EFFICIENT SYNTHESES OF A NEW PENEM ANTIBIOTIC, SODIUM (5*R*,6*S*)-2-(2-FLUOROETHYLTHIO)-6-[(1*R*)-1-HYDROXYETHYL]PENEM-3-CARBOXYLATE[1]

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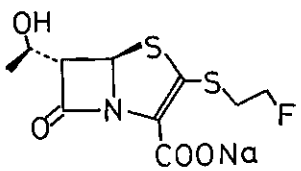
Abstract — Two useful routes to sodium (5*R*,6*S*)-2-(2-fluoroethylthio)-6-[(1*R*)-1-hydroxyethyl]penem-3-carboxylate (1) via trithiocarbonate (3) are reported. An intramolecular Wittig reaction of 6 and an oxalimide cyclization of 9 with phosphite are employed as key steps.

In a proceeding paper,[2] we described that sodium (5*R*,6*S*)-2-(2-fluoroethylthio)-6-[(1*R*)-1-hydroxyethyl]penem-3-carboxylate (1) had potent *in vitro* activity against both gram-positive and gram-negative organisms.



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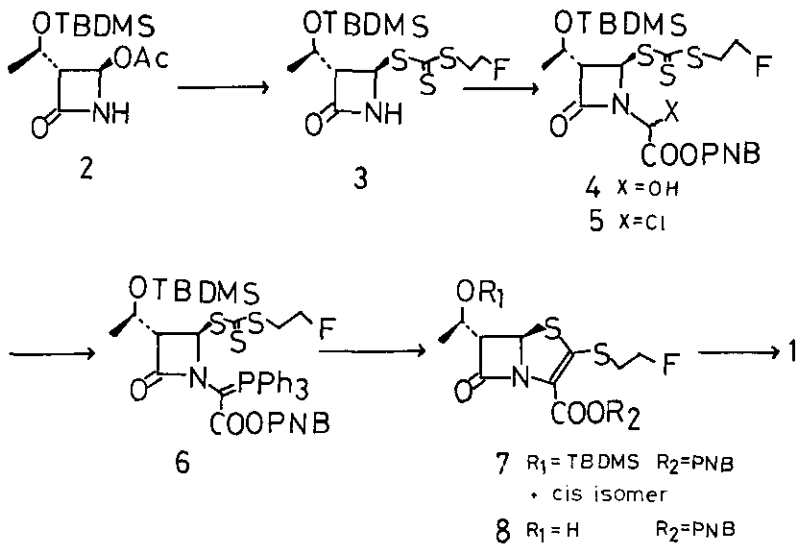
In the previous synthesis, alkylation of thioxopenam for the introduction of 2-fluoroethylthio side chain had been effected, but with less satisfactory results from the viewpoint of practical synthesis. Consequently, a more efficient and practical route to 1 was required. We report here efficient syntheses of 1 via trithiocarbonate 3. In the first attempt, the trithiocarbonate 3 could not be prepared from (3*R*,4*R*)-4-acetoxy-3-[(1*R*)-1-(t-butyldimethylsilyloxy)ethyl]-2-azetidinone (2) under usual conditions,[3] because of instability of 2-fluoroethyl mercaptide anion and 2-fluoroethyl trithiocarbonate anion.[4] Very limited reaction conditions, that is, low temperature and addition of lithium or sodium methoxide to the coexistence of carbon disulfide and 2-fluoroethyl thioacetate, were useful for the preparation of trithiocarbonate 3.

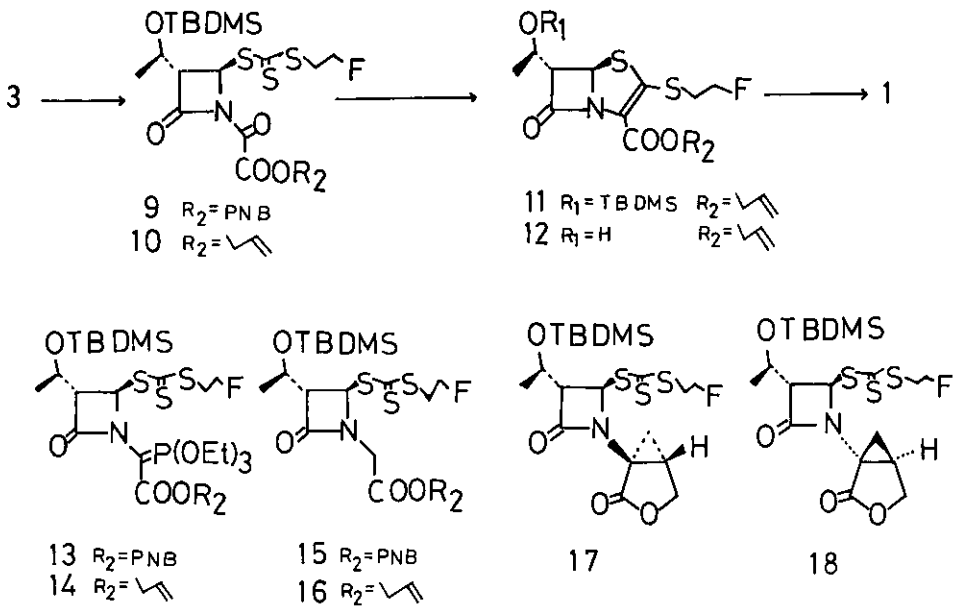
Scheme 1



TBDMS = t-Butyldimethylsilyl, PNB = p-Nitrobenzyl

Thus, lithium methoxide was added to the mixture of 2-fluoroethyl thioacetate and carbon disulfide (equimolar amounts) in methanol at -15°C and the mixture was stirred at -15°C for 30-35 min. To this solution, 4-acetoxyazetidinone 2 was added at -15∿-18°C and the mixture was stirred at the same temperature for 2 h. After addition of acetic acid, the usual work-up gave 3 in 78.2% yield. Under a similar condition, sodium methoxide was also effective to afford 3 in 70% yield. Reaction of 3 with *p*-nitrobenzylglyoxylate hydrate led to the diastereomeric mixture of hemiaminals 4 in 97% yield.[5] Conversion of 4 into the chloride 5 was carried out by reacting with thionyl chloride and 2,6-lutidine in tetrahydrofuran at -15∿-20°C. To this solution, triphenylphosphine and 2,6-lutidine were added without isolation of 5, and the mixture was mildly heated to give the phosphorane 6 in a yield of 50% over the two steps. Cyclization of 6 was achieved by heating at 120°C for 14 h in the presence of a small amount of hydroquinone. Chromatography of the reaction product gave a 74% yield of the *trans* penem 7 and a 15% yield of the *cis* penem. The formation of the *cis* penem can be explained by the equilibrium reaction of the *trans* and *cis* isomers via betaine intermediate[2] under the cyclization conditions of 6. As described in the previous paper,[2] 7 was converted into 1 by removal of t-butyldimethylsilyl and PNB groups. In this sequence, overall yield of 1 from 2 was 20%, which was improved in comparison with that of the previous thioxopenam route. In the second attempt, oxalimide cyclization reactions[6]

Scheme 2



which were independently developed by Sankyo research group and Schering research group have been applied to the more efficient penem synthesis of 1. The *p*-nitrobenzyloxalimide 9 was prepared in quantitative yield by the reaction of 3 with *p*-nitrobenzyloxalyl chloride and diisopropylethylamine in methylene chloride at 0∿5°C. Treatment of 9 with triethyl phosphite (2 eq.) in refluxing chloroform for 16 h afforded the *trans* penem 7 (53%), the phosphonium ylide 13 (13%) and the reduced product 15 (2%), which were separated by silica gel chromatography. On the other hand, preparation of allyloxalimide followed by cyclization reaction of 10 with triethyl phosphite gave the *trans* penem 11 in a high yield (71%), the phosphonium ylide 14 (8%), the reduced product 16 (2%), the cyclopropane compounds 17 (4%) and 18 (2%). The stereochemistry of 18 was established by X-ray crystallography as shown in Figure 1.[7] The conversion of 11 into 1 was achieved in a high yield of 80% over two steps, by removal of t-butyldimethylsilyl group followed by the McCombie procedure[8] for allyloxy cleavage. Thus, overall yields of 1 from 2 were 30% via the PNB ester 9 and 44.5% via the allyl ester 10, respectively. Evidently the overall yield of 1 was much improved by applying the oxalimide cyclization reaction. From the mechanistic points of view, the phosphonium ylides 13 and 14 were respectively refluxed in chloroform under similar conditions that employed for the cyclization of 9 and 10, but no detectable amount of cyclization

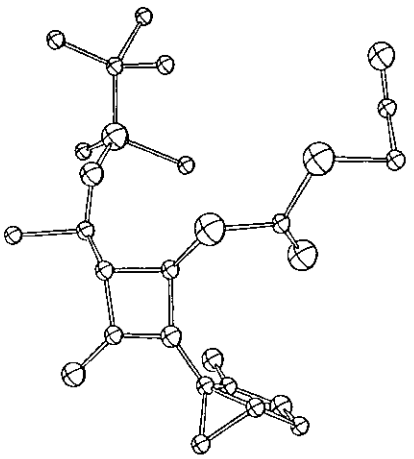
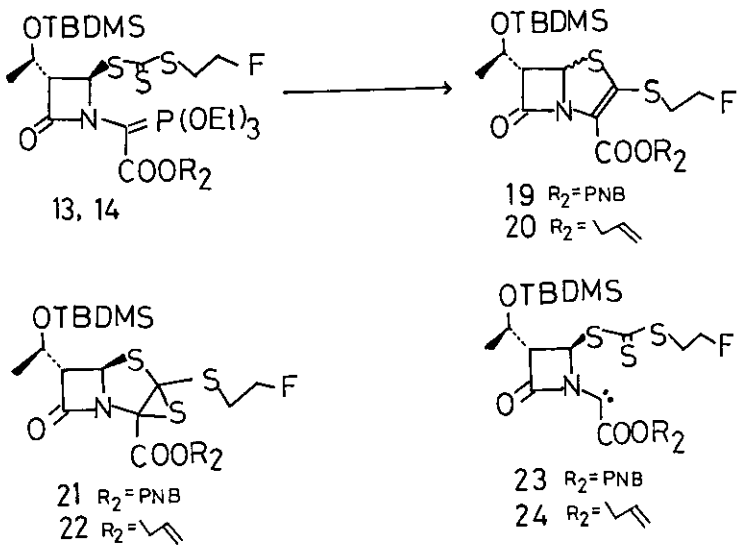


Figure 1. Projection of the structure of 18.

products (7 and 11) was observed. Cyclization of the ylides 13 and 14 proceeded at 125°C in xylene for 7 h to give *trans* and *cis* mixtures of 19 (*cis* : *trans* =

Scheme 3



ca. 1 : 3.5) and 20 (*cis* : *trans* = ca. 1 : 4) in 56% and 60% yield, respectively. These facts seem to show that the formation of the *trans* penems 7 and 11 is not via 13 and 14 but via episulfides 21 and 22, because episulfides are readily

desulfurized to olefins with triethyl phosphite. All the products in the oxalimide cyclization reaction can be explained by carbene intermediates 23 and 24 which are proposed by two groups.[6] The phosphonium ylides 13 and 14 are formed by the reactions of 23 and 24 with triethyl phosphite. The reduced products 15 and 16 are formed by hydrolysis of 13 and 14. The carbene 24 also reacts intramolecularly to the double bond to give the isomeric cyclopropane derivatives 17 and 18. In conclusion, the use of the above routes to 1, especially the oxalimide route, offers many practical advantages over utilizing alkylation of thioxopenam.

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4. Treatment of 2-fluoroethyl thioacetate with CD_3OLi in CD_3OD at -12 ∿ -15°C gave ethylene sulfide and CH_3COOCD_3 in quantitative yield. Furthermore, CD_3OLi was added to the mixture of 2-fluoroethyl thioacetate and carbon disulfide in CD_3OD at -14 ∿ -15°C, and then the mixture was stirred at 0 ∿ 5°C for 1 h to give a mixture of CH_3COOCD_3 (ca. 100%), ethylene trithiocarbonate (17%) and ethylene sulfide (83%).
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7. The crystal data are: a = 20.309 (5) Å, b = 10.314 (1) Å, c = 6.314 (1) Å, β = 91.18 (2)°, space group $P2_1$. Block-diagonal least-squares refinement with the anisotropic temperature factors reduced the R value to 0.142. The thermal parameters of the t-butyldimethylsilyl group of 18 are large due to

some disorder.

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9. Physical Data: Proton nmr chemical shifts in ppm with proton numbers, absorption patterns and coupling constants in Hz in parentheses (60 MHz nmr in $CDCl_3$, tetramethylsilane as an internal standard unless otherwise specified). 3: mp 106 – 107°C; nmr: 0.89 (9H, s), 1.21 (3H, d, 6), 3.20 (1H, t, 2), 3.68 (2H, dt, 21, 6), 4.00-4.50 (1H, m), 4.59 (2H, dt, 47, 6), 5.65 (1H, d, 2), 6.65 (1H, br s). 6: nmr: 0.68-0.95 (9H, m), 1.03-1.40 (3H, m), 2.30-3.14 (1H, m), 3.64 (2H, dt, 21.5, 6), 3.95-4.40 (1H, m), 4.55 (2H, dt, 46, 6), 4.62-5.38 (3H, m), 7.28-8.30 (19H, m). 11: mp 89-90°C; nmr (90 MHz): 0.88 (9H, s), 1.25 (3H, d, 6), 3.02-3.44 (2H, m), 3.67 (1H, dd, 4, 2), 4.60 (2H, dt, 46, 6), 4.03-4.38 (1H, m), 4.70 (2H, dm, 6), 5.12-5.53 (2H, m), 5.63 (1H, d, 2), 5.64-6.18 (1H, m). 13: nmr 0.85 (9H, s), 1.28 (3H, d, 6), 1.35 (9H, t, 6), 2.94-3.28 (1H, m), 3.68 (2H, dt, 27, 6), 3.78-4.41 (7H, m), 4.50 (2H, dt, 47, 6), 5.13 (2H, s), 6.15 (1H, m), 7.46, 8.12 (4H, A_2B_2, 9). 14: nmr: 0.86 (9H, s), 1.30 (2H, d, 6), 1.31 (9H, t, 6), 2.91-3.28 (1H, m), 3.63 (2H, dt, 21, 6), 3.88-4.60 (7H, m), 4.52 (2H, dt, 46, 6), 4.96-6.22 (4H, m). 15: nmr: 0.86 (9H, s), 1.30 (3H, d, 6), 3.32 (1H, dd, 6.5, 2.5), 3.66 (2H, dt, 21.5, 6), 3.94 (1H, d, 16), 4.32 (1H, d, 16), 4.60 (2H, dt, 46, 6), 5.32 (2H, s), 6.38 (1H, d, 2.5), 7.60, 8.26 (4H, A_2B_2, 9). 16: nmr (90 MHz): 0.88 (9H, s), 1.28 (3H, d, 6), 3.33 (1H, dd, 6, 2.5), 3.70 (2H, dt, 21.5, 6), 3.82, 4.20 (2H, AB, 18), 4.15-4.48 (1H, m), 4.60 (2H, dt, 46, 6), 4.65 (2H, d, 6), 5.18-5.50 (2H, m), 5.71-6.16 (1H, m), 6.10 (1H, d, 2.5). 17: nmr (90 MHz): 0.90 (9H, s), 1.23 (3H, d, 6), 1.30 (1H, t, 6), 1.98 (1H, dd, 9, 6), 2.40-2.65 (1H, m), 3.35 (1H, t, 2.5), 3.74 (2H, dt, 21.5, 6), 4.00-4.50 (3H, m), 4.63 (2H, dt, 46, 6), 6.28 (1H, d, 2.5). 18: mp 78-79°C; nmr (90 MHz): 0.90 (9H, s), 1.28 (3H, d, 6), 1.37 (1H, t, 6), 1.88 (1H, dd, 9, 6), 2.27-2.55 (1H, m), 3.28 (1H, dd, 6, 2.5), 3.75 (2H, dt, 21.5, 6), 3.95-4.50 (3H, m), 4.63 (2H, dt, 46, 6), 6.22 (1H, d, 2.5).

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