An Introduction to Reaction Stereoelectronics 2015-2016 OUTLINE MODEL ANSWERS

1 (a) (i) Protonation of the ketone by the per-acid, nucleophilic attack of the peroxycacid anion on the protonated ketone, 1,2-migration of the benzylic centre to the terminal oxygen (assisted by the lone pair on the hemi-acetal oxygen) with loss of benzoic acid:

(ii) The key Baeyer-Villiger 1,2-migration is under strict stereoelectronic control:

(iii) The migrating centre migrates with both electrons previously comprising the C-C bond. Therefore, the migrating centre retains 8-electrons and its tetrahedral geometry throughout the migration, resulting in retention of stereochemistry (see below).

(iv) In common with other 1,2-migrations the transition state for migration has a build-up of positive charge at the migrating centre. The group that can provide the greater stabilisation to this transient positive charge generally migrates the fastest. So in this case the benzyl group can stabilise the positive charge better than the methyl group:

(v) The secondary bridgehead methine carbon migrates in preference to the primary ring methylene because it is better able to stabilise the incipient positive charge (as above). This greater ability of a secondary carbon to stabilise positive charge relative to a primary one can be attributed induction and hyperconjugation (cf. carbocation stabilities). The double bond is not epoxidised because it is sterically shielded from the top face by the pendent benzylxoxymethyl group and from the bottom face by the methylene hydrogen at C2.
(b) (i) The 5-membered ($\gamma$-) lactone suffers nucleophilic attack at the carbonyl carbon to give a tetrahedral intermediate which breaks down to give an acyl imidazole after proton transfer. The overall result is cleavage of the acyl-oxygen bond of the lactone.

The 4-membered ($\beta$-) lactone suffers nucleophilic attack at the methylene ring carbon in an $S_N2$ fashion resulting in direct ring opening to give the $\alpha$-amino acid derivative following proton transfer. The overall result is cleavage of the alkyl-oxygen bond of the lactone.

(ii) The ‘usual’ mode of reactivity of an acyclic ester towards a nucleophile such as imidazole would be the attack at the carbonyl carbon as is observed for the $\gamma$-lactone. The anomalous behaviour of the $\beta$-lactam is therefore likely to be one or more of the three factors that were discussed in the lectures that affect the reactivity of functional groups when constrained into small (and medium) rings: 1) strain effects, 2) proximity effects, and 3) stereoelectronic effects. The most important factor favouring the $S_N2$ reaction for the $\beta$-lactone is likely to be the relief of compressive Baeyer angle strain.

(c) This is a Beckmann rearrangement. The indicated bonds need to be antiperiplanar to allow the rearrangement to proceed.