Formal Syntheses of N-Trifluoroacetyl-l-acosamine and N-Trifluoroacetyl-l-daunosamine from an Achiral Precursor, Methyl Sorbate

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N-Trifluoroacetyl-l-acosamine 20 and N-trifluoroacetyl-l-daunosamine 21 were formally synthesized from an achiral precursor, methyl sorbate 4, based on enzymatic chiral induction and diastereoselective 1,4-conjugated addition of benzylamine to the olefinic moiety of the α,β-unsaturated ester 12.

Keywords amino sugar; acosamine; daunosamine; conjugated addition; diastereoselective addition

The anthracyclines daunomycin (1a) and Adriamycin (1b) are highly effective in the treatment of childhood leukemia and several types of solid tumors,1,3 and contain an amino sugar called l-daunosamine (2). Conversion of l-daunosamine of adriamycin into l-acosamine (3), the 4-epimer, was reported to suppress the undesired toxic side effects while retaining the anti-tumor activity.2) Therefore extensive studies have been made on syntheses of this type of amino sugar.3) We wish to report formal syntheses of l-acosamine and l-daunosamine, starting with an achiral precursor, methyl sorbate 4, and employing enzymatic chiral induction and diastereoselective conjugated addition of benzylamine to the α,β-unsaturated double bond.

We reported previously that the reaction of (±)-(4,5)-trans-epoxy-(2E)-hexenoate (5) and thiophenol gave the racemic (4,5)-anti-5-hydroxy-4-thiophenoxy-(2E)-hexenoate (6), enzymatic acetylation of which afforded the (4S,SR)-5-acetoxy ester 7 (50.2% yield, 98% ee) and the (4R,SS)-5-hydroxy ester 6 (49.7% yield, >99% ee). Thus obtained (4R,SS)-6 (>99% ee) was converted into an inseparable mixture (trans:cis = 4:1) of (4S,SS)-trans-5 and (4R,SS)-cis-8 in 58% yield, while retaining high optical purity.4)

Conjugated addition of dimethylamine to the olefinic moiety of (±)-5 produced an inseparable 3.4:1 mixture of the lyxo- and xylo-hexonates 9 in 92% yield.5) On the other hand, the reaction of the (±)-α,β-unsaturated ester

![Chart 1](image1)

![Chart 2](image2)
10 with benzylamine furnished diastereoselectively the (3,4-syn)-3-benzylamino ester 11 in 85% yield.6 These examples of 1,4 addition of benzylamine to the olefinic moiety in (4R,5S)-acetonide 12 aroused our interest.

Treatment of a mixture (trans: cis = 4:1) of (4S,5S)-trans-5 and (4R,5S)-cis-8 with aqueous 1 N HClO₄ in tetrahydrofuran (THF) gave an inseparable mixture (anti: syn = 3:1) of diols, (4R,5S)-anti-13 and (4S,5S)-syn-14, in 63% yield along with 15% recovery of (4S,5S)-trans-5. This mixture was subjected to acetonide formation with 2,2-dimethoxypropane in the presence of p-TsOH to provide an acetonide mixture, which was separated to afford anti-(4R,5S)-12 (65% yield) and syn-(4S,5S)-15 (22% yield). The reaction of (4R,5S)-12 with benzylamine (2 eq) in the absence of solvent at room temperature afforded exclusively the diastereoselective 1,4-addition product 16 ([α]D +10.66° (c=1.2, CHCl₃)) in 68% yield along with 17% recovery of the starting material 12. In order to determine the stereochemistry of (+)-16, (+)-16 was converted into a known compound. Hydrogenolysis of (+)-16 in the presence of 10% Pd(OH)₂-C provided quantitatively the 3-amino ester 17,7 which was treated with benzoyl chloride in pyridine to furnish the 3-benzoylamino ester 18 in quantitative yield. Cleavage of the acetonide and the subsequent lactonization of 18 in aqueous 80% acetic acid at reflux produced the γ-lactone 19 in 71% overall yield. Physical data (mp 159°C, [α]D = -47.3° (c=1.13, EtOH)) of the present γ-lactone 19 were identical with those (mp 155°C, [α]D = -43.2° (c=1.1, EtOH)) of the reported (3S,4R,5S)-19.8 As conversions of (3S,4R,5S)-19 into N-trifluoroacetyl-l-α-casomine 20 and N-trifluoroacetyl-l-danosamine 21 have been reported,8 chiral syntheses of the above two amino sugar derivatives from an achiral precursor, methyl sorbate 4 could be achieved.

Although the stereoselection in the conjugated addition was reported9 to be explicable in terms of the Felkin-Anh model,10 it is difficult to explain unequivocally the present selectivity based on the above-mentioned model.

**Chart 3**

\[
(4S,5S)-5 + (4R,5S)-8 \xrightarrow{a} (4R,5S)-13 + (4S,5S)-14 \xrightarrow{b} (4R,5S)-12 \xrightarrow{c} (3S,4R,5S)-16 \xrightarrow{d} (3S,4R,5S)-17
\]

\[
a. 1N HClO₄ aq. \\
b. (MeO)₂CD₂/p-pTsOH \\
c. BnNH₂ \\
d. H₂ / Pd(OH)₂-C
\]

**Chart 4**

\[
(3S,4R,5S)-18 \xrightarrow{f} (3S,4R,5S)-19
\]

\[
a. 1) Ac₂O / pyridine \\
b. 80% AcOH aq., reflux
\]

**Chart 5**

\[
(3S,4R,5S)-22 \xrightarrow{a} (3S,4R,5S)-23
\]

\[
a. 1) Ac₂O / pyridine \\
b. Ac₂O / AcONa, 120°C
\]
Experimental
All melting points were measured on a Yanaco MP-S3 micro melting point apparatus and are uncorrected. IR spectra were measured on a JASCO A-3 spectrophotometer. NMR spectra were measured on a JEOL EX 4000 instrument. Spectra were taken for 5-10% (w/v) solutions in CDCl₃ with Me₄Si as an internal reference. Mass spectra were obtained with a JEOL JMS-D 300 or JEOL JMS-DX 303 (FAB) spectrometer. Optical rotations were measured on a JASCO DIP-370 polarimeter. All organic solvent extracts were washed with saturated brine and dried over anhydrous calcium sulfate (MgSO₄). All evaporation were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

Methyl (4RS,5S)-4-(isopropylidenedioxy)-(2E)-hexenoate (12) and Methyl (4S,5S)-4-(isopropylidenedioxy)-(2E)-hexenoate (15)
A solution of epoxy esters (4R,5S)-5 (4R,5S)-8 = 4.1, 2.2 g, 10% HClO₄ (2 ml), H₂O (2 ml) and IRF (40 ml) was stirred for 40 h at room temperature. The reaction mixture was diluted with saturated (NH₄)₂SO₄ aqueous solution and extracted with ether. Evaporation of the organic solvent provided a crude oily product, which was chromatographed on silica gel (150 g) to afford the recovered (4R,5S)-5 (0.57 g, 17% recovery) from the n-hexane-AcOEt (9:1) eluate and a pale yellow oil mixture (1.56 g, 63% yield) of (4R,5S)-13 and (4S,5S)-14 from the n-hexane-AcOEt (1:1) eluate. ii) A mixture of diols (4R,5S)-13 and (4S,5S)-14, 1.51 g, 2,2-dimethoxypropane (3 ml) and camphorsulfonic acid (CSA, 20 mg) in benzene (30 ml) was stirred for 1 h at room temperature. The reaction mixture was diluted with benzene (50 ml) and the benzene layer was washed with saturated NaHCO₃ aqueous solution. Evaporation of the organic layer afforded a crude oily product, which was chromatographed on silica gel (100 g) to give homogenuous compounds (4S,5S)-15 (0.41 g, 22% yield) and (4R,5S)-12 (1.22 g, 65% yield), in that order from the n-hexane-AcOEt (10:1) eluate. (4S,5S)-15: MS (FAB) m/z: 185 (M⁺-Me). [ξ]₂⁰o = 338° (c = 1.36, CHCl₃). IR (neat): 1721, 1610, 1050, 1010, 1000, 780, 750, 690, 650 cm⁻¹. NMR: δ = 1.32 (3H, d, J = 5.9, 5-Me), 1.42, 1.45 (each, 3H, s, MeCMe), 3.76 (3H, s, COOMe), 3.84 (1H, d, J = 8.3, 5.9, 5-H, 4-H), 4.08 (1H, ddd, J = 8.3, 5.9, 1.5, 4-H, 3.5-H), 1.14 (1H, dd, J = 1.5, 15.6, 2-H), 6.68 (1H, dd, J = 5.9, 15.6, 3-H). (4R,5S)-12: Anal. Calc. for C₁₅H₂₀O₅: C, 69.03; H, 8.23. MS (FAB) m/z: 239 (M⁺ + 39, in the presence of aqueous KCl). [ξ]₂⁰o = 47.3° (c = 1.13, EtOH). IR (CHCl₃): 3600, 3320, 1740, 1640 cm⁻¹. NMR δ = 1.36 (3H, d, J = 6.3, 5, 5-Me), 2.75 (1H, dd, J = 1.5, 17.5, 2-H, 3.5-H), 3.76 (1H, brs, 5-OMe), 4.19 (1H, d, J = 2.9, 3.5, 6.3-H), 4.33 (1H, dd, J = 2.9, 5.9, 8.4-H, 4.9), 4.95-5.01 (1H, m, 3-H).

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References and Notes
7) In a preliminary experiment, acetylation of (±)-17 followed by treatment with 80% AcOH aqueous solution gave the d,L-arabinono-3-acteinomono-2,3,6-trideoxyhexanoic acid d-lactone 22, which was converted into the known d,L-arabinono-3-acteomono-4-acteoyl-2,3,6-trideoxyhexanoic acid d-lactone 23. From this conversion experiment, the relative configuration of the conjugated addition product 16 was determined to be 3,4-syn (Chart 5).