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STEREOSELECTIVE CYCLOADDITIONS OF ACYL-NITROSO COMPOUNDS; AN APPROACH TO CARBAPENEM SYNTHESIS

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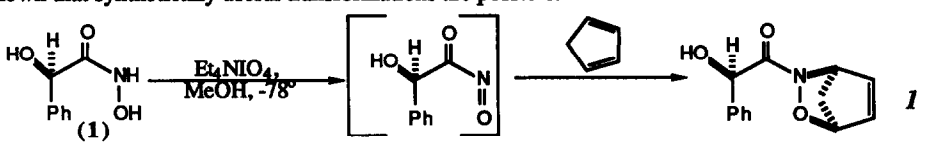
Summary : The adduct obtained from cyclopentadiene and benzohydroxamic acid under oxidising conditions has been used in a stereoselective synthesis of the N-benzoyl derivative of a known intermediate for carbapenem synthesis.

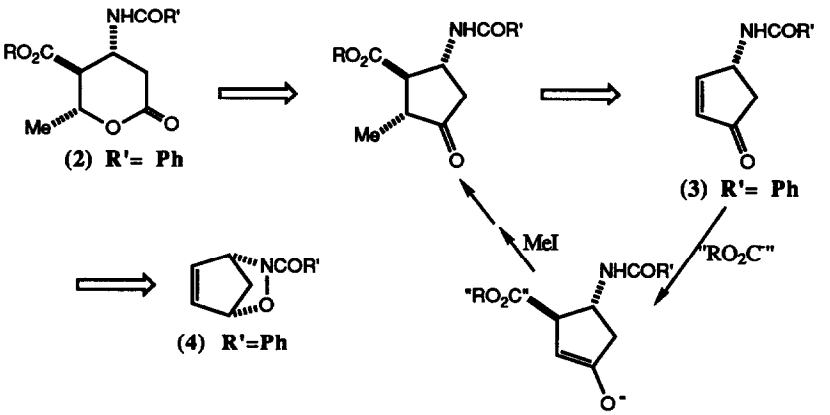
It has been shown that the cycloaddition between cyclic dienes and the chiral acyl-nitroso intermediate derived from the optically active hydroxamic acid (1) produces adducts in good yield and with good levels of diastereoselectivity (Reaction *1*).[1] As part of an initial investigation into the uses of this type of adduct we have shown that synthetically useful transformations are possible.[2]



In pursuance of further synthetic applications of these adducts we have explored the possibility of their use in the synthesis of carbapenems, in particular thienamycin. We report our preliminary work in the racemic series in this Letter. The plan was to synthesise a derivative of the lactone (2), which is an important intermediate in the Merck synthesis of thienamycin.[3]

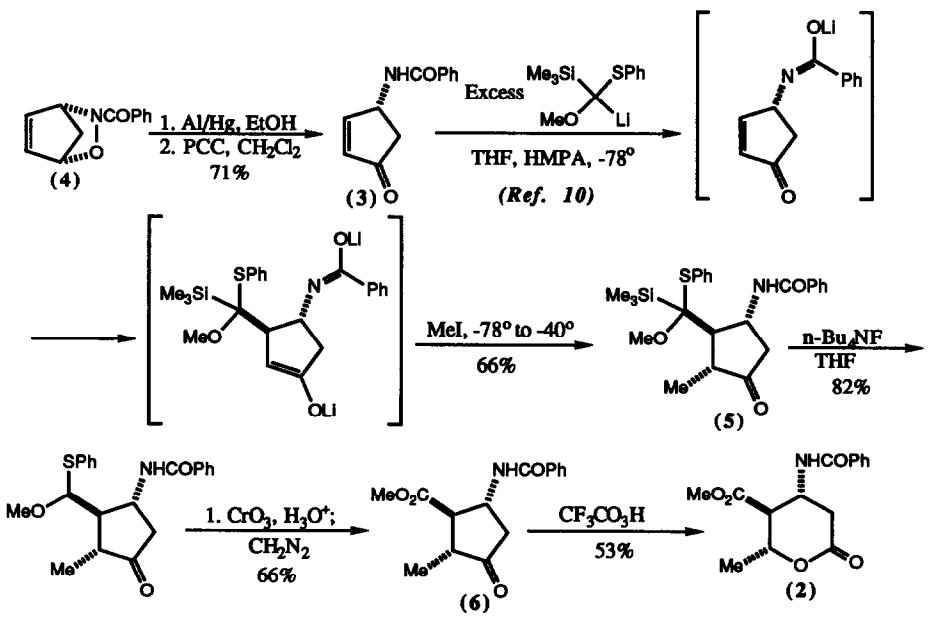
The overall synthetic approach is outlined in Scheme 1. This strategy has clear similarities with the conjugate addition-trapping approach to the synthesis of prostaglandins, which has ultimately proved successful but is not without its difficulties.[4]

Scheme 1



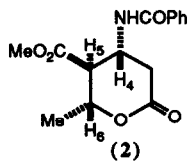
The enone (3) is readily obtained from adduct (4) (*vide infra*), but the conjugate addition-trapping with (3) as substrate has several complicating features. These potential problems are all associated with the presence of the secondary amide group. This group is expected to be deprotonated under the reaction conditions, and whereas this might decrease the possibility of β-elimination (*via* enolate equilibration), it could complicate the desired selective methylation of the enolate by itself undergoing methylation (the pK_a of aromatic amides is *ca.* 25).[5] Moreover it is conceivable that rather than directing the nucleophile to the opposite face of the enone as desired, this deprotonated amide function could deliver the nucleophile to the same side by coordination. Clearly these potential problems needed to be addressed, and to do this we used the adduct (4) as a convenient racemic starting material. The route which has been developed is shown in Scheme 2

Scheme 2



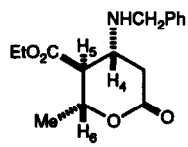
The enone (3) was prepared in good yield by reductive cleavage of the N-O bond[6] followed by oxidation. As yet we have been unable to isomerise the adduct (4) directly into the desired enone (3), but the reduction-oxidation sequence is both simple and convenient. A number of nucleophilic species were screened in the search for a suitable reagent for conjugate addition to (3), including H_2C=CHMgBr/Cu(I), $(PhS)_3CLi$,[7] $PhS(Me_3Si)CHLi$,[8] PhS(MeO)CHLi,[9] and $PhS(Me_3Si)(MeO)CLi$.[10] Of these only the last was found to be suitable for our purposes. It is necessary to use at least two equivalents of reagent, when only one equivalent is used complex mixtures are obtained (or no reaction occurs, depending on the conditions). We assume that the first equivalent of basic reagent deprotonates the amide group and that the conjugate addition takes place on the resulting lithium anion. The product (5) is of good stereochemical purity (> 8:1), implying that both the conjugate addition and trapping reactions are highly diastereoselective. The synthesis of the desired lactone (2) (R = Me, R' = Ph) was completed by conversion to the methyl ester (6) and Baeyer-Villiger oxidation. These last steps have not been optimised and there is scope for shortening this sequence. The stereochemistry of the lactone (2) follows from analysis of its 300 MHz ^{1}H nmr spectrum (Figure 1) and comparison of the coupling constants with published data.[3a,b] The large coupling constants between H_4 and H_5 and between H_5 and H_6 indicate that H_4, H_5 and H_6 are approximately *trans*-diaxial, as required.

Figure 1

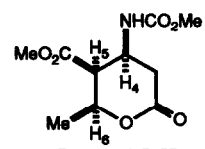


(2)

$J_{4,5}$ = 8.7 Hz
$J_{5,6}$ = 10.5 Hz



$J_{4,5}$ = 7.5 Hz
$J_{5,6}$ = 10.4 Hz
Ref. 3a



$J_{4,5}$ = 4.5 Hz
$J_{5,6}$ = 2.7 Hz
Ref. 3b

In conclusion we have demonstrated that it is possible to carry out a diastereoselective synthesis of a potential precursor to thienamycin and other carbapenems from a cyclopentadiene/acylnitroso adduct by a route which has the potential for producing enantiomerically enriched material using the previously described "asymmetric" version of the cycloaddition. We are currently working on this asymmetric synthesis, and investigating other related synthetic targets

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