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Novel Synthesis of 6,6-Dibromo-2'-Z-Chloromethyl and 2'-Z-Bromomethyl Anhydropenicillins from 6,6-Dibromo 2β-(Chloromethyl) and 2β-(Bromomethyl)-2α-Methyl-Penam-3α-Carboxylic Acid Via Anhydropenicillin Rearrangement

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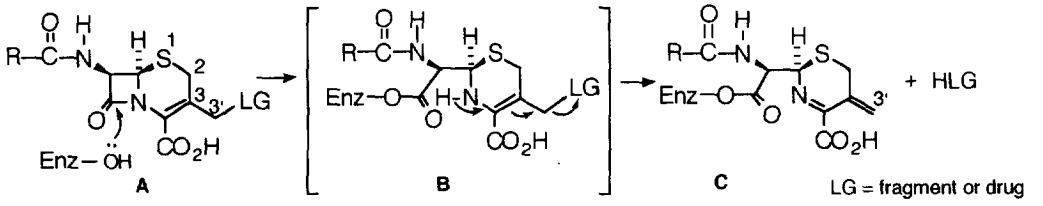
Abstract: We describe the preparation of isomerically pure 2'-Z-chloromethyl and 2'-Z-bromomethyl anhydropenicillins **2a** and **2b**, from 6,6-dibromo 2β-(chloromethyl) and 2β-(bromomethyl)-2α-methyl-penam-3α-carboxylic acid through the Wolfe rearrangement of anhydropenicillins.

It is well established that opening of the β-lactam ring of cephalosporins can be associated with release of a suitable leaving group (LG) on the side chain at position 3'[1] (Scheme 1). The nucleofugality of 3' substituents of the cephem nucleous was exploited in the use of cephalosporin compounds as elastase inhibitors.[2] X-Ray crystallographic analysis has demonstrated both acylation of the active site serine hydroxyl group and alkylation of the histidine by the 3'-exocyclic methylene group on what is commonly referred to as the *double hit mechanism*.[3] If the leaving group (LG) possesses intrinsic antibacterial activity then the cephalosporin exhibits a dual mode of action. The cephalosporin in addition to providing its own antibacterial activity acts as a targeted prodrug for the second antibacterial agent, delivering it close to its site of action. The bacteria are thus confronted by two different antibacterial agents. A variety of antibacterials have been selected as the second agent for incorporation into dual-action cephalosporins, with the fluoroquinolones[4] being the most used. Two new series of dual-action antibacterial agents have been designed and synthesized in which penems,[5,6] and carbapenems,[6] were linked at the 2' position to fluoroquinolones through either an ester or a carbamate moiety.

Scheme 1



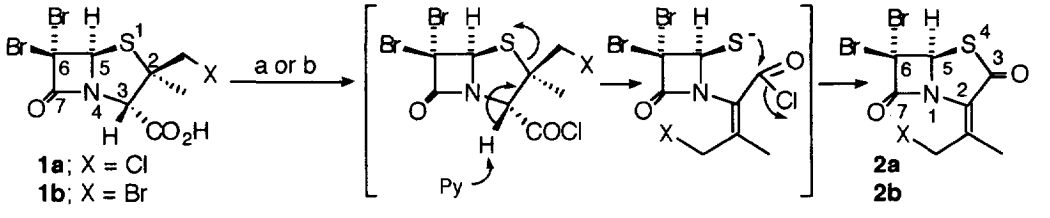
Antibody-Directed Enzyme Prodrug Therapy (ADEPT) also named Antibody Direct Catalysis (ADC) is a new conceptual approach designed to improve the selectivity of anticancer drugs.[7] ADEPT involving monoclonal antibody (MoAb)-β-lactamase conjugates as activating enzyme have received considerable attention in recent

years. The rationale for this choice is that β-lactamases catalyze the hydrolysis of the β-lactam ring of cephalosporins with quantitative expulsion of the LG at C-3' consequent to β-lactam cleavage. Cephalosporins substituted at the C-3' position with many different types of anticancer drugs, eg. aliphatic[8] and aromatic nitrogen mustards,[8-10] vinca alkaloid derivatives,[11,12] doxorubicin[13] and platinum compounds,[14] were synthesized as a potential prodrug for the treatment of solid tumors. One limitation is that the Δ-2 cephem olefin isomer is not a substrate for β-lactamases and therefore a LG at the allylic position, can not be eliminated.

In our search for the closet structural analogy to the cephalosporin series having a leaving group at the allylic position, the azetidinone-oxazolidinone structure was chosen as the target (Scheme 2). We envisioned a sequence in which a leaving group can be regioespecifically introduced at the 2β-methyl group of penicillins, and the application of the Wolfe rearrangement[15] of anhydropenicillins would selectively occur giving the (Z)-configuration of the newly formed double bond. We tested this idea with the stereocontrolled introduction of a leaving group regiospecifically at the Z allylic position of anhydropenicillins. The syntheses of the 6,6-dibromo-[2(2'-Z-chloromethyl-2'-methyl)-methylidene]-3,7-dioxo-4-thia-1-azabicyclo [3.2.0] heptane (**2a**) (6,6-dibromo-2'-Z-chloromethyl anhydropenicillin) and 6,6-dibromo-[2(2'-Z-bromomethyl-2'-methyl)-methylidene]-3,7-dioxo-4-thia-1-azabicyclo [3.2.0] heptane (**2b**) (6,6-dibromo-2'-Z-bromomethyl anhydropenicillin) are shown in Scheme 2. The starting materials were 6,6-dibromo 2β-(chloromethyl)-2α-methyl-penam-3α-carboxylic acid (**1a**) which was prepared by a similar procedure to that previously reported by us,[16] and 6,6-dibromo 2β-(bromomethyl)-2α-methyl-penam-3α-carboxylic acid (**1b**) prepared by a modified procedure, in which sulfuryl chloride was replaced by bromine. Conversion of **1a** into the corresponding anhydropenicillin **2a**[17] was achieved *via* the Wolfe methodology using pyridine and thionyl chloride in dichloromethane.

Treatment of compound **1b** using the same rearrangement conditions as used for the preparation of the anhydropenicillin **1a** (Py/Cl_2SO) resulted in the formation of a 1:2 mixture of products **2a** and **2b**. When the anhydropenicillin rearrangement was performed with [$Py/(CF_3CO)_2O/Et_3N$][18] at -60°C only the bromomethyl anhydropenicillin **2b**[17] was isolated.

Scheme 2



2a: a) Py/Cl_2SO, CH_2Cl_2, O°C;
2b: b) $Py/(CF_3CO)_2O/Et_3N$, CH_2Cl_2, -60°C.

Wolfe *et al*[19] have shown in the allylic bromination of methyl [2'β-chloro-3'β-phthalimido-4'-oxoazetidin-1'-yl]3-methylbut-2-enoate that the functionalization of the methyl groups on isopropylidine *via* free-radical intermediates occurs with no regiocontrolled selectivity. In this case, with two molar equivalents of NBS both methyl group are functionalized, with one molar equivalent of NBS a ratio 1:1 of Z:E monobrominated isomers was obtained.

In conclusion, we have been able to demonstrate that the Wolfe rearrangement of functionalized 2β-halomethylpenicillins is a suitable method for the synthesis of isomerically pure 2'-Z-chloromethyl and 2'-Z-bromomethyl anhydropenicillins **2a** and **2b**. The functionality present at the allylic position in **2a** and **2b** is ideally suited for elaboration into structural analogs. We are currently employing the same methodology toward the syntheses of 2α-chloromethyl penam derivatives[20] that can undergo the Wolfe rearrangement to form 2'-E-halomethyl anhydropenicillins.

Procedure for the synthesis of 6,6-dibromo-2'-Z-chloromethyl anhydropenicillin 2a: To a solution of 6,6-dibromo 2β-(chloromethyl)-2α-methyl-penam-3α-carboxylic acid (**1a**) (35 mg, 0.089 mmol) and dry CH_2Cl_2 (4 ml), was added pyridine (35 mg, 0.44 mmol) at 0°C. After 5 min. at 0°C the mixture was treated with 0.1 ml of a 10% solution of thionyl chloride (0.133 mmol) in dry CH_2Cl_2. After 15 min., the reaction was monitored by TLC for disappearance of the penicillanic acid. The mixture was diluted with CH_2Cl_2 (4 ml), washed with H_20, dried and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with hexane-ethyl acetate (98:2) to give compound **2a** (16.7 mg, 50%) as a colourless oil. ν_{max} (film) 1804 (β-lactam), 1711 cm^{-1} (C=O thiolactone), ^1H NMR (200 MHz, $CDCl_3$) δ 2.3 (s, 3 H, CH_3), 4.21 (d, 1 H, J 12.2, CH_2Cl), 4.48 (d, 1 H, J 12.2, CH_2Cl), 5.87 (s, 1 H, 5-H); MS,[17] (CI) m/z $[M+1]^+$ for $C_8H_6NO_2SBr_2Cl$: 374.

Procedure for the preparation of 6,6-dibromo-2'-Z-bromomethyl anhydropenicillin 2b: To a solution of 6,6-dibromo 2β-(bromomethyl)-2α-methyl-penam-3α-carboxylic acid (**1b**) (50 mg, 0.114 mmol) and dry CH_2Cl_2, (4 ml), was added 0.1 ml of 10% solution of pyridine (0.125 mmol) in dry CH_2Cl_2, at -60°C. After for 30 min., after the mixture was treated with 0.24 ml of a 10% solution of trifluoroacetic anhydride (0,171 mmol) in dry CH_2Cl_2. The resulting mixture was stirred at -60°C for 1 h, and was then treated with 0.3 ml of 10% solution of triethylamine (0.228 mmol) in dry CH_2Cl_2 and stirred for an additional 2 h, allowing it to warm to room temperature. After this time TLC showed the reaction to be complete. The resulting mixture was washed with saturated NH_4Cl (4 ml), 5% $NaHCO_3$ (4 ml) and (NaCl) (4 ml) solutions; dried, filtered and concentrated under reduced pressure. Chromatography as described for **2a**, provided the title compound **4** as a pale yellow oil (24 mg, 50%). ν_{max} (film) 1801 (β-lactam), 1700 cm^{-1} (C=O thiolactone); ^1H NMR (200 MHz, $CDCl_3$) δ 2.3 (s, 3 H, CH_3), 4.06 (d, 1 H, J 12.2, CH_2Br), 4.39 (d, 1 H, J 12.2, CH_2Br), 5.88 (s, 1 H, 5-H); MS,[17] (CI) m/z $[M+1]^+$ for $C_8H_6NO_2SBr_3$: 418.

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