Since modifications of C(1), C(7), C(8), and C(12) are not involved in the conversion **1** → **2** → **3**, these centers in **1** are fully defined. To determine the stereochemistry at C(9) through C(11), however, requires careful interpretation of the stereospecific chemical processes involved. Construction of molecular models indicates the stereochemical relationships between **1**, **2**, and **3**. Due to the extremely hindered "back" face of C(8) to C(12) in these molecules, solvolysis and elimination must involve substituents on the "front" face. The allylic displacements (S_N2') of epoxide **1** and of methoxy derivative **2** must involve the predicted syn orientation of displacing and leaving groups.[11] The ^1H NMR spectra of **1**–**3** support this contention. As a consequence of this reasoning, the epoxide stereochemistry at C(11) was established as *S*.

The structure of pseudopterolide[12] represents a novel monocyclic skeleton related only in part to cubitene,[13] a 12-membered ring with two isopropenyl groups oriented 1,3 instead of 1,7. While pseudopterolide can be dissected symmetrically into two geranyl units in two possible ways, perhaps suggesting a biogenesis involving dimerization, the prevalence of the 14-membered ring cembrenoids in marine soft corals suggests a mechanism involving ring contraction.

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Supplementary Material Available: Tables of fractional coordinates, bond distances, and bond angles for urethane **3** (5 pages). Ordering information is given on any current masthead page.

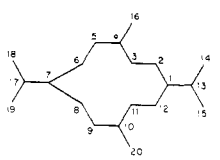
(8) Preliminary X-ray photographs of the urethane **3** showed orthorhombic symmetry and lattice constants of a = 12.470 (2) Å, b = 24.001 (2), and c = 9.356 (3) Å were determined by a least-squares fit of 15 moderate 2θ values measured on a diffractometer. Systematic extinctions, crystal density, and the presence of chirality were uniquely accommodated by space group $P2_12_12$ with a unit of $C_{28}H_{28}BrNO_7 \cdot H_2O$ forming the asymmetric unit. All unique diffraction maxima with $2\theta \leq 114°$ were collected on a four-circle diffractometer using graphite monochromated Cu K$\bar{\alpha}$ (1.541 78 Å) radiation and a variable-speed 1° ω scan. Of the 2189 reflections surveyed, 2041 (93%) were judged observed ($|F_o| \geq 3\sigma(F_o)$) after correction for Lorentz, polarization, and background effects. A phasing model was achieved by standard heavy-atom methods.[9] Full-matrix least-squares refinements using anisotropic non-hydrogen atoms, isotropic, fixed hydrogens, and anomalous scattering corrections for bromine have converged to a current residual of 0.095 for the structure shown and 0.099 for the enantiomer.[10]

(9) All crystallographic calculations were performed on a Prime 400 computer operated by the Materials Science Center and the Department of Chemistry, Cornell University. The principal programs used were as follows: REDUCE and UNIQUE, data reduction programs (Leonowicz, M. E., Cornell University, 1978); BLS78A, anisotropic block-diagonal least-squares refinement (Hirotsu, K.; Arnold, E., Cornell University, 1980); XRAY76 ("The X-ray System of Crystallographic Programs"; Stewart, J. M., Ed.; University of Maryland, Technical Report TR-445, March 1976); ORTEP, crystallographic illustration program (Johnson, C. K., Oak Ridge, TN, ORNL-3794); BOND, molecular metrics program (Hirotsu, K., Cornell University, 1978); MULTAN 78 ("A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Data"; University of York, England, Principal author P. Main). For literature description of MULTAN see: Germain, G.; Main, P.; Woolfson, M. W. *Acta Crystallogr., Sect. B* **1970**, *B26*, 274–285. Woolfson, M. M. *Acta Crystallogr., Sect. A* **1977**, *B33*, 219–225.

(10) Hamilton, W. C. *Acta Crystallogr.* **1965**, *18*, 502.

(11) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901.

(12) We propose the nomenclature "Pseudopterane" (i) to define this new ring system and the numbering sequence shown.



i

(13) Prestwich, G. D.; Wiemer, D. F.; Meinwald, J.; Clardy, J. *J. Am. Chem. Soc.* **1978**, *100*, 2560.

Stereocontrolled Synthesis of (+)-Negamycin from an Acyclic Homoallylamine by 1,3-Asymmetric Induction

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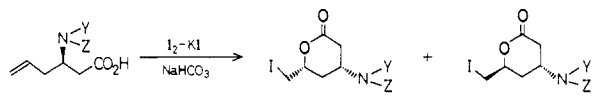
Negamycin 2-[(3*R*,5*R*)-3,6-diamino-5-hydroxyhexanoyl]-1-methylhydrazinoacetic acid (**1**), has attracted a great deal of synthetic study[1] since its isolation[2] and characterization,[3] because it possesses a strong inhibitory activity against Gram-negative bacteria, including *Pseudomonas* with low toxicity. However, none of the previous synthetic methods can afford the chiral β-amino acid effectively. We report here an efficient and enantioselective synthesis of negamycin **1** from the acyclic homoallylamine **3** in a highly stereocontrolled manner starting from methyl (*S*)-β-aminoglutarate (**4**).

A combination of enzymatic and chemical procedures was taken as our synthetic strategy as shown in Scheme I. The chiral homoallylamine **3** was considered to be a good intermediate for asymmetric induction, and the chiral half-ester **4** was chosen as the starting synthon, because it is now easily available in quantity by enzymatic hydrolysis of the prochiral precursor **5**.[4] Thus, the chiral half-ester **4** with *S* configuration was first converted to the chiral *tert*-butyl ester **6** with isobutene–H_2SO_4 (catalyst) in 88% yield, and then basic hydrolysis (0.25 N NaOH) afforded the chiral half-ester **7** with *R*-configuration quantitatively. The aldehyde **8** was prepared in 76% yield from **7** by treatment with dimethylpyrazole–DCC followed by reduction with $LiAlH_4$. Our key intermediate **9** was obtained in 80% yield by Wittig reaction of **8** with $Ph_3P{=}CH_2$ in THF at -78 °C. The compound **9** has a common double bond located at the δ,ε position and at the β,γ position for the carboxyl group and benzyloxycarbonyl (*Z*)-amino group, respectively. Therefore, asymmetric induction[5] is possible in two ways. Iodolactonization of **9a** and **9b** was first examined.



Treatment of **9a** with I_2–KI–$NaHCO_3$ in H_2O–CH_2Cl_2 at 0 °C for 4 h afforded a mixture of *cis*- and *trans*-iodo-δ-lactone (**10a**) in 94% yield, but the ratio was about 1.5:1 slightly in favor of the desired cis enantiomer. The ratio was improved to 6:1 *cis*–

(1) (a) Shibahara, S.; Kondo, S.; Maeda, K.; Umezawa, H.; Ohno, M. *J. Am. Chem. Soc.* **1972**, *94*, 4353. (b) Pierdet, A.; Nēdēlec, L.; Delaroff, V.; Allais, A. *Tetrahedron* **1980**, *36*, 1763. (c) Pasquet, G.; Boucherot, D.; Pilgrim, W. R. *Tetrahedron Lett.* **1980**, *21*, 931. (d) Kondo, S.; Iinuma, K.; Yoshida, K.; Yokose, K.; Ikeda, Y.; Shimazaki, M.; Umezawa, H. *J. Antibiot.* **1976**, *29*, 208. (e) Streicher, W.; Reinshagen, H. *Chem. Ber.* **1975**, *108*, 813.

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

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

(4) Ohno, M.; Kobayashi, S.; Iimori, T.; Wang, Yi-F.; Izawa, T. *J. Am. Chem. Soc.* **1981**, *103*, 2405. Originally, pig liver esterase was used as the enzyme, but **4** is now prepared by the enzyme of microbial origin (*Flavobacterium lutescens*), and the detailed study of the enzymatic process will be reported elsewhere.

(5) (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2 and references cited therein. (b) Bartlett, P. A.; Jernstedt, K. K. *J. Am. Chem. Soc.* **1977**, *99*, 4829.

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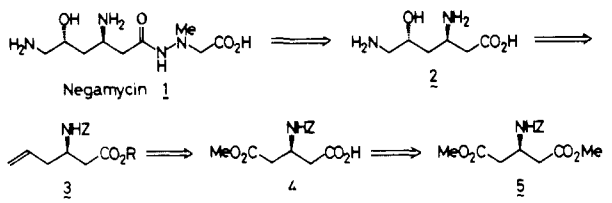
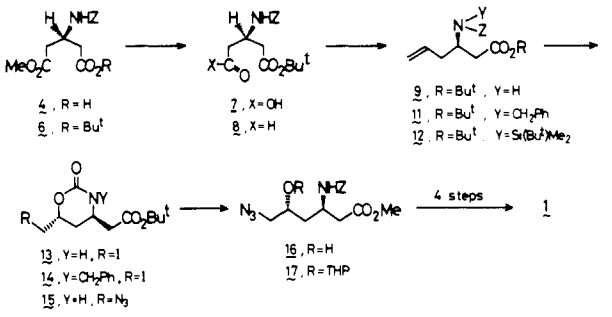
Scheme I



Scheme II



10b/*trans*-**10b**, when *N*-benzyl derivative[6] **9b** was subjected to iodolactonization under the same condition, but this approach (**6** → **9b** → **10b** → **1**) requires more steps for protection and removal of the benzyl group. Next, 1,3-asymmetric induction from the homoallylamino group of **9** was investigated. As illustrated in Scheme II, a new methodology named iodocyclocarbamation has been developed to accomplish the asymmetric functionalization of the double bond. No systematic study on 1,3-asymmetric induction from acyclic homoallylamines has been reported.[7] We found that treatment of **9** with I_2 in CH_2Cl_2 at 0 °C for 24 h resulted in cleavage of the N–Z protecting group to afford the cyclic carbamate **13** in excellent yield,[8] but in this case the desired enantiomer **13**, trans-cyclic carbamate, was obtained as a minor product (3:7 trans/cis). However, we reasoned that if the amino group could be protected further with a more bulky substituent than the CH_2CO_2R group at the α position, the opposite 1,3-asymmetric induction might be realized in a more highly specific manner. Thus, the *N*-benzyl derivative **11**[6,9] was subjected to iodocyclocarbamation (I_2 (3 equiv) in $CHCl_3$, 0 °C, 2.5 h), affording the corresponding cyclic carbamate **14** in 83% yield. The ratio of trans to cis isomers was found to be 23:1 after chromatography on silica gel, showing that a remarkably high 1,3-asymmetric induction was achieved (trans isomer, R_f 0.4; cis isomer, R_f 0.47, AcOEt–C_6H_6 (1:5)). Encouraged by this finding, the *tert*-butyldimethylsilyl (TBDMS) group was selected as a more convenient protective group, because of not only the ready introduction and removal but also the more straightforward synthesis of **1**. The acyclic carbamate **12**, prepared in situ from **9** and TBDMS triflate[10] in the presence of 2,6-lutidine in anhydrous CH_2Cl_2 at 0 °C for 40 min, was directly treated with I_2 (3 equiv) at 0 °C for 2 h. After usual workup and careful TLC on silica gel (3:1 ether/hexane, the desired trans-enantiomer **13** was obtained in 69% yield (mp 114–115 °C, $[\alpha]^{20}_D$ −51.2° (*c* 1.0, $CHCl_3$)), along with the cis isomer in 5% yield, (mp 112–113 °C, $[\alpha]^{20}_D$ −32.5° (*c* 2.0, $CHCl_3$)). The ratio of trans to cis was about 14:1.[11] The high 1,3-asymmetric induction developed here may be reasonably explained by an evaluation of two possible diastereomeric faces of transition-state conformations. The diastereomeric mixture of iodocyclocarbamate **13** was converted to the azidocyclocarbamate **15** in 98% yield. Hydrolysis of **15** with $Ba(OH)_2$ in aqueous THF followed by protection with Z–Cl/$NaHCO_3$ and esterification with CH_2N_2 afforded a diastereomeric mixture of **16** in 85% overall yields. The desired enantiomer **16** was most easily separated at this stage and purified by column chromatography on silica gel (**16**: mp 70–71 °C, $[\alpha]^{20}_D$ +49.8° (*c* 1.0, $CHCl_3$), R_f 0.30, 2:1 ether/hexane). The total synthesis of **1** was completed in five steps from **16** in 51% overall yield (protection of the hydroxyl group with DHP, saponification with 0.25 N NaOH, condensation with benzyl 1-methylhydrazinoacetate by mixed anhydride method,[1b] and removal of the protective group with H_2/Pd–C in aqueous AcOH). The synthetic material ($[\alpha]^{20}_D$ +2.4° (*c* 1.50, H_2O)) was confirmed to be identical with natural negamycin in all respects.[12]

Acknowledgment. This work was supported in part by a Grant-in-Aid for Special Project Research of the Ministry of Education, Science and Culture of Japan.

(6) This derivative was prepared from **6** as follows: (a) H_2–Pd/C, PhCHO, 81%; (b) Z–Cl–Et_3N, 86%; (c) 0.25 N NaOH, 77%; (d) 3,5-dimethylpyrazole–DCC, 89%; (e) $LiAlH_4$, 80%; (f) $Ph_3P^+CH_3I^-$–KH, 95%; (g) *p*-TsOH, 90%.

(7) (a) Fraser-Reid and his co-workers have made significant synthetic advances toward the amino sugar moiety by using oxyamination through five-membered cyclic urethanes from cyclic compounds, while our work is independently in progress. See: Georges, M.; Mackay, D.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1982**, *104*, 1101 and references cited therein. (b) 1,2-Asymmetric induction through five-membered urethanes from epoxy alcohol was achieved in a highly stereocontrolled manner. See: Minami, N.; Ko, S. S.; Kishi, Y. *Ibid.* **1982**, *104*, 1109. (c) 1,2-Asymmetric induction through a five-membered urethane from an epoxy amine was used in sugar chemistry to effect oxyamination. See: Noorzad, H. M.; Gross, D. H. *Carbohydr. Res.* **1973**, *31*, 229.

(8) Bartlett recently observed the similar result by treatment of the *N*-*tert*-butoxycarbonyl derivative of a homoallylic amine with I_2 in CH_3CN. Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *Tetrahedron Lett.* **1982**, *23*, 619.

(9) This compound was prepared from **6** as in the case[6] of **9b** except for the step of hydrolysis with *p*-TsOH.

(10) Corey, E. J.; Cho, H.; Rücker, C.; Hau, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.

(11) The silyl derivative **12** was found to be very unstable to result in facile cleavage of the N–Si bond by contact with H_2O. Therefore, it seemed likely that a partial cleavage of the silyl group occurred during the reaction, lowering the overall asymmetric induction.

(12) All new compounds were well characterized by spectroscopic analysis (IR, ^1H NMR, and MS).

1,1-Di-*tert*-butyldiazene

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1,1-Diazenes (aminonitrenes, *N*-nitrenes) are unstable species usually not isolated or directly observed.[2,3] The recent syntheses of kinetically persistent 1,1-diazenes, *N*-(2,2,6,6-tetramethylpiperidyl)nitrene and *N*-(2,2,5,5-tetramethylpyrrolidyl)nitrene, have allowed *direct* studies on this species.[4] These five- and six-membered cyclic 1,1-diazenes are equipped with a steric blockade to dimerization and are sufficiently long lived in solution at −78 °C to permit spectroscopic inspection and purification by

(1) Camille and Henry Dreyfus Teacher-Scholar, 1978–1983.

(2) For reviews of 1,1-diazene behavior see: (a) Lemal, D. M. In "Nitrenes"; Lwowski, W., Ed.; Interscience: New York, 1970; Chapter 10. (b) Ioffe, B. V.; Kuznetsov, M. H. *Russ. Chem. Rev.* (*Engl. Transl.*) **1972**, *41*, 131.

(3) For theoretical work on 1,1-diazenes see: (a) Baird, N. C.; Barr, R. F. *Can. J. Chem.* **1973**, *51*, 3303. (b) Lanthon, W. A.; Curtis, L. A.; Helve, W. J.; Lisle, J. B.; Pople, J. A. *Prof. Phys. Org. Chem.* **1974**, *11*, 1975. (c) Ahlrichs, R.; Staemmler, V. *Chem. Phys. Lett.* **1976**, *37*, 77. (d) Wagniere, G. *Theor. Chim. Acta* **1973**, *31*, 269. (e) Baird, N. C.; Wernette, D. A. *Can. J. Chem.* **1977**, *55*, 330. (f) Davis, J. H.; Goddard, W. A. *J. Am. Chem. Soc.* **1977**, *99*, 7111. (g) Gelbart, W. M.; Elert, M. L.; Heller, D. F. *Chem. Rev.* **1980**, *80*, 403.

(4) (a) Hinsberg, W. D., III; Dervan, P. B. *J. Am. Chem. Soc.* **1978**, *100*, 1608; (b) **1979**, *101*, 6142. (c) Schultz, P. G.; Dervan, P. B. *Ibid.* **1980**, *102*, 878. (d) Schultz, P. G.; Dervan, P. B. *Ibid.* **1981**, *103*, 1563. (e) Dervan, P. B.; Squillacote, M.; Lahti, P.; Sylwester, A.; Roberts, J. D. *Ibid.* **1981**, *103*, 1120. (f) Hinsberg, W. D., III; Schultz, P. G.; Dervan, P. B. *Ibid.* **1982**, *104*, 766. (g) Schultz, P. G.; Dervan, P. B. *Ibid.*, in press.

0002-7863/82/1504-6466$01.25/0