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

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Received May 23, 1994; accepted July 25, 1994

***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] 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-(2*E*)-hexenoate (**5**) and thiophenol gave the racemic (4,5)-*anti*-5-hydroxy-4-thiophenoxy-(2*E*)-hexenoate (**6**), enzymatic acetylation of which afforded the (4*S*,5*R*)-5-acetoxy ester **7** (50.2% yield, 98% ee) and the (4*R*,5*S*)-5-hydroxy ester **6** (49.7% yield, >99% ee). Thus obtained (4*R*,5*S*)-**6** (>99% ee) was converted into an inseparable mixture (*trans*:*cis*=4:1) of (4*S*,5*S*)-*trans*-**5** and (4*R*,5*S*)-*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

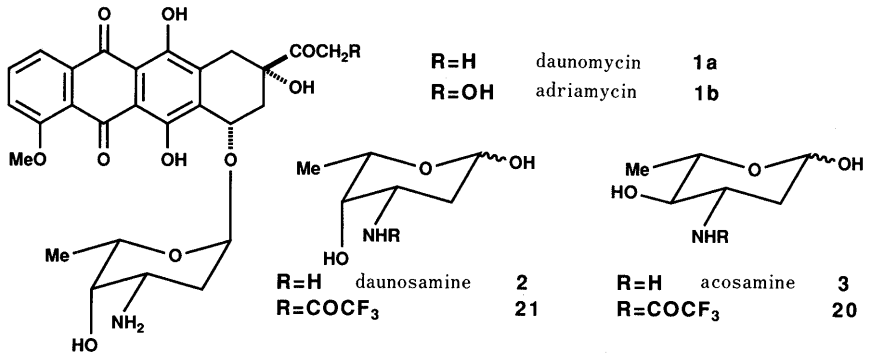

Chart 1

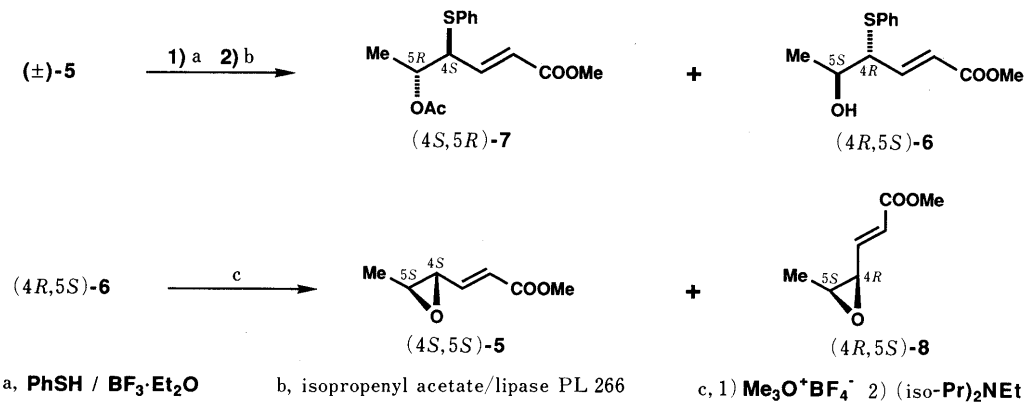

Chart 2

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 (4*R*,5*S*)-acetonide **12** aroused our interest.

Treatment of a mixture (*trans*:*cis*=4:1) of (4*S*,5*S*)-*trans*-**5** and (4*R*,5*S*)-*cis*-**8** with aqueous 1 N $HClO_4$ in tetrahydrofuran (THF) gave an inseparable mixture (*anti*:*syn*=3:1) of diols, (4*R*,5*S*)-*anti*-**13** and (4*S*,5*S*)-*syn*-**14**, in 63% yield along with 15% recovery of (4*S*,5*S*)-*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*-(4*R*,5*S*)-**12** (65% yield) and *syn*-(4*S*,5*S*)-**15** (22% yield). The reaction of (4*R*,5*S*)-**12** with benzylamine (2 eq) in the absence of solvent at room temperature afforded exclusively the diastereoselective 1,4-addition product **16** ($[\alpha]_D$ +10.66° (*c*=1.2, $CHCl_3$)) 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, $[\alpha]_D$ −47.3° (*c*=1.13, EtOH)) of the present γ-lactone **19** were identical with those (mp 155 °C, $[\alpha]_D$ −43.2° (*c*=1.1, EtOH)) of the reported (3*S*,4*R*,5*S*)-**19**.[8] As conversions of (3*S*,4*R*,5*S*)-**19** into *N*-trifluoroacetyl-L-acosamine **20** and *N*-trifluoroacetyl-L-daunosamine **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 reported[9] 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.

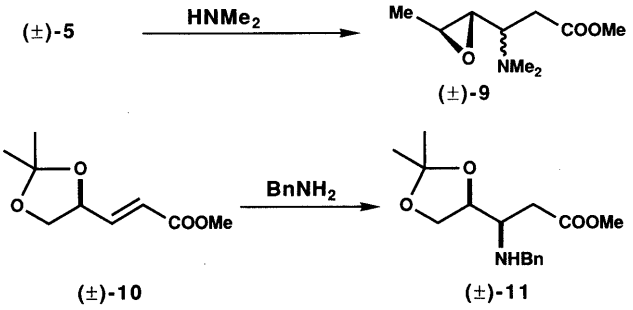

Chart 3

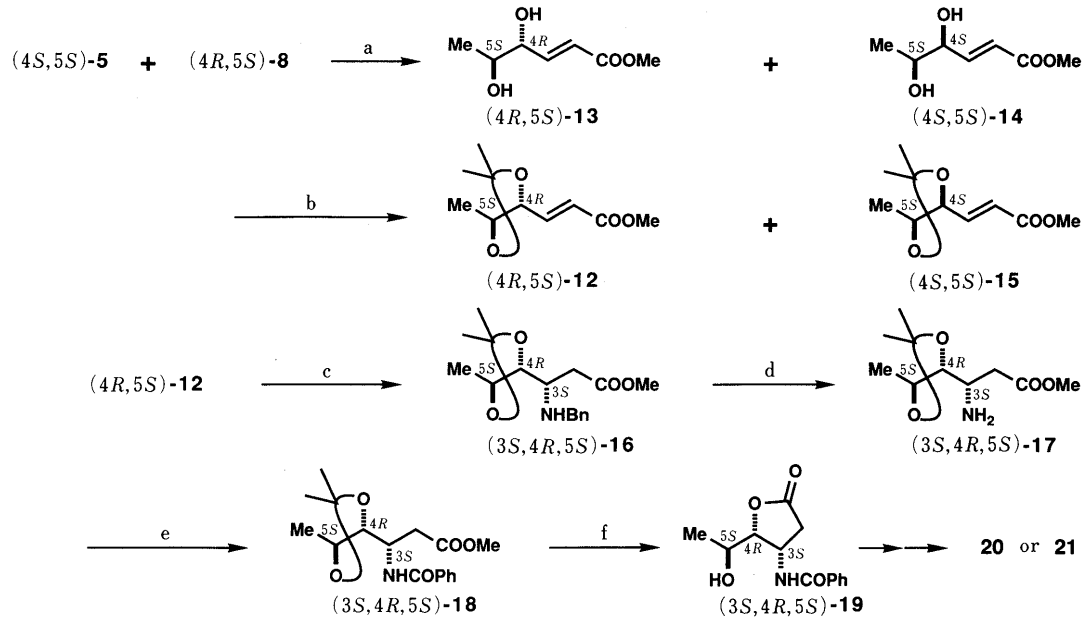

Chart 4

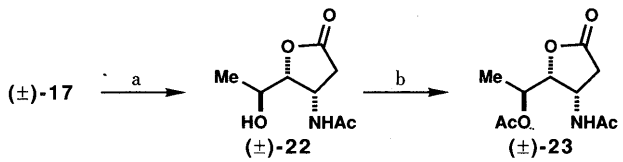

Chart 5

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 $CDCl_3$ with Me_4Si 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 magnesium sulfate ($MgSO_4$). All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

Methyl (4*R*,5*S*)-4,5-(Isopropylidenedioxy)-(2*E*)-hexenoate (12) and Methyl (4*S*,5*S*)-4,5-(Isopropylidenedioxy)-(2*E*)-hexenoate (15) i) A solution of epoxy esters ((4*S*,5*S*)-**5**:(4*R*,5*S*)-**8**=4:1, 2.2 g), 1 N $HClO_4$ (2 ml), H_2O (2 ml) and THF (40 ml) was stirred for 40 h at room temperature. The reaction mixture was diluted with saturated $(NH_4)_2SO_4$ 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 (4*S*,5*S*)-**5** (0.57 g, 15% recovery) from the *n*-hexane–AcOEt (9:1) eluate and a pale yellow oily mixture (1.56 g, 63% yield) of (4*R*,5*S*)-**13** and (4*S*,5*S*)-**14** from the *n*-hexane–AcOEt (1:1) eluate. ii) A mixture of diols ((4*R*,5*S*)-**13** and (4*S*,5*S*)-**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 $NaHCO_3$ aqueous solution. Evaporation of the organic layer afforded a crude oily product, which was chromatographed on silica gel (100 g) to give homogeneous oils, (4*S*,5*S*)-**15** (0.41 g, 22% yield) and (4*R*,5*S*)-**12** (1.22 g, 65% yield), in that order from the *n*-hexane–AcOEt (10:1) eluate. (4*S*,5*S*)-**15**: MS (FAB) *m/z*: 185 ($M^+ - Me$). $[\alpha]_D^{25}$ +3.38° (*c*=1.36, $CHCl_3$). IR (neat): 1728, 1660 cm^{-1}. NMR δ: 1.32 (3H, d, *J*=5.9 Hz, 5-Me), 1.42, 1.45 (each, 3H, s, MeCMe), 3.76 (3H, s, COOMe), 3.84 (1H, dq, *J*=8.3, 5.9 Hz, 5-H), 4.08 (1H, ddd, *J*=8.3, 5.9, 1.5 Hz, 4-H), 6.14 (1H, dd, *J*=1.5, 15.6 Hz, 2-H), 6.88 (1H, dd, *J*=5.9, 15.6 Hz, 3-H). (4*R*,5*S*)-**12**: *Anal.* Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.50; H, 8.23. MS (FAB) *m/z*: 239 (M^++39, in the presence of aqueous KCl). $[\alpha]_D^{25}$ −0.55° (*c*=1.10, $CHCl_3$). IR(neat): 1720, 1660 cm^{-1}. NMR δ: 1.16 (3H, d, *J*=6.3 Hz, 5-Me), 1.38, 1.51 (each 3H, s, MeCMe), 3.75 (3H, s, COOMe), 4.43 (1H, dq, *J*=6.3, 6.3 Hz, 5-H), 4.66 (1H, ddd, *J*=6.3, 5.9, 1.5 Hz, 4-H), 6.09 (1H, dd, *J*=1.5, 15.6 Hz, 2-H), 6.84 (1H, dd, *J*=5.9, 15.6 Hz, 3-H).

Methyl (3*S*,4*R*,5*S*)-3-Benzylamino-4,5-(isopropylidenedioxy)hexanoate (16) A mixture of (4*R*,5*S*)-**12** (1.17 g) and benzylamine (1.25 g) was stirred for 3 d. The reaction mixture was subjected to silica gel (55 g) column chromatography to provide the recovered (4*R*,5*S*)-**12** (0.2 g, 17% recovery) from the *n*-hexane–AcOEt (10:1) eluate and a pale yellow oil, (3*S*,4*R*,5*S*)-**16** (1.22 g, 68% yield) from the *n*-hexane–AcOEt (4:1) eluate. (3*S*,4*R*,5*S*)-**16**: *Anal.* Calcd for $C_{17}H_{25}NO_4$: C, 66.42; H, 8.20; N, 4.56. Found: C, 66.16; H, 8.46; N, 4.65. MS (FAB) *m/z*: 308 (M^++1). $[\alpha]_D^{25}$ +10.67° (*c*=1.20, $CHCl_3$). IR (neat): 3330, 1720 cm^{-1}. NMR δ: 1.26 (3H, d, *J*=6.4 Hz, 5-Me), 1.33, 1.45 (each, 3H, s, MeCMe), 1.81 (1H, s, NH), 2.50 (2H, d, *J*=5.9 Hz, 2-H_2), 3.18 (1H, dd, *J*=5.9, 6.4 Hz, 3-H), 3.68 (3H, s, COOMe), 3.78, 3.88 (each 1H, d, *J*=12.7 Hz, $NHCH_2$–), 4.10 (1H, dd, *J*=6.4, 6.4 Hz, 4-H), 4.31 (1H, dq, *J*=6.4, 6.4 Hz, 5-H), 7.23—7.36 (5H, m, aromatic-H).

Methyl (3*S*,4*R*,5*S*)-3-Amino-4,5-(isopropylidenedioxy)hexanoate (17) A solution of (3*S*,4*R*,5*S*)-**16** (1.18 g) in EtOH (15 ml) was hydrogenated at ordinary temperature and pressure over 10% $Pd(OH)_2$–C (50 mg). After hydrogen absorption had ceased, the catalyst was filtered off and the filtrate was evaporated to give (3*S*,4*R*,5*S*)-**17** (0.83 g, >99% yield) as a homogeneous oil. (3*S*,4*R*,5*S*)-**17**: *Anal.* Calcd for $C_{10}H_{19}NO_4$: C, 55.28; H, 8.82; N, 6.45. Found: C, 54.73; H, 8.92; N, 6.25. $[\alpha]_D^{25}$ −6.37° (*c*=1.35, $CHCl_3$). IR (neat): 1720 cm^{-1}. NMR δ: 1.28 (3H, d, *J*=6.3 Hz, 5-Me), 1.35, 1.48 (each 3H, s, MeCMe), 1.68 (2H, s, 3-NH_2), 2.35 (1H, dd, *J*=8.8, 15.6 Hz, 2-H), 2.43 (1H, dd, *J*=3.9, 15.6 Hz, 2-H), 3.28—3.33 (1H, m, 3-H), 3.71 (3H, s, COOMe), 3.87 (1H, dd, *J*=6.3, 6.3 Hz, 4-H), 4.30 (1H, dq, *J*=6.3, 6.3 Hz, 5-H).

Methyl (3*S*,4*R*,5*S*)-3-Benzoylamino-4,5-(isopropylidenedioxy)hexanoate (18) A mixture of (3*S*,4*R*,5*S*)-**17** (0.80 g) and benzoyl chloride (0.78 g) in pyridine (3 ml) was stirred for 10 min under ice-water cooling. The reaction mixture was diluted with CH_2Cl_2. The organic layer was washed. Evaporation of the organic solvent afforded a crude oil, which was chromatographed on silica gel (50 g) to provide a pale yellow oil, (3*S*,4*R*,5*S*)-**18** (1.18 g, >99% yield) from the *n*-hexane–AcOEt (4:1) eluate. (3*S*,4*R*,5*S*)-**18**: *Anal.* Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.97; H, 7.29; N, 4.38. MS (FAB) *m/z*: 322 (M^++1). $[\alpha]_D^{25}$ +5.48° (*c*=0.62, $CHCl_3$). IR (Nujol): 2280, 1720, 1630 cm^{-1}. NMR δ: 1.33 (3H, d, *J*=6.3 Hz, 5-Me), 1.40, 1.57 (each, 3H, s, MeCMe), 2.69 (1H, dd, *J*=8.3, 15.6 Hz, 2-H), 2.77 (1H, dd, *J*=5, 15.6 Hz, 2-H), 3.69 (3H, s, COOMe), 4.33 (1H, dd, *J*=1.5, 7 Hz, 4-H), 4.44—4.59 (2H, m, 3-H and 5-H), 6.69 (1H, d, *J*=7.8 Hz, NH).

L-*arabino*-3-Benzoylamino-2,3,6-trideoxyhexanoic Acid γ-Lactone (19) A solution of (3*S*,4*R*,5*S*)-**18** (1.14 g) in 80% AcOH aqueous solution (15 ml) was stirred for 4.5 h at reflux. The reaction mixture was diluted with toluene. Evaporation of the organic solvent gave a crude oil, which was chromatographed on silica gel (50 g) to furnish colorless crystals, (3*S*,4*R*,5*S*)-**19** (0.63 g, 71% yield). Recrystallization of (3*S*,4*R*,5*S*)-**19** from CH_2Cl_2–Et_2O gave colorless prisms. (3*S*,4*R*,5*S*)-**19**: mp 159 °C. *Anal.* Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.35; H, 6.18; N, 5.49. MS *m/z*: 249 (M^+). $[\alpha]_D^{26}$ −47.3° (*c*=1.13, EtOH). IR ($CHCl_3$): 3600, 3320, 1740, 1640 cm^{-1}. NMR δ: 1.36 (3H, d, *J*=6.3 Hz, 5-Me), 2.75 (1H, dd, *J*=1, 17.5 Hz, 2-H), 3.05 (1H, dd, *J*=6.3, 17.5 Hz, 2-H), 3.76 (1H, br s, 5-OH), 4.19 (1H, dq, *J*=2.9, 6.3 Hz, 5-H), 4.33 (1H, dd, *J*=2.9, 5.8 Hz, 4-H), 4.95—5.01 (1H, m, 3-H).

Acknowledgement This work was supported by a grant for the Biodesign Research Program from The Institute of Physical and Chemical Research (RIKEN) to H.A. and a Grant-in-Aid for Scientific Research (No. 06772082) from the Ministry of Education, Science and Culture of Japan to S.N.

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7) In a preliminary experiment, acetylation of (±)-**17** followed by treatment with 80% AcOH aqueous solution gave the D,L-*arabino*-3-acetoamino-2,3,6-trideoxyhexanoic acid δ-lactone **22**, which was converted into the known D,L-*arabino*-3-acetoamino-4-acetoxy-2,3,6-trideoxyhexanoic acid γ-lactone **23**.[11] From this conversion experiment, the relative configuration of the conjugated addition product **16** was determined to be 3,4-*syn*. (Chart 5).
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