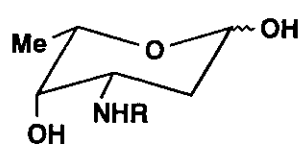
TOTAL SYNTHESES OF *N*-TRIFLUOROACETYL-L-DAUNOSAMINE, *N*-TRIFLUOROACETYL-L-ACOSAMINE, *N*-BENZOYL-D-ACOSAMINE, AND *N*-BENZOYL-D-RISTOSAMINE FROM AN ACHIRAL PRECURSOR, METHYL SORBATE

Machiko Ono,* Chikako Saotome, and Hiroyuki Akita*

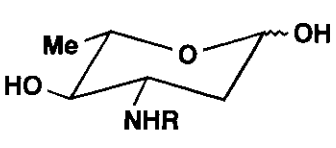
School of Pharmaceutical Science, Toho University, 2-2-1 Miyama, Funabashi, Chiba 274, Japan

Abstract -A conjugated addition of benzylamine to methyl (4*R*,5*S*)-4,5-(isopropylidenedioxy)-(2*E*)-hexenoate (**12**) followed by lactonization under acidic condition proceeds formally to the total syntheses of L-daunasamine (**1**) and L-acosamine (**2**). On the other hand, direct conjugated addition of benzylamine to methyl (4*S*,5*S*)-4,5-epoxy-(2*E*)-hexenoate (**4**) and the subsequent intramolecular nucleophilic attack by ester carbonyl group against epoxy ring of the substrates leads to the formal total syntheses of D-acosamine (**2**) and D-ristosamine (**3**).

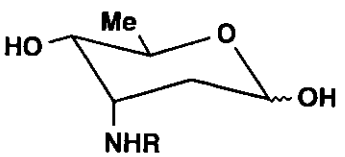
The anthracycline antibiotics daunomycin and adriamycin are highly effective in the treatment of childhood leukemia and several types of solid tumor,[1] and possess an amino sugar moiety, called L-daunosamine (**1**). Changing L-daunosamine of adriamycin with its 4-epimer, L-acosamine (**2**) was reported to suppress the cardiotoxicity while retaining the anti-tumor activity.[2] Therefore, considerable interest has been shown in developing syntheses of enantiomerically pure L-daunosamine (**1**) and its analogues in order to provide sufficient material for pharmaceutical structure-activity studies.[3] Of several syntheses of L-daunosamine (**1**), almost all of the chiral syntheses are based on conversion of natural carbohydrates such as D-mannose and L-rhamnose and D-glucose.[4] The approaches from non-carbohydrate precursors have also been reported, however, the known syntheses of **1** seem to be rather impractical.[5] We wish to report formal total syntheses of L-daunosamine (**1**), L-acosamine (**2**), D-acosamine (**2**) and D-ristosamine (**3**), starting with an achiral precursor, methyl sorbate, and employing enzymatic chiral induction and diastereoselective conjugated addition of benzylamine to the α,β-unsaturated ester.



R=H L-daunosamine (1)
R=$COCF_3$ 18

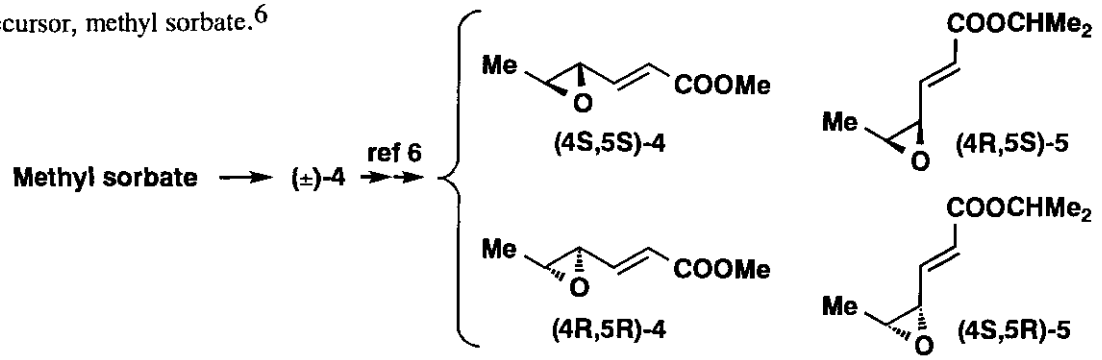


R=H L-acosamine (2)
R=$COCF_3$ 19

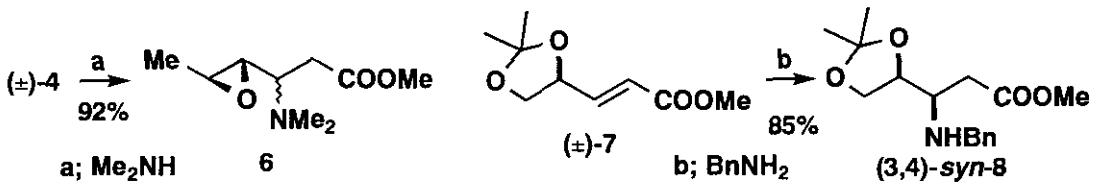


R=H D-ristosamine (3)
R=Bz 29

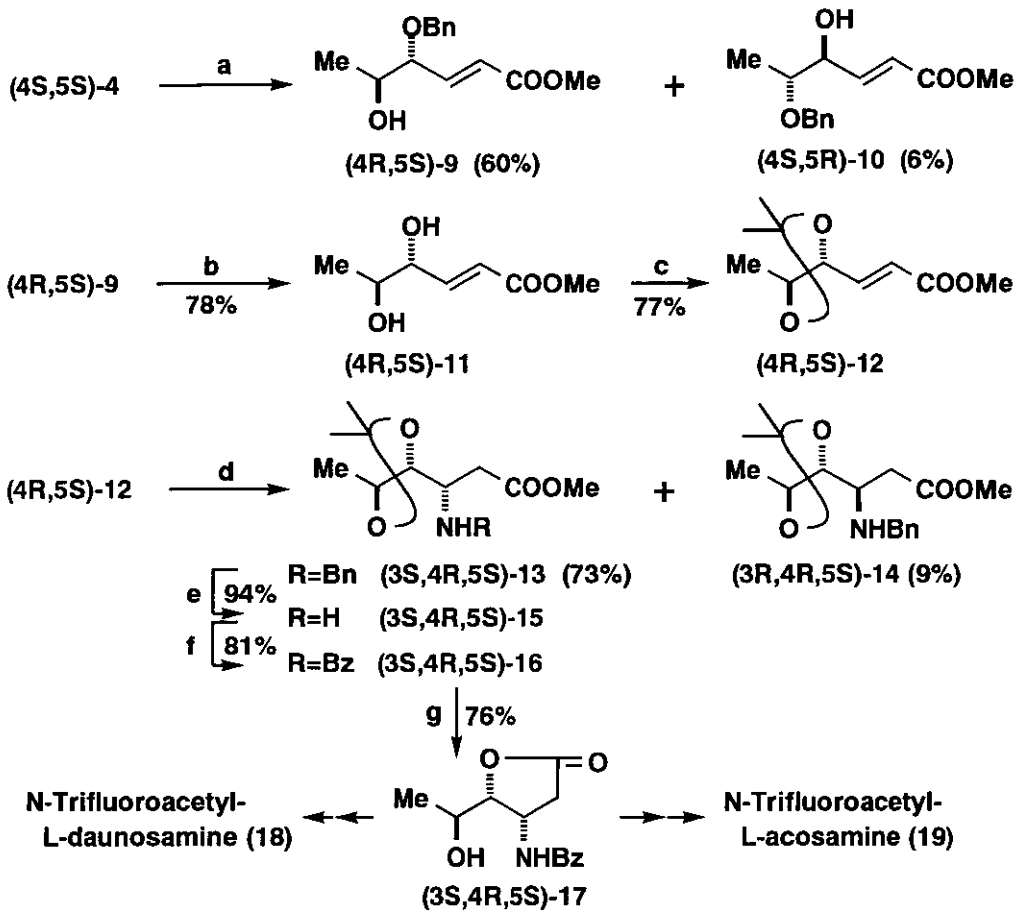
We reported previously syntheses of the each optically pure stereoisomer of (4,5)-epoxy-(2*E*)-hexenoates, (4*S*,5*S*)-**4**, (4*R*,5*R*)-**4**, (4*R*,5*S*)-**5** and (4*S*,5*R*)-**5** based on a chemoenzymatic method from an achiral precursor, methyl sorbate.[6]



Conjugated addition of dimethylamine to the olefinic moiety of (±)-**4** produced an inseparable 3.4:1 mixture of the *lyxo*- and *xylo*-hexonate (**6**),[7] while the reaction of (±)-unsaturated ester (**7**) with benzylamine furnished diastereoselectively the (3,4)-*syn*-3-benzylamino ester (**8**).[8] From these examples, the 1,4-addition of benzylamine to the olefinic moiety in (4*S*,5*S*)-**4** or (4*R*,5*S*)-acetonide (**12**) aroused our interest.



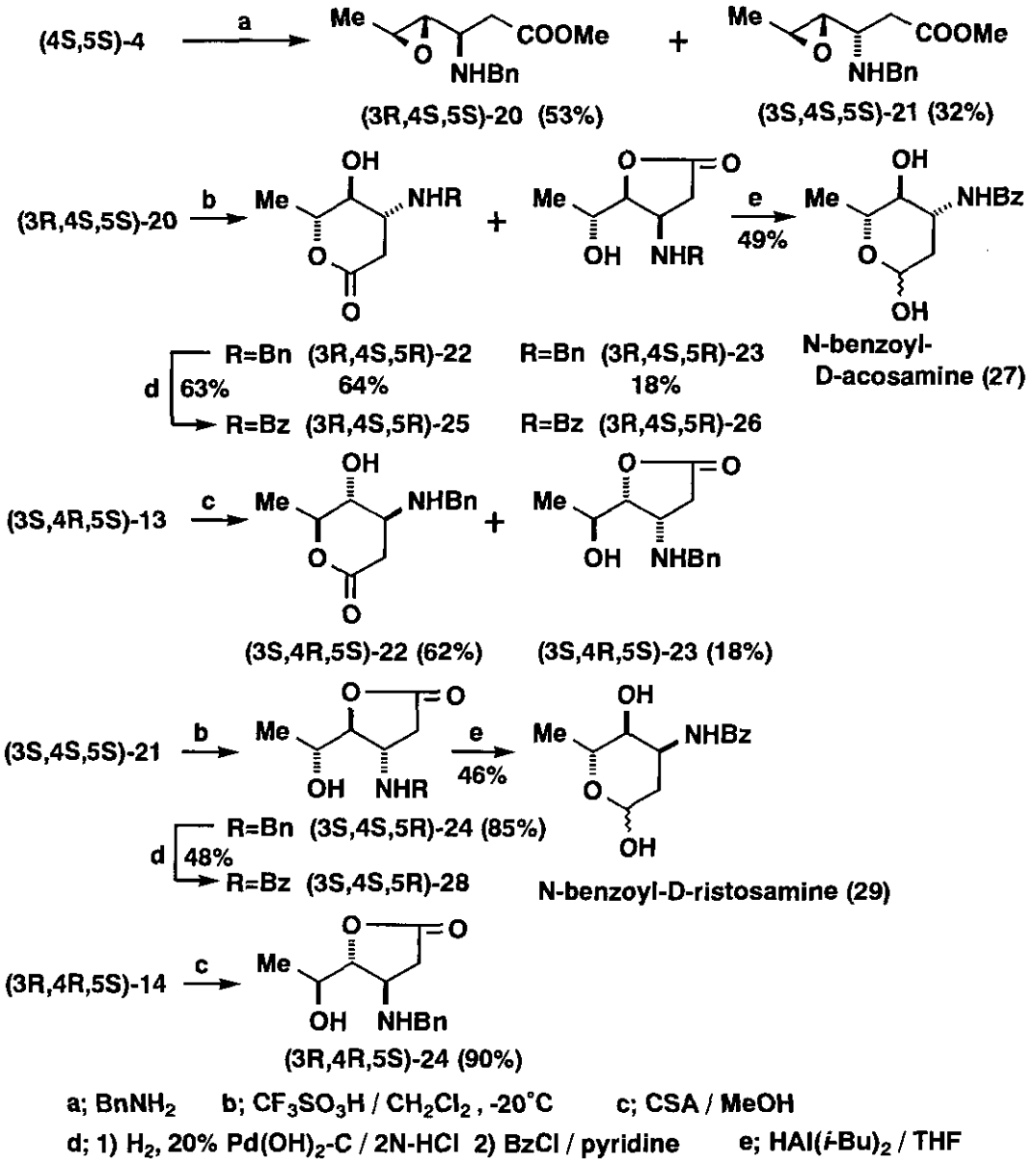
For the syntheses of the target molecules from (4*S*,5*S*)-**4**, two synthetic routes are considerable. One is the 1,4-addition of benzylamine to the α,β-unsaturated ester after epoxy ring opening of (4*S*,5*S*)-**4** by oxygen nucleophile such as benzyl alcohol. The other is the direct 1,4-addition of benzylamine to the (4*S*,5*S*)-**4** and the subsequent regioselective cleavage of epoxy ring with intramolecular nucleophilic attack by ester carbonyl group. The reaction of (4*S*,5*S*)-**4** with benzyl alcohol in the presence of $BF_3.Et_2O$ afforded regioselectively the (4*R*,5*S*)-**9**[9] ([α]$_D$ -71.6° (c=1.24, $CHCl_3$)) and (4*S*,5*R*)-**10** ([α]$_D$ -22.6° (c=0.19, $CHCl_3$)). NMR spectra of (4*R*,5*S*)-**9** and (4*S*,5*R*)-**10** were identical with those of the reported[6] (±)-**9** and (±)-**10**, respectively. Treatment of (4*R*,5*S*)-**9** with $AlCl_3$ in the presence of *m*-xylene[6] gave a diol (4*R*,5*S*)-**11** ([α]$_D$ +16.7° (c=0.86, $CHCl_3$), which was subjected to acetonide formation to provide an acetonide (4*R*,5*S*)-**12** ([α]$_D$ +0.49° (c=3.67, $CHCl_3$)). The reaction of (4*R*,5*S*)-**12** with benzylamine (2 equivalents) in the absence of solvent at room temperature afforded the 1,4-addition products, (3*S*,4*R*,5*S*)-**13** ([α]$_D$ +15.9° (c=1.92, $CHCl_3$)) and (3*R*,4*R*,5*S*)-**14** ([α]D -9.81° (c=0.43, $CHCl_3$)). In order to determine the stereochemistry of the main product ((+)-**13**), (+)-**13** was converted into the known compound. Hydrogenolysis of (+)-**13** followed by treatment of the 3-amino ester (**15**) ([α]D -4.8° (c=3.21, $CHCl_3$) with benzoyl chloride gave the 3-benzoylamino ester (**16**)([α]D +9.3° (c=2.84, $CHCl_3$)). Cleavage of the acetonide and the subsequent lactonization of **16** in aqueous 80% AcOH at reflux afforded the γ-lactone (**17**). Physical data (mp 139°, [α]$_D$ -47.3° (c=0.77, EtOH), IR and NMR) of the present γ-lactone (**17**) were identical with those (mp 155°C, [α]$_D$ -43.2° (c=1.1, EtOH), IR and NMR) of the reported (3*S*,4*R*,5*S*)-**17**.[5] Therefore, the stereochemistries of (+)-**13** and (-)-**14** were determined



a; BnOH, BF_3·Et_2O / CH_2Cl_2, -20°C b; $AlCl_3$, *m*-xylene / CH_2Cl_2, 0°C
c; $(MeO)_2CMe_2$, *p*-TsOH / acetone, 0°C d; $BnNH_2$
e; H_2, 20%-$Pd(OH)_2$ / MeOH f; BzCl / pyridine g; 80% AcOH, reflux

to be (3*S*,4*R*,5*S*)-configuration and (3*R*,4*R*,5*S*)-configuration, respectively. As conversions of (3*S*,4*R*,5*S*)-**17** into *N*-trifluoroacetyl-L-daunosamine (**18**) and *N*-trifluoroacetyl-L-acosamine (**19**) have been reported,[5] chiral syntheses of the above-mentioned two amino sugar derivatives from an achiral precursor, methyl sorbate could be achieved.

Then, the reaction of (4*S*,5*S*)-**4** with benzylamine (4 equivalents) at 40°C afforded the 1,4-addition products, (3*R*,4*S*,5*S*)-**20** ($[\alpha]_D$ -18.7° (c=0.77, $CHCl_3$)) and (3*S*,4*S*,5*S*)-**21** ($[\alpha]_D$ -21.1° (c=0.6, $CHCl_3$)). In order to determine the stereochemistry of the main product ((-)-**20**), (-)-**20** was treated with CF_3SO_3H in CH_2Cl_2 at -20°C to give the δ-lactone (**22**) ($[\alpha]_D$ -49.2° (c=0.47, $CHCl_3$)) and γ-lactone (**23**) ($[\alpha]_D$ -51.5° (c=0.71, $CHCl_3$)). For the purpose of comparison, the standard samples, δ-lactone ((3*S*,4*R*,5*S*)-**22**) ($[\alpha]_D$ +51.9° (c=0.4, $CHCl_3$)) and γ-lactone ((3*S*,4*R*,5*S*)-**23**) ($[\alpha]_D$ +45.3° (c=0.23, $CHCl_3$)) were obtained by the treatment of the above-mentioned (3*S*,4*R*,5*S*)-**13** with camphorsulfonic acid (CSA) in MeOH. Both δ-lactones were found to be an enantiomeric relationship because of spectromeric identification (IR and NMR) except for the sign of $[\alpha]_D$ of each enantiomer. Meanwhile, both γ-lactones



a; $BnNH_2$ b; CF_3SO_3H / CH_2Cl_2 , -20°C c; CSA / MeOH

d; 1) H_2, 20% $Pd(OH)_2$-C / 2N-HCl 2) BzCl / pyridine e; $HAl(i\text{-}Bu)_2$ / THF

of (*3R*,4*S*,5*R*)-**23** and the standard sample ((*3S*,4*R*,5*S*)-**23**) were also found to be an enantiomeric relationship. Therefore, the stereochemistry of (-)-**20** was determined to be (*3R*,4*S*,5*S*)-configuration. The stereochemistry of the minor product (-)-**21** was also determined to be (3*S*,4*S*,5S)-configuration, because physical data ($[\alpha]_D$ +38.4° (c=0.63, $CHCl_3$)) of (+)-γ-lactone (**24**) derived from (-)-**21** was consistent with those ($[\alpha]_D$ -37.2° (c=0.3, $CHCl_3$)) of (-)-γ-lactone ((*3R*,4*R*,5*S*)-**24**) derived from the above-mentioned (*3R*,4*R*,5*S*)-**14** except for the sign of $[\alpha]_D$ of each enantiomer. In the case of lactonization of the (3,4)-*syn* **20**, an intramolecular nucleophilic attack by ester carbonyl group upon C5-position results in the formation of the δ-lactone (**22**). At this reaction condition, the δ-lactone (**22**) comes to equilibrium with the γ-lactone (**23**). Meanwhile, in the case of lactonization of the (3,4)-*anti* **21**,

an intramolecular nucleophilic attack by ester carbonyl group upon C_5-position causes predominantly the formation of the δ-lactone, which was soon transfered to the γ-lactone (**24**).

Hydrogenolysis of (3*R*,4*S*,5*R*)-**22** thus obtained followed by treatment with benzoyl chloride gave a mixture (63% yield) of δ-lactone (**25**) and γ-lactone (**26**), which was reduced with diisobutylaluminum hydride (Dibal) to the *N*-benzoyl-D-acosamine ((3*R*,4*S*,5*R*)-**27**) ($[\alpha]_D$ +13.1° (c=0.6, EtOH), mp 216-217°C). The physical data (^{1}H-NMR and ^{13}C-NMR) of the present **27** were identical with those (^{1}H-NMR and ^{13}C-NMR) of the reported (3*R*,4*S*,5*R*)-**27**.[10] The (3*S*,4*S*,5*S*)-**21** was also converted into the *N*-benzoyl-D-ristosamine ((3*S*,4*S*,5*R*)-**29**) *via* (3*S*,4*S*,5*R*)-**28** ($[\alpha]_D$ -46.9° (c=0.78, THF) by the same way as in the case of the conversion of **20** to **27**. The (3*S*,4*S*,5*R*)-**29** ($[\alpha]_D$ +28.0° (c=0.23, EtOH), mp 131-133°C) thus obtained was consistent with the reported *N*-benzoyl-L-ristosamine ((3*R*,4*R*,5*S*)-**29**)[11] ($[\alpha]_D$ -12° (c=1, EtOH), mp 130-132°C) except for the sign of $[\alpha]_D$ of each enantiomer.

In conclusion, the syntheses of L-amino sugars such as L-daunosamine (**1**) and L-acosamie (**2**) and D-amino sugars such as D-acosamine (**2**) and D-ristosamine (**3**) were found to be distinguishable by changing the addition order of nucleophile against optically pure (4*S*,5*S*)-epoxy-(2*E*)-hexenoate (**4**).

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