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A New Synthesis of 3-Amino-2-alkenoates. Novel Synthetic Route to Amino Sugars *N*-Benzoyl-L-daunosamine and -L-acosamine

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Alkanoate esters are found to couple with various nitriles to give (*Z*)-3-amino-2-alkenoates in good yields with the aid of a magnesium amide prepared by the reaction of ethylmagnesium bromide and diisopropylamine. The C–C bond forming reaction was applied to (2*S*,3*S*)-2,3-(cyclohexylidenedioxy)butanenitrile and the resulting adduct was successfully converted into *N*-benzoyl-L-daunosamine in 41% overall yield through a sequence of functional group manipulation; acetylation, hydrogenation, hydrolysis and benzoylation, lactonization and finally reduction. By the similar process, (2*R*,3*S*)-2,3-(cyclohexylidenedioxy)butanenitrile was transformed to *N*-benzoyl-L-acosamine in 25% overall yield.

Carbonyl addition of the enolates of carboxylic acids and their esters is well-documented and widely used for the construction of carbon framework of various target molecules.[1] For this carbonyl addition, a variety of metal enolates are employed which exhibit characteristic reactivity with respect to stereo-selection.[2] Addition of the metal enolates with nitrogen analogs of aldehydes is especially useful for β-lactam synthesis.[3] However, nitriles as the substrates remained unexplored until recently, possibly due to low reactivity of conventional enolates.[4] In fact, when we examined the reaction of *t*-butyl lithioacetate with benzonitrile, we observed that no trace of the expected adduct was produced. The failure of the nitrile addition was ascribed to the incapability of the lithium ion to take a nitrile in its ligand sphere as well as to the instability of the primary adduct. Thus, we searched for higher valent metal counter ions appropriate to the C–C bond formation. Zinc enolates grew promising upon literature survey.[5] We could not, however, achieve the nitrile addition of the Reformatsky reagent in good yields, although Hannick and Kishi later established an improved procedure for the Blaise reaction.[6] After several screening experiments, we found the magnesium enolates of alkanoate esters undergo the desired reaction to afford 3-amino-2-alkenoates efficiently[7] and applied the reaction successfully to the synthesis of amino sugars *N*-benzoyl-L-daunosamine[8] and *N*-benzoyl-L-acosamine.[9] Details of the new transformation are reported herein.

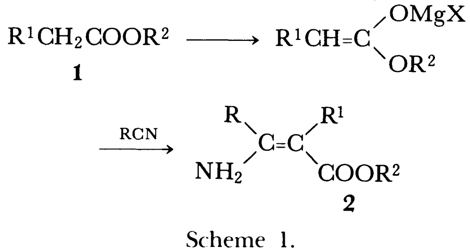
Results and Discussion

Nitrile Addition of Alkanoate Magnesium Enolates. The reaction of *t*-butyl acetate with benzonitrile was first studied. Magnesium amide was prepared by mixing equimolar amounts of ethylmagnesium bromide and a secondary amine[10] such as diisopropylamine, isopropylcyclohexylamine and hexamethyldisilazane. *t*-Butyl acetate was treated with each base at −10 to 0 °C in diethyl ether for 1 h and then with benzonitrile to give, after quenching with aqueous ammonium chloride solution and extractive workup followed by distillation, *t*-butyl 3-amino-3-phenylpropenoate (**2i**) in 53, 49, and 62% yield respectively. The yields were improved when the magnesium amide was prepared by 2 : 1 molar ratio of secondary amine and ethylmagnesium bromide. Diethyl ether was proved to be a superior solvent to tetrahydrofuran (THF). Although the structure of the magnesium amide reagent is unclear at present, a report by Wannagat and Kuckertz is informative.[11] They treated hexamethyldisilazane with a Grignard reagent in diethyl ether and obtained a complex $[(Me_3Si)_2N]_2Mg:MgX_2:OEt_2$ which upon treatment with more basic solvent dioxane gave $[(Me_3Si)_2N]_2Mg:(dioxane)_3$ and $MgI_2:(dioxane)_2$. Thus, we assumed the reagent generated from a 1 : 1 mixture of EtMgBr and $HN(i\text{-}Pr)_2$ would be a mixture of $[(i\text{-}Pr)_2N]_2Mg$ and $MgBr_2$ solvated by diethyl ether. By use of excess diisopropylamine, the Lewis acid $MgBr_2$ would be preferentially neutralized, and, as the results, the reactivity of the magnesium amide base is enhanced.

$$2\,EtMgBr + 4\,HN(i\text{-}Pr)_2 \longrightarrow Mg[N(i\text{-}Pr)_2]_2 + MgBr_2\cdot[HN(i\text{-}Pr)_2]_2$$

We employed diisopropylamine for all cases, as it is relatively cheap and volatile enough to be removed readily. At the early stage of our research,[7a] we employed 4 : 2 : 2 molar ratio of diisopropylamine, ethylmagnesium bromide and ester, but later found a 4 : 2 : 1 ratio is better for the reaction, since an excess ester sometimes underwent self-condensation.

The nitrile addition of magnesium ester enolate is applicable to various nitriles (Scheme 1). The mol ratio of the ester enolate to a nitrile was changed from 1 : 1 to large excess depending on the reactivity of the nitrile as summarized in Table 1. Nitriles having rela-



Scheme 1.

Table 1. Nitrile Addition of the Magnesium Enolates of Alkanoate Esters

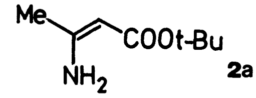
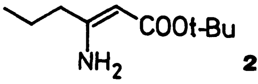
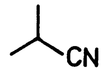
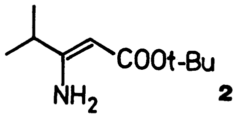
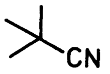
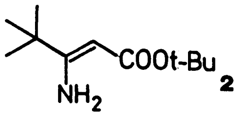
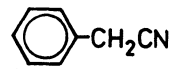
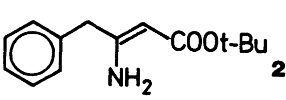
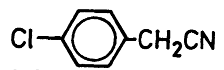
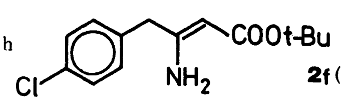
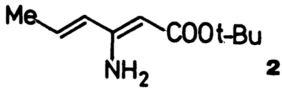
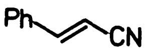
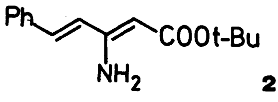
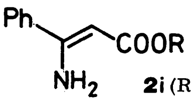
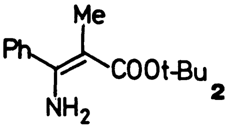
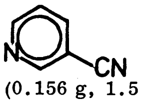
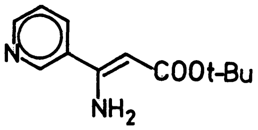
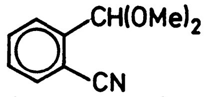
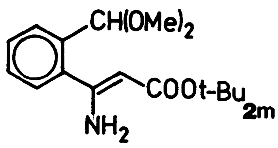
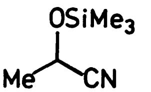
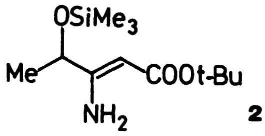
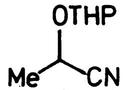
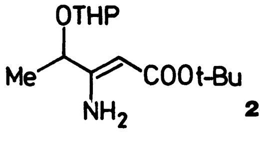
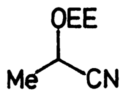
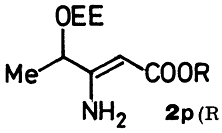
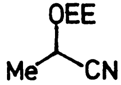
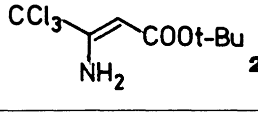
Run	Nitrile	Alkanoate Ester 1	Reaction Condition	Product (Yield)
1	MeCN (62 mg, 1.5 mmol)	AcOt-Bu (0.35 g, 3 mmol)[a]	0 °C, 3 h	 **2a** (0.156 g, 66%)
2	 (0.104 g, 1.5 mmol)	AcOt-Bu (0.35 g, 3 mmol)[a]	0 °C, 4 h	 **2b** (0.158 g, 57%)
3	 (0.104 g, 1.5 mmol)	AcOt-Bu (0.174 g, 1.5 mmol)[a]	0 °C, 1.5 h	 **2c** (0.21 g, 74%)
4	 (0.127 g, 1.5 mmol)	AcOt-Bu (0.174 g, 1.5 mmol)[a]	0 °C, 1.5 h	 **2d** (0.143 g, 48%)
5	 (0.176 g, 1.5 mmol)	AcOt-Bu (0.176 g, 1.5 mmol)[a]	0 °C, 1.5 h	 **2e** (94 mg, 27%)
6	 (0.23 g, 1.5 mmol)	AcOt-Bu (0.70 g, 6 mmol)[a]	0 °C, 0.7 h	 **2f** (0.120 g, 30%)
7	 (0.101 g, 1.5 mmol)	AcOt-Bu (0.174 g, 1.5 mmol)[a]	0 °C, 1.5 h	 **2g** (49 mg, 18%)
8	 (0.194 g, 1.5 mmol)	AcOt-Bu (0.35 g, 3 mmol)[b]	0 °C, 1.5 h	 **2h** (0.163 g, 44%)
9	PhCN (0.155 g, 1.5 mmol)	AcOt-Bu (0.134 g, 1.5 mmol)[b]	0 °C, 1 h	 **2i** (R = t-Bu, 0.27 g, 83%)
10	PhCN (0.155 g, 1.5 mmol)	AcOEt (0.26 g, 3 mmol)[b]	-78 °C to 0 °C, 1.5 h	**2j** (R = Et, 0.163 g, 57%)
11	PhCN (0.155 g, 1.5 mmol)	EtCOOt-Bu (0.195 g, 1.5 mmol)[b]	-78 °C, 5 h; then 0 °C	 **2k** (0.105 g, 30%)
12	 (0.156 g, 1.5 mmol)	AcOt-Bu (0.174 g, 1.5 mmol)[a]	0 °C, 1.5 h	 **2l** (0.22 g, 65%)
13	 (0.35 g, 2 mmol)	AcOt-Bu (0.91 g, 8 mmol)[a]	0 °C, 5 h	 **2m** (0.50 g, 85%)
14	 (2.14 g, 15 mmol)	AcOt-Bu (3.48 g, 30 mmol)[b]	0 °C, 3 h	 **2n** (2.52 g, 65%)

Table 1. (Continued)

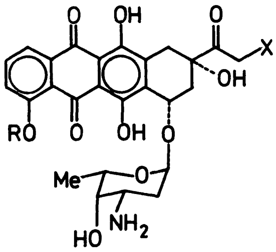
Run	Nitrile	Alkanoate Ester **1**	Reaction Condition	Product (Yield)
15	 (0.100 g, 0.65 mmol)[c)]	AcOt-Bu (87 mg, 0.75 mmol)[b)]	0 °C, 1.5 h	 **2o** (0.150 g, 86%)
16	 (12.9 g, 90 mmol)[c)]	AcOt-Bu (20.9 g, 180 mmol)[b)]	0 °C, 3 h	 **2p** (R = t-Bu, 18.9 g, 81%)
17	 (0.143 g, 1 mmol)[c)]	AcOEt (0.35 g, 4 mmol)[b)]	−78 °C to 0 °C, 5 h	**2q** (R = Et, 0.122 g, 53%)
18	CCl_3CN (0.29 g, 2 mmol)	AcOt-Bu (0.23 g, 2 mmol)[b)]	0 °C, 5 min	 **2r** (0.43 g, 83%)

a) A mol ratio of diisopropylamine:ethylmagnesium bromide:ester was 4:2:2. b) A mol ratio of diisopropylamine:ethylmagnesium bromide:ester was 4:2:1. c) THP is tetrahydropyran-2-yl; EE is 1-ethoxyethyl group.

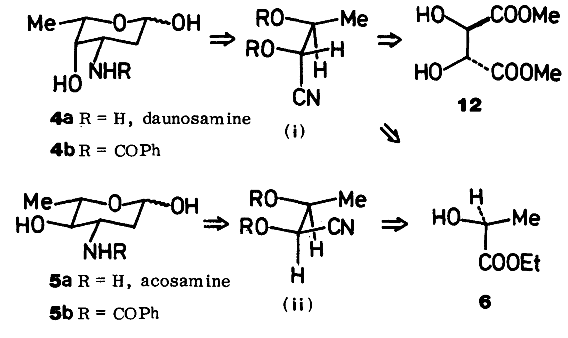
tively acidic α-hydrogen(s) gave slightly lower yields of adducts (Runs 5 and 6). The yields were not improved even by use of 6 fold mol of the ester enolate. 3-Butenenitrile did not give the desired adduct at all. The nitrile addition was applied particularly effectively to α-alkoxy nitriles or protected cyanohydrins (Runs 14 to 17). Ethyl acetate and *t*-butyl propionate can be employed in place of *t*-butyl acetate, but these required milder conditions: Both generation of magnesium enolate and the reaction with benzonitrile were preferably carried out at −78 °C, and the reaction mixture was allowed to warm up gradually (Runs 10, 11, and 17) to avoid self-condensation of the esters.

The configuration of the products **2** is all assigned as (Z) on the basis of ^{1}H NMR spectra. For example, **2a** and **2c** showed olefinic singlet absorptions at δ 4.42 and 4.47 respectively consistent with the literature values δ 4.49 and 4.56 for the ethyl ester of Z-configuration corresponding to **2a** and **2c** respectively.[12)] The Z-preference is ascribed to intramolecular hydrogen bonding between amino and alkoxycarbonyl groups.[12)] The geometrical preference was retained after the 3-amino-2-alkenoates were acetylated, though small amounts of (E)-isomers were produced. The resultant 3-acetamido-2-alkenoates are stable to moisture and was readily purified by preparative TLC or column chromatography in contrast to the parent compounds **2**.

As 3-amino-2-alkenoates are versatile synthetic intermediates for heterocycles such as pyridines,[13)] pyrimidines, indoles,[14)] and isothiazoles,[15)] and, in addition, some *N*-aroyl derivatives of 3-amino-2-alkenoic acids exhibit anti-inflammatory activity,[16)] various synthetic approaches have appeared.[6,17)] The magnesium enolate-nitrile addition reported herein can be characterized by simple experimental version coupled with wide applicability. We applied the new synthetic method to the total synthesis of physiologically active amino sugars.



3a R=Me, X=OH adriamycin
3b R=Me, X=H daunomycin
3c R=H, X=H carminomycin



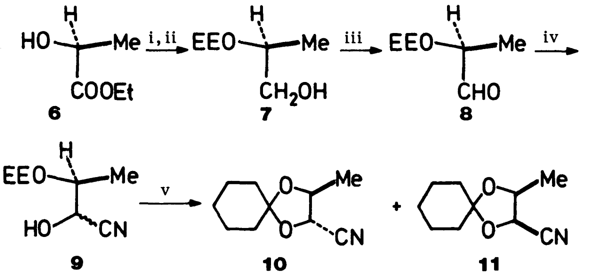
Scheme 2.

Synthesis of *N*-Benzoyl-L-daunosamine and -L-acosamine. The nitrile-ester enolate coupling reaction is applied to the synthesis of amino sugars such as L-daunosamine (**4a**) and L-acosamine (**5a**). These are sugar moieties of highly potent antitumor antibiotics adriamycin, daunomycin, and carminomycin.[18)] Particularly, the cardiotoxicity is lowered remarkably by changing the sugar part of adriamycin from daunosamine to acosamine.[19] The structural features of these amino sugars led us to retrosynthetic analysis as shown in Scheme 2. Addition of acetic acid ester enolate to the nitrile (i) or (ii) followed by stereoselective reduction of the resulting configurationally fixed C=C bond and appropriate functional group manipulation should afford daunosamine or acosamine derivatives respectively. The requisite nitriles (i) and (ii) may be derived from ethyl (*S*)-(−)-lactate (**6**). Methyl L-tartrate (**12**) can be the precursor of the nitrile (i), as the tartrate possesses the needed C_4 framework, oxygen functional groups and stereochemical arrangements all in a single molecule. Synthetic operations were carried out according to the Schemes 3 and 4.

Ethyl (*S*)-(−)-lactate (**6**) was protected with ethyl vinyl ether, and reduced with lithium aluminium hydride to give (*S*)-2-ethoxyethyl ether of 1,2-propanediol (**7**). Oxidation of **7** with dimethyl sulfoxide (DMSO)[20] gave the aldehyde **8** which was isolated by distillation. Cyanohydrin formation was effected with acetone cyanohydrin and triethylamine catalyst. The resulting cyanohydrin **9** was converted into a cyclohexylidene acetal by acetal exchange reaction with cyclohexanone dimethyl acetal and bis(trimethylsily) sulfate catalyst.[21] The diastereomeric ratio of **10** and **11** was estimated before isolation to be 45 : 55. When the cyanohydrin formation was carried out with Me_3SiCN and Et_2AlCN catalyst, the diastereomeric ratio changed to 73 : 27. These nitriles were readily separated by column chromatography. ^1H NMR study with $Eu(tfc)_3$ showed >95% optical purity of **10** and **11**. Thus, no trace of racemization occurred during the oxidation of **7**, cyanohydrin formation or acetalization leading to **10** and **11**. All attempts to epimerize the C(2) stereocenter with base failed. Either recovery of the starting nitriles (NaOEt) or total decomposition ($LiN(i\text{-}Pr)_2$) was observed in sharp contrast to the facile epimerization of the corresponding aldehydes.[22]

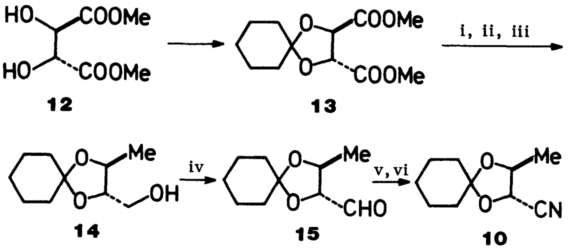
The (2S,3S)-isomer **10** was alternatively prepared according to the Scheme 4. Dimethyl L-tartrate (**12**) was acetalized to **13**[23] which was reduced with lithium aluminium hydride to a diol. Selective monotosylation followed by sodium borohydride reduction of the resulting tosylate gave an alcohol **14**. Oxidation by the Swern's method[20] afforded **15**.[24] Derivatization of **15** to its oxime followed by dehydration gave **10**.

With the required nitriles now at hand, we studied subsequent C_2 homologation. The (2*S*,3*S*)-nitrile **10**



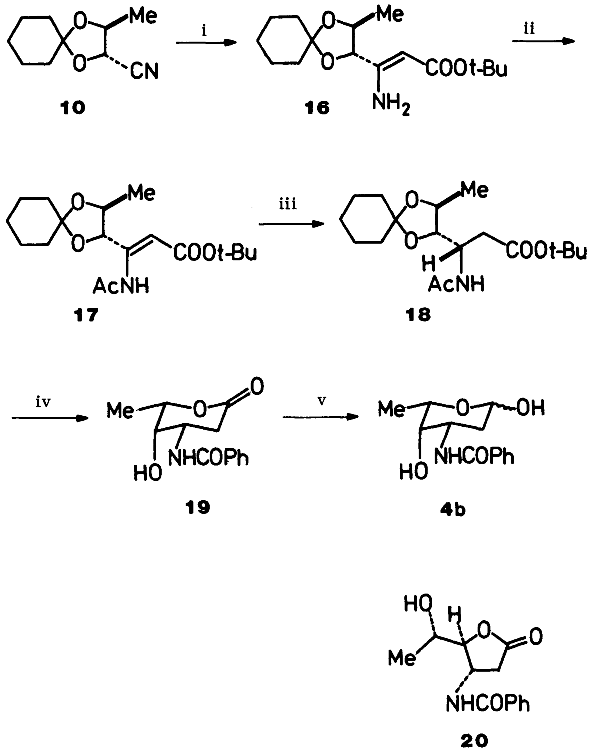
i) $CH_2{=}CHOEt$, PyH·OTs, CH_2Cl_2, 0 °C to r.t.
ii) $LiAlH_4$, Et_2O, reflux
iii) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −65 to −70 °C
iv) $Me_2C(OH)CN$, Et_3N, 0 °C
v) $(CH_2)_5C(OMe)_2$, $(Me_3SiO)_2SO_2$, Molecular Sieve 4A, 0 °C to r.t.

Scheme 3.



i) $LiAlH_4$, Et_2O, 0 °C to reflux
ii) TsCl, Et_3N, CH_2Cl_2, 0 °C
iii) $NaBH_4$, DMSO
iv) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2
v) $NH_2OH·HCl$, Py, 80 °C
vi) CCl_4, Ph_3P, Et_3N, 80 °C

Scheme 4.



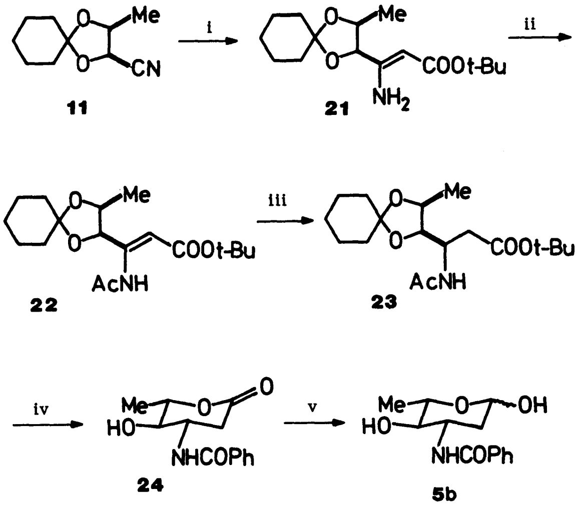
i) $CH_2{=}C(Ot\text{-}Bu)OMgX$, Et_2O, 0 °C
ii) Ac_2O, Py, 50 to 60 °C
iii) H_2(55 kg cm^{-2}=5.6×10^6 Pa), PtO_2, AcOEt, 70 °C
iv) 2M (1M=1 mol dm^{-3}) HCl, reflux; PhCOCl, sat aq $NaHOC_3$-acetone (5 : 2), r.t.; 2 M HCl
v) $i\text{-}Bu_2AlH$, THF, −60 to −50 °C

Scheme 5.

Table 2. Catalytic Hydrogenation of **17**

Run	Catalyst	Solvent	Temp	H_2	Reaction Time/d	Yield	**18**:Epimer
			°C	kg cm^{-2}[a]		%	
1	5% Rh/C	THF	55	60	0.6	90	1:2
2	5% Rh/C	THF-AcOH (40:1)	55	60	2.5	68	2:3
3	5% Pd/Al_2O_3	AcOEt	55	60	0.6	Quant.	1:2
4	PtO_2	AcOEt	55	1	3.5	31	3:2
5	PtO_2	AcOEt	70	55	1	98	5.1:1

a) 1 kg cm^{-2} = 1.01×10^5 Pa.



i) CH_2=C(O*t*-Bu)OMgX, Et_2O, 0 °C
ii) Ac_2O, Py, 50 to 60 °C
iii) H_2(70 kg cm^{-2}=7.1×10^6 Pa), Rh/C, THF, 55 °C
iv) 2M HCl, reflux; PhCOCl, sat aq $NaHOC_3$–acetone (5:2), r.t.; 2 M HCl
v) *i*-Bu_2AlH, THF, −60 to −50 °C

Scheme 6.

was revealed to be reactive enough to afford **16** in 99% yield (Scheme 5). Although the C=C bond of 3-amino-2-alkenoates is recorded to be reduced under several conditions,[25] the known conditions were not applicable to **16** possibly due to unrecognized electronic and/or steric reasons. To reduce the electron density of the C=C bond of **16**, we acetylated **16** to **17**. A part of the product isomerized to the (E)-isomer.[26] The acetamide **17** was proved to be acid-stable and was readily purified by chromatography. Catalytic hydrogenation was studied under various conditions. Results are summarized in Table 2. Platinum catalyst produced predominantly the desired product **18**, whereas rhodium and palladium catalysts preferred the formation of the epimer of **18**. Under the conditions of Run 5, **18** was isolated in 82% yield in a pure form. Its epimer was isolated in 16% yield. Treatment of **18** with hydrochloric acid induced hydrolysis of the acetal, ester and amide moieties all in a single operation. Subsequent benzoylation under the Schotten–Baumann conditions followed by lactonization gave a δ-lactone **19**. The lactonization was found to proceed stepwise: Initially a γ-lactone **20** was formed which gradually isomerized to **19**. Reduction of **19** with diisobutylaluminium hydride gave *N*-benzoyl-L-daunosamine.[27,28,31]

For the synthesis of *N*-benzoyl-L-acosamine (**5b**), (2*R*,3*S*)-2,3-(cyclohexylidenedioxy)butanenitrile (**11**) is a requisite starting material. Addition of the magnesium enolate of *t*-butyl acetate to **11** was found relatively sluggish and took place at 0 °C to give **21** in 54% yield after isolation by distillation. Acetylation under the standard conditions gave **22**. Again (E)-isomer of **22** accompanied. Hydrogenation of **22** with rhodium or platinum catalyst was satisfactory in respect to stereochemical outcome. Of these, rhodium on carbon was employed in an autoclave under a hydrogen pressure of 70 kg cm^{-2}. Hereby a single isomer **23** was isolated in 84% yield. It is worthy of note that the stereochemical course of the hydrogenation of C(2)=C(3) is oriented by the configuration of C(5) rather than that of C(4) (compare the reduction of **17** with that of **22**), even though C(4) is situated closer to the reaction site.[32] Hydrolysis of **23** followed by *N*-benzoylation and lactonization afforded **24** which exhibited spectral data fully identical with the reported values.[28a] Diisobutylaluminium hydride reduction gave finally *N*-benzoyl-L-acosamine.[28,29]

Experimental

Distillation of a sample of less than 1 g was carried out by bulb-to-bulb distillation technique with Kugelrohr (Büchi) or Glass Tube Oven GTO 250R (Shibata). Larger amount of sample was distilled by a micro distillation apparatus. Reactions were carried out under an argon atmosphere unless otherwise specified. All mps and bps were uncorrected values. ^1H NMR spectra were obtained on a Varian EM 390 or Varian XL-100A spectrometer, chemical shifts being given in ppm units from the tetramethylsilane standard. ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer with tetramethylsilane as the internal standard. IR spectra were taken on a JASCO A 202 spectrometer. Specific rotation was measured with a Horiba SEPA-200 or Union PM-201 machine. Low resolution mass spectra were recorded with a Hitachi RMU-6MG machine (70 eV); millimass with a Hitachi M-80A spectrometer. GLC analyses were performed with a Shimadzu GC-7A chromatograph with a FID detector. TLC analyses were performed on commercial glass plates coated with Merck Silica Gel 60 F_{254} in 0.25 mm thick layer. Preparative TLC plates were prepared using Merck Kieselgel 60 PF_{254}. Column chromatography was carried out using silica gel such as Wacogel C-100 (Wako) or Kieselgel 60 (Merck). THF and diethyl ether were distilled before use from sodium-benzophenone. Diisopropylamine, *t*-butyl acetate, and DMSO were distilled over calcium hydride.

***t*-Butyl 3-Amino-2-butenoate (2a). A Typical Procedure for Generation and Nitrile Addition of the Magnesium Enolate of *t*-Butyl Acetate.** Diisopropylamine (0.61 g, 6.0 mmol) was added to an ethereal solution (0.70 M, 4.3 ml) of ethylmagnesium bromide (3.0 mmol) at 0 °C, and the reaction mixture was stirred for 1 h. To the resulting turbid solution was added *t*-butyl acetate (0.35 g, 3.0 mmol) at 0 °C. After 0.5 h acetonitrile (62 mg, 1.5 mmol) was injected with the aid of a microsyringe to the reaction mixture and allowed to react for 3 h at 0 °C. Quenching with aqueous ammonium chloride solution, extraction with diethyl ether, and purification by distillation gave *t*-butyl 3-amino-2-butenoate (2a) (0.156 g, 66% yield). Bp 73 °C/0.3 Torr† (lit,[16] 66 °C/0.4 Torr). IR (neat) 3460, 3345, 1650, 1615, 1558 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.46 (s, 9H), 1.84 (s, 3H), 4.42 (s, 1H), 5.0—6.7 (br, 2H).

The *t*-butyl esters of 2 (Table 1) were prepared by the similar procedure described above, and the physical properties of these are listed below.

***t*-Butyl 3-Amino-2-hexenoate (2b):** Bp 78 °C/0.25 Torr; IR (neat) 3460, 3345, 1655, 1615, 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.93 (t, 3H), 1.45 (s, 9H), 1.5—1.8 (m, 2H), 2.05 (t, 2H), 4.43 (s, 1H), 5.3—6.6 (br, 2 H). Found: C, 64.89; H, 10.10; N, 7.42%. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56%.

***t*-Butyl 3-Amino-4-methyl-2-pentenoate (2c):** Bp 95 °C/0.7 Torr; IR (neat) 3460, 3345, 1660, 1615, 1545 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.14 (d, 6H), 1.47 (s, 9H), 2.1—2.5 (m, 1H), 4.47 (s, 1H), 5.8—6.8 (br, 2H). Found: C, 64.59; H, 10.23; N, 7.40%. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56%.

***t*-Butyl 3-Amino-4,4-dimethyl-2-pentenoate (2d):** Bp 104 °C/0.4 Torr; mp 75 °C; IR (neat) 3500, 3455, 3345, 1675, 1615, 1540 cm^{-1}; ^1H NMR δ=1.14 (s, 9H), 1.45 (s, 9H), 4.52 (s, 1H), 5.9—7.0 (br, 2H). Found: C, 66.16; H, 10.72; N, 7.01%. Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03%.

***t*-Butyl 3-Amino-4-phenyl-2-butenoate (2e):** Bp 116 °C/0.25 Torr (lit,[30] 120 °C/0.01 Torr); IR (neat) 3460, 3340, 1660, 1615, 1555 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.46 (s, 9H), 3.70 (s, 2H), 4.53 (s, 1H), 5.5—6.3 (br, 2H), 7.31 (s, 5H).

***t*-Butyl 3-Amino-4-(4-chlorophenyl)-2-butenoate (2f):** Bp 138 °C/0.25 Torr; IR (neat) 3450, 3340, 1660, 1610, 1555 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.48 (s, 9H), 3.36 (s, 2H), 4.49 (s, 1H), 5.4—6.4 (br, 2H), 7.0—7.5 (m, 4H); MS *m/z* (rel intensity) 269 (M^++2, 1), 267 (M^+, 3), 212 (28), 211 (19), 195 (27), 194 (20), 193 (43), 152 (18), 127 (11), 126 (13), 125 (30), 89 (11), 57 (100). Found: *m/z* 267.1027. Calcd for $C_{14}H_{18}NO_2Cl$: M^+ 267.1030.

***t*-Butyl 3-Amino-2,4-hexadienoate (2g):** Bp 103 °C/0.3 Torr; IR (neat) 3475, 3350, 1670, 1610, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.48 (s, 9H), 1.7—2.0 (m, 3H), 4.56 (br s, 1H), 5.1—6.9 (m, 5H); MS *m/z* (rel intensity) 183 (M^+, 11), 127 (100), 126 (14), 112 (77), 110 (41), 109 (13), 82 (14), 81 (17), 80 (11), 68 (31), 67 (30), 66 (11), 57 (28). Found: *m/z* 183.1270. Calcd for $C_{10}H_{17}NO_2$: M^+ 183.1260.

***t*-Butyl 3-Amino-5-phenyl-2,4-pentadienoate (2h):** Viscous oil, R_f=0.70 (hexane-ethyl acetate 3 : 1); IR (neat) 3460, 3340, 1655, 1635, 1605, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.48 (s, 9H), 4.76 (s, 1H), 5.9—6.3 (br, 2H), 6.37 (d, 1H), 6.90 (d, 1H), 7.2—7.5 (m, 5H). MS *m/z* (rel intensity) 245 (M^+, 5), 189 (9), 188 (4), 172 (10), 145 (13), 144 (100), 143 (20), 57 (10). Found: *m/z* 245.1417. Calcd for $C_{15}H_{19}NO_2$: M^+ 245.1416.

***t*-Butyl 3-Amino-3-phenyl-2-propenoate (2i):** R_f=0.51 (hexane-ethyl acetate 5 : 1); mp 93 °C; IR (KBr) 3460, 3425, 3345, 1665, 1645, 1615, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.49 (s, 9H), 4.86 (s, 1H), 5.8—6.8 (br, 2H), 7.3—7.6 (m, 5H). Found: C, 71.18; H, 7.77; N, 6.38%. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39%.

***t*-Butyl 3-Amino-3-(3-pyridyl)-2-propenoate (2l):** Bp 144 °C/0.25 Torr; mp 50—50.5 °C; IR (KBr) 3400, 3310, 3275, 3190, 1665, 1595, 1555 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.51 (s, 9H), 4.86 (s, 1H), 6.0—7.0 (br, 2H), 7.2—7.4 (m, 1H), 7.80 (dt, 1H), 8.62 (dd, 1H), 8.82 (d, 1H). Found: C, 65.46; H, 7.45; N, 12.48%. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72%.

***t*-Butyl 3-Amino-4-trimethylsilyloxy-2-pentenoate (2n):** Bp 72 °C/0.3 Torr; IR (neat) 3400, 3345, 1665, 1615, 1540 1140, 840 cm^{-1}; ^1H NMR (CCl_4) δ=0.18 (s, 9H), 1.38 (d, 3H), 1.48 (s, 9H), 4.25 and 4.30 (q and s, totally 2H), 5.9—7.4 (br, 2H). MS *m/z* (rel intensity) 259 (M^+, 10), 203 (37), 188 (21), 186 (34), 185 (100), 170 (16), 158 (13), 142 (10), 117 (10), 96 (16), 85 (12), 75 (25), 73 (49), 57 (18). Found: C, 55.64; H, 9.82; N, 5.32%. Calcd for $C_{12}H_{25}NO_3Si$: C, 55.56; H, 9.71; N, 5.40%.

***t*-Butyl 3-Amino-4-(tetrahydro-2-pyranyloxy)-2-pentenoate (2o):** Bp 160 °C/0.25 Torr; IR (neat) 3500, 3440, 1665, 1540 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.2—1.9 (m and s (δ=1.45), totally 18 H), 3.2—4.7 (m, 5H), 5.8—6.6 (br, 2H). Found: C, 62.19; H, 9.16; N, 5.08%. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16%.

***t*-Butyl 3-Amino-2-methyl-3-phenylpropenoate (2k):** Bp 112 °C/0.3 Torr; ^1H NMR (CCl_4): δ=1.50 (s, 9H), 1.53 (s, 3H), 6.2 (br, 2H), 7.30 (s, 5H); IR (neat) 3460, 3330, 3050, 2970, 2920, 1660, 1610, 1595, 1280, 1130, 1100, 770, 700 cm^{-1}; MS *m/z* (rel intensity) 233 (M^+, 15), 178 (13), 177 (100), 176 (26), 160 (29), 132 (40), 131 (43), 130 (25), 105 (11), 104 (57), 77 (20). Found: *m/z* 233.1427. Calcd for $C_{14}H_{19}NO_2$: M^+ 233.1416.

***t*-Butyl 3-Amino-3-[2-(dimethoxymethyl)phenyl]propenoate (2m):** Bp 159 °C/0.17 Torr; ^1H NMR ($CDCl_3$) δ=1.52 (s, 9H), 3.35 (s, 6H), 4.62 (s, 1H), 5.47 (s, 1H), 7.1—7.5 (m, 2H), 6.0—7.0 (br, 2H), 7.0—7.7 (m, 2H); IR (neat) 3450, 3330, 2960, 2920, 2830, 1660, 1605, 1545, 1360, 1310, 1200, 1140, 1090, 1070, 980, 790, 770, 750 cm^{-1}; MS *m/z* (rel intensity) 293 (M^+, 1), 278 (10), 261 (10), 223 (11), 222 (84), 206 (16), 205 (39), 204 (58), 174 (70), 172 (52), 160 (13), 156 (100), 146 (87), 130 (44), 129 (13), 128 (27), 57 (53). Found: *m/z* 293.1627. Calcd for $C_{16}H_{23}NO_4$: M^+ 293.1627.

***t*-Butyl 3-Amino-4-(1-ethoxyethoxy)-2-pentenoate (2p):** Bp 102 °C/0.37 Torr; ^1H NMR ($CDCl_3$) δ=1.1—1.6 (m+s (δ=1.47), 18H), 3.3—3.7 (m, 2H), 3.9—4.3 (m, 1H), 4.38 and 4.43 (2s, 1H), 4.57 and 4.67 (2q, 1H), 5.6—6.9 (br, 2H); IR (neat) 3500, 3440, 1660, 1615, 1540 cm^{-1}; MS *m/z* (rel intensity) 259 (M^+, 0.5), 187 (16), 171 (5), 170 (2), 158 (11), 131 (3), 115 (60), 114 (46), 113 (16), 97 (10), 96 (20), 85 (14), 73 (100), 57 (24). Found: *m/z* 259.1779. Calcd for $C_{13}H_{25}NO_4$: M^+ 259.1783. Found: C, 60.07; H, 9.99; N, 5.30%. Calcd for $C_{13}H_{25}NO_4$: C, 60.21; H, 9.72; N, 5.40%.

Ethyl 3-Amino-4-(1-ethoxyethoxy)-2-pentenoate (2q): Bp 98 °C/0.5 Torr; ^1H NMR (CCl_4) δ=1.0—1.6 (m, 12H), 3.4—

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† 1 Torr=133.322 Pa.

3.9 (m, 2H), 4.0—4.9 (m, 5H), 6.0—7.0 (br, 2H); IR (neat) 3450, 3340, 2970, 2920, 1660, 1620, 1560, 1265, 1150, 1070, 1040 cm^{-1}; MS *m/z* (rel intensity) 231 (M^+, 0.1), 186 (M^+—OEt, 5), 170 (3), 160 (2), 159 (23), 143 (28), 124 (11), 114 (32), 113 (14), 97 (12), 96 (27), 85 (14), 73 (84), 69 (9), 68 (7), 54 (6), 45 (100). Found: *m/z* 231.1460. Calcd for $C_{11}H_{21}NO_4$: M^+ 231.1469.

***t*-Butyl 3-Amino-4,4,4-trichloro-2-butenoate (2r):** Bp 123 °C/0.3 Torr; mp 37—39 °C; ^{1}H NMR ($CDCl_3$) δ=1.49 (s, 9H), 5.41 (s, 1H), 6.0—7.1 (br, 2H); IR (KBr) 3445, 3330, 2980, 1665, 1625, 1620, 1545, 1365, 1275, 1250, 1140, 820, 775 cm^{-1}; MS *m/z* (rel intensity) 263 (M^++4, 0.7), 262 (M^++2, 2), 259 (M^+, 2), 224 (4), 207 (12), 205 (36), 203 (37), 188 (12), 186 (12), 170 (12), 168 (19), 86 (11), 68 (27), 57 (100). Found: *m/z* 258.9927. Calcd for $C_8H_{12}NO_2Cl_3$: M^+ 258.9907.

Ethyl 3-Amino-3-phenyl-2-propenoate (2j). The magnesium amide was prepared by the addition of diisopropylamine (0.61 g, 6.0 mmol) to an ethereal solution (4.3 ml) of ethylmagnesium bromide (3 mmol) at 0 °C and by stirring the solution of 1 h. To the base solution cooled at −78 °C, ethyl acetate (0.132 g, 1.5 mmol) was added drop by drop and the resulting enolate solution was stirred at −78 °C for 30 min. Benzonitrile (0.155 g, 1.5 mmol) was then added, and the reaction mixture was allowed to warm to 0 °C and stirred for 1.5 h. Workup as before followed by distillation gave **2j** (0.163 g, 57% yield). Bp 112 °C/0.3 Torr (lit,[30] bp 110—112 °C/0.2 Torr).

Acetylation of 2n. A mixture of *t*-butyl 3-amino-4-trimethylsilyloxy-2-pentenoate (**2n**) (1.00 g, 3.9 mmol), acetic anhydride (10 ml) and pyridine (0.53 g, 6.6 mmol) was heated at 80 °C for 9 h. Excess acetic anhydride and pyridine was evaporated under reduced pressure, and the residue was purified by column chromatography (silica gel, hexane-ethyl acetate 3 : 1) to give *t*-butyl (*Z*)-3-acetamido-4-acetoxy-2-pentenoate (R_f=0.56, 0.68 g, 65% yield). IR (neat) 3230, 1745, 1720, 1660, 1630 cm^{-1}; ^{1}H NMR (CCl_4) δ=1.42 and 1.46 (d and s, totally 12 H), 2.03 (s, 3H), 2.11 (s, 3H), 4.99 (s, 1H), 6.31 (q, 1H), 12.2 (br, 1H). Found: C, 57.24; H, 7.66; N, 4.84%. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16%.

The (E) isomer (R_f=0.13, 0.198 g) also was obtained in 19% yield. Mp 104—105.5 °C; IR (KBr) 3350, 1745, 1710 (sh), 1695, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.43 and 1.46 (d and s, totally 12H), 2.09 (s, 3H), 2.14 (s, 3H), 6.68 and 6.80 (q and s, 2H), 7.2 (br, 1H).

(*S*)-2-(1-Ethoxyethoxy)-1-propanol (7). A dichloromethane (26 ml) solution of pyridinium *p*-toluenesulfonate (1.53 g, 0.01 mol) was added drop by drop to a mixture of ethyl (*S*)-lactate (11.8 g, 0.10 mol), ethyl vinyl ether (10.8 g, 0.15 mol) and dichloromethane (100 ml), and the mixture was stirred at 0 °C for 50 min and at room temperature for 1 h. The reaction mixture was diluted with diethyl ether (300 ml) and washed twice with brine (50 ml) and then twice with water (50 ml). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. Distillation at 77—78 °C/26 Torr gave ethyl (*S*)-*O*-ethoxyethyl lactate (18.4 g, 97% yield). ^{1}H NMR ($CDCl_3$) δ=1.06—1.50 (m, 12H), 3.33—3.90 (m, 2H), 4.20 (q, *J*=7.5 Hz, 2H), 4.30 (q, *J*=6.0 Hz, 1H), 4.76 (q, *J*=6.0 Hz). IR (neat) 3000, 2950, 1750, 1445, 1390, 1370, 1270, 1200, 1175, 1150, 1090, 1055, 1025, 965 cm^{-1}. MS *m/z* (rel intensity) 189 (M^+ −1, 1), 175 (15), 145 (99), 117 (53), 102 (73), 101 (44), 74 (49), 73 (100), 72 (15), 55 (13), 45 (100). $[\alpha]_D^{24}$ −54.1° (*c* 3.87, $CHCl_3$); $[\alpha]_D^{28}$ −71.7° (*c* 4.18, MeOH). Found: C, 57.05; H, 9.77%. Calcd for $C_9H_{18}O_4$: C, 56.82; H, 9.54%.

The above lactate (14.9 g, 78.3 mmol) dissolved in diethyl ether (100 ml) was added to an ethereal solution (100 ml) of lithium aluminium hydride (4.05 g, 0.100 mol) over 25 min. After the addition was completed, the reaction mixture was heated to reflux for 7 h. Quenching the excess hydride was effected by dropwise addition of aqueous saturated solution of sodium sulfate and successively by the addition of magnesium sulfate. Filtration through a Hyflosupercell pad, concentration, followed by distillation, gave **7** (10.9 g, 94% yield). Bp 77—79 °C/17 Torr; ^{1}H NMR ($CDCl_3$) δ=1.06—1.38 (m, 9H), 2.62 and 3.20 (dd, *J*=(6.8, 5.3 Hz) and (8.3, 4.1 Hz) respectively, totally 1H, OH), 3.37—3.96 (m, 5H), 4.70 and 4.78 (2q, *J*=5.3 Hz each, totally 1H); IR (neat) 3450, 3000, 2950, 1450, 1380, 1340, 1130, 1105, 1060, 970 cm^{-1}; MS *m/z* (rel intensity) 147 (M^+—1, 1), 133 (2), 117 (5), 103 (15), 73 (92), 59 (43), 45 (100), 43 (12). $[\alpha]_D^{29}$ +42.2° (*c* 5.87, $CHCl_3$). Found: C, 56.91; H, 11.03%. Calcd for $C_7H_{16}O_3$: C, 56.73; H, 10.88%.

(*S*)-2-(1-Ethoxyethoxy)propanal (8). A dichloromethane (40 ml) solution of DMSO (7.9 g, 7.2 ml, 0.101 mol) was added drop by drop over 15 min to a dichloromethane (100 ml) solution of oxalyl dichloride (6.4 g, 4.4 ml, 0.050 mol) at −70 °C. After stirring for 10 min a dichloromethane (50 ml) solution of **7** (5.0 g, 0.034 mol) was added over 15 min, and the resulting mixture was stirred for 30 min at −70 °C before addition (over 15 min) of triethylamine (17.1 g, 23.5 ml, 0.168 mol). The mixture was stirred at −70 °C for 25 min, allowed to warm to 10 °C in 20 min, and then treated with brine (100 ml). The organic layer was separated, washed with brine (50 ml×2), dried over magnesium sulfate and concentrated. Distillation at 53—54 °C/17 Torr gave **8** (3.8 g, 78% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ=1.06—1.38 (m, 9 H), 3.20 (q, *J*=7.5 Hz, 2H), 3.70—4.27 (m, 1H), 4.71 and 4.81 (2q, *J*=5.3 Hz, totally 1H), 9.59 and 9.64 (2d, *J*=3.0 and 1.5 Hz respectively, totally 1H); IR (neat) 1735 cm^{-1}. $[\alpha]_D^{23}$ −56.9° (*c* 6.31, $CHCl_3$). The aldehyde was immediately used for the next transformation.

(3*S*)-3-(1-Ethoxyethoxy)-2-hydroxybutanenitrile (9). A mixture of **8** (2.2 g, 15 mmol), acetone cyanohydrin (bp 53—55 °C/8 Torr, 1.53 g, 1.64 ml, 18 mmol) and triethylamine (21 μl, 15 mg) was stirred in an ice bath for 1 h. TLC assay revealed the starting material **8** was all consumed. Evaporation of excess acetone cyanohydrin and triethylamine followed by brief column chromatography (Wacogel C-100, hexane-ethyl acetate 3 : 1 to 1 : 1) gave **9** (2.6 g, quantitative yield) as a viscous oil. ^{1}H NMR ($CDCl_3$) δ=1.10—1.40 (m, 9H), 3.36—4.14 (m, 3H), 4.25 and 4.28 (2d, *J*=1.5 and 4.5 Hz, respectively, totally 1H), 4.60—6.00 (m, 1H); IR (neat) 3425, 3000, 2950, 2250, 1450, 1395, 1340, 1130, 1070, 970, 940, 855, 810 cm^{-1}. The cyanohydrin was directly used for the next reaction.

(2*S*,3*S*)-2,3-(Cyclohexylidenedioxy)butanenitrile (10) and (2*R*,3*S*)-2,3-(Cyclohexylidenedioxy)butanenitrile (11). In a 100-ml flask were placed successively activated Molecular Sieve 4A (ca. 5 g), a dichloromethane (20 ml) solution of **9** (2.55 g, 14.7 mmol), a dichloromethane (20 ml) solution of 1,1-dimethoxycyclohexane (2.39 g, 16.5 mmol). The mixture was cooled to 0 °C and a 1 M dichloromethane solution of bis(trimethylsilyl) sulfate (0.45 ml, 0.45 mmol) was added and the resulting mixture was stirred at 0 °C for 10 min and at room temperature for 30 min. The reaction mixture was neutralized with pyridine (0.1 ml), and the insoluble material was filtered off. Concentration and purification by column chromatography (Kieselgel 60, hexane–ethyl acetate 10 : 1 to 6 : 1) afforded 10 (0.69 g, R_f=0.67, hexane–ethyl acetate 3 : 1, 28% yield) and **11** (1.05 g, R_f=0.55 (vide supra), 40% yield).

Physical properties of **10** are as follows. Bp 60—61 °C/0.25 Torr; ^{1}H NMR (CCl_4) δ=1.38 (d, J=6.0 Hz, 3H), 1.50—1.80 (m, 10H), 4.02 (d, J=7.5 Hz, 1H), 4.36 (quintet, J=6.0 Hz, 1H); IR (neat) 2950, 2870, 2250, 1450, 1370, 1285, 1160, 1120, 1065, 930, 910 cm^{-1}; MS m/z (rel intensity) 181 (M^+, 9), 152 (11), 138 (100), 55 (29), 41 (15); $[\alpha]_D^{24}$ +15.5° (c 8.84, $CHCl_3$). Found: C, 66.38; H, 8.39; N, 7.57%. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73%.

Physical properties of **11** are following. Bp 73—75 °C/0.25 Torr; ^{1}H NMR (CCl_4) δ=1.45, (d, J=6.0 Hz, 3H), 1.30—1.80 (m, 10H), 4.21 (quintet, J=6.0 Hz, 1H), 4.58 (d, J=5.3 Hz, 1H); IR (neat) 2950, 2875, 2250, 1450, 1370, 1285, 1240, 1170, 1120, 1080, 920 cm^{-1}. MS m/z (rel intensity) 181 (M^+, 9), 152 (12), 138 (100), 84 (10), 55 (31), 42 (10), 41 (15); $[\alpha]_D^{26}$ +26.4° (c 5.57, $CHCl_3$). Found: C, 66.40; H, 8.44; N, 8.09%. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73%. The optical purity of **11** was checked by ^{1}H NMR with a chiral shift reagent $Eu(tfc)_3$ (1.2 mol eq) in dry CCl_4 solution. Under these conditions the doublet methine proton of (±)-**11** splitted into base-line resolved two doublets. The sample of **11** prepared as above gave only one doublet at higher field and the other doublet was not detected even after 5 times enlargement. The sample of **10** also was subjected to the chirality check, and similar results were obtained. Thus, the optical purity of **11** as well as **10** was estimated to be more than 95%.

(2*S*,3*S*)-2,3-(Cyclohexylidenedioxy)-1-butanol (14). An ethereal (20 ml) solution of dimethyl (2*R*,3*R*)-2,3-(cyclohexylidenedioxy)butanedioate[23] (5.16 g, 20 mmol) was added to an ethereal (20 ml) solution of lithium aluminium hydride (2.0 g) at 0 °C. After the addition was completed, the reaction mixture was heated to reflux for 1 h, and the excess hydride was quenched by addition of saturated aqueous solution of sodium sulfate under cooling. The reaction mixture was further dried by addition of anhydrous magnesium sulfate under vigorous stirring. Filtration through a pad of Hyflo-supercell followed by concentration gave a crude oil of (2*S*,3*S*)-2,3-(cyclohexylidenedioxy)-1,4-butanediol (2.78 g, 69% yield). Mp 52—54 °C; ^{1}H NMR ($CDCl_3$) δ=1.4—1.8 (m, 10H), 2.90 (t, J=6 Hz, 2H), 3.68—4.03 (m, 6H); IR (KBr) 3400, 2940, 1450, 1160, 1120, 1040 cm^{-1}.

The diol (13.7 mmol) was dissolved in dichloromethane (10 ml) and triethylamine (3 ml, 21.4 mmol). To the solution was added at 0 °C *p*-toluenesulfonyl chloride (2.86 g, 15 mmol) dissolved in dichloromethane (15 ml) drop by drop over a period of 3 h with the aid of a syringe drive. Stirring was continued at 0 °C for 1 h and at room temperature for 1 h. Concentration under reduced pressure, trituration of the resulting solid with diethyl ether, filtration, concentration of the ethereal filtrate, followed by purification by column chromatography (Wacogel C-100, hexane–ethyl acetate 2 : 1), afforded a ditosylate (2.13 g, 30% yield). Further elution with hexane–ethyl acetate (1 : 1) gave a monotosylate (2.13 g, 44% yield, 70% yield based on the consumed diol). Elution with ethyl acetate and methanol afforded a recovered diol (0.96 g). The monotosylate exhibited ^{1}H NMR ($CDCl_3$) δ=1.2—1.7 (m, 10H), 2.10 (s, 1H), 2.43 (s, 3H), 3.5—3.8 (m, 2H), 3.8—4.2 (m, 4H), 7.33 (d, J=8 Hz, 2H), 7.88 (d, J=8 Hz, 2H); IR (neat) 3500, 2940, 1740, 1600, 1360, 1180, 810 cm^{-1}.

The monotosylate (2.05 g, 5.7 mmol) was dissolved in DMSO (5 ml). To this solution was added sodium borohydride (0.68 g, 18 mmol) and the reaction mixture was heated at 80 °C for 2 h. At the initial stage, foaming of the reaction mixture was observed which ceased at the end of the reaction time. The reaction mixture was diluted with dichloromethane and the excess hydride was carefully quenched with brine. Dichloromethane extraction followed by usual workup and purification by column chromatography (Wacogel C-100, hexane–ethyl acetate 3 : 1, R_f=0.27) gave **14** (0.94 g, 88% yield). ^{1}H NMR (CCl_4) δ=1.23 (d, J=6 Hz, 3H), 1.3—2.0 (m, 10H), 2.25 (br s, 1H), 3.3—3.7 (m, 3H), 3.88 (dq, J=8 and 6 Hz, 1H); IR (neat) 3450, 2940, 1440, 1360, 1160, 1100, 940 cm^{-1}.

(2*R*,3*S*)-2,3-(Cyclohexylidenedioxy)butanal (15). A dichloromethane (1 ml) solution of DMSO (0.34 ml, 4.8 mmol) was added to a dichloromethane (4 ml) solution of oxalyl dichloride (0.195 ml, 2.2 mmol) at −78 °C over a period of ca. 5 min, and the resulting solution was stirred at −78 °C for 10 min before the addition of a dichloromethane (2 ml) solution of **14** (0.375 g, 2.0 mmol) at −78 °C. After 15 min, triethylamine (1.4 ml) was added at −78 °C, and stirring was continued for 10 min. The reaction mixture was then warmed to room temperature, treated with water (ca. 6 ml), and vigorously stirred for 10 min. Separation of the organic layer, extraction of the aqueous layer with dichloromethane, drying the combined dichloromethane extract with anhydrous sodium sulfate, followed by concentration and purification by column chromatography (Wacogel C-100, CH_2Cl_2), afforded **15** (0.32 g, 87% yield). ^{1}H NMR (CCl_4) δ=1.33 (d, J=6.0 Hz, 3H), 1.4—2.0 (m, 10 H), 3.67 (dd, J=7.8 and 2.7 Hz, 1H), 4.00 (dq, J=7.8 and 6.0 Hz, 1H), 9.62 (d, J=2.7 Hz, 1H); IR (neat) 3450, 2940, 1740, 1370, 1100 cm^{-1}.

(2*S*,3*S*)-2,3-(Cyclohexylidenedioxy)butanenitrile (10). A mixture of **15** (0.29 g, 1.58 mmol), hydroxylamine hydrochloride (0.30 g, 4.3 mmol), ethanol (2 ml) and pyridine (2 ml) was heated at 80 °C for 2 h. Concentration followed by short column chromatography (Wacogel C-100, CH_2Cl_2) gave the oxime (0.32 g, quantitative yield) which exhibited ^{1}H NMR ($CDCl_3$) absorptions at δ=1.30 (d) and 1.43 (d) along with absorptions ascribed to aldoxime methine hydrogen at δ=6.80, 7.36, 7.68, and 8.60. Thus, syn-anti isomers as well as their conformational ones seem to coexist.

The oxime (40 mg, 0.20 mmol) dissolved in dichloroethane (1 ml) was heated in the presence of triphenylphosphine (80 mg, 0.30 mmol), triethylamine (42 µl, 0.3 mmol) and carbon tetrachloride (29 µl, 0.3 mmol) at 80 °C for 2 h. The reaction mixture was passed through an 8 cm column of Wacogel C-100 (CH_2Cl_2 elution) to give **10** (30 mg, 83% yield). Bp 150 °C/10 Torr.

***t*-Butyl (4*S*,5*S*,2*Z*)-3-Amino-4,5-(cyclohexylidenedioxy)-2-hexenoate (16).** The magnesium enolate of *t*-butyl acetate (0.42 ml, 3.3 mmol) was prepared as before using ethylmagnesium bromide (2.0 M ethereal solution, 3.3 ml, 6.6 mmol), diethyl ether (9.6 ml), diisopropylamine (1.96 ml, 14 mmol) at 0 °C. To this enolate solution was added an ethereal solution (3.0 ml) of **10** (0.30 g, 1.66 mmol) at 0 °C over a period of 5 min, and the mixture was stirred at 0 °C for 4 h. Workup gave a colorless solid **16** (0.49 g, 99% yield) which was homogeneous by silica gel TLC assay (R_f=0.70 (hexane–ethyl acetate 3 : 1)). Mp 102—103 °C (hexane). ^{1}H NMR ($CDCl_3$) δ=1.35 (d, J=5.3 Hz, 3H), 1.48 (s, 9H), 1.50—1.77 (m, 10H), 3.77—4.10 (m, 2H), 4.43 (s, 1H), 6.40 (br, 2H); IR (KBr) 3510, 3470, 3370, 3350, 2980, 2950, 1670, 1630, 1610, 1555, 1445, 1365, 1285, 1255, 1140, 1110, 1060, 1000, 935, 790 cm^{-1}; MS *m/z* (rel intensity) 297 (M^+, 6), 241 (22), 198 (85), 180 (19), 154 (15), 144 (16), 143 (56), 127 (13), 126 (100), 125 (15), 99 (13), 98 (12), 81 (13), 57 (34), 55 (24), 41 (38); $[\alpha]_D^{26}$ −62.5° (*c* 5.19, CHCl$_3$). Found: C, 64.57; H, 9.04; N, 4.63%. Calcd for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15; N, 4.71%.

***t*-Butyl (4*S*,5*S*,2*Z*)-3-Acetamido-4,5-(cyclohexylidenedioxy)-2-hexenoate (17).** A mixture of **16** (0.45 g), pyridine (4 ml) and acetic anhydride (4.0 ml) was heated at 50 °C for 6.5 d. Concentration in vacuo followed by preparative TLC (hexane-ethyl acetate 3 : 1) gave **17** (R_f=0.62, 0.31 g, 59% yield) along with its (E)-isomer (R_f=0.53, 97 mg, 19% yield) both as viscous oil. The compound **17** exhibited ^{1}H NMR (CDCl$_3$) δ=1.42 (d, *J*=6.0 Hz, 3H), 1.50 (s, 9H), 1.60—1.85 (m, 10H), 2.13 (s, 3H), 3.99 (quintet, *J*=6.0 Hz, 1H), 5.62 (s, 1H), 5.65 (d, *J*=6.0 Hz, 1H), 11.12 (br s, 1H, NH); IR (neat) 3450, 3250, 3000, 2950, 2880, 1720, 1635, 1490, 1450, 1370, 1250, 1150 cm^{-1}. The (E) isomer gave ^{1}H NMR (CDCl$_3$) δ= 1.37 (d, *J*=6.0 Hz, 3H), 1.47 (s, 9H), 1.60—1.80 (m, 10H), 2.08 (s, 3H), 3.80 (dq, *J*=8.3 and 6.0 Hz, 1H), 5.65 (d, *J*=8.3 Hz, 1H), 6.93 (br s, 1H), 7.87 (br s, 1H, NH).

***t*-Butyl (3*S*,4*S*,5*S*)-3-Acetamido-4,5-(cyclohexylidenedioxy)-hexanoate (18).** In an autoclave were placed **17** (34 mg, 0.1 mmol), ethyl acetate (2 ml) and platinum oxide (34 mg), and the atmosphere was replaced by hydrogen of 55 kg cm^{-2}. The autoclave was agitated at 70 °C for 24 h. Filtration of the catalyst through a Celite pad, concentration, followed by preparative TLC (hexane-ethyl acetate 1 : 1) afforded **18** (R_f=0.33, 28 mg, 82% yield) as a viscous oil. ^{1}H NMR (CDCl$_3$) δ=1.27 (d, *J*=6.0 Hz, 3H), 1.47 (s, 9H), 1.50—1.70 (m, 10H), 1.97 (s, 3H), 2.57 (dd, *J*=4.5 and 3.0 Hz, 2H), 3.55 (t, *J*=7.5 Hz, 1H), 3.75—4.10 (m, 1H), 4.15—4.50 (m, 1H), 6.40 (br d, *J*=7.5 Hz, 1H, NH); IR (neat) 3400 (br), 3100 (br), 2950, 1735, 1660, 1550, 1450, 1370, 1160, 1110, 950, 850 cm^{-1}; MS *m/z* (rel intensity) 341 (M^+, 16), 285 (18), 243 (18), 242 (100), 170 (61), 155 (37), 144 (31), 128 (35), 111 (27), 88 (23), 81 (20), 57 (35), 55 (24), 43 (40); $[\alpha]_D^{20}$ −4.8° (*c* 1.47, CHCl$_3$). Found: *m/z* 341.2186. Calcd for $C_{18}H_{31}NO_5$: M^+ 341.2200.

(3*R*)-Isomer (5 mg, 15% yield, R_f=0.60) also was isolated and showed ^{1}H NMR (CDCl$_3$) δ=1.30 (d, *J*=6.0 Hz, 3H), 1.45 (s, 9H), 1.50—1.70 (m, 10H), 1.97 (s, 3H), 2.50 (d, *J*=6.8 Hz, 2H), 3.40—3.85 (m, 1H), 6.0 (br d, *J*=10.5 Hz, 1H, NH).

(3*S*,4*S*,5*S*)-3-Benzamido-4-hydroxy-5-hexanolide (19). A mixture of the *t*-butyl ester **18** (73 mg, 0.22 mmol) and 2 M hydrochloric acid (3 ml) was heated to reflux for 5 h. Excess acid and volatile material were evaporated, and the residue was dissolved in saturated aqueous sodium hydrogencarbonate solution (7.5 ml) and acetone (2.6 ml). To the resulting solution was added benzoyl chloride (0.2 ml) at 0 °C. The mixture was stirred at room temperature for 2.5 h, then acidified with 2 M hydrochloric acid to pH 1, stirred for 20 min at room temperature and extracted with ethyl acetate. Workup and preparative TLC purification gave the desired lactone **19** (50 mg, 93% yield). Mp 138—140 °C (lit,[28b)] 125—127 °C); R_f=0.06 (hexane-ethyl acetate 1 : 1); IR (Nujol) 3500, 3350, 1745, 1740, 1640, 1530, 1460, 1380, 1035 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=1.14 (d, *J*=6.2 Hz, 3 H), 2.54 (AB dd, *J*=18.0 and 4.0 Hz, 1H), 2.94 (AB dd, *J*=18.0 and 9.0 Hz, 1H), 3.91 (m, 1H), 4.30 (t, *J*=3.0 Hz, 1H), 4.63 (m, 1H), 5.10 (d, *J*=5.1 Hz, 1H, OH), 7.40—7.65 (m, 3H), 7.82—8.02 (m, 2H), 8.92 (br d, *J*=7.0 Hz, 1H, NH); ^{13}C NMR (DMSO-d_6) δ=19.3 (C-6), 34.5 (C-2), 48.3 (C-3), 66.5 (C-5), 88.9 (C-4), 127.2, 128.2, 131.3, 133.7 (aromatic), 166.1 (NHCO), 175.7 (lactone C=O); $[\alpha]_D^{20}$ −20.5° (*c* 0.39, ethanol); lit,[28b)] $[\alpha]_D^{20}$ −15.8° (*c* 1, ethanol). Found: *m/z* 249.1024. Calcd for $C_{13}H_{15}NO_4$: M^+ 249.1000.

At the early stage of the lactonization, 1,4-lactone (**20**) was produced and isolated. The physical properties of **20** is as follows. R_f=0.13 (hexane-ethyl acetate 1 : 1); ^{1}H NMR (CDCl$_3$) δ=1.34 (d, *J*=6.2 Hz, 3H), 2.32 (br, 1H, OH), 2.60 (AB dd, *J*=18.0 and 4.0 Hz, 1H), 3.17 (AB dd, *J*=18.0 and 9.0 Hz, 1H), 4.16 (m, 1H), 4.41 (t, *J*=3.0 Hz, 1H), 4.85 (m, 1H), 6.89 (br d, *J*=7.0 Hz, 1H, NH), 7.45—7.62 (m, 3H), 7.76—7.92 (m, 2H). IR (CHCl$_3$) 3460, 3350, 2950, 1780, 1660, 1515, 1290, 1200, 1180, 1160, 990 cm^{-1}; $[\alpha]_D^{20}$ −10.6° (*c* 0.64, EtOH).

***N*-Benzoyl-L-daunosamine (4b).** A 1 M hexane solution of diisobutylaluminium hydride (0.07 ml, 5 mol equiv) was added to a THF (1.0 ml) solution of **19** (3.4 mg, 0.014 mmol) at −60 °C, and the resulting solution was stirred at −60 to −50 °C for 1.5 h before the addition of a 1 : 1 mixture (2 ml) of methanol and acetone. Warming up to room temperature, filtration through a Celite pad, concentration and purification by column chromatography (ethyl acetate) gave *N*-benzoyl-L-daunosamine (3.2 mg, 94% yield). Mp 153—155 °C (ether) (lit,[31)] 152 °C); $[\alpha]_D^{20}$ −109° (*c* 0.08, EtOH) (lit,[31)] −108° (*c* 0.5, EtOH)); ^{1}H NMR (DMSO-d_6) δ=1.10 and 1.15 (each d, *J*=6 Hz, 3H, Me of α,β-isomers), 1.35—2.16 (m, 2H, C(2)-H_2 of α,β-isomers), 3.14—4.90 (C(3-5)-H of α,β-isomers and C(1)-H of β-isomer, totally 7H), 5.18 (br m, 1H, C(1)-*H* of α-isomer), 6.18 (br d, *J*=3.8 Hz, 1H, OH of α-isomer), 6.50 (br d, *J*=6.3 Hz, 1H, OH of α-isomer), 7.38—7.66 (m, 3H, aromatic), 7.80—8.10 (m, aromatic and NH, 3H): ^{13}C NMR (DMSO-d_6) δ=17.1 (C-6), 30.2 (C-2 of α-isomer), 32.9 (C-2 of β-isomer), 45.6 (C-3 of α-isomer), 49.5 (C-3 of β-isomer), 65.4 C-5 of α-isomer), 66.8 (C-4 of β-isomer), 68.1 (C-4 of α-isomer), 70.8 (C-5 of β-isomer), 90.2 (C-1 of α-isomer), 94.1 (C-1 of β-isomer), 127.2, 128.0, 130.9, 134.6 (aromatic) and 165.5 (CONH), all consistent with the literature values.[28a)]

***t*-Butyl (4*R*,5*S*,2*Z*)-3-Amino-4,5-(cyclohexylidenedioxy)-2-hexenoate (21).** The nitrile **11** (1.40 g, 7.7 mmol) in diethyl ether (20 ml) was allowed to react at 0 °C for 3.5 h with the magnesium enolate of *t*-butyl acetate, which was prepared from ethylmagnesium bromide (31 mmol), diisopropylamine (8.7 ml, 62 mmol) and diethyl ether (40 ml) at 0 °C. Workup followed by distillation afforded **21** (1.23 g, 54% yield). Bp 112—113 °C/0.3 Torr; ^{1}H NMR (CDCl$_3$) δ=1.21 (d, *J*=6.0 Hz, 3H), 1.30—1.90 (m, 10H), 1.48 (s, 9H), 4.30—4.60 (m, 3H), 6.50 (br, 2H, NH$_2$); IR (neat) 3525, 3350, 1670, 1620, 1050 cm^{-1}; MS *m/z* (rel intensity) 297 (M^+, 8), 241 (28), 199 (14), 198 (93), 197 (28), 180 (30), 154 (26), 144 (20), 143 (72), 127 (14), 126 (100), 125 (29), 99 (24), 98 (15), 81 (19), 69 (14), 57 (44), 55 (33), 41 (41); $[\alpha]_D^{26}$ −7.40° (*c* 3.59, CHCl$_3$). Found: *m/z* 297.1937. Calcd for $C_{16}H_{27}NO_4$: M^+ 297.1938.

***t*-Butyl (4*R*,5*S*,2*Z*)-3-Acetamido-4,5-(cyclohexylidenedioxy)-2-hexenoate (22).** A mixture of **21** (0.143 g, 0.48 mmol), acetic anhydride (1 ml) and pyridine (1 ml) was heated at 50 to 60 °C for 2 d. Concentration followed by preparative TLC (silica gel, hexane-ethyl acetate 3 : 1) gave **22** (R_f=0.47, 0.125 g, 77% yield) along with its (E) isomer (R_f=0.37, 33 mg, 20% yield) both as viscous oil.

The spectral data of **22** are as follows. ^{1}H NMR (CDCl$_3$) δ=1.10 (d, *J*=6.0 Hz, 3H), 1.30—1.80 (m, 10H), 1.50 (s, 9H), 2.14 (s, 3H), 4.73 (quintet, *J*=6.0 Hz, 1H), 5.55 (d, *J*=1.0 Hz, 1H), 5.74 (dd, *J*=6.0 and 1.0 Hz, 1H), 11.34 (br, 1H, NH); IR (neat) 3525, 3250, 3000, 2950, 2875, 1720, 1670, 1635, 1490, 1450, 1370, 1320, 1250, 1150, 1115 cm^{-1}; MS *m/z* (rel intensity) 339 (M$^+$, 2) 283 (21), 241 (14), 240 (28), 185 (74), 168 (32), 167 (21), 151 (13), 150 (100), 143 (21), 142 (21), 141 (27), 126 (20), 125 (48), 124 (13), 123 (35), 99 (10), 98 (11), 97 (11), 81 (14), 69 (13), 57 (33), 55 (33), 43 (58), 41 (40). Found: *m/z* 339.2012. Calcd for $C_{18}H_{29}NO_5$: M$^+$ 339.2043. $[\alpha]_D^{20}$ −131.7° (*c* 2.26, $CHCl_3$). Spectral data of the (E) isomer of **22** are following. ^{1}H NMR ($CDCl_3$) δ=1.05 (d, *J*=6.0 Hz, 3H), 1.43 (s, 9H), 1.60—1.80 (m, 10H), 2.03 (s, 3H), 4.63 (quintet, *J*=6.0 Hz, 1H), 5.62 (br d, *J*=7.5 Hz, 1H), 6.77 (br s, 1H), 7.82 (br s, 1H, NH); IR (neat) 3420, 1720, 1700, 1635, 1500, 1370, 1235, 1135, 1110 cm^{-1}.

***t*-Butyl (3*S*,4*R*,5*S*)-3-Acetamido-4,5-(cyclohexylidenedioxy)-hexanoate (23).** In an autoclave were placed **22** (0.57 g, 1.67 mmol), THF (10 ml) and 5% rhodium on carbon (0.64 g) and the atmosphere was replaced by hydrogen of 70 kg cm^{-2}. The reaction mixture was heated at 55 °C for 24 h. Filtration, concentration and preparative TLC (hexane-ethyl acetate 1 : 1) gave recovered **22** (26 mg, 5%) and the desired product **23** (0.48 g, 84% yield) as a viscous oil. R_f=0.19 (silica-gel TLC, hexane-ethyl acetate 3 : 1), >99.3% pure by GLC assay (Diasolid ZS, 2 m, 180 °C, R_t=10.7 min). ^{1}H NMR ($CDCl_3$) δ=1.25 (d, *J*=6.0 Hz, 3H), 1.47 (s, 9H), 1.50—1.80 (m, 10H), 1.95 (s, 3H), 2.48 (d, *J*=6.8 Hz, 2H), 4.10—4.50 (m, 3H), 5.93 (br d, *J*=7.5 Hz, 1H, NH); IR (neat) 3450, 3200, 1730, 1660, 1370, 1160, 1120, 1070 cm^{-1}; MS *m/z* (rel intensity) 341 (M$^+$, 15), 285 (17), 243 (16), 242 (100), 188 (18), 187 (16), 170 (63), 155 (62), 144 (14), 137 (10), 131 (26), 130 (21), 128 (24), 111 (19), 99 (13), 88 (30), 81 (19), 70 (12), 60 (16), 57 (38), 55 (25), 43 (42), 41 (31); $[\alpha]_D^{26}$ +21.2° (*c* 2.04, $CHCl_3$). Found: *m/z* 341.2232. Calcd for $C_{18}H_{31}NO_5$: M$^+$ 341.2201.

(3*S*,4*R*,5*S*)-3-Benzamido-4-hydroxy-5-hexanolide (24). A mixture of **23** (17 mg, 0.050 mmol) and 2 M hydrochloric acid (1.0 ml) was heated to reflux for 12 h. Concentration in vacuo gave a solid which was treated with saturated sodium hydrogencarbonate (0.5 ml), acetone (0.1 ml) and benzoyl chloride (15 μl) at room temperature for 4 h. Then, the reaction mixture was acidified with 2 M hydrochloric acid to pH 1, diluted with brine (2 ml) and extracted with ethyl acetate (30 ml×3 times). The combined extract was dried over sodium sulfate, concentrated, and the residue was chromatographed to give **24** (9.1 mg, 73% yield). Mp 188 °C (MeOH) (lit,[28b)] 190 °C); R_f=0.25 (silica-gel TLC, hexane-ethyl acetate 1 : 2); ^{1}H NMR (acetone-d_6) δ=1.42 (d, *J*=6.2 Hz, 3H), 2.67 (AB dd, *J*=17.5 and 7.5 Hz, 1H), 3.17 (AB dd, *J*=17.5 and 7.5 Hz, 1H), 3.71 (dt, *J*=8.5 and 4.5 Hz, 1H), 4.33 (dq, *J*=8.5 and 6.0 Hz, 1H), 4.44 (m, 1H), 4.98 (d, *J*=4.5 Hz, 1H, OH), 7.30—7.60 (m, 3H), 7.70 (br m, 1H, NH), 7.85—8.05 (m, 2H); IR (Nujol) 3550—3200, 1735, 1720, 1640 cm^{-1}; MS *m/z* (rel intensity) 249 (M$^+$, 2), 231 (2), 192 (6), 144 (7), 122 (14), 105 (100), 77 (31), 51 (6). $[\alpha]_D^{20}$ +11.5° (*c* 0.80, EtOH) (lit,[28b)] +11.5° (*c* 1.1, EtOH)). Found: *m/z* 249.1035. Calcd for $C_{13}H_{15}NO_4$: M$^+$ 249.1000.

***N*-Benzoyl-L-acosamine (5b).** A 1.0 M hexane solution (0.11 ml) of diisobutylaluminium hydride (0.11 mmol) was added to a THF (1 ml) solution of **24** (5.4 mg, 0.022 mmol) at −60 °C, and the reaction mixture was stirred at −50 to −60 °C for 1.5 h before quenching with a 1 : 1 mixture (3 ml) of methanol and acetone. Warming to room temperature, filtration through a Celite pad and finally purification by preparative TLC (ethyl acetate) gave *N*-benzoyl-L-acosamine (**5b**) (5.3 mg, 98% yield). R_f=0.38 (silica-gel TLC, AcOEt); mp 218—220 °C (Et_2O); $[\alpha]_D^{20}$ −18.6° (*c* 0.30, EtOH, 3 h); ^{1}H NMR (DMSO-d_6) for α-isomer: δ=1.15 (C(6)-H), 4.85 (C(4)-OH), 5.12 (C(1)-H), 6.13 (C(1)-OH), 8.10 (NH) and for β-isomer: δ=1.20 (C(6)-H), 4.70 (C(1)-*H*), 4.85 (C(4)-O*H*), 6.49 (C(1)-O*H*), 8.22 (NH). ^{13}C NMR (DMSO-d_6) for α-isomer: δ=18.2 (C-6), 36.9 (C-2), 48.2 (C-3), 67.6 (C-5), 74.1 (C-4), 89.7 (C-1), and for β-isomer: δ=18.2 (C-6), 51.5 (C-3), 72.8 (C-5), 73.5 (C-4), 93.5 (C-1), and 127.2, 127.9, 130.8, 134.9 (aromatic), 166.0 (CONH). These data are fully consistent with the literature values.[28a)]

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