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SYNTHETIC STUDIES ON CARBAPENEM ANTIBIOTICS FROM PENICILLINS. III[1]. STEREOSELECTIVE RADICAL REDUCTION OF A CHIRAL 3-ISOCYANOAZETIDINONE: A TOTAL SYNTHESIS OF OPTICALLY ACTIVE CARPETIMYCINS[2]

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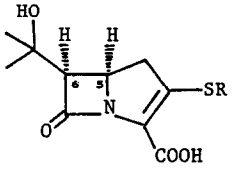
Summary: A new, efficient synthesis of the optically active carpetimycins 1 from penicillins has been achieved via, as key steps, aldol reaction of isonitrile 19, followed by n-Bu_3SnH reduction.

In recent years, there have been a number of reports concerning the chiral synthesis of carbapenem antibiotics[3]. As part of our work on ß-lactam antibiotics, we have also focused on the stereocontrolled synthesis of optically active carbapenems by utilization of the penicillin ß-lactam as a chiral precursor. We described in the preceding paper a synthesis of the 5,6-trans-carbapenems via trans introduction of alkyl side-chains at C-3 of the chiral 4-allylazetidinone 2 derived from penicillins[1]. We have now concentrated on introduction of alkyl side-chains at C-3, on the contrary, with cis stereochemistry to the 4ß-substituent of 2 for the synthesis of the 5,6-cis-carbapenems represented by carpetimycins 1[4]. Herein we report a successful approach for synthesizing 1 via, as key steps, aldol reaction of isonitrile 3, followed by radical reduction using trialkyltin hydride.

At the outset of this program we designed two schemes starting from 6 and 19 for the synthesis of 1. We considered that, on the hydride reduction of the aldol reaction products of 3, the hydride would attack from the α-face owing to a steric influence of the 4ß-substituents as depicted in 4.



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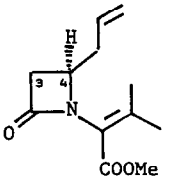

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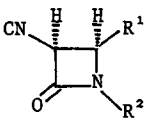

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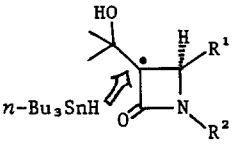
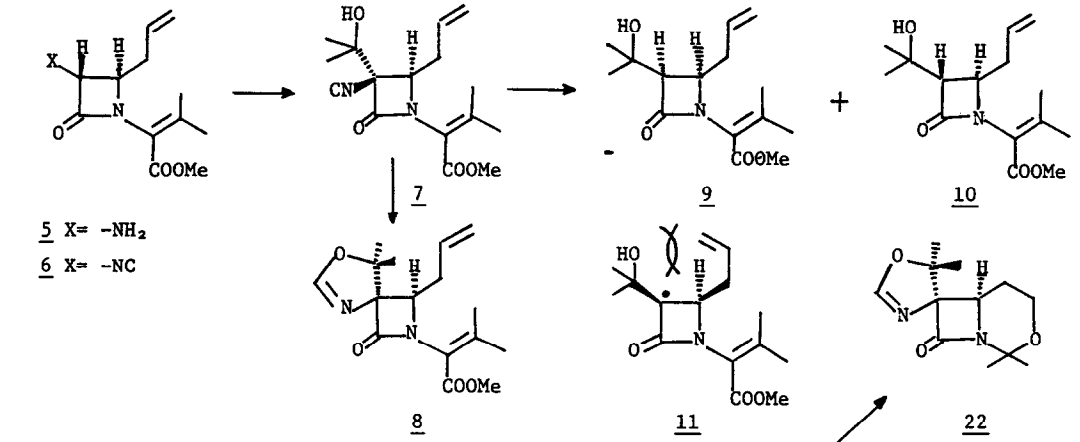


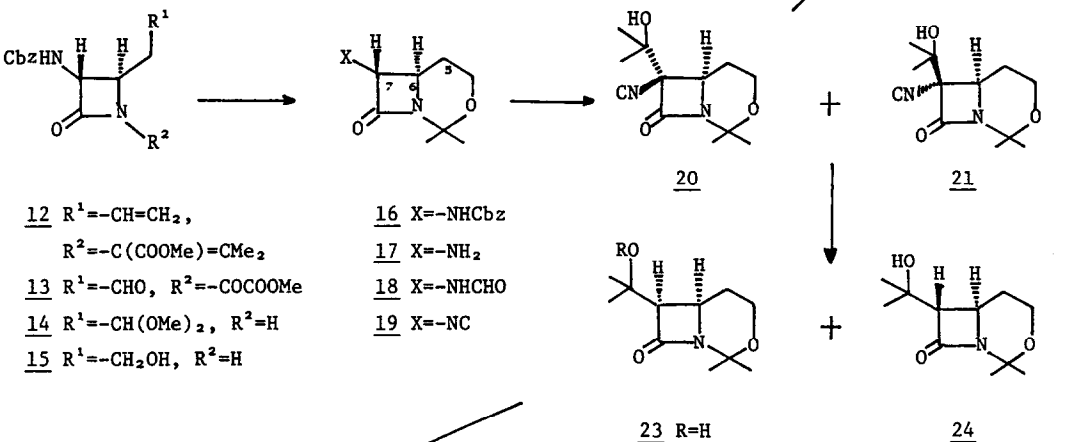
4

The starting material chosen for our initial examinations was isonitrile 6[1], which was treated with n-BuLi (1.2 equiv, THF, -78°C) and followed by addition of acetone (1.2 equiv, THF, -78°C) to afford stereospecifically the trans-substituted product 7 in 73% yield[5]. The stereochemistry of 7 was confirmed by conversion, by treatment with DBU in CH_2Cl_2, to oxazoline 8, in which a 17% NOE was observed between ß-Me (δ 1.17) and 4α-H (δ 4.13). In the above aldol reaction, acetone appeared to approach only from the less hindered α-face of the ß-lactam ring. Radical reduction of 7 was conducted using n-Bu_3SnH (1.3 equiv) in the presence of AIBN (0.1 equiv, benzene, reflux)[6]. Unfortunately, on this reduction the major product was the trans

compound 10 ($J_{3,4}$=3Hz), the ratio of 10 to the minor cis product 9 ($J_{3,4}$=6Hz) being 3:1 (97%)[7]. This result may be interpreted as follows. The steric hindrance between the 4-allyl group and the N-substituent might enforce the former to place in a rather restricted conformation in which the vinyl group of the 4-substituent is directed toward the 3-substituent as depicted in 11. The resulting severe steric repulsion might exceed that arising between the 4-substituent and the reagent and result in the predominant formation of the trans-product.

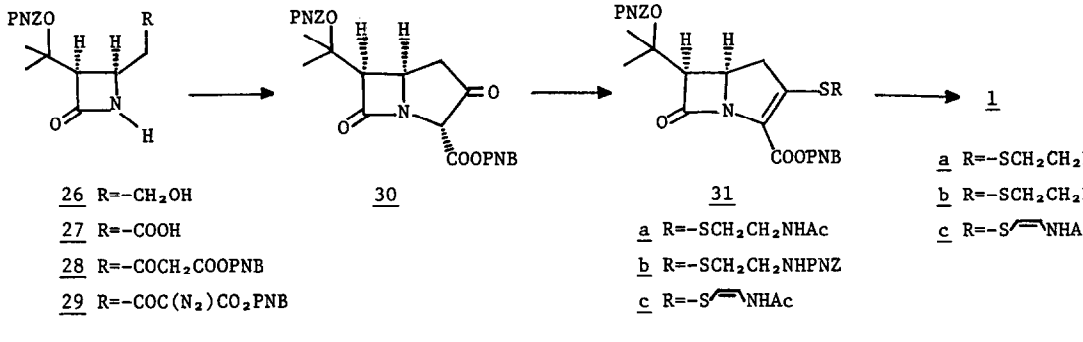


5 X= -NH_2
6 X= -NC



12 R^1=-CH=CH_2, R^2=-C(COOMe)=CMe_2
13 R^1=-CHO, R^2=-COCOOMe
14 R^1=-CH$(OMe)_2$, R^2=H
15 R^1=-CH_2OH, R^2=H

16 X=-NHCbz
17 X=-NH_2
18 X=-NHCHO
19 X=-NC



23 R=H
25 R=-COOPNB(=PNZ)

26 R=-CH_2OH
27 R=-COOH
28 R=-$COCH_2COOPNB$
29 R=-$COC(N_2)CO_2PNB$

30

31
a R=-SCH_2CH_2NHAc
b R=-SCH_2CH_2NHPNZ
c R=-S⟨═⟩NHAc

1
a R=-SCH_2CH_2NHAc
b R=-$SCH_2CH_2NH_2$
c R=-S⟨═⟩NHAc

We therefore directed to leading the substrate 6 to a more compact molecule 19 in which the steric repulsion between the 4-substituent and the N-substituent vanishes and the smallest hydrogen atoms on C-5 are directed toward the 3-substituent. The resulting steric repulsion might thus be much smaller than that discussed above and the approach of the reagent would be controlled to be of trans direction to the tetrahydrooxazine ring. Isonitrile 19 was prepared from 5 as follows. After protection of the amino group in 5 with the Cbz group ($C_6H_5CH_2OCOCl$, 2,6-lutidine, CH_2Cl_2, 0°C, 99%), the product 12 was subjected to ozonolysis (1. O_3, MeOH, -60°C; 2. Me_2S) to yield oxalimide 13, which, after protection of its aldehyde group [$CH(OMe)_3$, TsOH, 50°C], further subjected to methanolysis (reflux) to produce acetal 14 in 74% yield from 12. Reduction of 14 with $NaBH_3CN$ in 2N HCl-THF gave in 70% yield alcohol 15, which was then treated with 2,2-dimethoxypropane (BF_3-Et_2O, CH_2Cl_2) to give acetonide 16 in 89% yield. Deprotection of the Cbz group in 16 by hydrogenation (H_2/Pd-C, AcOEt) to amine 17, followed by formylation and dehydration according to our previous work[1] provided the requisite isonitrile 19 in 80% yield from 16.

Aldol reaction of 19 with acetone was conducted in a manner similar to that for 7 to form a 5:1 mixture of 20 and 21 in 97% yield[8]. The major product 20 was converted, in a similar way to 7, to oxazoline 22, in which a 18% NOE was observed between ß-Me (δ 1.37) and 4α-H (δ 3.82) indicating that 20 is trans and hence the minor product 21 is cis. The fact that 21 was formed, though as the minor product, implys that the steric hindrance of the 5-CH_2 group in 19 is indeed less than that of the allyl group in 6. Radical reduction of 20 as for 7 afforded, as expected, the cis compound 23 ($J_{6,7}$=5Hz) as a major product. The ratio of 23 to the minor trans product 24 ($J_{6,7}$=2Hz) was 2.6:1 (97%) and the isolated yield of 23 was 62%. The reduction of 21 also gave the same ratio of 23 and 24 in 95% yield[9].

For the synthesis of carpetimycins, the hydroxy group in 23 was protected with the PNZ group to 25 [1. *n*-BuLi(1.05 equiv), THF, -78°C; 2. PNBOCOCl(1.05 equiv), -78°C ~ 0°C, 76%], which was followed by removal of the acetonide group (AcOH-H_2O, 65°C) to give 26 (96%). Finally, 26 was transformed to 1 by employing the Merck method[10] [1. oxidation to 27 (86%); 2. diazotization to 29 (100%); 3. cyclization to 30 (100%); 4. activation of the carbonyl, followed by reaction with thiols to 31; 5. hydrogenation to 1 (yield from 30: 1a, 40%; 1b, 46%; 1c; 26%)[3f,8,11]].

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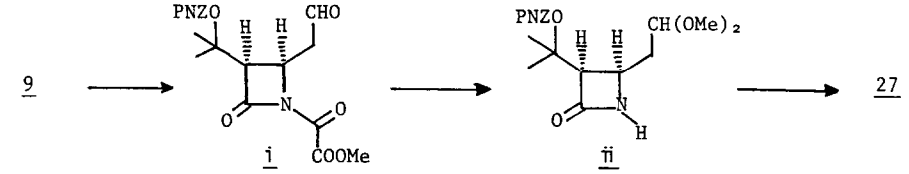
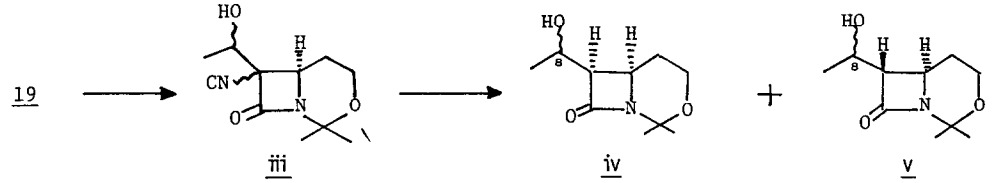
6. This reduction was carried out according to the reported procedures in the literature: (a) D. I. John, E. J. Thomas, and N. D. Tyrrell, J. Chem. Soc., Chem. Commun., 345(1979); (b) D. H. R. Barton, G. Bringmann, and W. B. Motherwell, Synthesis, 68(1980).

7. The cis product 9 was isolated (21%) and, after protection of the hydroxy group with the PNZ group (1. *n*-BuLi; 2. PNBOCOCl), transformed to 27 (61%) by a sequence of reactions [1. ozonolysis to i; 2. treatment with $CH(OMe)_3$/TsOH, followed by methanolysis to ii; 3. treatment with aq. AcOH, followed by Jones oxidation to 27].



8. After completion of our work, a similar approach for the synthesis of (+)-carpetimycins has been appeared: H. Natsugari, Y. Matsushita, N. Tamura, K. Yoshioka, and M. Ochiai, J. Chem. Soc. Perkin Trans. I, 403(1983).

9. Aldol reaction of 19 with acetaldehyde in a similar manner gave a mixture of the cis (8R and 8S isomers) and trans (8R and 8S isomers) product iii (93%), which was subjected, without separation, to *n*-Bu_3SnH reduction to yield the cis product iv (8R:8S =1:1.2) and the trans product v (8R:8S =1:3.7) in a ratio of 4.3:1 (84%).



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12. Selected data are as follows. 1c: UV $\lambda_{max}(H_2O)$ 308nm(ε=11650). 7: ^1H NMR($CDCl_3$) δ4.24(t, 1H, J=7Hz). 8: ^1H NMR(d_6-benzene) δ1.17(s, 3H), 4.13(t, 1H, J=7Hz). 9: ^1H NMR($CDCl_3$) δ 3.30(d, 1H, J=6Hz), 4.12(dt, 1H, J=6 and 7Hz). 10: ^1H NMR($CDCl_3$) δ2.90(d, 1H, J=3Hz), 3.81(dt, 1H, J=3 and 7Hz). 19: mp 150-151°C; IR(CH_2Cl_2) 2140cm^{-1}; ^1H NMR($CDCl_3$) δ4.30(d, 1H, J=2Hz). 20: mp 137-138°C. 21: mp 139-147°C(dec.). 22: mp 133-134°C; ^1H NMR($CDCl_3$) δ 1.37(s, 3H), 3.82(dd, J=5 and 10Hz). 23: mp 139-141°C; ^1H NMR($CDCl_3$) δ3.15(d, 1H, J=5Hz). 24: ^1H NMR($CDCl_3$) δ2.81(d, 1H, J=2Hz). 25: mp 117-119°C. 28: mp 126.5-127.5°C. 30: mp 94-99°C(dec.); ^1H NMR($CDCl_3$) δ3.77(d, 1H, J=6HZ), 4.34(dt, 1H, J=6 and 8Hz).

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