excellent yield.[19] Deprotection of DMPM groups with DDQ in the presence of MPM protections usually proceeded with excellent selectivity,[1,7,10] but unfortunately **13** gave only unsatisfactory results (3.0–4.3:1 selectivity).[20] The C-3 hydroxy compound **14**, $[\alpha]_D^{13.5}$ −2.6°, was readily converted to the C-3 keto compound **18** by Swern oxidation. The final conversion of **18** into **1** proceeded efficiently without any detectable formation of kromycin; namely, when **18** was retreated with a large excess of DDQ at room temperature, rapid deprotection of the MPM group occurred within 5 min and then the Bn group was gradually removed to give pikronolide (**1**)[21] in high yield[22] (Scheme II).

Acknowledgment. We are grateful to Professor M. Yamaguchi for providing his reagent and helpful discussions. We are indebted to N. Kakusawa for technical assistance.

Supplementary Material Available: $[\alpha]_D$, ^1H NMR, mass, and IR data for **1**, **3**, **5–9**, **12–14**, **18** (6 pages). Ordering information is given on any current masthead page.

(19) The ester **15**, synthesized similarly via **5**, was also subjected to the macrocyclization.[18] The reaction required a rather long time (20 h) and the 14-membered ring enone (**16**) was isolated in moderate yield (66%).

(20) When the *O*-acetate of **7** was treated with DDQ (1.2 equiv) in toluene–H_2O (20:1) at −10 to −5 °C for 5.5 h, deprotection of the DMPM group proceeded with excellent selectivity (22:1).

(21) Mp 140–141.5 °C (*n*-hexane–EtOAc), $[\alpha]_D^{18.5}$ +66° (*c* 0.187, MeOH) [lit.[3b] mp 139 °C, $[\alpha]_D$ +70°(MeOH)].

(22) So far, attempts to obtain **1** by oxidation of **17** derived from **16** have been unsuccessful; i.e., Swern oxidation gave only the C-5 keto compound, which was also obtained very slowly by $RuCl_2(PPh_3)_3$ oxidation.[23]

(23) Tomita, H.; Takai, K.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1605.

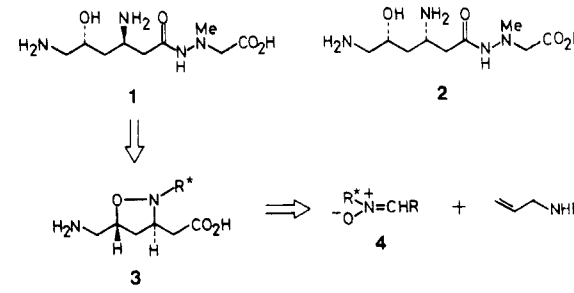
Enantioselective Total Synthesis of (+)-Negamycin and (−)-Epinegamycin by an Asymmetric 1,3-Dipolar Cycloaddition

Hideo Iida, Katsura Kasahara, and Chihiro Kibayashi*

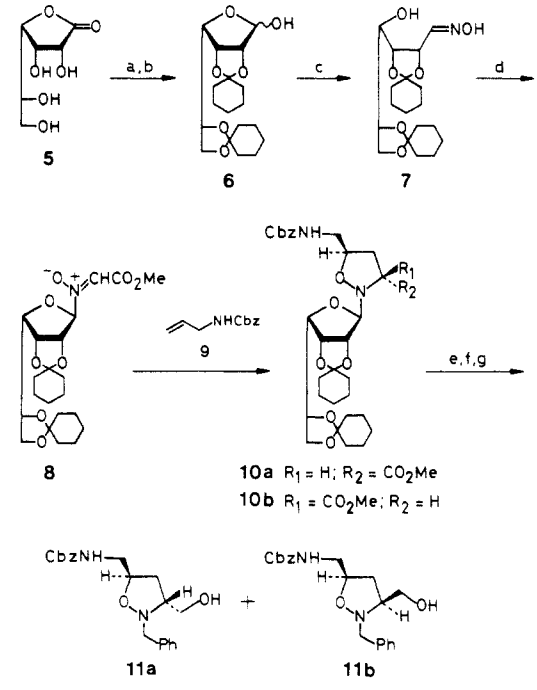
Tokyo College of Pharmacy
Horinouchi, Tokyo 192-03, Japan
Received December 12, 1985

Negamycin (**1**),[1] a structurally unique peptide-like natural product which exhibits striking activity against Gram-negative bacteria, including *Pseudomonas aerginosa*,[2] has attracted considerable synthetic interest[3,4] since its structure elucidation in 1971.[5] Herein we report an efficient chiral entry into (+)-negamycin in natural form (**1**) and the unnatural isomer (−)-3-epinegamycin (**2**). Our strategy for the synthesis of (+)-**1** is outlined retrosynthetically in Scheme I. The key step envisioned would involve a highly enantioselective 1,3-dipolar cycloaddition of an appropriate chiral nitrone[6] (**4**) to the allylamine. This cycloaddition would simultaneously create two new asymmetric centers adaptable to the 3*R*,5*R* stereochemistry of (+)-**1**. Our first objective was to develop a suitable, chiral nitrone and to demonstrate acceptable diastereoselection during the cycloaddition. Toward this end, we chose the carbohydrate as the chiral template (Schemes II).

Scheme I



Scheme II[a]



[a] (a) 1,1-Dimethoxycyclohexane, TsOH, benzene, reflux, 10 h; (b) DIBAL, toluene/THF (1:1), −78 °C, 1 h; (c) NH_2OH·HCl, py, room temperature, 2 h; (d) (**7** → **10**) methyl glyoxylate, **9**, toluene, reflux, 14 h; (e) 10% HCl/MeOH (3:8), 90 °C, 4 h; (f) $PhCH_2Br$, K_2CO_3, DMF, 50 °C, 1 h; (g) $LiAlH_4$, Et_2O, room temperature, 30 min.

D-Gulono-γ-lactone (**5**) was first converted to 2,3:5,6-di-*O*-cyclohexylidene-D-*gulo*-furanose (**6**), $[\alpha]^{20}_D$ −12.3° ($CHCl_3$), by treatment with 1,1-dimethoxycyclohexane (benzene, TsOH) followed by DIBAL reduction in 88% yield from **5**. Compound **6** was converted quantitatively to the oxime **7**, $[\alpha]^{20}_D$ +45.5° ($CHCl_3$). The nitrone **8**, generated in situ by the reaction of **7** with methyl glyoxylate probably as a mixture of *E* and *Z* isomers, was allowed to react with the allylamine derivative **9** (toluene, reflux, 14 h) to produce an inseparable mixture of the 3*R*,5*R*-trans (**10a**) and 3*S*,5*R*-cis (**10b**) adducts in 84% yield. After removal of the D-gulosyl auxiliary group by acid hydrolysis, the product was subjected to N-benzylation ($PhCH_2Br$, K_2CO_3, DMF) followed by $LiAlH_4$ reduction to provide the chromatographically separable (silica gel, 50:1 $CHCl_3$/MeOH) trans alcohol **11a**, mp 99–100 °C, $[\alpha]^{25}_D$ −16.7° ($CHCl_3$), and cis alcohol **11b**, $[\alpha]^{25}_D$ −29.0° ($CHCl_3$), in a ratio of 2:3 (55% overall yield from **10a** + **10b**). Thus utilization of the D-gulosyl chiral template in this process resulted in a highly stereobiased synthesis of **11a** and **11b**

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

(2) Korzybski, T.; Kowszyk-Gindifer, Z.; Kurytowicz, W. *Antibiotics*; American Society of Microbiology: Washington, DC, 1978; Vol. 1, pp 343–346.

(3) For syntheses of racemic negamycin, see: (a) Streicher, W.; Reinshagen, H.; Turnowsky, F. *J. Antibiot.* **1978**, *31*, 725. (b) Pierdet, A.; Nédélec, L.; Delaroff, V.; Allais, A. *Tetrahedron* **1980**, *36*, 1763. (c) Pasquet, G.; Boucherot, D.; Pilgrim, W. R. *Tetrahedron Lett.* **1980**, *21*, 931.

(4) For synthesis of (+)-negamycin in natural form, see: (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.

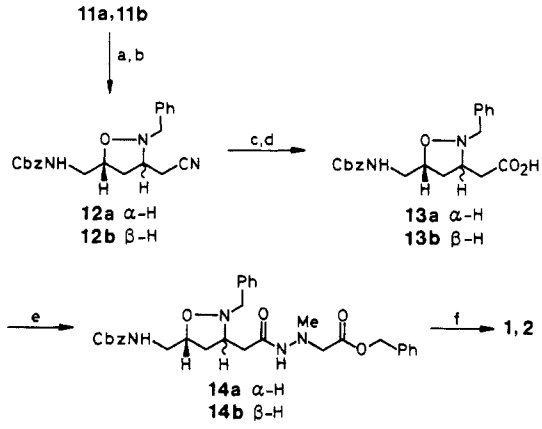
(5) Kondo, S.; Shibahara, S.; Takahashi, S.; Maeda, K.; Umezawa, H.; Ohno, M. *J. Am. Chem. Soc.* **1971**, *93*, 6305.

(6) For cycloaddition with chiral nitrones, see: (a) Vasella, A. *Helv. Chim. Acta* **1977**, *60*, 426, 1273. (b) Oppolzer, W.; Petrzilka, M. *Ibid.* **1978**, *61*, 2755. (c) Belzecki, C.; Panfil, I. *J. Org. Chem.* **1979**, *44*, 1212. (d) Wovkulich, P. M.; Uskoković, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 3956. (e) Vasella, A.; Voeffray, R. *J. Chem. Soc., Chem. Commun.* **1981**, 97. (f) Vasella, A.; Voeffray, R. *Helv. Chim. Acta* **1982**, *65*, 1134. (g) Vasella, A.; Voeffray, R. *Ibid.* **1983**, *66*, 1241. (h) Tice, C. M.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 5048. (i) Kametani, T.; Nagahara, T.; Honda, T. *Ibid.* **1985**, *50*, 2327.

(7) Ness, R. K.; Diehl, H. W.; Flecher, Jr., H. G. *J. Am. Chem. Soc.* **1954**, *76*, 763.

0002-7863/86/1508-4647$01.50/0

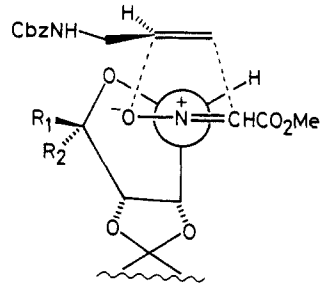
Scheme III[a]



[a] (a) TsCl, $(i\text{-Pr})_2NEt$, Et_3N/CH_2Cl_2 (1:1), 0 °C → room temperature, 10 h; (b) NaCN, $(Me)_2SO$, room temperature (2 h) → 50 °C (10 h); (c) HCl/EtOH, 0 °C → room temperature, 12 h; (d) 4% aqueous NaOH/MeOH (1:2), room temperature, 3 h; (e) $ClCO_2$ Et, Et_3N, toluene, 0 °C, 25 min, then benzyl (1-methylhydrazino)acetate, 0 °C (2 h) → room temperature (10 h); (f) H_2, Pd/C, 10% aqueous AcOH/MeOH (1:2), 3 atm, 12 h.

in 93.7% ee and 94.2% ee (determined as the (+)-MTPA esters[8]), respectively.

Both trans (**10a**) and cis (**10b**) products obtained in this cycloaddition using the *nonconjugated olefin*[9] as the dipolarophile must arise (applying Diels-Alder terminology) from the exo transition state;[10] the *E* isomer of the nitrone **8** yields the trans adduct **10a**, while the *Z* isomer yields the cis adduct **10b**. The facial selectivity observed in this cycloaddition with the *E* and *Z* nitrones may be interpreted in terms of "O-endo" transition-state model[6a,11] as shown in A, wherein, by analogy to recent reports,[12-14]



A

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 orbital overlap of the participating centers, leading to the favored *re* face approach at the prochiral olefin. A similar approach to a prochiral diene has been observed in pericyclic cyclocondensation reactions of chiral sugars.[15]

(8) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(9) The nitrone cycloadditions with monosubstituted electron-rich dipolarophiles, incapable of secondary orbital interactions, proceed through exo transition states and are described as dipole LUMO controlled, resulting in 5-substituted isoxazolidines (cf.: Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2, Chapter 9).
(10) Endo transition states would greatly be restricted by suffering from unfavorble steric interactions between the CH_2NHCbz group in the incoming dipolarophile **9** and the furan ring oxygen atom of the nitrone **8**.
(11) "O-Exo" transition states should be disfavored due to serious nonbonded interactions between the furan ring oxygen atom and the $CHCO_2Me$ group.
(12) DeShong, P.; Leginus, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1686.
(13) Jäger, V.; Schohe, R.; Paulus, E. F. *Tetrahedron Lett.* **1983**, *24*, 5501.
(14) 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.
(15) Danishefsky, S. J.; Marring, C. J.; Barbachy, M. R.; Segmuller, B. E. *J. Org. Chem.* **1984**, *49*, 4565.

Compound **11a** was converted to (+)-negamycin in six steps (Scheme III). Tosylation of **11a** followed by substitution (NaCN, Me_2SO) gave the nitrile **12a**, $[\alpha]^{17}_D$ +31.4° ($CHCl_3$), in 72% overall yield. Compound **12a** was converted to the carboxylic acid **13a**, $[\alpha]^{14}_D$ +31.7° ($CHCl_3$), in 79% yield via ethanolysis and subsequent saponification. Condensation of **13a** with benzyl (1-methylhydrazino)acetate was carried out using the mixed carboxylic acid anhydride method ($ClCO_2Et$, Et_3N)[16] affording the hydrazide **14a**, $[\alpha]^{16}_D$ +20.4° ($CHCl_3$), in 67% yield. Hydrogenolysis resulted in combined debenzylation and N-O bond cleavage; purification of the crude product by silica gel chromatography[17] gave (+)-negamycin (**1**), mp 108-115 °C dec (lit.[5] mp 110-120 °C dec), $[\alpha]^{20}_D$ +2.3° (*c* 4.07, H_2O) (lit.[5] $[\alpha]^{29}_D$ +2.5° (*c* 2, H_2O), in 75% yield. This material was found to be identical with natural negamycin (TLC, ^1H NMR, and antibacterial activity[18]).

We then completed the synthesis of optically active 3-epinegamycin (**2**) by transformation of the 3*S*,5*R*-cis isomer **11b** (Scheme III). Compound **11b** was converted in four steps to the carboxylic acid **13b**, $[\alpha]^{20}_D$ +26.0° ($CHCl_3$), which was then worked up in a manner similar to that described for **13a**, giving rise to the hydrazide **14b**, $[\alpha]^{20}_D$ +17.4° ($CHCl_3$), in 34.4% overall yield from **11b**. Hydrogenolysis of **14b** followed by silica gel chromatography[17] afforded (-)-3-epinegamycin (**2**) in 65% yield, $[\alpha]^{20}_D$ -3.2° (*c* 4.42, H_2O), mp 165-195 °C dec (for (±)-**2** lit.[3c] mp 150-180 °C dec), which had an identical ^1H NMR spectrum in a D_2O solution with that of (±)-**2**. Antibacterial activity for synthetic (-)-**2** is under investigation.

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 a spectrum of racemic epinegamycin. We also thank Professor M. Kono and Dr. K. O'hara of Tokyo College of Pharmacy for cooperating in antibacterial tests.

(16) Vaughan, J. R., Jr.; Osato, R. L. *J. Am. Chem. Soc.* **1952**, *74*, 676.
(17) Elution was initiated with $CHCl_3$/MeOH (4:1), containing 0.5% of concentrated NH_4OH, continued with gradient solvent system and finally conducted with MeOH including 1% concentrated NH_4OH.
(18) Kono, M.; O'hara, K.; Ohmiya, K.; Iida, H.; Kibayashi, C.; Kasahara, K. *Jpn. J. Antibiot.* **1986**, *39*, 247.

On the Characterization of Intermediates in the Mitomycin Activation Cascade: A Practical Synthesis of an Aziridinomitosene

Samuel J. Danishefsky* and Melissa Egbertson

Department of Chemistry, Yale University
New Haven, Connecticut 06511

Received March 4, 1986

Mitomycin C (mutamycin) is already a significant resource in cancer chemotherapy.[1,2] Potential second generation mitomycins are in various stages of preclinical development. It has long been recognized that mitomycins (**1**) are not per se biologically potent but require reductive priming.[3] One mode of action of suitably primed mitomycins involves the alkylation and cross-linking of DNA.[4] Furthermore, the reductive process seems to generate

(1) Carter, S. K.; Crooke, S. T. *Mitomycin C: Current Status and New Developments*; Academic Press: New York, 1979.
(2) (a) Cassady, J. M.; Duorose, J. D. *Anticancer Agents Based On Natural Product Models*; Academic Press: New York, 1980. (b) Remers, W. A. *Antineoplastic Agents*; Wiley: New York, 1980.
(3) (a) Iyer, V. N.; Szybalski, W. *Proc. Natl. Acad. Sci. U.S.A.* **1963**, *50*, 355. (b) Iyer, V. N.; Szybalski, W. *Science (Washington, D.C.)* **1964**, *145*, 55. (c) Nagata, C.; Matsuyama, A. *Prog. Antimicrob. Anticancer Chemother. Proc. Int. Congr. Chemother., 6th, 1969* **1970**, *2*, 423.

0002-7863/86/1508-4648$01.50/0