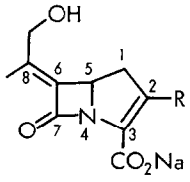
Tetrahedron Letters,Vol.25,No.21,pp 2237-2240,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

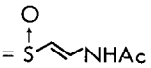
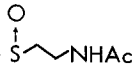
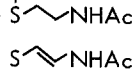
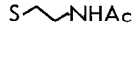
TOTAL SYNTHESIS OF dl-ASPARENOMYCINS A, B AND C, NOVEL CARBAPENEM ANTIBIOTICS

Hisao Ona and Shoichiro Uyeo*
Shionogi Research Laboratories, Shionogi & Co., Ltd.,
Fukushima-ku, Osaka, 553 JAPAN

Summary: Total synthesis of dl-asparenomycins was accomplished with direct conversion of carbonates 13a, 13b and 14a, 14b to asparenomycin esters 15 and 16 and carboxy deprotection by the $AlCl_3$-anisole method.

Asparenomycin A 1, a broad spectrum antibiotic with potent β-lactamase inhibitory activity, which was recently isolated from Streptomyces tokunonensis sp. nov. at our laboratories, has been shown to have a carbapenem structure with a hitherto unknown 1-(hydroxymethyl)ethylidene side-chain at C_6.[1] Three related antibiotics, asparenomycins B 2, C 3[1] and 6643-X 4[2] also were isolated. Recent publication[3] by M. Ohno and his associates on the total synthesis of natural asparenomycin C has prompted us to report our own work in this field.[4]



1 asparenomycin A R = 
2 asparenomycin B R = 
3 asparenomycin C R = 
4 6643-X R = 

N-Silylated allylazetidinone 5[5] was deprotonated (LDA, THF, -70°) and reacted with trimethylsilyloxyacetone to give, after acid treatment (AcOH, MeOH, r.t.), a 2:1 mixture of 5,6-trans azetidinones 6a and 6b isomeric at C_8 in 90% yield. No cis isomers were obtained. After separation by silica gel chromatography, the α-glycol groups of 6a and 6b were protected as cyclic carbonates 7a and 7b ($COCl_2$, py., CH_2Cl_2, 0°) and then N-desilylated [$(n\text{-But})_4NF$,AcOH, THF] to afford crystalline azetidinones 8a and 8b respectively in ca. 75% overall yields in both series. X-ray crystallographic analysis[6] showed that 8a had a 5RS, 6SR, 8RS (carbapenem numbering) stereochemical structure, and therefore the other isomer 8b should have a 5RS, 6SR, 8SR structure.

Conversion of 8a and 8b to bicyclic systems 12a and 12b was achieved in a straightforward manner according to the reported procedure.[7] Thus, 8a and 8b were oxidized (O_3, CH_2Cl_2, -70°, then Jones') to acids 9a and 9b (ca. 90% yields), which were converted, via β-keto-p-methoxybenzyl esters 10a and 10b

[Im_2CO, THF,] $Mg(OCOCH_2CO_2PMB)_2$, CH_3CN] and diazo derivatives 11a and 11b (p-TsN_3, Et_3N, CH_3CN), into bicyclic keto-esters 12a and 12b [$Rh_2(OAc)_4$, C_6H_6] in ca. 50% overall yields. Introduction of alkylthio groups [$ClPO(OPh)_2$, $(iPr)_2NEt$, CH_3CN followed by $AgSC_2H_2NHAc$, NaI or HSC_2H_4NHAc, $(iPr)_2NEt$] furnished carbapenems 13a and 13b as well as 14a and 14b in 60-70% yields. Direct conversion of the carbonates 13 and 14 into asparenomycin esters 15 and 16 was achieved not only from 13b and 14b having a favorable stereochemical arrangement for an E2 reaction but also from the stereochemically unfavorable epimers, 13a and 14a by the following simple operation. A solution of 13b or 14b in CH_3CN was treated with a catalytic amount of DBU at 20° for 30 min to give 15 or 16 respectively as a major product. On the other hand, conversion of 13a or 14a into 15 or 16 was effected in a different solvent system of C_6H_6-CH_2Cl_2.[8] Thus we can utilize both isomers 12a and 12b for synthesis of asparenomycins. We assume that this interesting elimination reaction goes predominantly through a typical E2 mechanism in a polar solvent whereas in a nonpolar solvent the leavability of the carbonate is insufficient for effecting the E2 elimination, thereby advancing an E1cB-type mechanism via a β-lactam enolate or C_6-carbanion, leading to the opposite direction (Fig. 1).

Removal of the carboxy protective group and isolation of the antibiotic in pure form usually constitute crucial steps in carbapenem syntheses. This elaboration was nicely achieved by applying the $AlCl_3$-anisole carboxy depro-

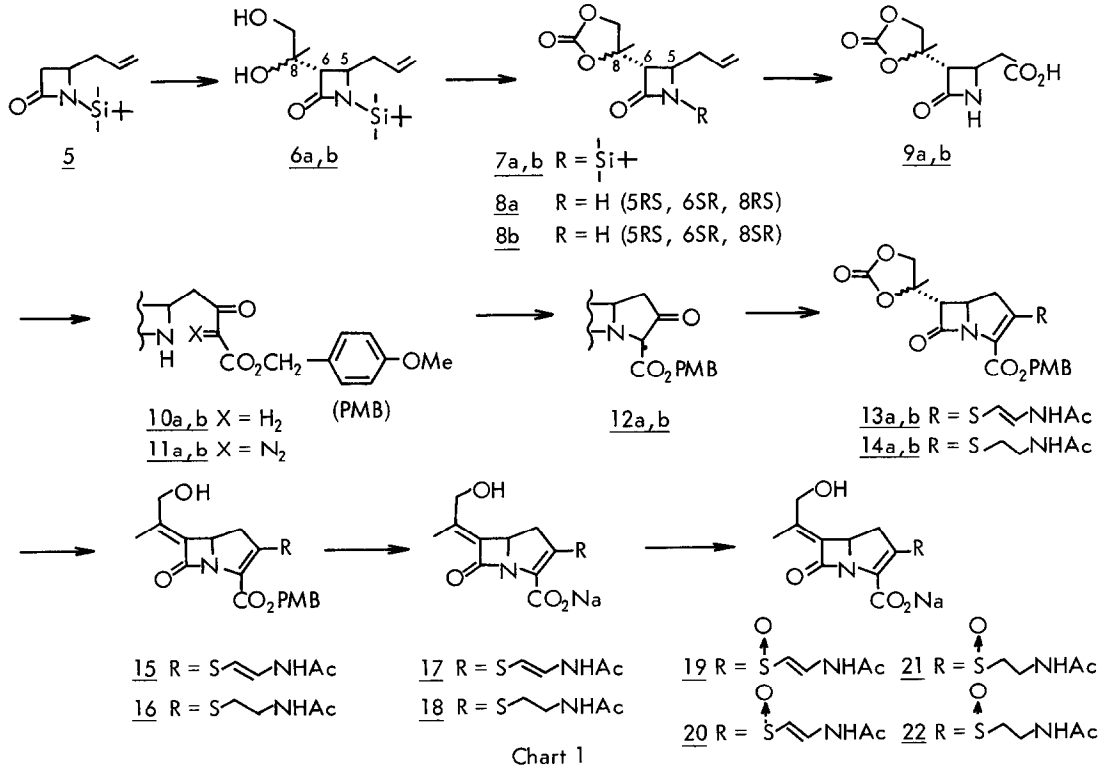


Chart 1

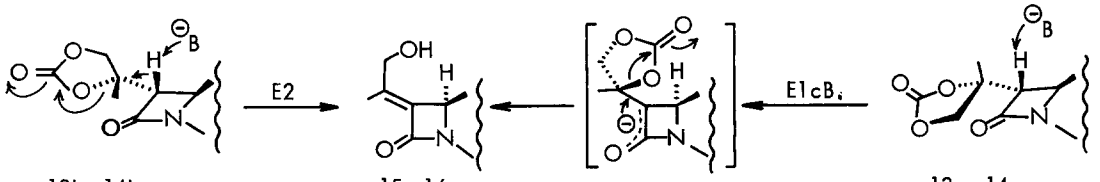


Fig. 1

tection procedure[9] (2.5 mol eq, CH_2Cl_2, -65°, 20 min) followed by purification on a Diaion HP-20 column and freeze-drying. Thus, pure sodium salt 17 was obtained as amorphous powder in 40% overall yield from 13b. This material was proved to be dl-asparenomycin C by identity of its spectral data and HPLC retention times with those of an authentic sample. Oxidation of 17 with m-CPBA in a two-phase solvent system (pH 7 phosphate buffer, CH_2Cl_2) at 0° gave a mixture of isomeric sulfoxides which were separated by preparative HPLC (Nucleosil $30C_{18}$, pH 7 phosphate buffer). Pure sodium salt 19, identified as dl-asparenomycin A, and its sulfoxide isomer 20 were obtained in 59% and 30% yields respectively. By following the same sequence of reactions, dl-asparenomycin B 21 and its sulfoxide isomer 22 were synthesized via 18 (dl-6643-X) from 16. The racemic compounds 17, 19 and 21 synthesized above showed one half the antibacterial activity against representative Gram-positive and Gram-negative bacteria when compared with the corresponding natural products.

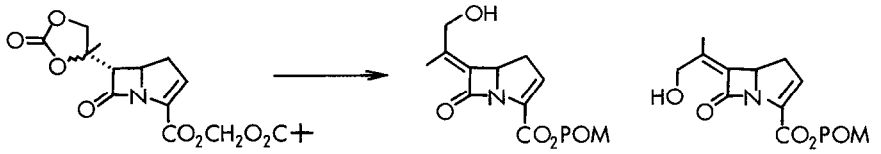
Since the cyclic carbonate grouping is stable under reaction conditions usually employed for carbapenem syntheses, and our carboxy deprotection method is convenient, the methodology described here can be used successfully for synthesizing various carbapenem and penem derivatives having the asparenomycin-type side-chain. Our work along these lines will be published in separate papers.[10]

Acknowledgement: The authors thank the following scientists of our laboratories: Drs. W. Nagata and M. Narisada (discussions), M. Shiro (X-ray crystallography), N.Tsuji and J. Shoji (samples of asparenomycins), T. Yoshida (antibacterial assay), Y. Terui (NMR) and Y. Nakagawa (mass spectroscopy).

References and Notes

1. (a) K. Tanaka, J. Shoji, Y. Terui, N. Tsuji, E. Kondo, M. Mayama, Y. Kawamura, T. Hattori, K. Matsumoto and T. Yoshida, J. Antibiot. 34, 909 (1981). (b) J. Shoji, H. Hinoo, R. Sakazaki, N. Tsuji, K. Nagashima, K. Matsumoto, Y. Takahashi, S. Kozuki, T. Hattori, E. Kondo and K. Tanaka, J. Antibiot. 35, 15 (1982). (c) N. Tsuji, K. Nagashima, M. Kobayashi, J. Shoji, T. Kato, Y. Terui, H. Nakai and M. Shiro, J. Antibiot. 35, 24 (1982).
2. S. Tanabe, M. Okuchi, M. Nakayama, S. Kimura, A. Iwasaki, T. Mizoguchi, A. Murakami, H. Itoh and T. Mori, J. Antibiot. 35, 1237 (1982).
3. K. Okano, Y. Kyotani, H. Ishihama, S. Kobayashi and M. Ohno, J. Am. Chem.

Soc. 105, 7186 (1983).
4. Our preliminary account has appeared in the form of Japanese Patent Publication (Kokai) 82-176982 (Oct. 30, 1982).
5. A. J. G. Baxter, K. H. Dickinson, P. M. Roberts, T. C. Smale and R. Southgate, J. Chem. Soc., Chem. Comm. 236 (1979).
6. This was carried out by Dr. M. Shiro.
7. T. N. Salzmann, R. W. Ratcliffe, B. G. Christensen and F. A. Bouffard, J. Am. Chem. Soc. 102, 6163 (1980).
8. This reaction was first studied in some detail using simpler carbapenems 23a and 23b in deuterated solvents by NMR spectroscopy. In $CDCl_3$, 23a gave 24E as a major product together with 24Z (ca. 20%) which decomposed to another product, probably a lactone, after aqueous work-up. In CD_3CN, 23a gave mostly the decomposed product accompanied by some 24Z. In contrast, 23b gave 24E in CD_3CN and 24Z in $CDCl_3$ as a major product.



23a,b (POM) 24E 24Z

9 Cf. T. Tsuji, T. Kataoka, M. Yoshioka, Y. Sendo, Y. Nishitani, S. Hirai, T. Maeda and W. Nagata, Tetrahedron Lett. 20, 2793 (1979). The present procedure is a modification of the original procedure which was developed for cephem and oxacephem syntheses and was successfully applied to carbapenems by Drs. M. Narisada and M. Ohtani for the first time.
10. Selected IR and NMR data.
8a: IR ($CHCl_3$) 3410, 1810, 1775 cm^{-1}; NMR ($CDCl_3$) δ 1.55 (s, 3H, C_8-Me), 2.45 (t, J = 6 Hz, 2H, C_5-CH_2), 3.07 (d, J = 2 Hz, 1H, C_6-H), 3.72 (dt, J = 2 and 6 Hz, 1H, C_5-H), 4.14 and 4.68 (ABq, J = 8 Hz, 2H, C_8-CH_2), 4.9-6.1 (m, 3H, -CH=CH_2), 6.6 (br s, 1H, NH).
8b: IR ($CHCl_3$) 3410, 1815, 1780 cm^{-1}; NMR ($CDCl_3$) δ 1.60 (s, 3H, C_8-Me), 2.47 (t, J = 6 Hz, 2H, C_5-CH_2), 3.12 (d, J = 2 Hz, 1H, C_6-H), 3.62 (dt, J = 2 and 6 Hz, 1H, C_5-H), 4.10 and 4.47 (ABq, J = 8 Hz, 2H, C_8-CH_2), 4.9-6.2 (m, 3H, -CH=CH_2), 6.5 (br s, 1H, NH).
15: IR ($CHCl_3$) 3400-3300, 1740, 1695, 1620 cm^{-1}; NMR ($CDCl_3$) δ 1.93 (s, 3H, Ac) 1.98 (s, 3H, C_8-Me), 3.04 (br d, J = 9 Hz, 2H, C_1-H_2), 3.73 (s, 3H, OMe), 4.15 (br s, 2H, C_8-CH_2), 4.79 (br t, J = 8 Hz, 1H, C_5-H), 5.16 (s, 2H, CO_2CH_2), 5.72 (d, J = 13 Hz, 1H, SCH=), 6.7-7.4 (m, 5H, =CHN and Ar-H), 8.57 (br d, J = 10 Hz, 1H, NH).
16: IR ($CHCl_3$) 3450, 3360, 1755, 1700 (sh), 1670, 1615 cm^{-1}; NMR ($CDCl_3$) δ 1.82 (s, 3H, Ac), 1.91 (s, 3H, C_8-Me), 2.91 (br d, J = 6.3 Hz, 2H, C_1-H_2), 3.1-3.5 (m, 4H, SC_2H_4N), 3.77 (s, 3H, OMe), 4.13 (br s, 2H, C_8-CH_2), 4.83 (br t, J = 9 Hz, 1H, C_5-H), 5.14 (s, 2H, CO_2CH_2), 6.7-7.1 (m, 1H, NH), 6.91 and 7.37 (A_2B_2q, J = 9 Hz, 4H, Ar-H).

(Received in Japan 10 February 1984)