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THE SYNTHESIS OF AN ASPARENOMYCIN ANALOG

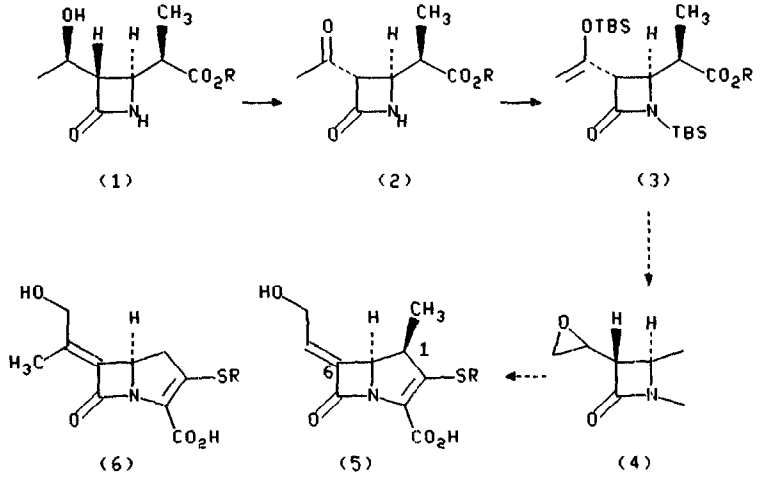
Gilles Bouthillier, Harold Mastalerz* and Marcel Ménard

Bristol-Myers Squibb Company
100 Industrial Blvd., Candiac, QC. Canada, J5R 1J1

Summary: The synthesis of an analog of the carbapenem antibiotics, the asparenomycins, is described. This analog lacks the methyl group in the 6-alkylidene side chain while a methyl group has been placed at the 1β-position. The key step involved the Lewis acid-catalyzed rearrangement of an epoxide to an allylic alcohol.

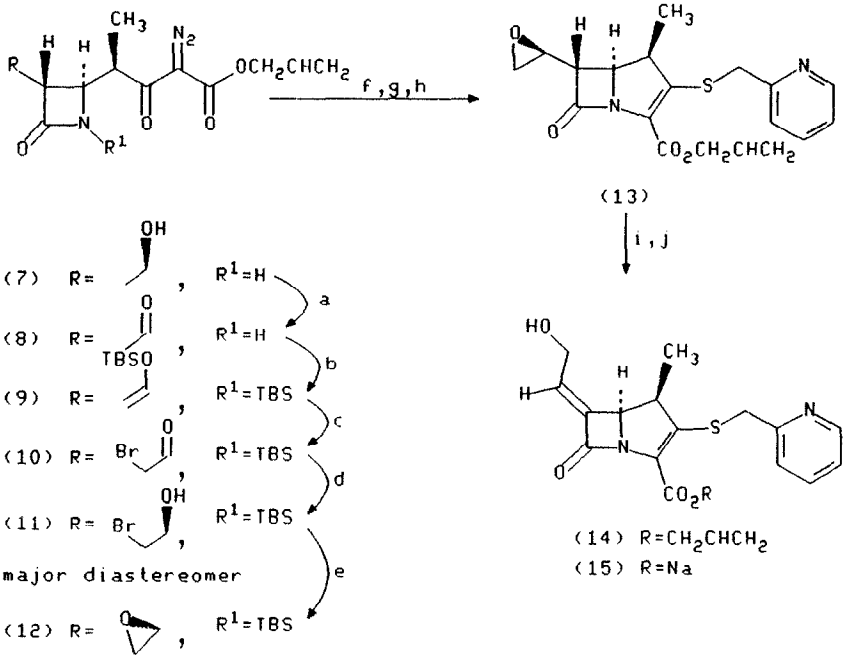
The asparenomycins, (6), are carbapenem antibiotics[1] which inhibit [2] a wide range of β-lactamases by irreversibly acylating the β-lactamase enzyme. We would like to describe the synthesis of an analog of asparenomycin, (5), in which a methyl group has been added to the β-face at position 1 and a methyl group has been removed from the alkylidene side chain at position 6. It was thought that the former modification would provide improved chemical stability[3] while the latter would result in a sterically less hindered and hence more reactive β-lactam.

Our approach to the synthesis of (5) utilizes a recently described reaction[4] in which the ketone (2) [available by Jones oxidation of (1)] is converted to the kinetic silyl enol ether (3). It was thought that the silyl enol ether (3) could be converted to the epoxide (4) and that the latter could subsequently be induced to rearrange to the asparenomycin analog (5).



The synthesis is outlined in Scheme 1. To reduce the number of steps, we began with the azetidinone (7) which already possesses the diazo sidechain that is required[3] for carbapenem formation. The first two steps, [(7) → (8) → (9)], proceeded as had been described for the formation of the simpler ester analog (3). We decided to convert the enol function of (9) to an epoxide via the bromohydrin (11). Thus treatment of the silyl enol ether (9) with bromine gave the α-bromoketone (10). It was taken directly and reduced with sodium borohydride in methanol at -78°C. This reaction was found to proceed with a high degree of regioselectivity and stereoselectivity[5]. The product is predominantly one bromohydrin isomer (11) (diastereomer ratio is 7:1 by ^{1}H NMR, stereochemistry was assigned by analogy with the work described below). This mixture of diastereomers was treated with sodium hydride in THF to afford a separable mixture of epoxide isomers. The major isomer (12) was separated and used to complete the synthesis. Removal of

SCHEME 1

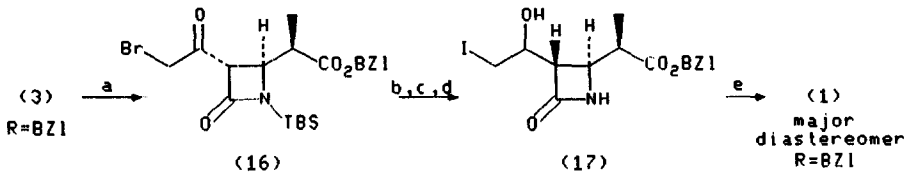


a. Jones reagent, acetone, 4°C, 95%). b. TBSOTf (2 equiv), Hünig's base (2 equiv), CH_2Cl_2, -20°C to RT 91% c. Br_2, THF, -78°C to 0°C, 76% d. $NaBH_4$, MeOH, -78°C, 71% e. NaH, THF, RT, 87% f. TBAF, HOAc, (2.6 equiv), THF, -15°C, 75% g. Rh (octonoate)$_2$ (cat.), EtOAc:hexane (3:1), 60°C, 15 min h. $ClPO(O\phi)_2$, Hünig's base, CH_3CN, -5°C, 0.5 h. then 2-picolyl methanethiol (1.75 equiv), Hünig's base, -15°C, 0.5 h 43% i. DBU (0.8 equiv), $ZnCl_2$ (0.2 equiv), CH_2Cl_2:φH (1:1), -15°C, 1 day 40% j. Sodium ethylhexanoate (1.1 equiv), Pd(dba)$_2$ (0.05 equiv), $P\phi_3$ (0.2 equiv), THF, 5 min, 48%.

the N-silyl group followed by the usual[3] sequence of reactions furnished the carbapenem (13). The rearrangement of this material to the alkylidene compound (14) was then examined. After looking at a variety of conditions, it was found that this was best effected by treating the epoxide (13) with DBU in the presence of a catalytic amount of $ZnCl_2$[6]. The product (14) is assumed to have the desired olefin configuration since the other possible isomer would be expected to be unstable and readily lactonize[7]. Palladium catalyzed deprotection afforded the asparenomycin analog[8] (15).

We tried to determine the stereochemistry of the major bromohydrin diastereomer (11) by performing a radical dehalogenation of (11) and then comparing the resulting 6-(1'-hydroxyethyl) compound with material of known configuration. Unfortunately, attempts to dehalogenate the bromohydrin (11), or the corresponding iodohydrin, using standard conditions did not lead to any characterizable products. It was assumed that the diazo function in the side chain was interfering and therefore this reaction was examined with the ester (17). This compound was prepared (Scheme 2) in the same manner as (11). Reduction of the α-bromoketone (16) was again fairly selective (diastereomer ratio, 4:1). Halogen exchange followed by removal of the N-silyl group afforded (17). This time the expected radical dehalogenation did occur and a comparison of the ^1H NMR of the resulting mixture of 3-(1'-hydroxyethyl) isomers with that of authentic (1)[9] indicated that the major diastereomer was (1). By analogy, it seems reasonable to assume that the carbon bearing the alcohol function in the major bromohydrin diastereomer (11) has the S configuration.

SCHEME 2



a. Br_2, THF, -78°C to RT, 80% b. $NaBH_4$, MeOH, -78°C to RT, 88% c. NaI (2.5 equiv), acetone, reflux, 2.5 h, 80% d. aq. HCl, MeOH, RT, 1h, 71% e. $HSnBu_3$ (5 equiv), AIBN (cat.), ϕCH_3, reflux 1 h, 78%

In summary, the synthesis of a modified asparenomycin[8] has been achieved. Noteworthy features are the selectivity observed in the reduction of 3-(2-bromo-1-oxo-ethyl) azetidinones and the stability of the diazo sidechain to different reaction conditions. The α-bromoketone (10) is a useful starting material for the synthesis of a variety of novel 6-substituted carbapenems and further examples will be reported in the future.

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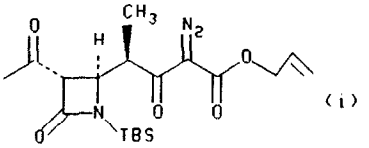
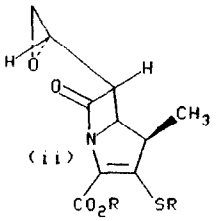
2. K. Murakami, M. Doi and T. Yoshida, J. Antibiotics, 1982, **35**, 39 and other papers in this series.
3. D.H. Shih, F. Baker, L. Cama, B.G. Christensen, Heterocycles, 1984, **35**, 39.
4. E.H. Ruediger and C. Solomon, "Novel Conversion of a 3-(1-Hydroxyethyl)-azetidinone to a 3-Hydroxy-1-β-methyl-carbapenem", ORGN 0080, The Third Chemical Congress of North America, June 5-10, 1988, Toronto, Canada. A manuscript describing this work is in preparation.
5. Previous work did not lead us to expect any significant selectivity with borohydride as reducing agent: F.A. Bouffard and B.G. Christensen, J. Org. Chem., 1981, **46**, 2208. This was confirmed by the observation that reduction of (i) using conditions that were identical to those that were used to reduce (10) afforded a 1:1 mixture of alcohol isomers. We are unable to account for the selectivity observed in the reduction of (10).



(i)

6. The need for a Lewis acid catalyst would appear to stem from the 1β-methyl group in (ii) rendering the 6β-hydrogen atom kinetically less acidic.



(ii)

7. This has been observed in an asparenomycin synthesis; See reference 8 in: H. Ona and S. Uyeo, Tet. Letters, 1984, **25**, 2237.
8. The analog (15) has a half life (pH 7.4, 37°C) of 225 h which is about three times that of the analogous carbapenem bearing the thienamycin, 6-(1'R-hydroxyethyl), side chain and approximately four times that of asparenomycin A (reference 2). The antibacterial and β-lactamase inhibitory activity of (15) will be reported elsewhere.
9. We thank Philippe Lapointe for a sample of (3) and the ^{1}H NMR spectrum of (1).

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