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Nitrate Ester Derivatives from Epoxides Using CAN: Efficient Preparation of Key Intermediates in the Synthesis of 4-Alkoxytrinems.

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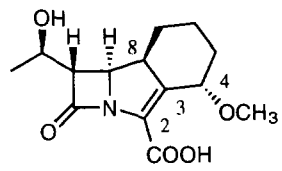
Abstract: A regio and stereoselective opening reaction of epoxide with CAN (0.5 equivalents) in aprotic solvents is descried. This novel reaction allowed the preparation of versatile nitrate ester derivatives as useful intermediates in the synthesis of trinems widely substituted at the position C-4. © 1997 Elsevier Science Ltd.

Trinems, formerly named tribactams, are novel tricyclic β-lactam derivatives discovered[1] by GlaxoWellcome some years ago, endowed with outstanding chemical and metabolic stability. In particular, sanfetrinem **1**, shown in Fig.1, is a broad-spectrum antibacterial agent highly resistant to β-lactamases and dehydropeptidases currently undergoing clinical trials.

Figure 1



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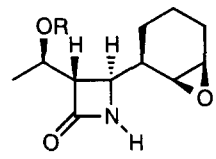

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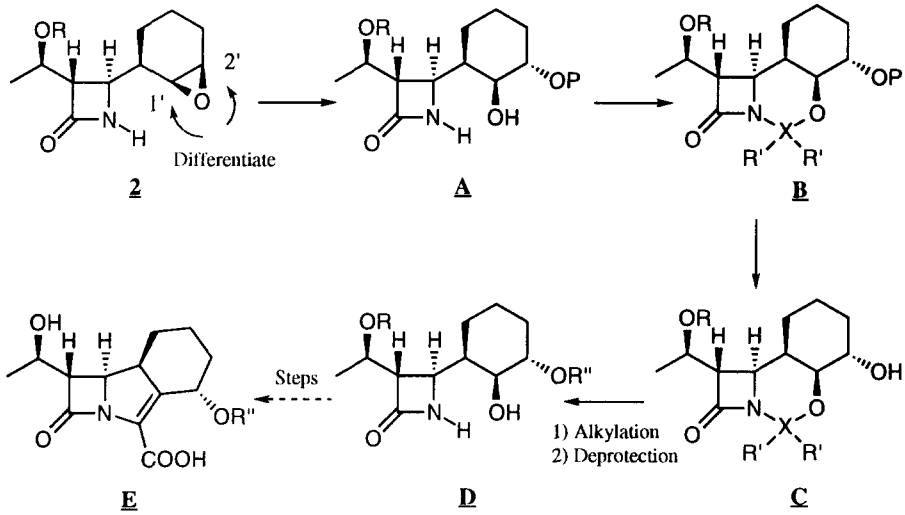
Its stereoselective synthesis[2] was efficiently performed, starting from the commercially available 4-acetoxy-3-[(R)-1-*tert*-butyldimethylsilyloxyethyl]-2-azetidinone[3], following different synthetic routes. Epoxide derivative **2**, depicted in Fig.1 (R=TBS), was identified[4] as a key synthetic intermediate in the preparation of this tricyclic β-lactam template. The acid catalysed (TsOH) opening reaction of the epoxide with MeOH gave in high yield secondary alcohol derivative **3** (R' = CH_3), shown in Scheme 2, with complete regio and stereocontrol. This reaction was found to be efficient only with few simple alcohols (MeOH, EtOH, i-PrOH, Ethylene glycol), used as solvent[5] and thus, in order to synthesise a wider range of 4-alkoxytrinems, we wished to explore alternative routes.

The general synthetic strategy we decided to adopt is shown in Scheme 1. In this approach, the key step is represented by the opening reaction of the epoxide derivative **2** with a suitable POH reagent to give the intermediate **B**, depicted in Scheme 1, where P should be a suitable "masking group" easy to be chemoselectively removed to restore the desired free alcoholic group, after protection of C-1' hydroxyl

group. Then, the following derivative C could allow a smooth functionalization of the C-4 position, introducing different side chains, easy to be further elaborated. Finally, the removal of the protecting group followed by the oxidation of the secondary C-1' hydroxyl group and the 5-membered ring closure[6] should give a variety of target trinem derivatives E.

Scheme 1



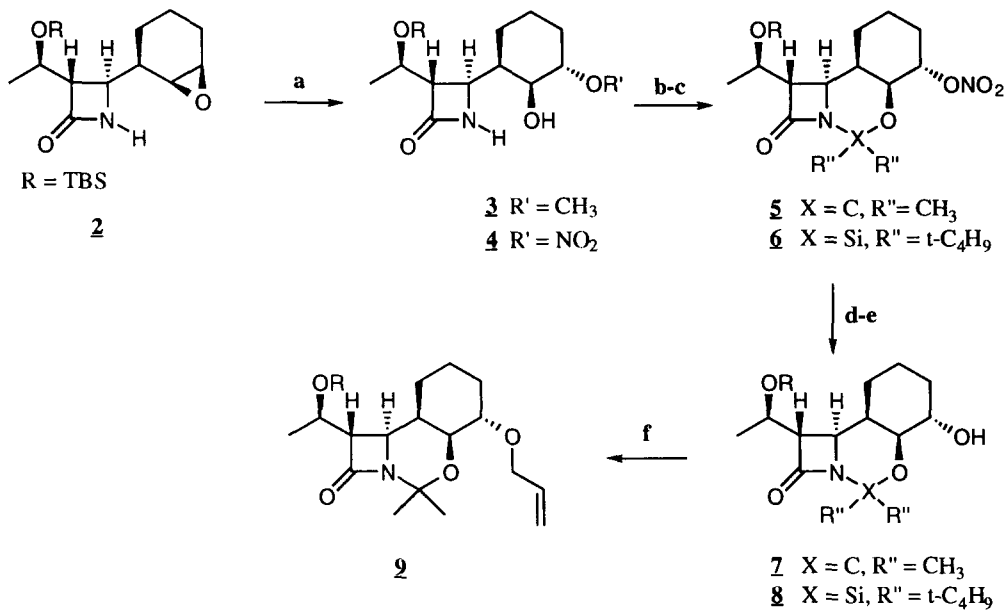
It was known[7] that CAN was able to catalyse efficiently the opening reaction of different epoxides when simple alcohols were used, once again, as solvent. When this reaction was attempted on the epoxide derivative **2**, using MeOH as solvent in the presence of stoichiometric amount of CAN, at 0°C for 10 min, a mixture of the desired methoxy derivative **3**, shown in Scheme 2 (R'= CH_3), and a by-product, then identified as the chemically stable nitrate ester derivative **5**, were obtained. Any attempt of optimising this process in terms of ratio **3** *vs.* **4**, reducing the amount of CAN used or slowing down its addition into the reaction mixture, was unsuccessful. Compound **3** was always isolated in poor yield in the presence of variable amount of derivative **4**.

Considering than the nitro group could behave as a "protecting group" (removal could be easily accomplished by catalytic hydrogenation or in basic reaction conditions)[8], the process was modified trying to address the reaction towards the exclusive formation of compound **4**: when MeOH was replaced by CH_3CN, in the presence of 0.5 equivalents of CAN, the nitrate derivative **4** was the only reaction product isolated in 55% yield after purification by flash chromatography. After the optimisation of this key reaction[9], the simultaneous protection of amido group and the free secondary alcohol was smoothly accomplished using acetone dimethylketal in CH_2Cl_2 in the presence of $BF_3{\cdot}OEt_2$, obtaining compound **5** (X = C, R" = CH_3) in 60 % yield. During this reaction the control of the temperature and the reaction time were crucial to avoid the concomitant removal of the TBS protecting group, whereas the final nitrate derivative was found to be completely stable during both the reaction and the purification by flash chromatography. The following removal of the "nitro protecting group", to give the intermediate **7**, was performed in quantitative yield by catalytic hydrogenation (H_2, 10% Pd/C, EtOH, 30 min). This compound,

obtained in three step from epoxide **2**, in view of the presence of the free secondary alcohol, can be considered as a *useful intermediate in the preparation of different 4-alkoxy substituted trinems..*

Compound **7** was smoothly alkylated (NaH, allyl bromide, TBAI, THF) to give the derivative **9** in 78% yield. In view of the presence of an olefinic function within the C-4 side chain, a number of potential modifications could be accomplished.

Scheme 2



a) CAN (0.5 eq), CH_3CN, 0°C, 10 min; b) acetone dimethylketal, $BF_3 \cdot OEt_2$, CH_2Cl_2, 0°C, 12 h; c) $(TfO)_2Si(t\text{-}C_4H_9)_2$, 2,6 Lutidine, CH_2Cl_2, 0°C, 12 h; d) 10 % Pd/C, H_2 (p = 1 atm), EtOH, 30 min; e) 10 % Pd/C, H_2 (p = 1 atm), AcOEt, 2 h; f) NaH, allyl bromide, TBAI, THF, r.t., 12h.

Due to the potential problems associated with the deprotection of the isopropylidene protecting group, the original synthetic pathway was slightly modified replacing it with the more labile di-*tert*-butylsilyl analogue.[10] In this event, the nitrate derivative **4** (Scheme 2) was treated with stoichiometric amount of $(TfO)_2Si(t\text{-}C_4H_9)_2$ and 2,6-lutidine in CH_2Cl_2 at 0°C, to give the stable compound **6** (X = Si, R" = t-C4H9) in 80% yield after purification by flash chromatography. Finally, the following hydrogenation reaction (H_2, 10 % Pd/C, AcOEt, 30 min) allowed the isolation of compound **8** in quantitative yield. In conclusion, a versatile preparation of nitrate derivatives from epoxides using CAN (0.5 equivalents) in aprotic solvent has been described. This synthetic procedure allowed the preparation of some key intermediates[11] useful in the synthesis of different classes of 4-alkoxytrinems.

Acknowledgments

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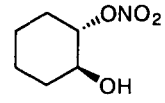
9. This reaction was proven to be general using different types of epoxides. In particular, when the reaction was attempted on cyclohexene oxide and styrene oxide the nitro derivatives **10** and **11** were obtained with complete regio and stereoselection, in reasonable yields after purification by flash cromatography.



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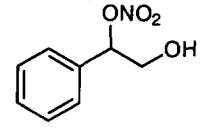

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11. All new compounds were characterised by routine analytical and spectroscopic methods.

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