# 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

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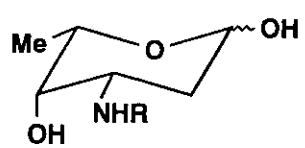
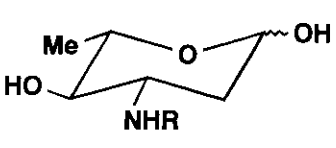
**Abstract** -A conjugated addition of benzylamine to methyl (4*R*,5*S*)-4,5-(isopropylidenedioxy)-(2*E*)-hexenoate (**12**) followed by lactonization under acidic condition proceeds formally to the total syntheses of L-daunasamine (**1**) and L-acosamine (**2**). On the other hand, direct conjugated 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**).

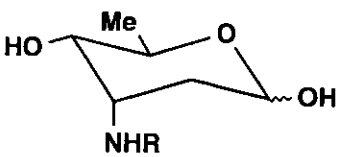
The anthracycline antibiotics daunomycin and adriamycin are highly effective in the treatment of childhood leukemia and several types of solid tumor,[1] and possess an amino sugar moiety, called L-daunosamine (**1**). Changing L-daunosamine of adriamycin with its 4-epimer, L-acosamine (**2**) was reported 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

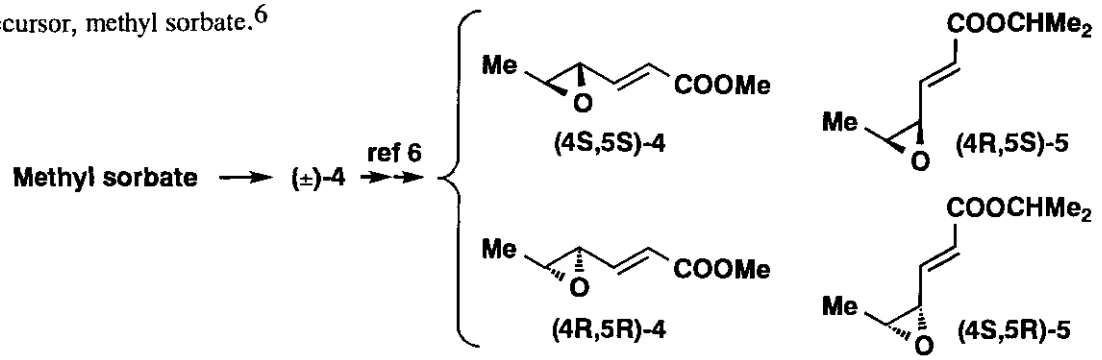



R=H L-acosamine (2)
R=$COCF_3$ 19

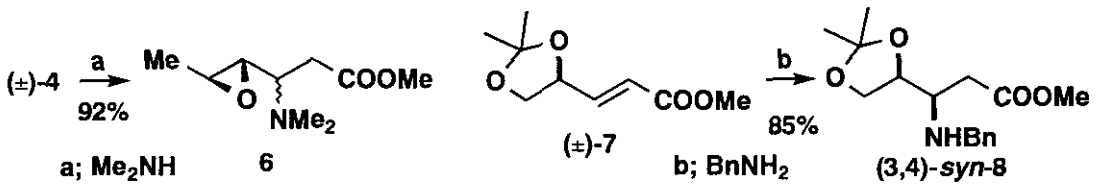



R=H D-ristosamine (3)
R=Bz 29

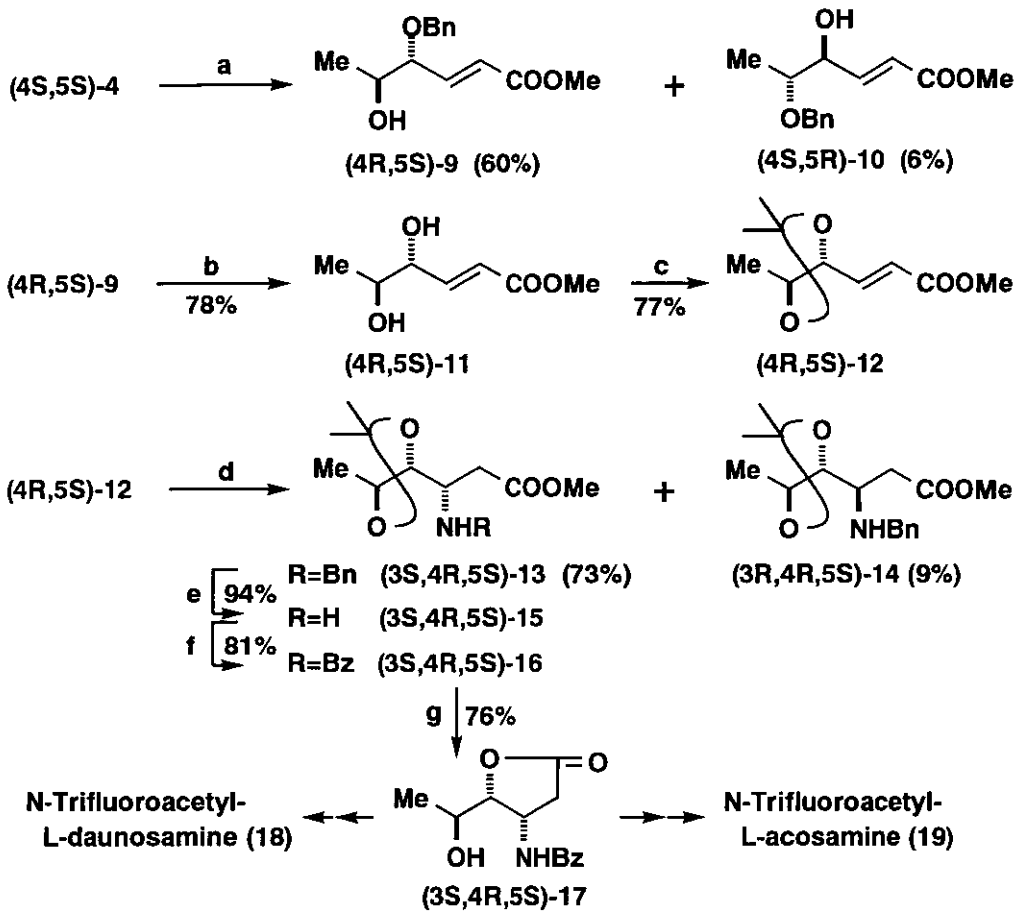
We reported previously syntheses of the each optically pure stereoisomer of (4,5)-epoxy-(2*E*)-hexenoates, (4*S*,5*S*)-**4**, (4*R*,5*R*)-**4**, (4*R*,5*S*)-**5** and (4*S*,5*R*)-**5** based on a chemoenzymatic method from an achiral precursor, methyl sorbate.[6]




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.



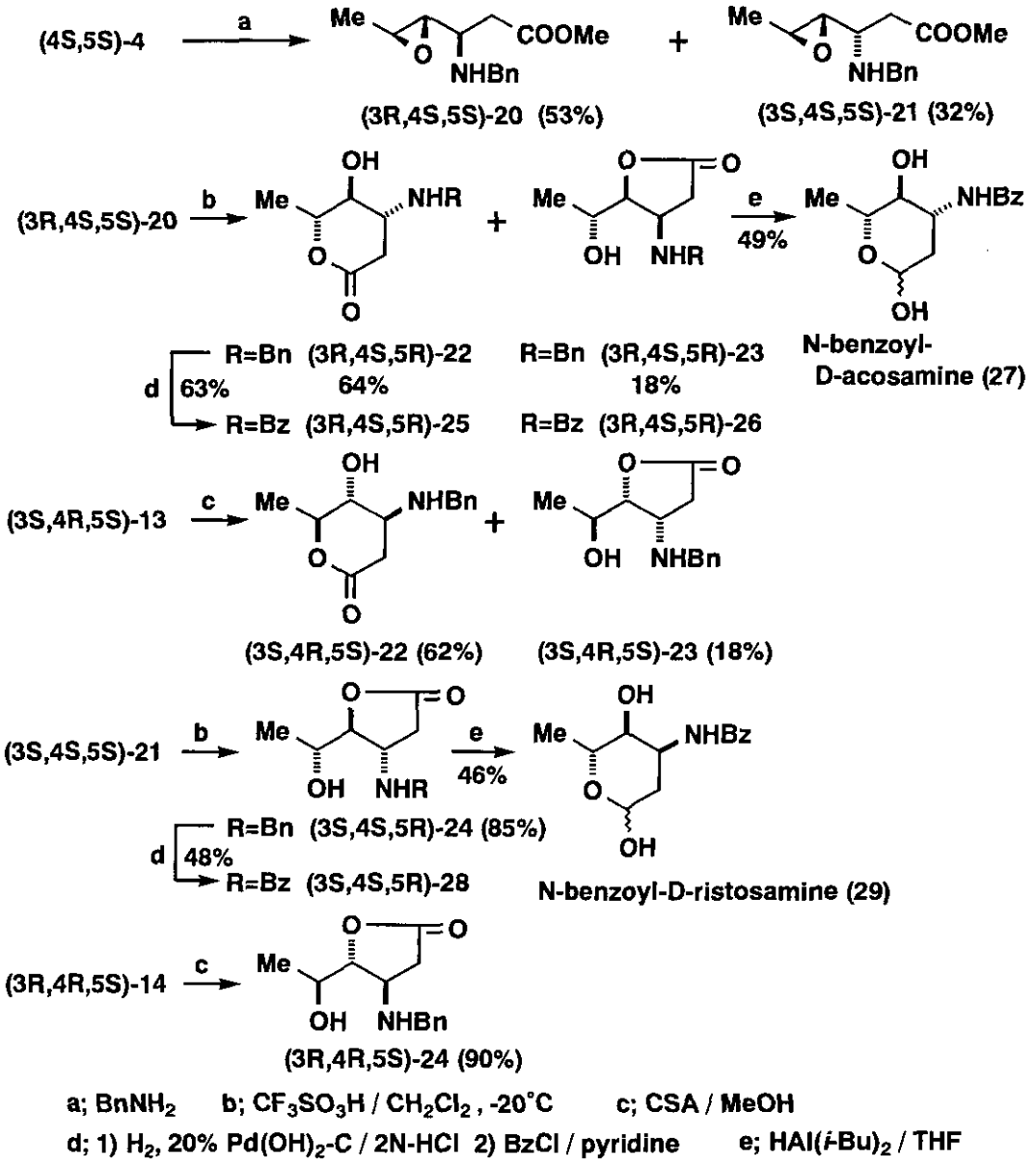

For the syntheses of the target molecules from (4*S*,5*S*)-**4**, two synthetic routes are considerable. One is the 1,4-addition of benzylamine to the α,β-unsaturated ester after epoxy ring opening of (4*S*,5*S*)-**4** by oxygen nucleophile such as benzyl alcohol. The other is the direct 1,4-addition 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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## REFERENCES AND NOTES

1. F. Arcramone, "Topics in Antibiotic Chemistry," vol. 2, ed. by P. G. Sammes, Ellis Horwood Ltd., Chichester, 1978.
2. F. Arcamone, S. Penco, A. Vigevani, S. Redaelli, G. Franchi, A. Di Marco, A. M. Casazza, T. Dasdia, F. Formelli, A. Necco, and C. Soranzo, *J. Med. Chem.*, 1975, **18**, 703.
3. More recent syntheses of daunosamine; S. T. Davies and G. D. Smyth, *Tetrahedron:Asymmetry*, 1996, **7**, 1273 and references cited therein.
4. F. M. Hauser and S. Ellenberger, *Chem. Rev.*, 1986, **86**, 35.
5. G. Fronza, C. Fuganti, and P. Grasselli, *J. Chem. Soc. Chem. Commun*, **1980**, 442.
6. M. Ono, C. Saotome ,and H. Akita, *Tetrahedron:Asymmetry*, 1996, **7**, 2595.
7. I. Dyong and H. Bendlin, *Chem. Ber.*, 1979, **112**, 717.
8. H. Matsunaga, T. Sakamaki, H. Nagaoka, and Y. Yamada, *Tetrahedron Lett.*, 1983, **24**, 3009.
9. Satisfactory analytical data were obtained for all new compounds.
10. G. Fronza, C. Fuganti, and P. Grasselli, *J. Chem. Soc., Perkin Trans. I*, **1982**, 885.
11. G. Fronza, C. Fuganti, and P. Grasselli, *Tetrahedron Lett.*, 1980, **21**, 2999.

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