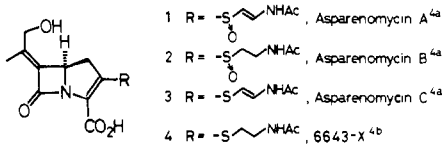
does not have a collinear arrangement of the two terminal carbon atoms and the migrating hydrogen. Such a collinear structure must be higher in energy. While inclusion of correlation might reduce the energy difference between **2** and **3**, we believe it unlikely that it would reverse the order of these two possible transition structures and conclude that the transition structure of the [1,5]-sigmatropic hydrogen transfer in **1** most likely possesses C_s symmetry and is therefore not a transition structure with a collinear hydrogen transfer.

Stereocontrolled Synthesis of an Ene-Carbapenem Antibiotic, (-)-Asparenomycin C

Kazuo Okano, Yoshinori Kyotani,[1] Hiroshi Ishihama,[1] Susumu Kobayashi, and Masaji Ohno*

Faculty of Pharmaceutical Sciences
University of Tokyo
Hongo, Bunkyo-ku, Tokyo 113, Japan
Received June 30, 1983

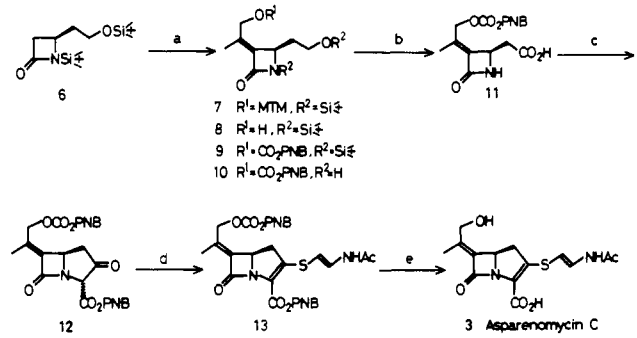
Naturally occurring carbapenem antibiotics can be classified into three groups (trans, cis, and ene types according to the structural mode of the side chain of the β-lactam ring.[2] Synthetically, trans-substituted carbapenem antibiotics have been most extensively studied by a number of research groups,[3a] and a cis-carbapenem antibiotic, (-)-carpetimycin A, was recently elaborated starting with (*S*)-3-[((benzyloxy)carbonyl)amino]-4-(methoxycarbonyl)butyric acid.[3b] However, there is no successful report for the enantioselective synthesis of asparenomycins **1**–**4**,



which belong to the third class of naturally occurring carbapenem antibiotics recently isolated.[4] They are structurally unique, because the common side chain at C-6 is a 1-(hydroxymethyl)-ethylidene group in *E* form and they have only one asymmetric carbon at C-5 with *R* configuration. We now wish to report here the first chiral and stereocontrolled synthesis of (-)-asparenomycin C starting with (*S*)-4-[(methoxycarbonyl)methyl]azetidin-2-one (**5**) as shown in Scheme I. The characteristic feature of the present synthesis includes a stereocontrolled elaboration of the required *E* tetrasubstituted olefin by a combination (one-pot reaction) of chelation-controlled aldol reaction and Peterson olefination as shown in Scheme II.

The fully silylated derivative **6** of 4-(hydroxyethyl)azetizin-2-one now easily available[5] from **5** was selected as the starting synthon. Introduction of alkylidene groups at C-3 of 2-azetidinone first studied by Shibuya et al.[6] showed that 3-alkylideneazetidin-2-ones are easily obtained by reaction of 3-(trimethylsilyl)azetidin-2-one with usual carbonyl compounds. We become interested in direct introduction of (*E*)-1-(hydroxymethyl)ethylidene group in a stereocontrolled manner by using hydroxyacetone derivatives. Thus, one-pot reaction of **6** with trimethylsilyl chloride (1 equiv)

Scheme I



a (i) 2 LDA, TMSCl, $CH_3COCH_2OCH_2SCH_3$/THF (6→7) (ii) $HgCl_2$, $CaCO_3$/aq CH_3CN (7→8) (iii) $ClCO_2PNB$, DMAP/CH_2Cl_2 (8→9) (iv) conc. HCl/MeOH (9→10); b CrO_3/Py; c (i) CDI/THF (ii) $(CO_2PNB\text{-}CO_2)_2Mg$ (iii) TsN_3, Et_3N/CH_3CN (iv) cat. $Rh_2(OAc)_4$/C_6H_6; d (i) $Cl\text{-}P(OPh)_2$, i-Pr_2NEt, DMAP/CH_3CN (ii) NaI, AgS-NHAc/CH_3CN; e H_2, Pd-C/pH 7.5 phosphate buffer, dioxane

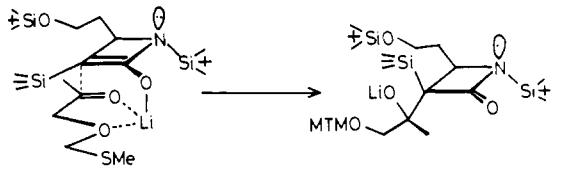
in the presence of LDA (2.3 equiv) at −78 °C (15 min) and then with [(methylthio)methoxy]acetone[7] (1.6 equiv) at −78 °C (15 min) was studied and 3-(1-(((methylthio)methoxy)methyl)-ethylidene)azetidin-2-one (**7**) was obtained as the single product in 98% yield.[7] **7**: oil, $[\alpha]^{20}_D$ −25.26° (*c* 2.01, $CHCl_3$). The stereochemistry of the olefinic moiety was assigned the *E* form based on the comparison of ^1H NMR of **7** and reference compounds[8] and proved to be the desired *E* form by eventual conversion to natural asparemonycin C. The remarkable success of the stereoselectivity could be reasonably explained by the chelation-controlled aldol reaction from the α-face followed by Peterson olefination or syn elimination[9] of Me_3SiOLi, as depicted in Scheme II.

The similar complete stereoselectivity was also observed in each case of (((benzyloxy)carbonyl)oxy)- or ((methoxymethyl)oxy)-acetone, giving the corresponding *E* isomer as the sole product. These results clearly indicate that the chelation between lithium cation and oxygens[10] plays a key role at the transition state A to control the stereochemistry of the intermediate B. The MTM group was selectively cleaved by mercuric chloride–calcium carbonate in aqueous acetonitrile[11] at 40 °C, and the resultant unstable allyl alcohol **8**, $[\alpha]^{20}_D$ −38.6° (*c* 1.99, $CHCl_3$), was reprotected with *p*-nitrobenzyl (PNB) chloroformate and 4-(dimethylamino)pyridine to give **9** in 90% yield.[12] It was gratifying to be able to isolate **8** in 84% yield by catalytic hydrogenolysis (H_2–Pd/C) of **9**, showing that hydrogenolysis of the *p*-nitrobenzyl group is much faster than the hydrogenation of the double bond of the enone moiety of the β-lactam.[13] The confirmation of this crucial step allowed us to proceed the present synthetic path from monocyclic **9** to bicyclic **13**. Deprotection of the two silyl groups was quantitatively carried out with HCl in MeOH. Oxidation of **10** with Sarett reagent afforded an acid derivative **11**, $[\alpha]^{20}_D$

(1) Research chemists of Tokyo Research Laboratories, Kowa Co., Ltd.
(2) Recently, 6-unsubstituted and very unstable carbapenem, SQ27,860, was isolated and this may belong to a new class of carbapenems, but it is synthetically considered to be a simpler precursor. Parker, W. L.; Rathnum, M. L.; Wells, J. S.; Trejo, W. H.; Principe, P. A.; Sykes, R. B. *J. Antibiot.* **1982**, *35*, 653.
(3) (a) Okano, K.; Izawa, T.; Ohno, M. *Tetrahedron Lett.* **1983**, *24*, 217 and references cited therein. (b) Iimori, T.; Takahashi, Y.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1983**, *105*, 1659, and references cited therein.
(4) Tsuji, N.; Nagashima, K.; Kobayashi, M.; Shoji, J.; Kato, T.; Terui, Y.; Nakai, H.; Shiro, M. *J. Antibiot.* **1982**, *35*, 24, and references cited therein.
(5) (a) Ohno, M.; Kobayashi, S.; Iimori, T.; Wang, Y.-F.; Izawa, T. *J. Am. Chem. Soc.* **1981**, *103*, 2405. (b) Kobayashi, S.; Iimori, T.; Izawa, T.; Ohno, M. *Ibid.* **1981**, *103*, 2406.
(6) Kano, S.; Ebata, T.; Funaki, K.; Shibuya, S. *Synthesis* **1978**, 746.
(7) ((Methylthio)methoxy)acetone was prepared directly from hydroxyacetone and (methylthio)methyl chloride according to Yamaguchi's method; Suzuki, K.; Inanaga, J.; Yamaguchi, M. *Chem. Lett.* **1979**, 1277. The intermediate **6a**, trimethylsilyl derivative of **6**, was able to be isolated and characterized.[16]
(8) 3-Isopropylidene derivative **C** was prepared from **6** and acetone in a similar manner, and we tentatively assigned the *E* stereochemistry for **7**. **7**: ^1H NMR ($CDCl_3$) δ 2.05. **C**: ^1H NMR ($CDCl_3$) δ 2.03 (cis methyl), 1.74 (trans methyl). See also: Johnston, D. B. R.; Schmitt, S. M.; Bouffard, E. A.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 313.
(9) For reviews, see: (a) Weber, W. P. "Silicon Reagents for Organic Synthesis"; Springer-Verlag: Berlin and Heidelberg, 1983. Chapter 6. (b) Colvin, E. W. "Silicon in Organic Synthesis"; Butterworths: London 1981.
(10) For instance, see: Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526.
(11) Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1976**, 3269.
(12) The direct preparation of **9** from **6** with [(((*p*-nitrobenzyl)oxy)-carbonyl)oxy]acetone in the similar manner was found to be unsuccessful.
(13) This point was considered to be a crusial step in the present synthesis, since we previously observed that a simple double bond conjugated to the carbonyl of the β-lactam was easily hydrogenated during the synthesis of PS-6 series. Okano, K.; Ohno, M., unpublished results.

0002-7863/83/1505-7186$01.50/0

Scheme II



A B

+47.82° (*c* 1.18, $CHCl_3$). The final phase of the synthesis or the construction of the bicyclic system was performed in a straightforward manner according to the known procedures. The β-keto ester **12** was obtained in 63% yield from **11** (4 steps) and conversion of **12** to the enol phosphate followed by the direct treatment with NaI (11.2 equiv) and powdered silver (*E*)-2-acetamido-1-ethenethiolate (1.1 equiv) in CH_3CN[14] afforded the desired *E* isomer **13** in 82% yield along with *Z* isomer[4a] in 17% yield.[15] Catalytic hydrogenolysis of **13** (H_2, 40 psi, 10% Pd–C, phosphate buffer solution–dioxane, pH 7.5, 49% yield) completed the total synthesis of **3**[16] identical in all respects[16] with natural asparenomycin C including the antibacterial activity. It should be mentioned here that the optically active half-ester in (*S*) form prepared by an enzyme-mediated hydrolysis of the prochiral dimethyl β-aminoglutarate can be now converted to any type of naturally occurring carbapenem antibiotics[3,5] in principle.

Acknowledgment. This work was financially supported in part by a Grant-in-Aid Special Project Research 57118002 of the Ministry of Education, Science, and Culture of Japan. We express our cordial thanks to Drs. W. Nagata and N. Tsuji of Shionogi Research Laboratories, Shionogi & Co., Ltd., for kind donation of natural asparenomycins.

Supplementary Material Available: Listings of physical properties of new compounds (9 pages). Ordering information is given on any current masthead page.

(14) Kametani, T.; Huang, S.-P.; Nagahara, T.; Ihara, M. *Heterocycles* **1981**, *16*, 65.
(15) The ratio of silver thiolate and **12** was critical in this reaction. The use of excess silver thiolate decreased the ratio of **13** and *Z* isomer, and *Z* isomer was easily lactonized after removal of the protected group.
(16) All materials described here gave satisfactory MS, IR, NMR spectra consistent with their structure (supplementary material).

Nucleophilic Trapping of 7,11-Dideoxyanthracyclinone Quinone Methides

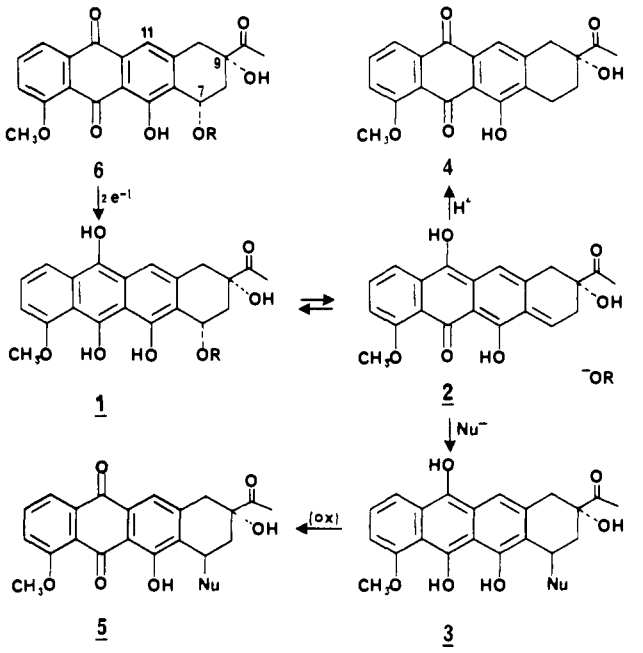
K. Ramakrishnan and Jed Fisher*

Department of Chemistry, University of Minnesota Minneapolis, Minnesota 55455

Received June 13, 1983

The anthracycline glycosides comprise an important class of antitumor antibiotics. A chemical basis for the expression of some of their biological activities has been sought in the ability of their anthraquinone moiety to undergo enzyme-catalyzed reduction to semiquinone and hydroquinone states. In the presence of O_2, both reduced states are oxidized;[1] in the absence of O_2, the hydroquinone eliminates the C-7 glycoside to provide a quinone methide.[2-4] This quinone methide has been suggested as a plausible intermediate in the covalent labeling of cellular macromolecules.[2,4] Until recently, the only known reaction of the quinone methide was irreversible solvent protonation at C-7.[5,6]

Scheme I



Kleyer and Koch[7] have now observed that the 7-deoxydaunomycinone quinone methide is efficiently trapped by a second electrophile, benzaldehyde. We report here that the quinone methides of 11-deoxyanthracyclinones possess reactivity as electrophiles, reacting with thiol and thiolate nucleophiles by addition at C-7.

Since the circumstances required for the isolation of the resultant adducts are unusual, a brief discussion of the quinone methide is necessary. All evidence indicates that the equilibrium between the hydroquinone **1** and the quinone methide **2** and free glycoside strongly favors quinone methide formation. Thus, nucleophile addition will provide an *unstable* adduct, **3**, as quinone methide formation remains favored. In order to prevent the eventual (and irrevocable) loss of the quinone methide to solvent protonation (to give **4**), it is necessary to provide to the nucleophile an oxidant, to trap **3** and convert it to the stable quinone adduct **5** (Scheme I). In searching for the requisite conditions, we have observed that the anthracycline glycoside itself is a most suitable oxidant and that the nucleophile adducts may be isolated under the following circumstances. After initial quinone methide formation and nucleophile addition, the hydroquinone adduct is trapped by disproportionation. The anthracycline glycoside hydroquinone from the disproportionation eliminates to a second quinone methide; this is also sequentially trapped by nucleophile addition and disproportionation. Hence, in the presence of a suitable nucleophile, quinone methide formation is autocatalytic. If the rate of nucleophile addition and of the disproportionation exceeds that of solvent protonation at C-7, an excellent yield for conversion of the anthracycline to the adduct may be expected. This has proven to be the case for the 11-deoxyanthracycline glycosides 11-deoxydaunomycin (**6**, R = daunosamine), aclacinomycin A, and marcellomycin, with thiol and thiolate nucleophiles.

The method that is used to initiate (and sustain) quinone methide formation is enzyme-catalyzed reduction. A typical reaction is described: To a 10.0-mL anaerobic solution of potassium ethyl xanthate (10 mM), 11-deoxydaunomycin (0.91 mM), and NADH (0.18 mM) in 35 mM potassium phosphate pH 7.0 buffer is added *V. harveyi* oxidoreductase (0.26 μmol min^{-1} NADH oxidized by riboflavin).[6] After 6 h at ambient temper-

(1) Bachur, N. R.; Gordon, S. L.; Gee, M. V.; Kon, H. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 954–957.
(2) Moore, H. W.; Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249–280.
(3) Komiyama, T.; Oki, T.; Inui, T. *J. Antibiot.* **1979**, *32*, 1219–1221.
(4) Kleyer, D. L.; Koch, T. *J. Am. Chem. Soc.* **1983**, *105*, 2504–2505.
(5) Smith, T. H.; Fujiwara, A. N.; Henry, D. W.; Lee, W. W. *J. Am. Chem. Soc.* **1976**, *98*, 1969–1971.
(6) Fisher, J.; Ramakrishnan, K.; Becvar, J. E. *Biochemistry* **1983**, *22*, 1347–1355.
(7) Kleyer, D. L.; Koch, T. *J. Am. Chem. Soc.* **1983**, *105*, 5154–5155.

0002-7863/83/1505-7187$01.50/0