ZINC MEDIATED REDUCTION OF BROMOHYDRINS IN AZETIDINONES AND PENEMS. APPLICATION TO THE SYNTHESIS OF FCE 22891

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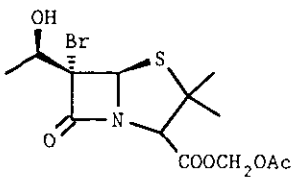
Abstract - A route to penems is described in which dehalogenative reduction of bromohydrins is carried out after ring opening of the penam nucleus. Reduction on some newly synthesized bromopenems suffered from low yields. Better yields and acceptable stereoselectivity were obtained on free-hydroxyethyl azetidinone substrates. Some parameters of the reduction are discussed.

The trans oriented 1(R)-hydroxyethyl substituent is considered to play an important role in determining the antibacterial activity of penems as well as of carbapenem antibiotics. Several studies have been devoted to the development of a synthetic methodology for the insertion of this essential moiety in the penicillin nucleus.[3] Until recently,[4] this side chain has been usually introduced on a penam magnesium bromoenolate by way of an aldol condensation. The reductive dehalogenation of the thus obtained 6α-bromo-6β-1(R)-hydroxyethylpenicillanate (e.g., 1) proceeds with inversion at C-6 position, yielding the 6α-hydroxyethylpenam with good (approx. 9:1) stereoselectivity.[3]

Figure 1



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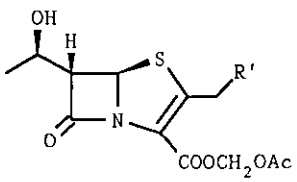
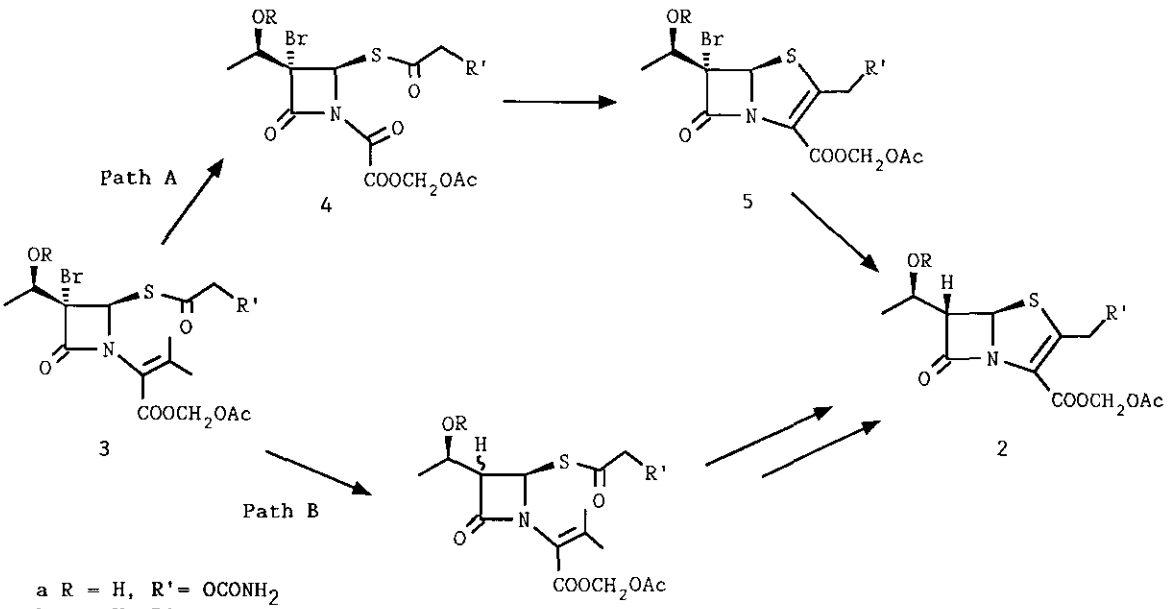


2a R'= $OCONH_2$
2b R'= OCH_3
2c R'= H

Previous studies showed that bromohydrin (**1**) is a better substrate than the corresponding dehalogenated derivative in the silver assisted 1,2 cleavage of penams.[5] Therefore in order to develop a practical, high yield synthesis of the orally active penem FCE 22891 (**2a**),[6] we examined pathways where the reductive debromination is carried out at the penem (path A) or azetidinone level (path B).

Figure 2



a R = H, R'= $OCONH_2$
b R = H, R'= OCH_3
c R = H, R'= H
d R =TMS, R'= $OCONH_2$
e R =TMS, R'= OCH_3
f R =TMS, R'= H

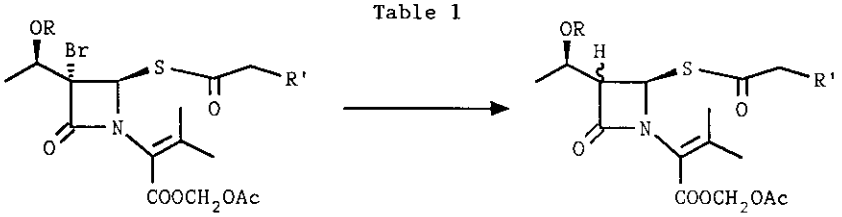
The unprotected bromohydrin (**1**) was converted into thioesters (**3a-c**)[7] as single isomers[8] (1.1 equiv. of AgCl, 1.1 equiv. of tetramethylguanidine, acetonitrile, -15°C, 60 min, then 2.5 mol equiv. of R'COCl, 10 min, 0°C; 72%, 73%, and 85% yield, respectively). According to path A, the trimethylsilyl derivatives (**3d-f**),[7] obtained by TMS protection of the OH group (TMSCl, Py, CH_2Cl_2, 30 min, room temperature), were subjected to ozonolysis (O_3, CH_2Cl_2, -70°C) to yield the dicarbonyl compounds (**4d-f**),[9] which underwent phosphite-mediated reductive condensation[10] to afford the

novel bromopenems (**5d-f**).[11] Upon aqueous acidic work-up (THF, aq. HCl, 10 min, room temperature) the desired penems (**5a-c**) were obtained in 33%, 43%, and 28% overall yield, respectively. Although reduction of the penem bromohydrins (**5a**,**b**) proved to be highly stereoselective (>95:5 of the desired α-oriented hydroxyethyl products (**2a**,**b**), the yields were unsatisafactory (35 and 38 % respectively in the best conditions), due to extensive decomposition of the substrates in all conditions tested.[12] No improvement was obtained by carrying out the reaction either using as substrate the TMS protected analogs (**5d-e**) or the more stable 2-methyl derivatives (**5c**, **5f**).[12]

Following this result, reduction of 3α-bromo-3β-1(R)-hydroxyethyl-4-acylthioazetidinones (**3**) was investigated (path B). The reductive debromination of 3,4-disubstituted azetidinones has been hardly studied and reported to be poorly diastereoselective, yielding mixtures of 3,4-trans and 3,4-cis products (approx. 6:4).[3d,13] In addition, at least in bicyclic systems, trans selectivity in the reduction of bromohydrins has been reported to increase with the steric hindrance of the hydroxyethyl protecting group (e.g., best results were obtained with t-butyldimethylsilyl as protecting group).[17] In agreement with these precedents, the reduction (Zn/1M aq. NH_4OAc, ethyl ether, room temperature)[14] of the less hindered azetidinone (**3f**), chosen as a model substrate, yielded **6f**[15] as a 1:1 trans/cis mixture. It has recently been suggested[16] that the stereochemical outcome in a palladium mediated reduction on 6,6-dihalopenams may be rationalized by assuming coordination of the metal from the β face of the intermediate enolate. A proton of the solvent bound to the metal would then effect the final step of the reduction, approaching from the same face. We speculated that the free OH group in our substrates could similarly favor trans selectivity by coordination to the metal. Therefore, we subjected the free hydroxyethyl azetidinone (**3c**) to reduction, and found an unprecedented good selectivity (Table 1, Entry 3). This outcome prompted us to extend the study to

azetidinones (**3a**) and (**3d**). Reaction times and temperatures, yields, α/β ratios, and solvent effect on **3a** and **3d** are summarized in Table 1; the corresponding reduction of 6α-bromo-6β-1(R)-hydroxyethylpenicillanate (**1a**) (Entry 1) is reported for comparison.

Table 1



Entry	Compound	temp.(°C)	α/β[a)]	Yield(%)	Solvent	Time(h)
1	1	25	90/10	82	Ether	0.67
2	3f	25	50/50	70	Ether	4.0
3	3c	25	81/19	82	Ether	1.5
4	3d	25	-	-[b)]	Ether	4.0
5	3d	25	-	-[b)]	CH_2Cl_2	4.0
6	3d	25	60/40	61	Acetone	2.0
7	3d	25	62/38	63	Acetonitrile	2.0
8	3a	25	84/16	33[c)]	Ethyl acetate	4.0
9	3a	25	82/18	70	Acetonitrile	0.75
11	3a	-5	85/15	76	Acetonitrile	1.25
12	3a	-15	88/12	75	Acetonitrile	1.30
13	3a	-10	81/19	69	THF	2.0

a) Nmr monitoring of the crude product. α/β ratios were determined by nmr from the coupling costants H(3)-H(4) in the reduction products.[15] b) All unreacted starting material recovered. c) 30% unreacted starting material recovered, 50% conversion.

The rate of the reduction of **3a** resulted significantly affected by the reaction solvent. In fact in CH_2Cl_2 and ethyl ether the reaction did not occurr at all, and only to a little extent in ethyl acetate (Entry 8, see also ref. 7). To avoid the possible influence of the poor solubility of **3a** on the reaction rate, we examined the soluble TMS derivative (**3d**). It was unaffected in CH_2Cl_2 and ethyl ether (Entries 4 and 5), while in polar

media a smooth reaction occurred, though with low trans selectivity (Entries 6 and 7). A detrimental effect of the TMS group on the reaction rate (about 2.5 times) was also observed (Entries 2 vs. 3 and 7 vs. 9). The temperature appeared to affect only moderately the α/β ratio (Entries 11 and 12).

Taking advantage of these findings a straightforward synthesis of FCE 22891 (compound **2a**) was realized. The azetidinone intermediate (**6a**) was silylated to **6d**, and then subjected to ozonolysis and phosphite-mediated carbonyl coupling. After acidic work-up, the crystalline penem (**2a**) was obtained as a single isomer in 28% overall yield.

In summary, reduction of the new bromopenems (**5a-f**) (path A) proved to be higly stereoselective. 6-Hydroxyethylpenems with the correct trans geometry (≥95%) were obtained, but overall yields were poor. On the other hand, reduction of 6-bromo-6-1(R)-hydroxyethyl-azetidinones (**3**) (path B), albeit less selective (88/12 of the desired trans isomer), offered distinct advantages in term of higher yields and practicality. This route to our selected oral penem FCE 22891 favorably compares with the ones previously described.[18]

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7. Selected physical data for azetidinone thioesters (**3**): **3a**: amorphous solid, $[\alpha]_D^{25}$ +24.9° (c=0.1, $CHCl_3$), ir (KBr) ν, cm^{-1}: 3480, 1770, 1740, 1690; ^1H nmr (300 MHz, $CDCl_3$) δ, ppm: 1.35 (3H, d, J=7.0 Hz, $C\underline{H}_3CH$), 2.10, 1.95, 1.85 (3x3H, s, CH_3), 3.83 (1H, m, $CH_3C\underline{H}$), 4.48 (2H, ABq, J=17.5 Hz, $SCOC\underline{H}_2$), 5.63 (2H, ABq, J=5 Hz, $COOC\underline{H}_2OCOCH_3$), 5.75 (2H, br s, $CONH_2$), 5.85 (1H, s, 4-H); **3b**: amorphous solid, ir (KBr) ν, cm^{-1}: 3470, 1765, 1750, 1710; ^1H nmr (300 MHz, $CDCl_3$) δ, ppm: 1.55 (3H, d, J=6.7 Hz), 2.05, 2.15, and 2.28 (3x3H, s), 2.5-3.0 (1H, br s), 3.48 (3H, s), 4.05-4.15 (3H, m), 5.75 and 5.87 (2H, two d, J=5.5 Hz), 6.05 (1H, s); **3c**: amorphous solid, $[\alpha]_D^{25}$ +28.5° (c=0.1, $CHCl_3$), ir (KBr) ν, cm^{-1}: 3480, 1770, 1745, 1710; ^1H nmr (300 MHz, $CDCl_3$) δ, ppm: 1.55 (3H, d, J=6.7 Hz), 2.05, 2.12, 2.27, 2.35 (4x3H, s), 2.80 (1H, br s), 4.15 (1H, m), 5.73 and 5.97 (2H, two d, J=5.4 Hz); **3d**: oil, ir ($CHCl_3$) ν, cm^{-1}: 1770, 1750, 1700; **3f**: oil, ^1H nmr (300 MHz, $CDCl_3$) δ, ppm: 0.18 (9H, s), 1.55 (3H, d, J=6.1 Hz), 1.95, 2.13, 2.24, 2.32 (4x3H, s), 4.15 (1H, q, J=6.1 Hz), 5.85 (2H, ABq, J=6.0 Hz), 6.05 (1H, s).

8. The correct 4(R) stereochemistry of **3a** was ascertained after reduction to **6a** by comparison with an authentic sample of the latter compound[5]

obtained by silver mediated ring opening.

9. Selected physical data for oxamides (**4d-e**): **4d**: foam, ^{1}H nmr (300 MHz, $CDCl_3$) δ, ppm: 0.20 (9H, s), 1.55 (3H, d, J=6.5 Hz), 2.15 (3H, s,), 4.18 (1H, q, J=6.5 Hz), 4.82 (2H, ABq, J=18.5 Hz), 5.1 (2H, br s), 5.90 (2H, ABq, J=4.1 Hz), 6.23 (1H, s), **4e**: oil,^{1}H nmr (300 MHz, $CDCl_3$) δ, ppm: 0.20 (9H, s), 1.55 (3H, d, J=6.4 Hz), 2.15 (3H, s,), 3.50 (3H, s), 4.13-4.22 (3H, m), 5.90 (2H, s), 6.22 (1H, s).

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11. Selected physical data for penems (**5a-f**): **5a**: amorphous solid, $[\alpha]_D^{25}$ +90.1° (c=0.5, $CHCl_3$), ir ($CHCl_3$ film) ν, cm^{-1}: 3480, 3375, 1800, 1770, 1725; ^{1}H nmr (300 MHz, $CDCl_3$) δ, ppm: 1.30 (3H, d, J=6.7 Hz), 2.13 (3H, s), 2.70 (1H, br s), 4.38 (1H, m), 5.05 and 5.47 (2H, two d, J=16.5 Hz), 4.98 (2H, br s), 5.81 (1H, s), 5.75 and 5.87 (2H, two d, J=5.5 Hz); **5b**: foam, ir ($CHCl_3$) ν, cm^{-1}: 1795, 1760, 1720; ^{1}H nmr (300 MHz, $CDCl_3$) δ, ppm: 1.33 (3H, d, J=6.1 Hz), 2.13 (3H, s), 2.60 (1H, br s), 3.41 (3H, s), 4.40 (1H, m), 4.64 (2H, ABq, J=16.0 Hz), 5.76 (1H, s), 5.87 (2H, ABq, J=5.9 Hz); **5c**: oil, $[\alpha]_D^{25}$ +98.8° (c=0.5, $CHCl_3$), ir ($CHCl_3$) ν, cm^{-1}: 1795, 1775, 1725, ^{1}H nmr (300 MHz, $CDCl_3$) δ, ppm: 1.30 (3H, d, J=6.5 Hz), 2.12 (3H, s), 2.40 (3H, s), 2.90 (1H, br s), 4.35 (1H, m), 5.75 (1H, s), 5.90 (2H, ABq, J=6.3 Hz); **5d**: oil, uv (MeOH), λ_{max} nm: 225, 322; ^{1}H nmr (300 MHz, $CDCl_3$) δ, ppm: 0.13 (9H, s), 1.28 (3H, d, J=6.5 Hz), 2.10 (3H, s), 4.33 (1H, q, J= 6.5 Hz), 5.15 and 5.47 (2H, two d, J=16.0 Hz), 4.95 (2H, br.s), 5.75 (1H, s), 5.83 and 5.89 (2H, two d, J=6.0 Hz); **5e**: oil, ^{1}H nmr (300 MHz, $CDCl_3$) δ, ppm: 0.13 (9H, s), 1.30 (3H, d, J=6.4 Hz), 2.13 (3H, s), 3.40 (3H, s), 4.37 (1H, q, J=6.4 Hz), 4.64 (2H, ABq, J=16.0 Hz), 5.24 (1H, s), 5.85 (2H, ABq, J=6.4 Hz); **5f**: oil, ir ($CHCl_3$) ν, cm^{-1}: 1795, 1770, 1720; ^{1}H nmr (300 MHz, $CDCl_3$) δ, ppm: 0.13 (9H, s), 1.30 (3H, d, J=6.5 Hz), 2.12 (3H, s), 2.40 (3H, s), 4.35 (1H, q, J=6.5 Hz), 5.71 (1H, s), 5.85 (2H, ABq, J=6.4 Hz).

12. Experimental conditions for the reduction of **5a-f** are as follows:

0.5 mmol of substrate, 10 ml of solvent, 4-6 mmol of reducing agent, 2.5 ml of a 1M ammonium acetate solution. The reaction temperature was 25°C. Reaction carried out at 0°C showed no significant differences in yields or degradation pattern. Reaction on **5a**, **5b** and **5e**, run in dioxane, isopropanol, and DMF led to decomposition. In all cases the amount of β isomer in the crude reaction mixture is ≤ 5%. Some relevant data are reported in table below:

Compound	Reducing agent	Time(min)	Solvent	Yields(%)
5a	Zn	30	Acetonitrile[a)]	35
5a	Zn/Ag	45	Acetonitrile	34
5a	Fe	120	Acetonitrile	-
5d	Zn	15	Acetonitrile[b)]	27
5b	Zn	120	Ether[c)]	38
5b	$Pd/CaCO_3$	120	Ethanol	24
5e	Zn	120	Acetonitrile or THF[d)]	10[e)]
5c	Zn	5	Acetonitrile[d)]	-[f)]
5f	Zn	5	Acetonitrile[d)]	-[f)]

a) No reaction in CH_2Cl_2 and ether; 15% and 28% of 2a were obtained in ethyl acetate and in THF respectively. b) No reaction in CH_2Cl_2, ether and ethyl acetate. In THF 22% of 2d was isolated. c) In CH_2Cl_2 trace amounts of 2b were isolated. In ethyl acetate, and CH_3CN 2b was obtained with 25% and 20% yield respectively. In THF only decomposition occurred. d) Almost no or no reaction in CH_2Cl_2, ether and ethyl acetate. e) Partial conversion (about 40%). f) Trace amounts; no starting material recovered.

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15. Selected physical data for azetidinones (**6a**, **c** and **6d**, **f**): **6a**, ir ($CHCl_3$) ν, cm^{-1}: 1760 (br), 1700 (sh); **6a** trans: ^1H nmr (300 MHz, $CDCl_3$) δ, ppm: 1.30 (3H, d, J=6.3 Hz), 1.94, 2.10, and 2.20 (3x3H, s), 3.15-3.25 (1H, br s), 3.28 (1H, dd, J_{3-4}=2.3 Hz, J=6.1 Hz), 4.27 (1H, m), 4.63 (2H, ABq, J=16 Hz), 5.36 (2H, br s), 5.63 (1H, d, J=2.4 Hz), 5.73 and 5.85 (2H, two d, J=7 Hz); **6a** cis, inter alia: 1.42 (3H, d, J=6.5 Hz), 3.65 (1H, dd, J_{3-4}=3.7 Hz, J=5.5 Hz); **6d**, ir ($CHCl_3$) ν, cm^{-1}: 1760 (br), 1710, 1690; **6d** trans: ^1H nmr (300 MHz, $CDCl_3$) δ ppm: 0.15 (9H, s), 1.25 (3H, s), 1.98, 2.10, and 2.26 (3x3H, s), 3.25 (1H,

dd, J_{3-4}=1.9 Hz, J=5.1 Hz), 4.30 (1H, m), 4.67 (2H, s), 4.95-5.12 (2H, br s), 5.75 (1H, d, J=2.0 Hz), 5.7-5.9 (2H, two d, J=6.3 Hz); **6d** cis inter alia: 1.42 (3H, d, J=6.8 Hz), 3.65 (1H, dd, J_{3-4}=3.9 Hz, J_{3-8}=1.5 Hz); **6c** trans : 1.30 (3H, d, J=6.3 Hz), 1.93, 2.10, 2.22, 2.28 (4x3H, s), 2.65-2.85 (1H, br s), 3.25 (1H, dd, J_{3-4}=2.5 Hz, J=6.3 Hz), 4.27 (1H, m)), 5.61 (1H, d, J= 2.5 Hz), 5.73, 5.85 (2H, 2d, J=6.3 Hz); **6c** cis, inter alia: 1.40 (3H, d, J=5.5 Hz), 3.63 (1H, dd, J_{3-4}=3.7 Hz, J=5.7 Hz); **6f** trans: 1.23 (3H, d, J=6.7 Hz), 1.93, 2.07, 2.20, 2.28 (4x3H, s), 3.18 (1H, dd, J_{3-4}=2.1 Hz, J=6.2 Hz), 4.25 (1H, m), 5.65 (1H, d, J=2.2 Hz), 5.65-5.75 (2H, m); **6f** cis inter alia: 1.40 (3H, d, J=6.6 Hz), 1.95, 2.12, 2.21, 2.26 (4x3H, s), 3.58, (1H, dd, J_{3-4}=3.7 Hz, J_{3-8}=1.9 Hz), 4.05 (1H, dq, J=1.8 Hz, J=6.6 Hz).

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