3-(2-Alkoxy-1-hydroxyethyl)azetidin-2-ones: Potential Intermediates for the Synthesis of Novel Carbapenems

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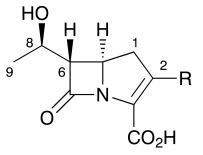
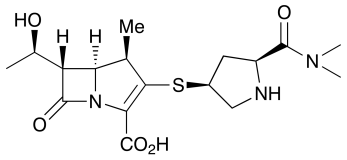
3-Vinyl and 3-isopropenylazetidin-2-ones can be transformed into the corresponding 3-(2-alkoxy-1-hydroxyethyl)azetidin-2-ones and 3-(1-alkoxy-2-hydroxypropan-2-yl)azetidin-2-ones by regioselective alcoholysis of 3-(1,2-epoxyethyl)azetidin-2-ones; 4-acetoxy-3-(1-hydroxy-2-methoxyethyl)-1-(4-methoxyphenyl)azetidin-2-one **14** is a synthetic precursor for carbapenems having both alcohol and alkoxyalcohol substituents at C-8.

The 1-hydroxyethyl substituent at C-6 is a characteristic feature of many carbapenems isolated and synthesised to date and the presence of this group consistently demonstrates potent antibacterial activity *e.g.* thienamycin **1a**, imipenem **1b** and meropenem **2**.[1] Extensive carbapenem modifications have been reported, the vast majority of which involve the substituents at C-1 and C-2.[2] However, Mastalerz *et al.* have reported a study on the synthesis and antibacterial activity of 6-aminoalkylcarbapenems[4] and related compounds. Other C-6 modifications that have been investigated include 6-(1-fluoroethyl),[5] 6-ethylidene,[6] 6-heteroethylidene[7] and 6-[1-(hydroxymethyl)ethylidene] carbapenems (asparenomycins).[8] The cholesterol absorption inhibition of 3-(2-aryloxy-1-hydroxyethyl)azetidin-2-ones has also been reported.[9]



1a R = $SCH_2CH_2NH_2$
1b R = $SCH_2CH_2NH-CH=NH$



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The synthesis of a 4-acetoxy-3-(1-hydroxy-2-methoxyethyl)-1-(4-methoxyphenyl)azetidin-2-one **14** and related compounds is now described with a view to the introduction of alkoxyalkyl and related substituents at C-8 of carbapenems. We investigated the regioselective epoxide ring opening of 3-(1,2-epoxyethyl)azetidin-2-ones with alcohols and other oxygen nucleophiles under the mild and neutral conditions[12,14,15] required for β-lactam chemistry. The required epoxides **5a–f** were obtained as illustrated in Scheme 1.

The 3-vinyl-β-lactams **4a–f** were obtained by reaction of crotonyl chloride or 3,3-dimethylacryloyl chloride with the appropriate Schiff bases **3a–f**. We have reported the use of 3-vinylazetidin-2-ones as intermediates in the synthesis of asparenomycin type carbapenem antibiotics[10] while Manhas *et al.* have reported their use as intermediates for the PS series of carbapenems.[11] The epoxides **5a–f** were prepared by oxidation of the 3-vinyl β-lactams **4a–f** with *m*CPBA and were obtained as diastereomeric mixtures. Treatment of the epoxides **5a–f** with methanol, ethanol or acetic acid with Woelm 200 neutral alumina[12] was then carried out and the epoxides **5a–f** were opened regioselectively in each case to afford the corresponding β-alkoxyalcohols **6a–h** and related esters as diastereomeric mixtures. The *trans* nature of the β-lactam protons was maintained throughout the procedure. The regioselectivity of the process was evident from the ^{1}H NMR spectrum. Diol **8** is produced in 25% yield from epoxide **5a** together with required β-alkoxy alcohol **6a** if conditions are not anhydrous. Oxidation of the β-alkoxyalcohols **6a–c** to the corresponding carbonyl compounds **7a–c** with pyridinium chlorochromate provided conclusive proof of the regioselectivity of the alumina method for opening the 3-(1,2-epoxyethyl)azetidin-2-ones with alcohols. This procedure allowed the introduction of the alcohols methanol and ethanol at C-6 while the use of acetic acid as nucleophile allowed the introduction of an ester substituent of C-6.

Regioselective methanolysis of 3-(1,2-epoxyethyl)-4-(4-methoxyphenyl)-1-phenylazetidin-2-one **5b** by DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone)[14] was achieved giving rise to the corresponding β-methoxy alcohol **6b** as a diastereomeric mixture in 49% yield. A similar alcoholysis reaction was carried out on β-lactam epoxides **5a**, **f** using cerium ammonium nitrate (CAN) as the catalyst[15] to afford the β-alkoxyalcohol products **6a, i, j, k**. The alumina, CAN and DDQ methods are suitable for use in β-lactam chemistry where mild neutral conditions are required to avoid unwanted reactions.

In order to demonstrate the utility of the procedure for carbapenem synthesis we then examined the preparation of suitably modified 4-acetoxyazetidin-2-ones, well recognised as intermediates for carbapenem synthesis.[19] This regioselective alcoholysis of 3-(1,2-epoxyethyl)azetidin-2-ones was therefore applied to a 4-acetoxy substituted azetidin-2-one which would afford products which could be considered as precursors for carbapenems having the β-alkoxy alcohol type substituent at C-6. The 4-acetoxy-3-vinylazetidin-2-one **12** was obtained from the corresponding 4-formyl-3-vinylazetidin-2-one[20] (Scheme 2) by oxidation to the carboxylic acid followed by decarboxylation–acetoxylation.[10] Epoxidation of the vinyl compound **12** afforded the epoxide product **13** as a diastereomeric mixture which was then reacted with methanol in the presence of alumina to afford the corresponding β-methoxy alcohol **14** as a diastereomeric mixture.

A procedure for the synthesis of β-lactams containing a β-alkoxy alcohol type substituent at C-3 is described. This reaction gives access to β-lactam products which have the characteristic hydroxy group at C-5 of the side chain as found in clinically important carbapenems, and contain an additional alkoxyalkyl substituent at C-6. The development of this methodology for the stereoselective introduction of varied nucleophiles at C-9 of carbapenems is currently in progress.

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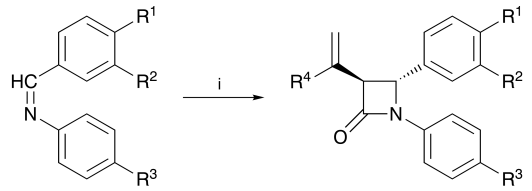
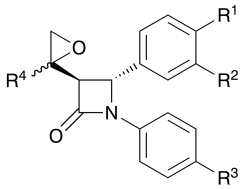
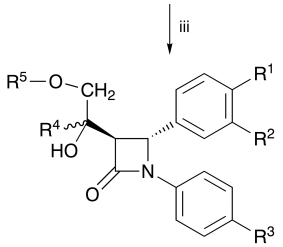


3a–f

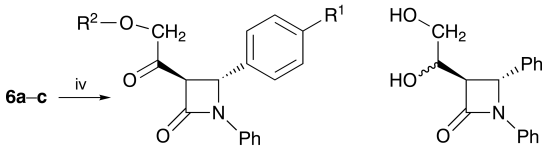
4a R^1 = H, R^2 = H, R^3 = H, R^4 = H
b R^1 = OMe, R^2 = H, R^3 = H, R^4 = H
c R^1R^2 = OCH_2O, R^3 = CO_2Me, R^4 = H
d R^1 = F, R^2 = H, R^3 = CO_2Me, R^4 = H
e R^1R^2 = OCH_2O, R^3 = CO_2Me, R^4 = Me
f R^1 = H, R^2 = H, R^3 = OMe, R^4 = H



5a R^1 = H, R^2 = H, R^3 = H, R^4 = H
b R^1 = OMe, R^2 = H, R^3 = H, R^4 = H
c R^1R^2 = OCH_2O, R^3 = CO_2Me, R^4 = H
d R^1 = F, R^2 = H, R^3 = CO_2Me, R^4 = H
e R^1R^2 = OCH_2O, R^3 = CO_2Me, R^4 = Me
f R^1 = H, R^2 = H, R^3 = OMe, R^4 = H



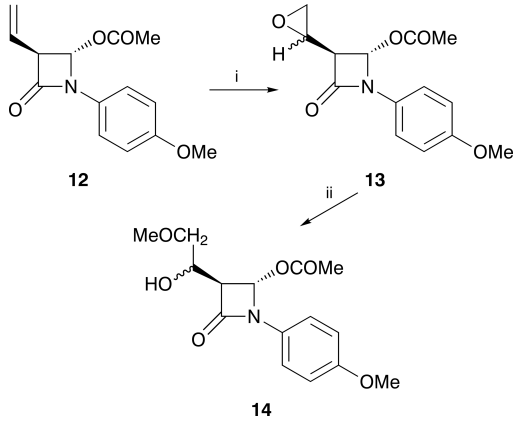
6a R^1 = H, R^2 = H, R^3 = H, R^4 = H, R^5 = Me
b R^1 = OMe, R^2 = H, R^3 = H, R^4 = H, R^5 = Me
c R^1R^2 = OCH_2O, R^3 = CO_2Me, R^4 = H, R^5 = Et
d R^1 = F, R^2 = H, R^3 = CO_2Me, R^4 = H. R^5 = Me
e R^1R^2 = OCH_2O, R^3 = CO_2Me, R^4 R^5 = Me
f R^1 = OMe, R^2 = H, R^3 = H, R^4 = H, R^5 = Et
g R^1 = OMe, R^2 = H, R^3 = H, R^4 = H, R^5 = COMe
h R^1R^2 = OCH_2O, R^3 = CO_2Me, R^4 = H, R^5 = COMe
i R^1 = H, R^2 = H, R^3 = H, R^4 = H. R^5 = Et
j R^1 = H, R^2 = H, R^3 = OMe, R^4 = H, R^5 = Me
k R^1 = H, R^2 = H, R^3 = OMe, R^4 = H, R^5 = $CHMe_2$



7a R^1 = H, R^2 = Me
b R^1 = OMe, R^2 = Me
c R^1 = OMe, R^2 = Et

8

Scheme 1 *Reagents and conditions*: i, MeCH=CHCOCl or $(Me)_2C$=CHCOCl, Et_3N; ii, *m*CPBA; iii, R^5OH, alumina, DDQ, or CAN; iv, pyridinium chlorochromate



12 **13** **14**

Scheme 2 *Reagents and conditions*: i, *m*CPBA, CH_2Cl_2; ii, MeOH, alumina

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Techniques used: ^1H and ^{13}C NMR, IR, mass spectrometry, TLC

Schemes: 2

Tables: 1

References: 23

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