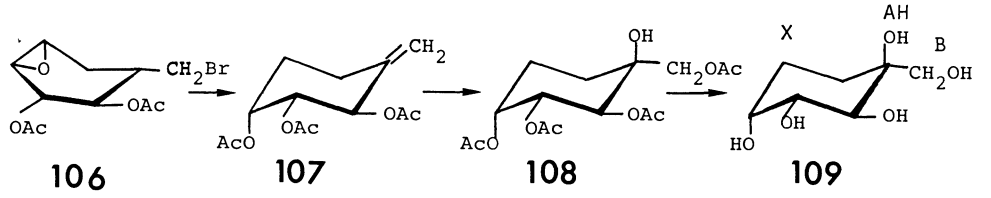


94 95 96 97 98 99

SYNTHESIS OF PSEUDO-β-FRUCTOPYRANOSES

D-Fructose is the sweetest sugar known in naturally occurring carbohydrates, and its intense sweetness arises only from a β-D-fructopyranose form (refs. 31, 32, 33). The sweetness eliciting units, AH (a proton donor) and B (a proton acceptor) components are assigned to be the anomeric hydroxyl group on C-2 and the hydroxyl group on C-1, respectively, and the methylene group on C-6 is ascribed to a third hydrophobic component (X) (ref. 34), completing the sweetness eliciting triplet. Since pseudo-β-D-fructopyranose furnishes the triplet in its molecule, this pseudo-sugar is expected to be fairly sweet. To demonstrate its sweetness, pseudo-β-DL-fructopyranose (109) has been synthesized, as well as the two enantiomers. There are two synthetic routes : (A) Dehydrobromination of 1,2-di-O-acetyl-(1,3/2)-3-bromomethyl-5-cyclohexene-1,2-diol (100) (ref. 15) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the diene (101). Preferential epoxidation of the exocyclic C=C bond with m-chloroperoxybenzoic acid (MCPBA) gave the spiro epoxide (102) in 52% yield. Opening of the oxirane ring with an acetate anion and successive acetylation gave the tetraacetate (103), which was converted into the epoxide (104). Reductive opening of the oxirane ring with lithium aluminium hydride, followed by acetylation afforded pseudo-β-DL-fructopyranose pentaacetate (105) in 5.8% over-all yield ; (B) Hydrolysis of (100) and successive epoxidation, followed by acetylation gave the compound (106). Dehydrobromination with silver fluoride and subsequent reductive opening of the oxirane ring gave the triacetate (107), after acetylation. Epoxidation of (107) with MCPBA and successive opening of the oxirane ring with an acetate anion gave pseudo-β-DL-fructopyranose tetraacetate (108), after conventional acetylation. Exhaustive acetylation of (108) gave the pentaacetate (105) in 21% over-all yield from (100). Deacetylation of (105) or (108) gave pseudo-β-DL-fructopyranose (109) (ref. 35).





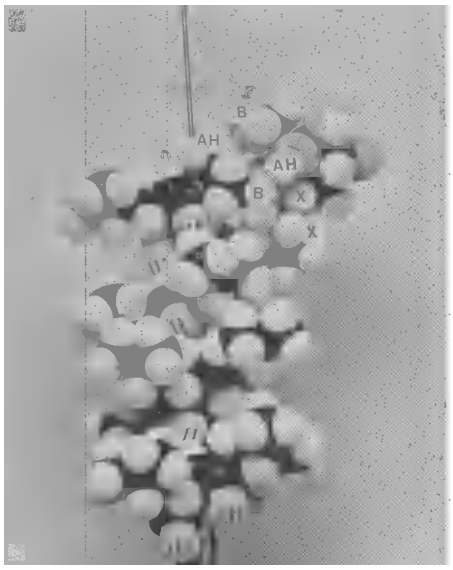
Pseudo-β-D-fructopyranose (110), $[\alpha]_D$ -56.9° (methanol), and pseudo-β-L-fructopyranose (111), $[\alpha]_D$ +57.2° (methanol), have been synthesized from the optically active antipodes of the Diels-Alder adduct, (57) and (58) (ref. 21), by the analogous reaction employed in the latter synthesis of the racemate (ref. 36).

MOLECULAR MECHANISM OF SWEET TASTE

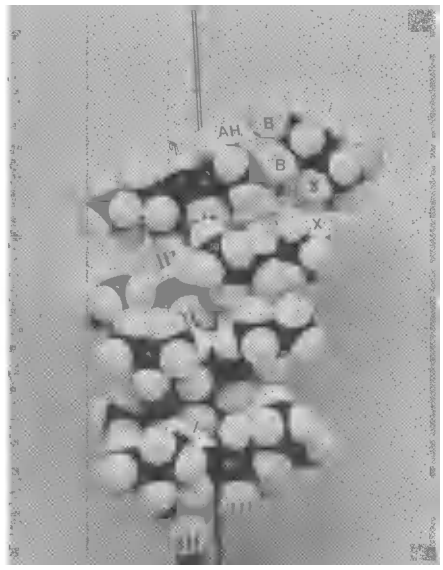
A common molecular feature of sweet tasting compounds has been established as a bifunctional entity of AH (a proton donor) and B (a proton acceptor) components, together with a third hydrophobic site (X) (refs. 31, 37, 38). A required distance between AH and B is 3.0 A, and X is located approximately 3.5 A apart from AH and 5.5 A from B (refs. 34, 37). In the D-glucopyranose molecule, the hydroxyl group on C-4 is assigned as AH, the hydroxyl group on C-3 is ascribed to B, and the methylene group on C-6 is attributed to X (ref. 39). A pseudo-sugar resembles closely to a true sugar, and a geometry of the pyranose ring is practically the same as that of the cyclohexane ring (ref. 40). Therefore, the glucophores (AH and B) and the hydrophobic site (X) may exist in some pseudo-sugars. In fact, pseudo-β-DL-gluco-pyranose (26), pseudo-α-DL-galactopyranose (25) and pseudo-β-DL-fructopyranose (109) are almost equally sweet as D-glucose, D-galactose and D-fructose, respectively (refs. 35, 41). Also, a relative sweetness of L-glucose is about the same as that of the D-enantiomer (ref. 42), and hence, pseudo-L-glucopyranose may taste as sweet as its D-enantiomer.

But it was suggested that a relative sweetness of L-fructose may not be the same as D-fructose, and this might be true in pseudo-β-fructopyranoses (ref. 35). Very recently, it was revealed that pseudo-β-D-fructopyranose (110) was some what sweeter than the L-enantiomer (111). To elucidate the difference in their sweet taste, their CPK molecular models have been inspected. At the same time, a molecular structure of a sweet-receptor must be learned. There are some investigations of the isolation of a sweet-sensitive protein (a sugar-binding protein) from a tongue epithelium (refs. 43 - 47), but concerning the molecular structure of the sugar-binding protein, little is known. So if the sugar-binding protein is assumed to constitute an essential part of the receptor, secondarily, a formation of hydrogen bonds between the sugar-binding protein and a sweet tasting substance is presumed to be a primary manner for perception of sweetness, and thirdly, the protein is supposed to be an alpha helix of a polypeptide having L-serine or L-threonine as a N-terminal amino acid residue, the molecular mechanism of sweet taste will be fairly well comprehensible. The hypothesis is exemplified in the case of enantiomeric pseudo-β-fructopyranoses, (110) and (111), as well as L and D-leucine as typical non-sweet and sweet tasting amino acids.

There is another AH-B system on the receptor, which is attributed to NH_3^+ and OH groups of the N-terminal L-serine or L-threonine residue. These AH and B components bind contrariwise to the AH and B components of a sugar by hydrogen bonds, and the hydrophobic site (X) of the sugar binds to a hydrophobic alkyl group (X) of the fourth amino acid residue of the receptor, counting from the N-terminal end, if both X sites get close. In the case of pseudo-β-D-fructopyranose (110), these two X sites locate close to each other, as shown in the photo picture of the CPK molecular model (below left), but in the case of the less sweet L-enantiomer (111), they do not come as close as the former case (below right).

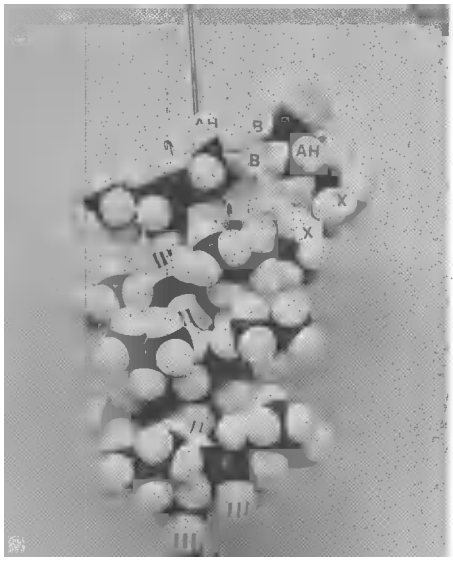


PSEUDO-β-D-FRUCTOPYRANOSE (110)

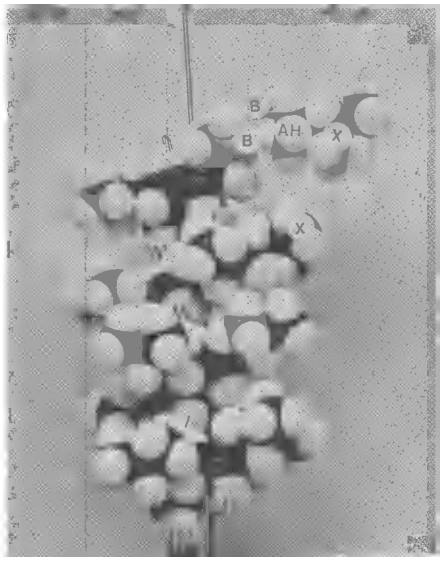


PSEUDO-β-L-FRUCTOPYRANOSE (111)

In the case of L and D-leucine, the difference is more clearly recognized. The AH and B components of leucine are ascribed to NH_3^+ and COO^- groups, respectively, which bind to the B and AH components of the receptor. A hydrophobic alkyl group (X) of D-leucine approaches very closely to the hydrophobic site (X) of the fourth amino acid residue of the receptor, and accordingly, D-leucine is very sweet (below left). On the contrary, the X site of L-leucine stands far away from the X site of the receptor, and hence, L-leucine is not sweet any more (below right).



D-LEUCINE



L-LEUCINE

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