Anal. Calcd for $C_{16}H_{26}N_2O_4Si$: C, 56.73; H, 7.74; N, 8.27. Found: C, 56.69; H, 7.82; N, 8.23.

Method B. From 2′,3′-*O*-Thionocarbonate 40b. A solution of **40b** (55 mg, 0.15 mmol) and 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (0.4 mL) in THF (2 mL) was stirred for 24 h. The solvent was removed under reduced pressure, and the residue was purified by chromatography using $CHCl_3$–MeOH (50:1) as the eluent to obtain 24 mg (52%) of **41b**.

2′,3′-Didehydro-2′,3′-dideoxyuridine (42). Compound **41a** (0.38 g, 1.17 mmol) was deprotected with a 1 M solution of tetra-*n*-butylammonium fluoride (1.5 mL, 1.5 mmol). The solvent was evaporated, and the residue was purified by chromatography on a silica gel column using $CHCl_3$–MeOH (20:1) to obtain 0.164 g (67%) of **42**: mp 153–155 °C (MeOH) (lit.[13] mp 155–156 °C); ^{13}C NMR (DMSO-d_6) δ 162.7 (C-4), 150.4 (C-2), 140.3 (C-6), 134.6, 125.2 (C-2′ and C-3′), 101.1 (C-5), 89.1 (C-1′), 87.0 (C-4′), 62.2 (C-5′).

2′,3′-Didehydro-2′,3′-dideoxy-5-methyluridine (5). A solution of **41b** (80 mg, 0.23 mmol) was converted to **5** by the procedure described above and purified by chromatography using $CHCl_3$–MeOH (30:1) as the eluent to obtain 41 mg (80%) of **5** as a colorless solid: mp 164 °C (lit.[6] mp 165–166 °C); ^1H NMR (DMSO-d_6) δ 1.90 (3 H, d, J = 1.17 Hz, 5-CH_3), 3.62 (2 H, dd, J = 3.52, 4.98 Hz, 5′-H), 4.75 (1 H, m, 4′-H), 4.95 (1 H, t, J = 4.98 Hz, 5′-OH, exchangeable), 5.85 (1 H, br d, J = 6.2 Hz, 2′-H), 6.40 (1 H, br d, J = 6.2 Hz, 3′-H), 6.80 (1 H, m, 1′-H), 7.62 (1 H, d, J = 1.17 Hz, 6-H), 11.25 (1 H, s, NH, exchangeable).

X-ray Crystallography. 2′,3′-Dideoxyadenosine (10). Crystals were obtained by slow evaporation of an aqueous acetone solution of 2′,3′-dideoxyadenosine (**10**). A crystal with approximate dimensions of 0.2 × 0.2 × 0.3 mm was used for the data collection on a Nicolet P3 diffractometer using Ni-filtered Cu Kα radiation (λ = 1.5418 Å). The crystal was cooled to 165 (2) K by means of a forced nitrogen stream. The space group is $P2_12_12_1$, and the cell dimensions are a = 9.959 (1) Å, b = 14.028 (1) Å, c = 7.666 (1) Å, V = 1070.95 Å^3, Z = 4, M_r = 235, D_{calcd} = 1.46 g cm^{-1}. Total data (876) with 4° < 2θ < 115° were measured. The structure was determined by direct methods, using the program MULTAN,[32] and refined by full-matrix least squares. All hydrogen atoms except the one bonded to the C-5′ atom were located in difference maps and refined. Final R values are R_w = 0.059, R_{unw} = 0.043 for the 873 observed data [$F > 3\sigma(F)$] and R_{all} = 0.043 for all 876 data. The final difference electron density map showed no features greater than 0.64 e Å^{-3}. Other programs used include data reduction program package DREAM.[33]

2′,3′-Didehydro-2′,3′-dideoxyadenosine (7). Crystals were obtained by slow evaporation of an acetone solution of **7**. The crystal used had approximate dimensions of 0.1 × 0.25 × 0.55 mm. The space group is $P2_12_12_1$, and the cell dimensions are a = 10.035 (2) Å, b = 13.866 (4) Å, c = 7.828 (2) Å, V = 1089.27 Å^3, Z = 4, M_r = 233, D_{calcd} = 1.42 g cm^{-1}. Data were measured at room temperature on an Enraf-Nonius CAD4 diffractometer, using Ni-filtered Cu Kα radiation. Unique data (1322) in the range 3.0° < 2θ < 154° were measured. The structure was determined by direct methods, using the program MULTAN,[32] and refined with full-matrix least squares. All non-hydrogen atoms were refined with anisotropic thermal parameters. All hydrogen atoms were located in difference maps and were refined. Final R values are R_w = 0.057, R_{unw} = 0.043 for the 1305 observed data [$F > 3\sigma(F)$] and R_{all} = 0.043 for all 1322 data. The final difference electron density map showed no features greater than 0.42 e Å^{-3}.

Acknowledgment. This research was supported by Grants AI26055, AI25899, and CA34769 from the National Institutes of Health, U.S. Public Health Service.

Supplementary Material Available: Anisotropic thermal parameters, hydrogen atom coordinates, bond lengths, and bond angles for 2′,3′-dideoxy- and 2′,3′-didehydro-2′,3′-dideoxyadenosine and ORTEP stereodiagram showing 2′,3′-dideoxy- and 2′,3′-didehydro-2′,3′-dideoxyadenosine superimposed by least-squares fitting of the atoms of the bases (6 pages). Ordering information is given on any current masthead page.

(32) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A: Cryst. Phys., Diffr., Theor. Gen. Crystallogr.* **1971**, *A27*, 368.
(33) Blessing, R. H. *Cryst. Rev.* **1987**, *1*, 3.

Asymmetric Total Synthesis of (+)-Negamycin and (−)-3-Epinegamycin via Enantioselective 1,3-Dipolar Cycloaddition

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Received September 22, 1988

Enantioselective total synthesis of (+)-negamycin [(+)-**1**] and (−)-3-epinegamycin [(−)-**2**] has been achieved by the introduction of asymmetry through 1,3-dipolar cycloaddition with chiral nitrones modified with carbohydrates. For the model study, the *trans*-isoxazolidine-3-carboxylate (±)-**6a**, obtained by 1,3-dipolar cycloaddition of the nitrone **4** with *N*-(benzyloxycarbonyl)allylamine (**5**), was converted into the hydrazide (±)-**13** via six steps, catalytic hydrogenation of which resulted in deprotection and N–O bond cleavage at the same time, affording (±)-negamycin [(±)-**1**]. This sequence was next applied to the synthesis of (+)-negamycin. Thus the enantioselective 1,3-dipolar cycloaddition of nitrones modified with carbohydrates, such as D- and L-gulose, D-ribose, and D-mannose derivatives, with **5** was investigated. Among these nitrones the gulosyl series proved to produce the best results. The trans adduct D-**19a** with 94% ee thus obtained by using *N*-D-gulosylnitrone D-**18** was converted into (+)-negamycin [(+)-**1**] by hydrolytic removal of the chiral auxiliary followed by a similar sequence for the synthesis of (±)-**1**. Similarly, the cis adduct D-**19b** with 94% ee obtained by cycloaddition with the D-gulosylnitrone D-**18** was transformed into (−)-**3**-epinegamycin [(−)-**2**]. With synthetic (+)-**1** and (−)-**2** in hand, antibacterial activity was examined.

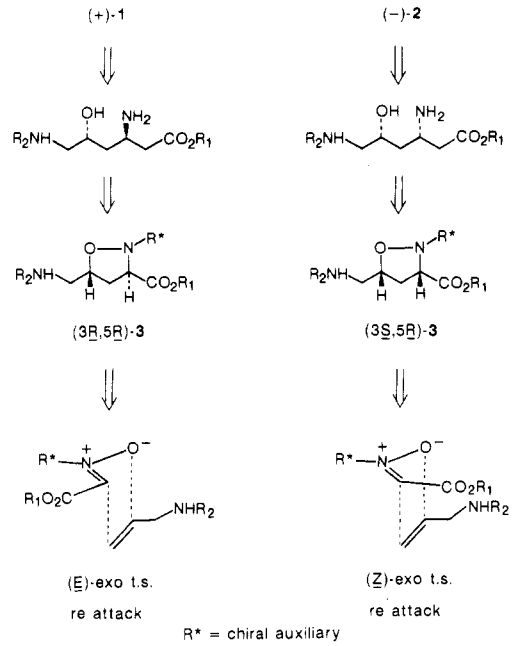
(+)-Negamycin is a rare and unusual peptidelike antibiotic containing a hydrazide moiety, first isolated in 1970 by Umezawa et al. from *Streptomyces purpeofuscus*[1] and characterized to be [2-[(3*R*,5*R*)-3,6-diamino-5-hydroxyhexanoyl]-1-methylhydrazino]acetic acid [(+)-**1**] in 1971.[2] (+)-Negamycin inhibits growth of Gram-negative and Gram-positive bacteria and is especially notable among antibiotics with regard to low toxicity and its activity

(1) Hamada, M.; Takeuchi, T.; Kondo, S.; Ikeda, Y.; Naganawa, H.; Maeda, K.; Okami, Y.; Umezawa, H. *J. Antibiot.* **1970**, *23*, 170.

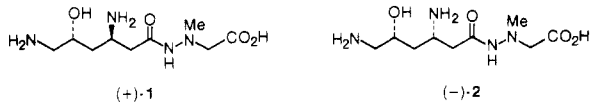
(2) Kondo, S.; Shibahara, S.; Takahashi, S.; Maeda, K.; Umezawa, H.; Ohno, M. *J. Am. Chem. Soc.* **1971**, *93*, 6305.

0022-3263/89/1954-2225$01.50/0

Scheme I

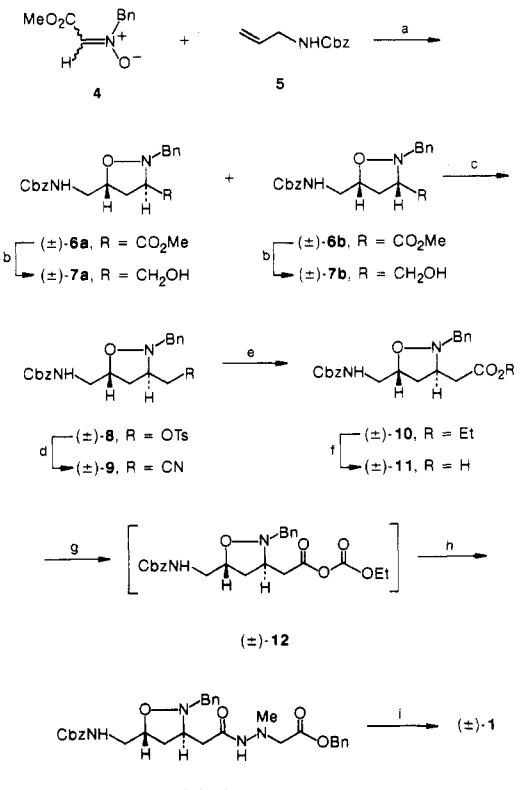


against Pseudomonas and multiple drug-resistant Gram-negative bacteria.[1] It has been shown to inhibit protein synthesis and to cause genetic miscording.[3-6] The significant antibiotic activity and the unique structural features of negamycin have stimulated considerable interest in the syntheses of this antibiotic in both racemic[7] and optically active[8] forms as well as its analogues[7a,9,10] and diastereomeric congeners such as epinegamycin in racemic form [(±)-2].[7a,c] For natural (+)-negamycin the published syntheses have relied on the methods utilizing chiral pools[8a,c] and an enzymatically derived chiral building block.[8b] In this paper, we present the full details of our total synthesis of (+)-negamycin as well as (−)-3-epinegamycin by the introduction of asymmetry through 1,3-dipolar cycloaddition with chiral nitrones.[11]



Our synthetic strategy is shown in Scheme I. The pivotal step in this approach is enantioselective 1,3-dipolar cycloaddition of a nitrone modified with an appropriate chiral auxiliary to allow approach to the *re* face of a prochiral olefin in an exo manner. In this manner with *E* and *Z* nitrones, two sets of new asymmetric centers adaptable to the 3*R*,5*R* and 3*S*,5*R* stereochemistry of (+)-1 and (−)-2, respectively, would be simultaneously created via the formation of *trans*- and *cis*-isoxazolidines **3**.

Scheme II[a]



[a] (a) Toluene, reflux; (b) $LiAlH_4$, Et_2O, 0 °C → room temperature; (c) TsCl, EtN(*i*-Pr)$_2$, CH_2Cl_2, 0 °C → room temperature; (d) NaCN, Me_2SO, 80 °C; (e) HCl, MeOH, room temperature; (f) 4% aqueous NaOH, MeOH, room temperature; (g) EtOCOCl, Et_3N, toluene, 0 °C; (h) $H_2NN(Me)CO_2Bn$, toluene, 0 °C → room temperature; (i) H_2 (3 atm), 10% Pd–C, MeOH–10% aqueous AcOH.

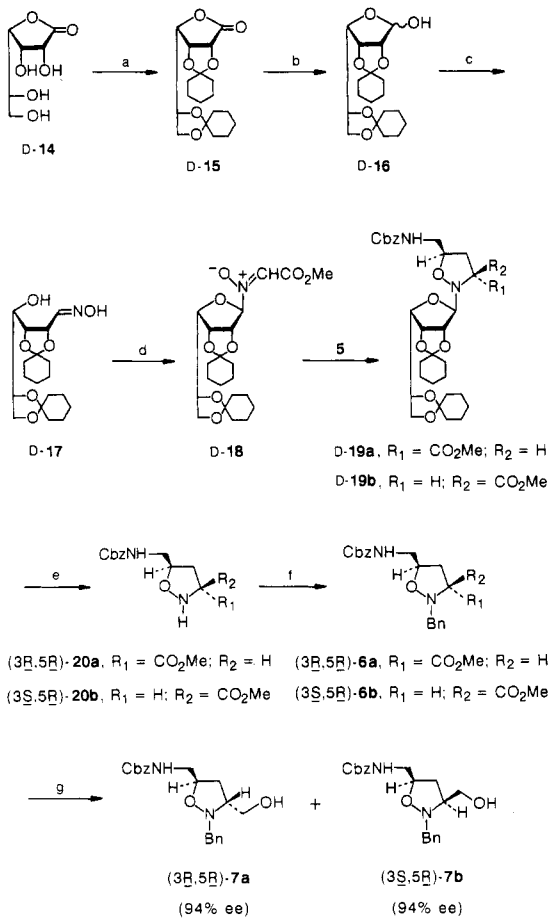
Results and Discussion

(1) Synthesis of (±)-Negamycin. In order to evaluate the retrosynthesis approach as outlined in Scheme I, we initially undertook as a model experiment the synthesis of racemic negamycin [(±)-1] by using the achiral nitrone (Scheme II). Thus nitrone **4** (5:3 *E*/*Z* equilibrium mixture), generated by condensation of methyl glyoxylate with *N*-benzylhydroxylamine, was subjected to cycloaddition with *N*-(benzyloxycarbonyl)allylamine (**5**) to give a 3:2 mixture of trans (from the *E* nitrone) and cis (from the *Z* nitrone) adducts [(±)-**6a** and (±)-**6b**]. Since it was difficult to separate preparatively, this mixture of the products was converted by $LiAlH_4$ reduction to the corresponding alcohols (±)-**7a** and (±)-**7b** separable by chromatography. The major crystalline isomer, the trans alcohol (±)-**7a**,[12] was subjected to tosylation followed by displacement (NaCN, Me_2SO) to produce the nitrile (±)-**9** in 57% overall yield from (±)-**7a**. The nitrile (±)-**9** was converted to the carboxylic acid (±)-**11** in 78% overall yield via ethanolysis by ethanolic hydrochloric acid and subsequent alkaline hydrolysis. Transformation to the hydrazide (±)-**13** was carried out by using the mixed anhydride method.[13] Thus, (±)-**11** was converted to the ethyl car-

(3) Mizuno, S.; Nitta, K.; Umezawa, H. *J. Antibiot.* **1970**, *23*, 581.
(4) Mizuno, S.; Nitta, K.; Umezawa, H. *J. Antibiot.* **1970**, *23*, 589.
(5) Uehara, Y.; Kondo, S.; Umezawa, H.; Suzukake, K.; Hori, M. *J. Antibiot.* **1972**, *25*, 685.
(6) Uehara, Y.; Hori, M.; Umezawa, H. *Biochim. Biophys. Acta* **1976**, *442*, 251.
(7) (a) Streicher, W.; Reinshagen, H.; Turnowsky, F. *J. Antibiot.* **1978**, *31*, 725. (b) Pierdet, A.; Nédélec, L.; Delaroff, V.; Allais, A. *Tetrahedron* **1980**, *36*, 1736. (c) Pasquet, G.; Boucherot, D.; Pilgrim, W.; Wright, B. *Tetrahedron Lett.* **1980**, *21*, 931.
(8) (a) Shibahara, S.; Kondo, S.; Maeda, K.; Umezawa, H.; Ohno, M. *J. Am. Chem. Soc.* **1972**, *94*, 4353. (b) Wang, Y.-F.; Izawa, T.; Kobayashi, S.; Ohno, M. *Ibid.* **1982**, *104*, 6465. (c) Tanner, D.; Somfai, P. *Tetrahedron Lett.* **1988**, *29*, 2373.
(9) Streicher, W.; Reinshagen, H. *Chem. Ber.* **1975**, *108*, 813.
(10) Kondo, S.; Iinuma, K.; Yoshida, K.; Yokose, K.; Ikeda, Y.; Shimazaki, M.; Umezawa, H. *J. Antibiot.* **1976**, *29*, 208.
(11) A preliminary account of some of this work has appeared in: Iida, H.; Kasahara, K.; Kibayashi, C. *J. Am. Chem. Soc.* **1986**, *108*, 4647.

(12) At this stage, it was not clear that the major isomer was the trans alcohol (±)-**7a** or cis alcohol (±)-**7b**, though in the ^1H NMR spectra some appreciable differences were observed between these isomers (see Experimental Section). Actually, it was verified to be the trans isomer (±)-**7a** by its transformation into the final product, which was identified as (±)-negamycin not (±)-epinegamycin.
(13) Vaughan, J. R., Jr.; Osato, R. L. *J. Am. Chem. Soc.* **1952**, *74*, 676.

Scheme III[a]



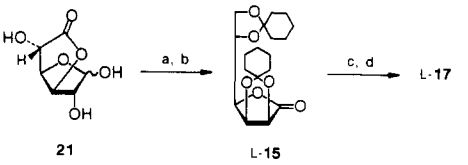
[a] (a) 1,1-Dimethoxycyclohexane TsOH, benzene, reflux; (b) DIBAL, toluene, −78 °C; (c) NH_2OH·HCl, pyridine, room temperature; (d) methyl glyoxylate, toluene, reflux; (e) 10% HCl, MeOH, 40 °C; (f) BnBr, K_2CO_3, DMF, 50 °C; (g) $LiAlH_4$, Et_2O, 0 °C → room temperature.

bonate (±)-**12**, which without isolation was coupled with benzyl (1-methylhydrazino)acetate to provide (±)-**13** in 67% yield. Catalytic hydrogenation (3 atm of H_2, Pd–C) of (±)-**13** resulted in deprotection and N–O bond cleavage at the same time; purification of the crude product on ion-exchange resin yielded racemic negamycin [(±)-**1**]. Spectral characteristics (^1H NMR) and TLC behavior of this product were identical with those of natural (+)-negamycin kindly provided by Professor M. Ohno.

(2) Enantioselective 1,3-Dipolar Cycloaddition. The next step in the project for preparing the target natural product required induction of asymmetry at the prochiral olefin to elaborate the two stereogenic centers with the proper absolute stereochemistry. Therefore, our efforts focused on enantioselective cycloaddition of a nitrone modified with an appropriate chiral auxiliary to the allylamine derivative **5**.

Of reported chiral inductor groups in asymmetric nitrone cycloaddition,[14,15] carbohydrate derivatives initially developed by Vasella[15] seem to be most attractive by virtue of availability and versatility. Accordingly, our objective was to develop efficient chiral *N*-glycosyl nitrones and to demonstrate acceptable diastereoselection during the cycloaddition.

Scheme IV[a]



[a] (a) Reference 17; (b) 1,1-dimethoxycyclohexane, TsOH, benzene, reflux; (c) DIBAL, toluene, −78 °C; (d) NH_2OH·HCl, pyridine, room temperature.

Treatment of D-gulonic γ-lactone (D-**14**) with 1,1-dimethoxycyclohexane followed by DIBAL reduction afforded 2,3:5,6-*O*-dicyclohexylidene-D-gulose (D-**16**) in 85% overall yield, which was then quantitatively converted to the oxime D-**17** as outlined in Scheme III. The nitrone D-**18**, generated in situ by condensation of D-**17** with methyl glyoxylate, was allowed to react with the allylamine derivative **5** in refluxing toluene to furnish a mixture of the trans (D-**19a**) and cis (D-**19b**) adducts in total yield of 84% yield. After removal of the D-gulosyl auxiliary by acid hydrolysis, the product was subjected to N-benzylation followed by $LiAlH_4$ reduction to provide the chromatographically separable trans [(3*R*,5*R*)-**7a**] and cis [(3*S*,5*R*)-**7b**] alcohols in a ratio of 1:2 (50% overall yield from D-**19a**/D-**19b**). Utilization of the D-gulosyl chiral template in this process was found to be very effective, both the trans and cis alcohols achieving the highly biased asymmetric induction of 94% ee according to analysis of the corresponding (+)-MTPA esters.[16]

Due to the above demonstrated capacity of the D-gulosyl auxiliary to create the chiral centers with high selectivity, the opposite enantiomeric chiral induction by the asymmetric nitrone cycloaddition was then investigated. In this regard, as an easily available and inexpensive enantiomeric chiral template the L-gulose oxime L-**17** was prepared from D-glucurono 6,3-lactone (**21**) according to Scheme IV. The L-gulonic γ-lactone derivative L-**15**, prepared from **21** by hydrogenation[17] and protection, was subjected to DIBAL reduction to give the L-gulose derivative L-**16**, which was converted to the oxime L-**17**. Cycloaddition with the L-gulosyl nitrone L-**18** and the following reactions were carried out in the same manner as described in Scheme III for the D-gulosyl series. The trans [(3*S*,5*S*)-**7a**] and cis [(3*R*,5*S*)-**7b**] alcohols were obtained in this way with high optical purity (93% and 92%, respectively) and were identical in all respects except the sign of optical rotation with the products previously prepared from the D-gulosyl nitrone D-**18**.

We next examined cycloaddition with the D-ribosyl nitrone **23** generated from the corresponding oxime **22**[18] as outlined in Scheme V. This reaction provided an unseparable mixture of the (3*R*,5*R*)-trans (**24a**) and (3*S*,5*R*)-cis (**24b**) adducts in total yield of 91%. Acidic hydrolysis of this mixture and subsequent $LiAlH_4$ reduction gave a mixture of **25a** and **25b**, which was converted via N-benzylation (benzyl bromide, K_2CO_3, DMF) to the trans

(14) For enantioselective cycloaddition with chiral nitrones, see: (a) Oppolzer, W.; Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 2755. (b) Belzecki, C.; Panfil, I. *J. Org. Chem.* **1979**, *44*, 1212. (c) Wovkulich, P. M.; Uskoković, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 3956. (d) Tice, C. M.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 5048. (e) Kametani, T.; Nagashima, T.; Honda, T. *Ibid.* **1985**, *60*, 426.

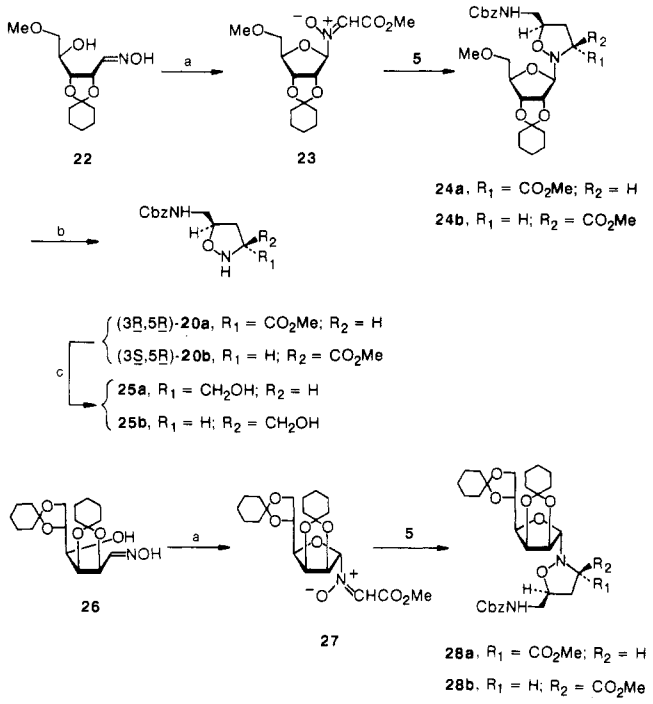
(15) (a) Vasella, A. *Helv. Chim. Acta* **1977**, *60*, 426. (b) Vasella, A. *Ibid.* **1977**, *60*, 1273. (c) Vasella, A.; Voeffray, R. *J. Chem. Soc., Chem. Commun.* **1981**, 97. (d) Vasella, A.; Voeffray, R. *Helv. Chim. Acta* **1982**, *65*, 1134. (e) Vasella, A.; Voeffray, R.; Pless, J.; Huguehin, R. *Ibid.* **1983**, *66*, 1241.

(16) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 3543.

(17) Ishidate, M.; Imai, Y.; Hirasaka, Y.; Umemoto, K. *Chem. Pharm. Bull.* **1965**, *13*, 173.

(18) Preparation of **22** from D-ribose is recorded in the supplementary material.

Scheme V[a]



[a] (a) Methyl glyoxylate, toluene, reflux; (b) 10% HCl, MeOH, 40 °C; (c) $LiAlH_4$, Et_2O, 0 °C → room temperature.

[(3*R*,5*R*)-**7a**] and cis [(3*S*,5*R*)-**7b**] alcohols in a ratio of 4:9 (total yield: 51% from **25a**/**25b**), after chromatographical separation. The enantiomeric excess of the product [(3*R*,5*R*)-**7a**] was determined to be 74% by analysis of the Mosher's (+)-MTPA ester.

On the other hand, cycloaddition with the D-mannosyl nitrone **27** generated from the oxime **26**[19] was carried out (Scheme V), and the cis isomer (3*R*,5*S*)-**7b** obtained by a sequence similar to that for the D-gulosyl series (Scheme III) was found to have 80% optical purity.

Thus, among the *N*-glycosyl nitrones (D-**18**, L-**18**, **23**, and **27**) employed, the gulosyl series proved to produce the best results.

Both trans and cis products obtained in these cycloadditions of sugar-modified nitrones with the nonconjugated olefin **5** as the dipolarophile must arise from (applying Diels–Alder terminology) the exo transition state since the endo transition state would be greatly restricted from unfavorable steric interactions between the CH_2NHCbz group in the incoming dipolarophile **5** and the furan ring oxygen atom of the furanose nitrone existing in *E*/*Z* equilibrium; the *E* isomer of the nitrone thus yields the trans adduct (D-**19a**, L-**19a**, **24a**, or **28a**), while the *Z* isomer yields the cis adduct (D-**19b**, L-**19b**, **24b**, or **28b**). The facial selectivity observed in these cases with the *E* and *Z* nitrones may be interpreted in terms of "O-endo" transition model (A) as shown in Figure 1 [representing the case of using the D-gulosyl (D-**18**) and D-ribosyl (**23**) nitrones] wherein, by analogy to recent reports,[20] the electron-donating group (secondary alkyl) rather than the polar group (alkoxy) is perpendicular to the plane of the nitrogen–carbon double bond to permit the maximum

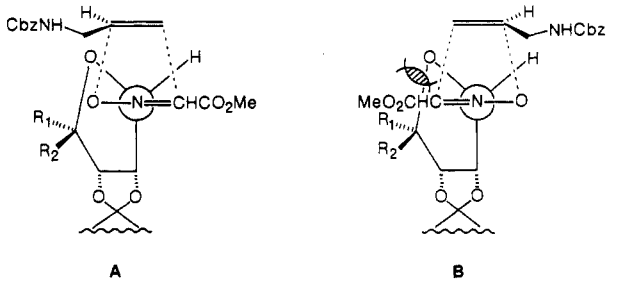


Figure 1.

orbital overlap of the participating centers, leading to the favored *re* face approach at the prochiral olefin; this gives rise to the adducts with the 5*R* configuration (D-**19a**/D-**19b** and **24a**/**24b**). An alternative "O-exo" transition state model[15b] (B) should be disfavored due to serious nonbonded interaction between the furan ring oxygen and the $CHCO_2Me$ group. Alternatively, the opposite enantiomeric chiral induction with nitrones L-**18** and **27** can be accounted for in terms of the *si* approach via the transition model enantiomeric to that illustrated as A in Figure 1; it results in the adducts with the 5*S* configuration (L-**19a**/L-**19b** and **28a**/**28b**). Although the proposed model A is tentative and speculative, it seems to predict consistently the direction of asymmetric induction.[21] A similar approach to a prochiral diene has been observed in pericyclic cycloaddition reaction of chiral sugars.[22]

(3) Synthesis of (+)-Negamycin. Introduction of the 3*R*,5*R* asymmetric centers required for (+)-negamycin was now accomplished via high level of enantioselective 1,3-dipolar cycloaddition by using the D-gulosyl nitrone D-**18**. The six-step synthesis of (+)-negamycin starting with the trans alcohol (3*R*,5*R*)-**7a** with high enantiomerical purity, derived from the D-gulosyl nitrone D-**18**, was executed by following in the exactly same manner described for (±)-negamycin (Scheme II). Tosylation of (3*R*,5*R*)-**7a** followed by substitution (NaCN, Me_2SO) gave the nitrile (3*S*,5*R*)-**9** in 72% overall yield, which was converted to the carboxylic acid (3*R*,5*R*)-**11** in 79% yield via ethanolysis followed by saponification. Condensation of (3*R*,5*R*)-**11** with benzyl (1-methylhydrazino)acetate was carried out by using the mixed anhydride method leading to the hydrazide (3*R*,5*R*)-**13** in 67% yield. Deprotection followed by purification by silica gel chromatography provided (+)-negamycin [(+)-**1**] in 75% yield. This material was found to be identical with natural negamycin in all respects.

The antibacterial activity of synthetic (+)-negamycin against a variety of bacteria has been proved to be almost the same as compared to that reported for naturally obtained negamycin[23] and also to be effective to *Pseudomonas aeruginosa* harboring multiple drug-resistant plasmid kR102.[24]

(4) Synthesis of (−)-3-Epinegamycin. Next we planned to apply this sequence to the synthesis of optically active 3-epinegamycin [(−)-**2**] by transformation of the cis alcohol (3*S*,5*R*)-**7b**. Compound (3*S*,5*R*)-**7b**, derived from the D-gulosyl nitrone D-**18**, was converted in five steps to

(19) Preparation of **26** from D-mannose is recorded in the supplementary material.

(20) (a) DeShong, P.; Leginus, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1686. (b) Jäger, V.; Schohe, R.; Paulus, E. F. *Tetrahedron Lett.* **1983**, *24*, 5501. (c) Houk, K. N.; Susan, R. M.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. *J. Am. Chem. Soc.* **1984**, *106*, 3880. (d) Houk, K. N.; Duh, H.-Y.; Wu, Y.-D.; Moses, S. R. *Ibid.* **1986**, *108*, 2754.

(21) Chirality induction in a similar manner has been interpreted in terms of kinetic anomeric effect.[15a]

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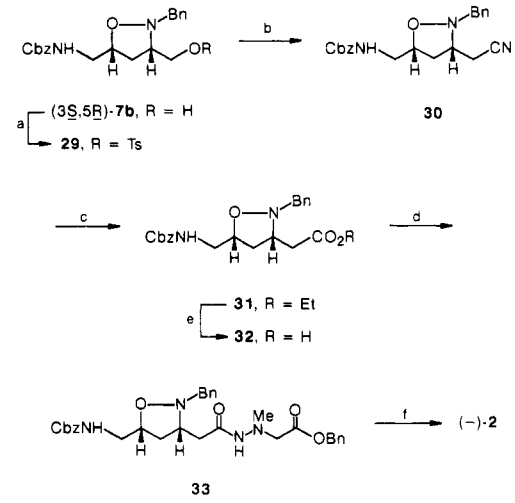
(24) For antibacterial activity of the synthetic material of (+)-negamycin in detail, see: Kono, M.; O'hara, K.; Ohmiya, K.; Iida, H.; Kibayashi, C.; Kasahara, K. *Jpn. J. Antibiot.* **1986**, *39*, 247.

Scheme VI[a]



[a] (a) TsCl, EtN(*i*-Pr)$_2$, CH_2Cl_2, 0 °C → room temperature; (b) NaCN, Me_2SO, 80 °C; (c) HCl, EtOH, room temperature; (d) 4% aqueous NaOH, MeOH, room temperature; (e) EtOCOCl, Et_3N, toluene, 0 °C, then $H_2NN(Me)CO_2Bn$, toluene, 0 °C → room temperature; (f) H_2 (3 atm), 10% Pd–C, MeOH–10% aqueous AcOH.

the hydrazide **33** in 36.7% overall yield (Scheme VI) by using the same procedure as described for the preparation of negamycin. Hydrogenolysis followed by silica gel chromatography afforded (−)-**3**-epinegamycin [(−)-**2**] in 68% yield, which had spectra (IR and ^{1}H NMR) identical with authentic spectra of (±)-epinegamycin kindly provided by Dr. W. R. Pilgrim.

It has been reported that among several racemic negamycin analogues, only epinegamycin possesses weak antibacterial activity.[7a] Otherwise, racemic epinegamycin has been reported to be more active than racemic negamycin against *Staphylococcus aureus* in in vivo mouse protection tests.[7c] (−)-3-Epinegamycin thus synthesized for the first time was tested for activity against a variety of Gram-negative and Gram-positive bacteria, and it was found to be virtually inactive against any of these bacteria including *Staphylococcus aureus*.[25]

Conclusion

In conclusion, the enantioselective total synthesis of (+)-negamycin and (−)-3-epinegamycin has been achieved in six steps from chiral isoxazolidine derivatives (3*R*,5*R*)-**7a** and (3*S*,5*R*)-**7b**, respectively. The key intermediates (3*R*,5*R*)-**7a** and (3S,5*R*)-**7b** in this synthesis were prepared via enantioselective 1,3-dipolar cycloaddition of nitrones modified with the readily available carbohydrate, i.e. the *N*-D-gulosyl nitrone D-**18**, which proceeds in stereocontrolled and predictable manner with a high degree of enantioselectivity. Because of the availability of both enantiomers, this methodology involving asymmetric induction based on nitrone cycloaddition is also applicable to the preparation of optically active congeners and analogues of negamycin, which are of interest in connection with their pharmacological activity and structure–activity relationship.[5,26]

Experimental Section

General Method. Melting points are uncorrected. Mass spectra were obtained at an ionizing potential of 70 eV. TLC was run on Wako precoated silica gel 70 FM plates. Merck silica gel 60 (200–400 mesh) was used for column chromatography.

***N*-Benzyl-*C*-(methoxycarbonyl)nitrone (4).** Compound **4** was prepared from *N*-benzylhydroxylamine and methyl glyoxylate according to the reported method:[27] yield 75%; mp 91–92 °C; IR ($CHCl_3$) 1725, 1560 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.96 and 4.00 (total 3 H in a ratio of 3:5, each s), 4.97 and 5.68 (total 2 H in a ratio of 3:5, each s), 7.40 and 7.45 (total 1 H in a ratio of 3:5, each s), 7.50–7.78 (5 H); mass spectrum, *m/z* (relative intensity) 193 (M^+, 4), 192 ($M^+ - 1$, 4), 176 (9), 91 (100). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.36; H, 5.80; N, 7.55.

Methyl (3*R,5*R**)- and (3*S**,5*R**)-*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]isoxazolidine-3-carboxylate [(±)-6a and (±)-6b].** A mixture of **4** (3.90 g, 20 mmol, *E*:*Z* = 5:3) and **5** (3.86 g, 20 mmol) in toluene (50 mL) was refluxed for 15 h. The reaction mixture was concentrated in vacuo, and the resulting residue was purified by chromatography on silica gel with benzene–chloroform (1:1) to give a mixture of the cycloadducts (6.76 g, 87%) (±)-**6a** (major) and (±)-**6b** (minor) as a pale yellow oil in a ratio of 3:2, as determined by GLC analysis: IR ($CHCl_3$) 3440, 1750, 1720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.21 and 2.31 [total 1 H in a ratio of 2:3, dt, *J* = 12.4, 8.2 Hz for (±)-**6b** and dt, *J* = 12.9, 5.6 Hz for (±)-**6a**, respectively], 2.55 and 2.68 [total 1 H in a ratio of 2:3, quintet, *J* = 6.6 Hz for (±)-**6b** and dt, *J* = 12.9, 8.7 Hz for (±)-**6a**, respectively], 3.33 and 3.54 [total 1 H in a ratio of 3:2, dt, *J* = 14.3, 6.0 Hz for (±)-**6a** and dd, *J* = 8.9, 6.2 Hz for (±)-**6b**, respectively], 3.38–4.49 (2 H, m), 3.64 and 3.67 (total 3 H in a ratio of 3:2, each s), 3.69 (1 H, dd, *J* = 9.0, 5.3 Hz), 3.97, 4.06 and 4.04, 4.09 [total 2 H in a ratio of 3:2, each AB q, *J* = 13.2 Hz for (±)-**6a** and *J* = 13.6 Hz for (±)-**6b**, respectively], 4.26 and 4.40 (total 1 H in a ratio of 2:3, each br m), 4.96 and 5.27 (total 1 H in a ratio of 2:3, each br s), 5.10 (2 H, s), 7.27–7.38 (10 H, m); mass spectrum, *m/z* (relative intensity) 384 (M^+, 1.4), 325 (11), 91 (100); exact mass calcd for $C_{21}H_{24}N_2O_5$ (M^+) 384.1684, found 384.1687.

(3*R,5*R**)- and (3*S**,5*R**)-*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]-3-(hydroxymethyl)isoxazolidine [(±)-7a and (±)-7b].** To an ice-cold stirred suspension of $LiAlH_4$ (6.72 g, 177 mmol) in ether (200 mL) was added dropwise a solution of the mixture (45.29 g, 118 mmol) of (±)-**6a** and (±)-**6b** described above in ether (150 mL) over a period of 30 min. After additional stirring during 30 min at room temperature, the reaction mixture was quenched with water and filtered through Celite. The filtrate was dried ($MgSO_4$) and evaporated in vacuo. The residue was chromatographed on silica gel with chloroform to afford the cis isomer (±)-**7b** (13.57 g, 32%) as a colorless oil: IR ($CHCl_3$) 3455, 1710 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.53–1.80 (1 H, m), 2.31–2.62 (2 H, m), 3.09–3.44 (5 H, m), 3.82 and 4.02 (2 H, AB q, *J* = 13.2 Hz), 4.2–4.5 (1 H, m), 5.08 (2 H, s), 5.23 (1 H, br t, *J* = 6.5 Hz), 7.31 and 7.33 (total 10 H); mass spectrum, *m/z* (relative intensity) 356 (M^+, 0.4), 355 ($M^+ - 1$, 0.3), 325 (14), 91 (100); exact mass calcd for $C_{20}H_{24}N_2O_4$ (M^+) 356.1735, found 356.1739.

The further elution with chloroform afforded the trans isomer (±)-**7a** (19.53 g, 46%) as colorless needles: mp 98–99 °C (benzene–hexane); IR ($CHCl_3$) 3440, 1740 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) δ 2.02–2.40 (3 H, m), 2.98–3.51 (total 5 H, m with 2 H, d, *J* = 4.5 Hz at δ 3.48), 3.96–4.24 (total 3 H, m with 2 H, s at δ 3.99), 5.02 (1 H, br s), 5.10 (2 H, s), 7.31 and 7.35 (total 10 H); mass spectrum, *m/z* (relative intensity) 356 (M^+, 1.2), 325 (15), 91 (100). Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.53; H, 6.82; N, 7.47.

(3*R,5*R**)-*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]-3-[[(*p*-tolylsulfonyl)oxy]methyl]isoxazolidine [(±)-8].** To an ice-cold stirred mixture of (±)-**7a** (1.74 g, 4.88 mmol) and *N*-ethyl-*N*,*N*-diisopropylamine (821 mg, 6.35 mmol)

(25) Minimum inhibitory concentrations of the synthetic (−)-3-epinegamycin to various bacteria were determined as follows: *Providencia rettgeri* N-149 A was inhibited by 100 mcg/mL. *Staphylococcus aureus* TERAJIMA, *Staphylococcus aureus* 209 P, *Bacillus subtilis* ATCC 6633, *Micrococcus luteus* ATCC 12708, and *Escherichia coli* NIHJ were inhibited by >200 mcg/mL, and *Serratia marcescens* TCP 3628 and *Klebsiella pneumoniae* JK 66 by 200 mcg/mL.

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in dichloromethane (2 mL) was added a solution of *p*-toluenesulfonyl chloride (1.21 g, 6.35 mmol). After being stirred for 10 h at room temperature, the reaction mixture was diluted with dichloromethane (30 mL), washed with water, and dried ($MgSO_4$). The solvent was evaporated in vacuo, and the residue was chromatographed on silica gel with benzene–chloroform (1:1) to give (±)-**8** (1.90 g, 76%) as an oil: IR ($CHCl_3$) 3460, 1715, 1365, 1175 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.04 (2 H, t, J = 8.4 Hz), 2.43 (3 H, s), 3.06–3.40 (3 H, m), 3.80–4.15 (1 H, br with 2 H, d, J = 5.7 Hz at δ 3.93 and 2 H, s at δ 3.94), 4.85–5.13 (1 H, br with 2 H, s at δ 5.07), 7.26 and 7.33 (total 12 H, each s with 2 H, A part of AB q at the base of the peaks), 7.73 (2 H, B part of AB q, J = 7.8 Hz); mass spectrum, m/z (relative intensity) 510 (M^+, 0.4), 172 (3), 108 (23), 91 (100); exact mass calcd for $C_{27}H_{30}N_2O_6S$ (M^+) 510.1823, found 510.1792.

(3*S,5*R**)-*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]-3-(cyanomethyl)isoxazolidine [(±)-9].** To a stirred solution of NaCN (214 mg, 4.37 mmol) in dimethyl sulfoxide (5 mL) was added a solution of (±)-**8** (1.85 g, 3.36 mmol) in dimethyl sulfoxide (5 mL) at room temperature. The mixture was then heated at 80 °C with stirring for 4 h. The reaction mixture was poured into ice–water (20 mL) and extracted with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography on silica gel with benzene–chloroform (3:1) to give (±)-**9** (920 mg, 75%) as colorless crystals: mp 86–87 °C (benzene–hexane); IR ($CHCl_3$) 3450, 2250, 1715 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.09–2.40 (4 H, m), 3.02–3.50 (3 H, m), 3.96 (2 H, d, J = 1.5 Hz), 4.08–4.32 (1 H, m), 4.80–5.15 (1 H, br with 2 H, s at δ 5.10), 7.34 (10 H, s); mass spectrum, m/z (relative intensity) 365 (M^+, 1.2), 325 (6), 91 (100). Anal. Calcd for $C_{21}H_{23}N_3O_3$: C, 69.02; H, 6.34; N, 11.50. Found: C, 68.80; H, 6.34; N, 11.31.

Ethyl (3*R,5*R**)-[*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]isoxazolidin-3-yl]acetate [(±)-10].** A solution of (±)-**9** (920 mg, 2.5 mmol) in ethanol saturated with hydrogen chloride (25 mL) was stirred at room temperature. After 12 h, the reaction mixture was concentrated in vacuo, and ice–water (5 mL) was added to the residue. The resulting mixture was basified with $NaHCO_3$ and extracted with chloroform. The extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The crude product was purified by chromatography on silica gel with benzene–chloroform (1:1) to give (±)-**10** (820 mg, 79%) as a colorless oil: IR ($CHCl_3$) 3430, 1710 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.23 (3 H, t, J = 7.4 Hz), 2.07–2.33 (2 H, m), 2.42–2.70 (2 H, m), 3.10–3.60 (3 H, m), 3.92 (2 H, s), 4.13 (2 H, q, J = 7.4 Hz with 1 H, br at the base of the peak), 5.08 (1 H, br s, $W_{1/2}$ = 13.5 Hz), 5.10 (2 H, s), 7.33 and 7.37 (total 10 H, each s); mass spectrum, m/z (relative intensity) 413 (M^+ + 1, 0.6), 412 (M^+, 3), 325 (6), 321 (12), 217 (6), 132 (6), 108 (7), 106 (7), 91 (100); exact mass for $C_{23}H_{28}N_2O_5$ (M^+) 412.1997, found 412.2013.

(3*R,5*R**)-[*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]isoxazolidin-3-yl]acetic Acid [(±)-11].** To a solution of (±)-**10** (100 mg, 0.24 mmol) in methanol (4 mL) was added 4% aqueous NaOH solution (2 mL), and the mixture was stirred at room temperature for 3 h. The reaction mixture was concentrated in vacuo, and water (3 mL) was added to the residue. The resulting aqueous solution was washed with ether, and the aqueous layer was neutralyzed by addition of hydrochloric acid and extracted with dichloromethane. The extract was dried ($MgSO_4$), and the solvent was removed in vacuo to leave the solid, which was recrystallized from benzene–hexane to afford (±)-**11** (92 mg, 99%) was colorless crystals: mp 109–110 °C: IR ($CHCl_3$) 3430, 1710 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 2.00–2.70 (4 H, m), 3.15–3.47 (3 H, m), 3.96 (2 H, s), 4.17 (1 H, br m), 5.03 (1 H, br s, $W_{1/2}$ = ca. 12 Hz), 5.10 (2 H, s), 7.30 and 7.33 (total 10 H, each s), 10.10 (1 H, br s, $W_{1/2}$ = ca. 12 Hz); mass spectrum, m/z (relative intensity) 384 (M^+, 0.5), 259 (4), 245 (4.5), 195 (18), 194 (14), 132 (18), 91 (100). Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.57; H, 6.26; N, 7.26.

Benzyl (3*R,5*R**)-[2-[[*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]isoxazolidin-3-yl]acetyl]-1-methylhydrazino]acetate [(±)-13].** To an ice-cold stirred mixture of (±)-**11** (400 mg, 1.04 mmol) and triethylamine (148 mg, 1.46 mmol) in toluene (10 mL) was added dropwise a solution of ethyl chloroformate (158 mg, 1.46 mmol) in toluene (3 mL). After being stirred for 30 min at 0 °C, a solution of benzyl (1-methylhydrazino)acetate (243 mg, 1.25 mmol) in toluene (3 mL) was added dropwise to the reaction mixture with stirring at 0 °C. The stirring was continued for 2 h at 0 °C and then 10 h at room temperature. The reaction mixture was diluted with benzene (10 mL), and the resulting precipitates (triethylamine hydrochloride) were filtered. The filtrate was washed with water and then with saturated aqueous solution of $NaHCO_3$ and dried ($MgSO_4$). After evaporation of the solvent, the crude product was purified by chromatography on silica gel with benzene–ethyl acetate (1:2) to provide (±)-**13** (390 mg, 67%) as a pale yellow oil: IR ($CHCl_3$) 3430, 1710, 1680 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ (200 MHz, $CDCl_3$) δ 1.81 (1 H, br s, $W_{1/2}$ = 15 Hz), 1.97–2.39 (total 4 H with 1 H, dd, J = 14.4, 6.4 Hz at δ 2.18 and 1 H, dd, J = 15.2, 6.4 Hz at δ 2.33), 2.67 and 2.75 (total 3 H, each s), 3.18–3.61 (4 H, m), 3.70 (2 H, s), 3.88 and 3.93 (2 H, AB q, J = 11.0 Hz), 4.13 (1 H, br s, $W_{1/4}$ = 15 Hz), ca. 5.0 (1 H, br m), 5.10 (2 H, s), 5.15 (2 H, s), 7.32 (15 H, s); mass spectrum, m/z (relative intensity) 561 (M^+ + 1, 0.3), 560 (M^+, 0.2), 383 (1.8), 91 (100); exact mass for $C_{31}H_{36}N_4O_6$ (M^+) 560.2637, found 560.2644.

(±)-Negamycin [(±)-1]. A solution of (±)-**13** (232 mg, 0.41 mmol) in methanol–10% acetic acid (2:1, 40 mL) including 10% palladium on carbon (180 mg) was shaken under 3 atm of hydrogen for 12 h on a Parr apparatus. The catalyst was filtered off, and the solution was concentrated to dryness and neutralized by addition of aqueous ammonia. A solution of the resulting crude product was applied to a column of 100 mL of Amberlite CG 50 (NH_4^+) and eluted with 0.1% aqueous ammonia. The elute was lypophilized to give (±)-**1** (65 mg, 63%) as a colorless hygroscopic powder, which was found identical (^1H NMR and TLC) with an authentic sample of natural (+)-**1**: mp 110–120 °C dec; ^1H NMR (200 MHz, D_2O) δ 1.5–1.8 (2 H, unresolved), 2.36 (2 H, d, J = 7.2 Hz), 2.60 (3 H, s), 2.8–3.1 (3 H, m), 3.3–3.65 (1 H, m with 2 H, s at δ 3.36), 4.0 (1 H, br s, $W_{1/2}$ = 18 Hz).

2,3:5,6-*O*-Dicyclohexylidene D-*gulono*-Lactone (D-15). A mixture of D-**14** (5.00 g, 28.1 mmol), 1,1-dimethoxycyclohexane (12.20 g, 84.6 mmol), and *p*-toluenesulfonic acid (50 mg) in benzene (80 mL) was heated at reflux through molecular sieves (4A) with a Soxhlet extractor. After 10 h, the reaction mixture was cooled to room temperature, washed with saturated aqueous Na_2CO_3 solution and then with water, and dried ($MgSO_4$). The solvent was evaporated, and the residue was purified by recrystallization from benzene–hexane to give D-**15** (9.20 g, 97%): mp 163–165 °C; $[\alpha]^{20}_D$ −53.0° (*c* 2.17, $CHCl_3$); IR ($CHCl_3$) 1785 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.27 to ca. 2.0 (m, 20 H), 3.74–3.96 (1 H, m), 4.18 (1 H, t, J = 6.0 Hz), 4.28–4.48 (2 H, m), 4.65–4.85 (2 H, m); mass spectrum, m/z (relative intensity) 340 (M^+, 28), 309 (14), 296 (18), 295 (100). Anal. Calcd for $C_{18}H_{26}O_6$: C, 63.89; H, 7.74. Found: C, 64.16; H, 7.84.

2,3:5,6-*O*-Dicyclohexylidene-D-gulofuranose (D-16). To a cooled (−78 °C) stirred solution of D-**15** (7.07 g, 20.9 mmol) in toluene–THF (1:1, 140 mL) was added dropwise a 1 M solution of DIBAL (31.4 mL, 31.4 mmol) in toluene. After being stirred for 1 h at −78 °C, the reaction mixture was quenched with water (15 mL) and filtered through Celite. The organic layer was separated, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by silica gel chromatography with hexane–ethyl acetate (5:1) to give D-**16** (6.24 g, 88%) as a colorless syrup: $[\alpha]^{20}_D$ −12.3° (*c* 0.89, $CHCl_3$); IR ($CHCl_3$) 3580 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.50 and 1.62 (total 20 H), 3.40 (1 H, d, J = 2.4 Hz), 3.71 (1 H, t, J = 6.6 Hz), 4.02–4.47 (3 H, m), 4.47–4.73 (2 H, m), 5.46 (1 H, d, J = 2.4 Hz); mass spectrum, m/z (relative intensity) 342 (M^+ + 2, 1), 341 (M^+ + 1, 6), 340 (M^+, 29), 311 (11), 297 (100), 199 (44); exact mass calcd for $C_{18}H_{28}O_6$ (M^+) 340.1884, found 340.1878.

2,3:5,6-*O*-Dicyclohexylidene-D-gulose Oxime (D-17). A mixture of D-**16** (6.24 g, 18.4 mmol) and hydroxylamine hydrochloride (15.31 g, 221 mmol) in pyridine (50 mL) was stirred at room temperature for 1 h. The reaction mixture was poured into water (150 mL) and extracted with dichloromethane. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The crude product was chromatographed on silica gel with hexane–ethyl acetate (3:1) to give D-**17** (6.23 g, 96%) as a colorless vitreous substance: $[\alpha]^{20}_D$ +45.5° (*c* 3.14, $CHCl_3$); IR ($CHCl_3$) 3580, 3350 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.59 (total 20 H, s with a series of signals at the base

of the peak), 3.30–4.36 (6 H, m), 4.73 and 5.27 (total 1 H, t, J = 7.5 Hz and dd, J = 7.8, 4.1 Hz, respectively), 7.11 and 7.54 (total 1 H, d, J = 4.1 Hz and d, J = 7.8 Hz, respectively), 8.42 and 9.04 (total 1 H, each br s, $W_{1/2}$ = 8 Hz); mass spectrum, m/z (relative intensity) 355 (M^+, 20), 312 (49), 294 (35), 141 (64), 79 (100); exact mass for $C_{18}H_{29}NO_6$ (M^+) 355.1993, found 355.2009.

Methyl (3*R*,5*R*)- and (3*S*,5*R*)-5-[[(Benzyloxycarbonyl)amino]methyl]-*N*-(2,3:5,6-*O*-dicyclohexylidene-D-gulofuranosyl)isoxazolidine-3-carboxylate (D-19a and D-19b). A mixture of D-**17** (4.63 g, 13.0 mmol), methyl glyoxylate (1.26 g, 14.3 mmol), and **5** (2.74 g, 14.3 mmol) in toluene (40 mL) was refluxed in the presence of molecular sieves (4A) for 14 h. The reaction mixture was filtered, and the solution was washed with water, dried ($MgSO_4$), and concentrated in vacuo. The crude material obtained was purified by chromatography on silica gel with hexane–ethyl acetate (5:1) to give a diastereomeric mixture (6.72 g, 84%) of D-**19a** and D-**19b** as a colorless syrup: $[\alpha]^{20}_D$ +4.8° (c 1.65, $CHCl_3$); IR ($CHCl_3$) 3450, 1760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.36–1.76 (20 H, m), 2.22–2.37 (1 H, m), 2.54–2.70 (1 H, m), 3.28–3.50 (3 H, m), 3.68 and 3.69 (total 3 H, each s), 4.05–4.46 (6 H, series of m), 4.67–4.70 (1 H, m), 4.95 (1 H, dd, J = 11.5, 6.0 Hz), 5.10 (2 H, s), 5.22 (br, 1 H), 7.29–7.38 (5 H); mass spectrum, m/z (relative intensity) 616 (M^+, 0.7), 323 (41), 225 (25), 141 (20), 127 (28), 91 (100); exact mass for $C_{32}H_{44}N_2O_{10}$ (M^+) 616.2993, found 616.3005.

(3*R*,5*R*)- and (3*S*,5*R*)-5-[[(Benzyloxycarbonyl)amino]methyl]-3-(methoxycarbonyl)isoxazolidine [(3*R*,5*R*)-20a and (3*S*,5*R*)-20b]. A solution of the above diastereomeric mixture (D-**19a** + D-**19b**, 6.72 g, 10.9 mmol) in 10% HCl–methanol (3:8, 50 mL) was stirred at 40 °C. After 4 h, the reaction mixture was concentrated in vacuo, and the residue was basified with 10% aqueous Na_2CO_3 and extracted with dichloromethane. The organic extracts were combined, washed with brine, and dried ($MgSO_4$). Evaporation of the solvent followed by chromatography on silica gel with chloroform gave a diastereomeric mixture (2.97 g, 93%) of (3*R*,5*R*)-**20a** and (3*S*,5*R*)-**20b** as a colorless syrup: IR ($CHCl_3$) 3420, 1720 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.94–2.23 (1 H, m), 2.41–2.74 (1 H, m), 3.10–3.44 (2 H, m), 3.71 (3 H, s), 3.93–4.27 (2 H, m), 5.10 (2 H, s), 5.3 (1 H, br s, $W_{1/2}$ = 18 Hz), 5.9 (1 H, br s). Anal. Calcd for $C_{14}H_{18}N_2O_5$: C, 57.14; H, 6.16; N, 9.52. Found: C, 57.14; H, 5.95; N, 9.44.

Methyl (3*R*,5*R*)- and (3*S*,5*R*)-*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]isoxazolidine-3-carboxylate [(3*R*,5*R*)-6a and (3*S*,5*R*)-6b]. A mixture of the above described mixture [(3*R*,5*R*)-**20a** + (3*S*,5*R*)-**20b**, 110 mg, 0.37 mmol], K_2CO_3 (52 mg, 0.37 mmol), and benzyl bromide (64 mg, 0.37 mmol) in DMF (2 mL) was stirred at 50 °C for 1 h. The reaction mixture was worked up in a similar manner to that described above for the preparation of (3*R*,5*R*)-**7a** and (3*S*,5*R*)-**7b** and then purified by silica gel chromatography with hexane–ethyl acetate (5:1) to give a diastereomeric mixture (123 mg, 86%) of (3*R*,5*R*)-**6a** and (3*S*,5*R*)-**6b** as a pale yellow syrup.

$LiAlH_4$ Reduction of (3*R*,5*R*)-6a and (3*S*,5*R*)-6b. Formation of (3*R*,5*R*)-7a and (3*S*,5*R*)-7b. To an ice-cold, stirred suspension of $LiAlH_4$ (210 mg, 5.53 mmol) in ether (20 mL) was added dropwise a solution of the above mixture [(3*R*,5*R*)-**6a** + (3*S*,5*R*)-**6b**, 1.41 g, 3.67 mmol] in ether (10 mL). After the resulting mixture was stirred at room temperature for 30 min, and the reaction mixture was quenched with water, filtered, and dried ($MgSO_4$). Removal of the solvent followed by chromatography on silica gel with chloroform gave (3*S*,5*R*)-**7b** (550 mg, 42%) as a colorless oil: $[\alpha]^{25}_D$ +11.2° (c 0.25, $CHCl_3$).[28]

Further elution with chloroform gave (3*R*,5*R*)-**7a** (280 mg, 21%) as colorless needles: mp 99–100 °C (benzene–hexane); $[\alpha]^{25}_D$ +39.0° (c 0.35, $CHCl_3$).[28] Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.45; H, 6.86; N, 7.85.

These products (3*R*,5*R*)-**7a** and (3*S*,5*R*)-**7b** had spectra (^1H NMR and mass) identical with those of (±)-**7a** and (±)-**7b** previously obtained and were both found to be 94% enantiomerically pure by 400-MHz ^1H NMR analysis of the corresponding (+)-(*R*)-MTPA esters.

(28) The optical rotation value previously reported[11] has been erroneous owing to measurement with a polarimeter under unfavorable conditions.

2,3:5,6-*O*-Dicyclohexylidene-L-gulose Oxime (L-17). By the procedure for the preparation of D-**17**, L-**16** (5.38 g, 15.8 mmol), prepared from L-**15** in the same manner as described for the preparation of D-**16**, was converted to L-**17** (5.30 g, 94%).

(3*S*,5*S*)- and (3*S*,5*S*)-*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]-3-(hydroxymethyl)isoxazolidine [(3*S*,5*S*)-7a and (3*R*,5*S*)-7b]. In the exactly same procedure described for the D-series, from L-**17** was obtained (3*S*,5*S*)-**7a** and (3*R*,5*S*)-**7b**. For (3*S*,5*S*)-**7a**: mp 99–100 °C; $[\alpha]^{22}_D$ −38.4° (c 0.20, $CHCl_3$). For (3*R*,5*S*)-**7b**: $[\alpha]^{20}_D$ −11.0° (c 0.34, $CHCl_3$).

These materials of (3*S*,5*S*)-**7a** and (3*R*,5*S*)-**7b** were estimated to be 93% and 92% ee, respectively, based on the optical rotation value of (3*R*,5*R*)-**7a** and (3*S*,5*R*)-**7b** derived from the D-gulosyl nitrone D-**18**.

Methyl (3*R*,5*R*)- and (3*S*,5*R*)-5-[[(Benzyloxycarbonyl)amino]methyl]-*N*-(2,3-*O*-cyclohexylidene-5-*O*-methyl-D-ribofuranosyl)isoxazolidine-3-carboxylate (24a and 24b). In the same manner as described for the cycloaddition using D-**17** to give D-**19a** + D-**19b**, 550 mg (2.21 mmol) of 2,3-*O*-cyclohexylidene-5-*O*-methyl-D-ribose oxime (**22**)[18] was allowed to react with methyl glyoxylate (203 mg, 2.31 mmol) and **5** (440 mg, 2.31 mmol) in toluene (30 mL) to give a diastereomeric mixture (1.00 g, 91%) of **24a** and **24b** [and their diastereomers 3*S*,5*S* and 3*R*,5*S* cycloadducts as minor products] as a colorless syrup: $[\alpha]^{15}_D$ +6.2° (c 2.44, $CHCl_3$); IR ($CHCl_3$) 3430, 1720, 1730 (sh) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.2–1.6 (10 H, m), 2.15–2.40 (1 H, unresolved), 2.4–2.75 (1 H, m), 3.1–3.55 (total 6 H, series of signals containing two s at δ 3.33 and 3.44), 3.55–3.9 (total 2 H, series of signals containing s at δ 3.69), 4.0–4.9 (6 H, m), 5.0–5.5 (total 3 H containing s at δ 5.11), 7.34 (5 H, s); mass spectrum, m/z (relative intensity) 521 (M^+ + 1, 0.6), 520 (M^+, 1.7), 227 (96), 169 (89), 91 (100). Anal. Calcd for $C_{28}H_{36}N_2O_9$: C, 59.99; H, 6.97; N, 5.38. Found: C, 60.01; H, 6.92; N, 5.31.

Hydrolysis of 24a and 24b. Formation of (3*R*,5*R*)-20a and (3*S*,5*R*)-20b. In the same manner as described for the hydrolysis of D-**19a** + D-**19b** to give (3*R*,5*R*)-**20a** + (3*S*,5*R*)-**20b**, the above-described product (**24a** + **24b**, 322 mg, 0.62 mmol), prepared by cycloaddition with the D-ribosyl nitrone **23** was hydrolyzed to give a diastereomeric mixture (170 mg, 93%) of (3*R*,5*R*)-**20a** and (3*S*,5*R*)-**20b** (and their enantiomers as minor products) as a colorless syrup: $[\alpha]^{15}_D$ +16.7° (c 3.41, $CHCl_3$).

(3*R*,5*R*)- and (3*S*,5*R*)-5-[[(Benzyloxycarbonyl)amino]methyl]-3-(hydroxymethyl)isoxazolidine (25a and 25b). To an ice-cold suspension of $LiAlH_4$ (14 mg, 0.35 mmol) in ether (5 mL) was added a solution of the above-described product [(3*R*,5*R*)-**20a** + (3*S*,5*R*)-**20b**, 68 mg, 0.23 mmol], derived from **23**, in ether (5 mL) with stirring. After being stirred at room temperature for 30 min, the reaction mixture was quenched with water, filtered, and dried ($MgSO_4$). Evaporation of the solvent followed by silica gel chromatography with chloroform–methanol (50:1) gave a diastereomeric mixture (43 mg, 70%) of **25a** and **25b** (and their enantiomers as minor products) as a colorless syrup: $[\alpha]^{18}_D$ −28.8° (c 2.36, $CHCl_3$); IR ($CHCl_3$) 3640, 3460, 1710 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.25–1.7 (1 H, m), 2.15–2.55 (1 H, m), 3.08–3.66 (total 9 H, series of signals containing at δ 3.47), 3.83 to ca. 4.5 (3 H, br m), 5.11 (2 H, s), 5.52 (1 H, br m), 7.36 (5 H, s). Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.64; H, 6.81; N, 10.52. Found: C, 58.46; H, 6.81; N, 10.29.

(3*R*,5*R*)- and (3*S*,5*R*)-*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]-3-(hydroxymethyl)isoxazolidine [(3*R*,5*R*)-7a and (3*S*,5*R*)-7b]. A mixture of the above-described product (**25a** + **25b**, 183 mg, 0.69 mmol), K_2CO_3 (95 mg, 0.69 mmol), and benzyl bromide (118 mg, 0.69 mmol) in DMF (3 mL) was stirred at 50 °C for 1 h. The reaction mixture was poured into water and extracted with chloroform. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed on silica gel with chloroform, affording (3*S*,5*R*)-**7b** (86 mg, 35%) as a colorless syrup: $[\alpha]^{25}_D$ +8.5° (c 2.02, $CHCl_3$).

Further elution with chloroform gave (3*R*,5*R*)-**7a** (39 mg, 16%) as colorless needles: mp 99–100 °C (benzene–hexane); $[\alpha]^{25}_D$ +29.3° (1.25, $CHCl_3$). These products (3*R*,5*R*)-**7a** and (3*S*,5*R*)-**7b** had spectra (^1H NMR and mass) identical with those of (±)-**7a** and (±)-**7b** previously obtained. The trans isomer (3*R*,5*R*)-**7a** was found to be 74% enantiomerically pure by 400-MHz ^1H NMR analysis of the corresponding (+)-(*R*)-MTPA ester.

Methyl (3*R*,5*R*)- and (3*S*,5*R*)-5-[[(Benzyloxycarbonyl)amino]methyl]-*N*-(2,3:5,6-*O*-dicyclohexylidene-D-mannofuranosyl)isoxazolidine-3-carboxylate (28a and 28b). In the same manner as described for the cycloaddition of D-17 to give D-19a + D-19b, 4.63 g (13.0 mmol) of 2,3:5,6-*O*-dicyclohexylidene-D-mannose oxime (26)[19] was allowed to react with methyl glyoxylate (1.26 g, 14.3 mmol) and 5 (2.74 g, 14.3 mmol) to give a diastereomeric mixture (7.00 g, 87%) of 28a and 28b as a colorless syrup.

Hydrolysis of 28a and 28b. Formation of (3*S*,5*S*)-20a and (3*R*,5*S*)-20b. In the same manner as described for the hydrolysis of the mixture of D-19a and D-19b to give (3*R*,5*R*)-20a and (3*S*,5*R*)-20b, the above diastereomeric mixture (28a + 28b, 3.39 g, 5.50 mmol) was hydrolyzed to afford a diastereomeric mixture (1.04 g, 64%) of (3*S*,5*S*)-20a and (3*R*,5*S*)-20b.

(3*R*,5*S*)-*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]-3-(hydroxymethyl)isoxazolidine [(3*R*,5*S*)-7b]. The above diastereomeric mixture [(3*S*,5*S*)-20a + (3*R*,5*S*)-20b] was subjected to benzylation followed by $LiAlH_4$ reduction and chromatographical separation in the exactly same manner as described above for the preparation of (3*S*,5*R*)-7b; this procedure gave (3*R*,5*S*)-7b: $[\alpha]^{25}_D$ −9.5° (*c* 0.12, $CHCl_3$). This material was estimated to be 80% ee based on the optical rotation value of (3*S*,5*R*)-7b derived from the D-gulosyl nitrone D-27.

(3*R*,5*R*)-*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]-3-[[(*p*-tolylsulfonyl)oxy]methyl]isoxazolidine [(3*R*,5*R*)-8]. In the same manner as described for (±)-8, (3*R*,5*R*)-7a (140 mg, 0.39 mmol), derived from D-17, was converted to (3*R*,5*R*)-8 (172 mg, 86%) as a pale yellow oil: $[\alpha]^{17}_D$ +29.8° (*c* 7.2, $CHCl_3$).

(3*S*,5*R*)-*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]-3-(cyanomethyl)isoxazolidine [(3*S*,5*R*)-9]. In the same manner as described for (±)-9, (3*R*,5*R*)-8 (137 mg, 0.27 mmol) was converted to (3*S*,5*R*)-9 (83 mg, 85%) as colorless needles: mp 90–93 °C (benzene–hexane); $[\alpha]^{17}_D$ +31.4° (*c* 5.98, $CHCl_3$).

Ethyl (3*R*,5*R*)-[*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]isoxazolidin-3-yl]acetate [(3*R*,5*R*)-10]. In the same manner as described for (±)-10, (3*R*,5*R*)-9 (167 mg, 0.46 mmol) was converted to (3*R*,5*R*)-10 (152 mg, 80%) as colorless oil: $[\alpha]^{14}_D$ +32.5° (*c* 2.48, $CHCl_3$).

(3*R*,5*R*)-[*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]isoxazolidin-3-yl]acetic Acid [(3*R*,5*R*)-11]. In the same manner as described for (±)-11, (3*R*,5*R*)-10 (120 mg, 0.29 mmol) was converted to (3*R*,5*R*)-11 (110 mg, 98%) as a colorless vitreous substance: $[\alpha]^{16}_D$ +31.7° (*c* 2.19, $CHCl_3$).

Benzyl (3*R*,5*R*)-[2-[[*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]isoxazolidin-3-yl]acetyl]-1-methylhydrazino]acetate [(3*R*,5*R*)-13]. In the same manner as described for (±)-13, (3*R*,5*R*)-11 (110 mg, 0.29 mmol) was converted to (3*R*,5*R*)-13 (107 mg, 67%) as a pale yellow oil: $[\alpha]^{16}_D$ +20.4° (*c* 2.11, $CHCl_3$).

(+)-Negamycin [(+)-1]. In the same manner as described for (±)-1, (3*R*,5*R*)-13 (42 mg, 0.075 mmol) was converted to (+)-1 (14 mg, 75%) as colorless hygroscopic crystals, which were found to be identical with an authentic sample of natural (+)-1 in all respects: mp 108–115 °C dec [lit.[2] mp 110–120 °C]; $[\alpha]^{20}_D$ +2.3° (*c* 4.07, H_2O) [lit.[2] $[\alpha]_D$ +2.5° (H_2O)]; ^1H NMR, see above described for (±)-1.

(3*S*,5*R*)-*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]-3-[[(*p*-tolylsulfonyl)oxy]methyl]isoxazolidine (29). In the same manner as described for (±)-8, (3*S*,5*R*)-7b (1.40 g, 3.93 mmol), derived from D-17, was converted to 29 (1.69 g, 84%) as a pale yellow oil: $[\alpha]^{20}_D$ +17.1° (*c* 3.17, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 1.52–1.99 (2 H, m), 2.29–2.61 (1 H, m with 3 H, s at δ 2.38), 3.04–3.44 (2 H, m), 3.69–4.03 (3 H, m), 4.25 (1 H, br), 5.05 (2 H, s with 1 H, br at the base of the peak), 7.21 and 7.29 (total 12 H), 7.66 (2 H, a part of AB q, J = 7.8 Hz); mass spectrum, m/z (relative intensity) 513 (M^+ + 3, 2), 512 (M^+ + 2, 9), 511 (M^+ + 1, 29), 510 (M^+, 24), 509 (M^+ − 1, 2), 419 (100), 346 (62), 325 (71), 249 (40), 226 (39), 181 (39), 172 (72).

(3*R*,5*R*)-*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]-3-(cyanomethyl)isoxazolidine (30). In the same manner as described for (±)-9, 29 (1.69 g, 3.31 mmol) was converted to 30 (1.03 g, 85%) as colorless needles: mp 107–109 °C (benzene–hexane); $[\alpha]^{20}_D$ +26.0° (*c* 3.30, $CHCl_3$); IR ($CHCl_3$) 3430, 2250, 1715 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.66–2.80 (4 H, m), 4.80–3.46 (3 H, m), 4.00 and 3.86 (2 H, AB q, J = 12.6 Hz), 4.38 (1 H, br), 5.10 (2 H, s with 1 H, br at the base of the peak), 7.34 (10 H); mass spectrum, m/z (relative intensity) 365 (M^+, 3), 325 (6), 181 (5), 91 (100). Anal. Calcd for $C_{21}H_{23}N_3O_3$: C, 69.02; H, 6.34; N, 11.50. Found: C, 69.32; H, 6.46; N, 11.34.

Ethyl (3*S*,5*R*)-[*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]isoxazolidin-3-yl]acetate (31). In the same manner as described for (±)-10, 30 (760 mg, 2.08 mmol) was converted to 31 (601 mg, 70%) as a colorless oil: $[\alpha]^{20}_D$ +27.8° (*c* 5.34, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 1.23 (3 H, t, J = 7.1 Hz), 1.60–2.03 (1 H, m), 2.21–2.81 (3 H, m), 3.26–3.54 (3 H, m), 3.91 (2 H, s), 4.11 (2 H, q, J = 7.1 Hz), 4.3 (1 H, br), 5.10 (2 H, s), 5.2 (1 H, br), 7.30 and 7.34 (total 10 H); mass spectrum, m/z (relative intensity) 413 (M^+ + 1, 3), 412 (M^+, 12), 325 (5), 321 (20), 217 (4), 160 (4), 91 (100).

(3*S*,5*R*)-[*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]isoxazolidin-3-yl]acetic Acid (32). In the same manner as described for (±)-11, 31 (267 mg, 0.65 mmol) was converted to 32 (224 mg, 90%) as a colorless vitreous substance: $[\alpha]^{20}_D$ +26.0° (*c* 3.32, $CHCl_3$); ^1H NMR δ 1.57–1.86 (1 H, m), 2.19–2.76 (3 H, m), 3.15–3.6 (3 H, br m), 3.91 (2 H, s), 4.1–4.15 (1 H, br), 5.09 (2 H, s), 5.35 (1 H, br s, $W_{1/2}$ = 11 Hz), 7.29 and 7.33 (total 10 H), 10.06 (1 H, br s, $W_{1/2}$ = 7.5 Hz).

Benzyl (3*S*,5*R*)-[2-[[*N*-Benzyl-5-[[(benzyloxycarbonyl)amino]methyl]isoxazolidin-3-yl]acetyl]-1-methylhydrazino]acetate (33). In the same manner as described for (±)-13, 32 (166 mg, 0.43 mmol) was converted to 33 (196 mg, 81%) as a pale yellow oil: $[\alpha]^{20}_D$ +17.4° (*c* 3.92, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 1.52 to ca. 2.8 (9 H, series of signals), 3.22–3.57 (4 H, m), 3.69 (1 H, s), 3.84 (2 H, s), 4.28 (1 H, br), 5.06 and 5.11 (each 1 H, s), 5.27 (1 H, br), 7.32 (15H).

(−)-3-Epinegamycin [(−)-2]. In the same manner as described for (±)-1, 33 (196 mg, 0.35 mmol) was converted to (−)-2 (59 mg, 68%) as colorless hygroscopic crystals, the spectroscopic data (IR, ^1H NMR) of which were identical with those of authentic spectra of (±)-2: mp 165–195 °C dec [for (±)-2: lit.[7c] mp 165–180 °C dec]; $[\alpha]^{20}_D$ −3.17° (*c* 4.42, H_2O); ^1H NMR (400 MHz, D_2O) δ 1.62–1.79 (2 H, m), 2.35 (1 H, dd, J = 14.8, 7.6 Hz), 2.48 (1 H, dd, J = 14.8, 5.4 Hz), 2.63 (3 H, s), 2.86 (1 H, dd, J = 13.1, 8.4 Hz), 3.05 (1 H, dd, J = 13.1, 3.2 Hz), 3.39 (2 H, s), 3.49 (1 H, quintet, J = 6.5 Hz), 3.97 (1 H, septet, J = 4.0 Hz).

Acknowledgment. We are indebted to Professor M. Ohno of Tokyo University for kindly providing a sample of natural (+)-negamycin and also to Dr. P. Siret of I.-C.I.-Pharma for IR and ^1H NMR spectra of racemic epinegamycin. We also thank Professor M. Kono and Dr. K. O'hara of Tokyo College of Pharmacy for cooperating in testing antibacterial activities of synthetic (+)-negamycin and (−)-3-epinegamycin.

Registry No. (+)-1, 33404-78-3; (±)-1, 68681-79-8; (−)-2, 103420-24-2; (*E*)-4, 77486-10-3; (*Z*)-4, 77486-09-0; 5, 5041-33-8; (±)-6a, 119680-68-1; (3*R*,5*R*)-6a, 119719-74-3; (±)-6b, 119680-69-2; (3*S*,5*R*)-6b, 119719-75-4; (±)-7a, 119719-68-5; (3*R*,5*R*)-7a, 103321-67-1; (3*S*,5*S*)-7a, 119680-79-4; (±)-7b, 119719-69-6; (3*S*,5*R*)-7b, 103321-68-2; (3*R*,5*S*)-7b, 119680-80-7; (±)-8, 119680-70-5; (3*R*,5*R*)-8, 119719-81-2; (±)-9, 119719-70-9; (3*S*,5*R*)-9, 103321-69-3; (±)-10, 119680-71-6; (3*R*,5*R*)-10, 119719-82-3; (±)-11, 119719-71-0; (3*R*,5*R*)-11, 103321-71-7; (±)-13, 119719-72-1; (3*R*,5*R*)-13, 103321-73-9; D-14, 6322-07-2; D-15, 119680-72-7; L-15, 119680-76-1; D-16, 103321-62-6; L-16, 119680-77-2; D-17, 103321-63-7; L-17, 119680-78-3; D-19a, 119680-73-8; D-19b, 119719-73-2; (3*R*,5*R*)-20a, 119680-74-9; (3*S*,5*S*)-20a, 119680-86-3; (3*S*,5*R*)-20b, 119680-75-0; (3*R*,5*S*)-20b, 119680-87-4; (*E*)-22, 119680-81-8; (*Z*)-22, 119693-77-5; (3*S*,5*S*)-24, 119719-77-6; (3*R*,5*S*)-24, 119719-78-7; 24a, 119680-82-9; 24b, 119719-76-5; 25a, 119680-83-0; 25b, 119680-84-1; 26, 119680-85-2; 28a, 119719-79-8; 28b, 119719-80-1; 29, 119719-83-4; 30, 103321-70-6; 31, 119719-84-5; 32, 103321-72-8; 33, 103321-74-0; $PhCH_2NHOH$, 622-30-0; OHCCOOMe, 922-68-9; $H_2NN(Me)CH_2COOBn$, 55501-33-2; $PhCH_2Br$, 100-39-0; 1,1-dimethoxycyclohexane, 933-40-4; benzyl D-*ribo*-furanoside, 119719-85-6; benzyl 2,3-*O*-cyclohexylidene-D-*ribo*-furanoside, 119694-05-2; benzyl 2,3-*O*-cyclohexylidene-5-*O*-methyl-D-*ribo*-furanoside, 119694-06-3; 2,3-*O*-cyclohexylidene-5-*O*-methyl-D-ribose, 119680-88-5; D-mannose, 3458-28-4; cyclohexanone, 108-

94-1; 2,3:5,6-*O*-dicyclohexylidene-D-mannose, 111025-78-6.

Supplementary Material Available: Procedures for the preparation of benzyl 2,3-*O*-cyclohexylidene-D-ribofuranoside, benzyl 2,3-*O*-cyclohexylidene-5-*O*-methyl-D-ribofuranoside, 2,3-*O*-cyclohexylidene-5-*O*-methyl-D-ribofuranose, 2,3-*O*-cyclohexylidene-5-*O*-methyl-D-ribose oxime, 2,3:5,6-*O*-dicyclohexylidene-D-mannofuranose, and 2,3:5,6-*O*-dicyclohexylidene-D-mannose oxime (4 pages). Ordering information is given on any current masthead page.

Notes

Highly Chemoselective and Stereocontrolled Catalytic Hydrogenolysis of the Carbon-6–Halogen Bond of (Pivaloyloxy)methyl 6,6-Dihalopenicillanate by Chlorotris(triphenylphosphine)rhodium(I) in Homogeneous Phase

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Received February 24, 1988

Catalytic hydrogenolysis of the carbon–halogen bond is an important and frequently encountered synthetic transformation in organic synthesis. A number of catalytic hydrogenolysis procedures using heterogeneous catalysts have been developed.[2] Homogeneous transition metal catalyst for this process are less common, although examples involving both molecular hydrogen[3] and hydrogen transfer from organic compounds[4,5] are known.

The transition metal complex chlorotris(triphenylphosphine)rhodium(I), $RhCl(PPh_3)_3$, known as Wilkimson's catalyst,[6,7] as well as a variant of it with chiral ligands,[8] has been thoroughly studied in the hydrogenation of alkenes by molecular hydrogen. This complex has also shown high catalytic activity in hydrogen transfer reactions from alcohols,[9] dioxane,[10] amines,[11] and various other organic compounds[11,12] to alkenes and other substrates. The mechanism of hydrogenation[6–8,13] and hydrogen transfer[9,10,14] has been extensively studied.

This paper describes in details the catalytic hydrogenolysis of the carbon-6–halogen bond in (pivaloyloxy)methyl (Pom) 6,6-dihalopenicillanates (**1**, **3**, **5**) by $RhCl(PPh_3)_3$ in the presence of molecular hydrogen and by a stoichiometric amount of $RhCl(PPh_3)_3$ in the absence of molecular hydrogen, in solutions containing methanol as cosolvent, in the presence of $CaCO_3$.

Results and Discussion

Pom 6β-iodo-6α-bromopenicillanate (**1**),[15a] and Pom 6,6-diiodopenicillanate (**3**)[15b] were effectively and stereoselectively hydrogenolyzed by $RhCl(PPh_3)_3$ in the presence of molecular hydrogen and $CaCO_3$ in 24 h by using a mixture of ethyl acetate and methanol (5:8, v/v) as solvent. The former (**1**) gave a mixture of Pom 6α-bromo- (**2a**) and 6β-bromo- (**2b**)[16] penicillanates, and the latter (**3**) a mixture of Pom 6α-iodo- (**4a**) and 6β-iodo- (**4b**) penicillanates, in a ratio 10:1, in 90% yield. Conversely, hydrogenolysis of Pom 6,6-dibromopenicillanate (**5**),[15b] gave only 10% yield of a mixture of **2a** and **2b** in a ratio of 10:1 along side 87% recovery of remaining starting material. Unequivocal proof of the configuration at carbon-6 was secured by ^1H NMR spectroscopy on the basis of the H(5)–H(6) coupling constant.[17]

Complete hydrogenolysis of compounds **1** and **3** in ethyl acetate under the same conditions required 72 h and gave mixtures of **2a** and **2b** from **1** and **4a** and **4b** from **3** in a ratio of 1:1. In contrast, compound **5**, under these conditions, did not react (see Table I, entries 1–6). These

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