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The design and synthesis of novel anomeric hydroperoxides: influence of the carbohydrate residue in the enantioselective epoxidation of quinones

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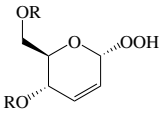
Abstract—We present a study of the base (DBU)-catalysed epoxidation of a number of important naturally occurring quinones using a series of pyranose-derived anomeric hydroperoxides. The absolute (viz. D or L) stereochemistry of the carbohydrate, electronic nature of the 6-substituent and ring substitution are all important variables, both for the formation of the hydroperoxide and its reactivity. Reactions studied were the epoxidation of a precursor of the natural antibiotic, alisamycin and a series of naphthoquinones related to Vitamin K. In the best case, an ee of 82% was obtained; either product enantiomer is accessible according to the absolute stereochemistry of the carbohydrate. Finally, a molecular modelling study of the reaction is reported, concluding that the reactions are under kinetic control and that the observed ees cannot be explained by considering transition states that involve only the quinone and peroxide anion. It seems likely that the DBU molecule may play a key role in the transition state.

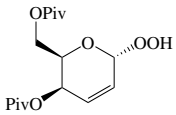
1. Background and introduction

The synthesis of enantiomerically pure epoxides is a fundamental challenge in organic chemistry.[1] Epoxides are both versatile building blocks in synthesis and significant in their own right as integral functional groups of important natural products. While impressive advances have been made in the asymmetric epoxidation of electron-rich alkenes[2] and electron-deficient *trans*-alkenes of the chalcone type,[3–5] there are few effective procedures for the asymmetric epoxidation of cyclic enones and quinones. Important examples of this type include the manumycin family of antibiotic/anticancer agents and naphthoquinone epoxides of the Vitamin K series.

Previously, we had utilised chiral phase-transfer catalysts[6,7] and chiral bases[8] to prepare quinone epoxides, and had published a preliminary report of the use of chiral pool epoxidants, namely carbohydrate anomeric hydroperoxides (AHPs), for the same purpose.[9] Chmielewski et al. also prepared AHPs[10,11] and used them in the oxidation of allyl alcohols and alkyl aryl sulfides, obtaining reasonable ees. In addition, Adam et al. employed chiral secondary benzylic hydroperoxides in the Ti-catalysed epoxidation of allylic alcohols and in the asymmetric epoxidation of chalcones.[12]



1 R = Piv, **2** R = Bn



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The above mentioned earlier publication[9] reported that the D-pyranose-derived hydroperoxides **1**–**3** were the most effective epoxidants of a number of D-glucose and D-galactose derivatives screened: the pivaloates (rather than acetates) were essential to give adequate

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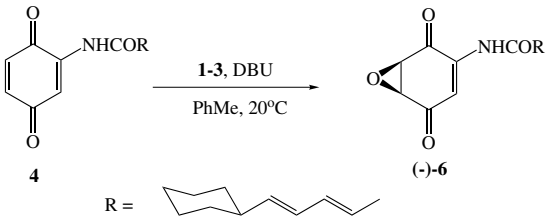
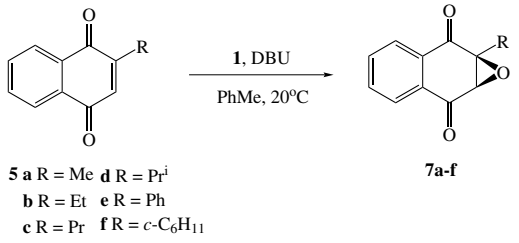
stability to the epoxidants. The test reactions used were epoxidations of the alisamycin[7,13,14] core amidoquinone (**4**→**6**) and, using **1** only, a series of naphthoquinones (**5**→**7**),[15] Schemes 1 and 2.



Scheme 1. Epoxidation of (−)-alisamycin precursor. Yields 38–64%, ee 42–64%.[9]



Scheme 2. Epoxidation of naphthoquinones. Yields 30–80%, ees 35–82%.[9]

General conclusions from this phase of the work were:

1. DBU was the most effective base: other organic and inorganic bases gave lower yields and/or ee.
2. Toluene was the most effective solvent in terms of ee.
3. Anomeric purity of the hydroperoxide was vital: the corresponding β-hydroperoxides gave the opposite enantiomeric product with lower selectivity.

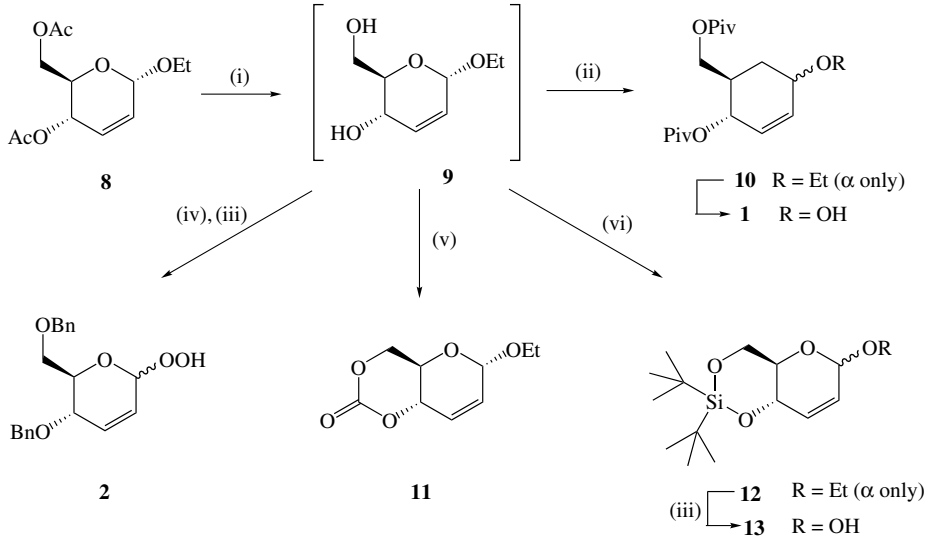
We set out to obtain a more complete picture by screening AHPS of other pyranose carbohydrates, varying in particular the 6-substituent, to determine the importance of electronic and stereochemical features. In particular we addressed one clear omission of the earlier examples, namely the lack of an L-series sugar (since the effect of anomeric configuration in itself appeared too small to overturn the ee to a useful extent).[9] In this way we hoped to access either enantiomer of a pair of epoxides with equal facility. The most accessible L-series sugar is L-rhamnose, and reactions with rhamnose-derived AHPs are described herein. Finally, we present our conclusions from a molecular modelling study of the epoxidation reaction.

2. Discussion

2.1. Preparation of carbohydrate intermediates

The D-glucose derived AHPs **1** and **2** were readily obtained from the known[16] 'pseudoglycal' or Ferrier rearrangement product **8** (Scheme 3). The switch from the known acetates to the novel pivaloates, via compounds **9** and **10**, was essential to improve the stability of the products under the basic conditions of the epoxidation reaction. Acid-catalysed anomeric displacement on **10** with hydrogen peroxide then afforded **1** as a separable α/β AHP mixture; alternatively, di-*O*-benzylation of diol **9**, followed by treatment with H_2O_2 and acid, afforded **2** as previously reported.[11,17]

The di-pivaloate AHP **1** was isolated as a crystalline material and proved suitable for X-ray structure determination (Fig. 1). This shows a half-chair conformation, in agreement with the NMR evidence [especially the H(4)–H(5) coupling of $J = 9.5$ Hz].



Scheme 3. Mono- and bicyclic anomeric hydroperoxides, D-glucose series. Reagents: (i) Et_3N, MeOH, cat. K_2CO_3, quant.; (ii) $Me_3C{\cdot}COCl$, pyridine; (iii) H_2O_2, dioxane, H_2SO_4, 50%, α:β, 2.2:1 for **1**; 64%, α:β, 2.7:1 for **2**; 87%, α:β, 5:1 for **13**; (iv) NaH, BnBr, DMF, 76%; (v) $Cl_3C{\cdot}CO{\cdot}CCl_3$, 59%; (vi) $Bu^t_2Si(OTf)_2$, pyridine, 68%.

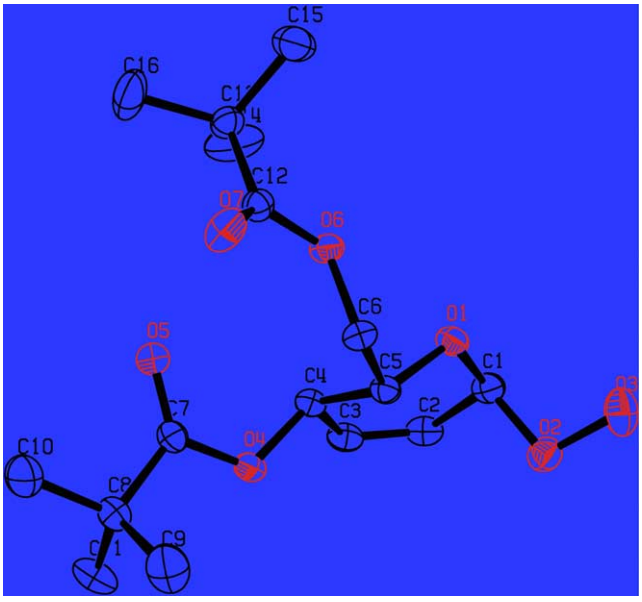
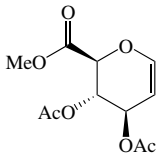


Figure 1. X-ray crystal structure of **1**. Hydrogen atoms have been omitted for clarity: ellipsoids are drawn at 50% probability.

In order to probe further the structure–reactivity relationships in this series, a novel bicyclic hydroperoxide was also prepared (Scheme 3). Thus Zemplen deprotection of the Ferrier intermediate **8** gave the presumed 4,6-diol **9**, which without isolation, was transformed by acylation with triphosgene (59%)[18] into the cyclic carbonate **11** or by base-catalysed silylation (68%) with di-*t*-butylsilyl ditriflate[19] into bicyclic ether **12**. Acid-catalysed reaction of **11** with H_2O_2 gave no reaction even after several days, whereas **12** reacted smoothly in 16 h to give hydroperoxide **13** in 75% yield (inseparable anomeric mixture, α:β = 5:1). The profound difference in reactivity between **11** and **12** is attributed to the destabilising effect of an electron-withdrawing C(6)-substituent on an incipient anomeric carbonium ion and is parallelled by the behaviour of monocyclic derivatives (vide infra).

The AHP **3** in the D-galactose series was obtained as an inseparable α:β mixture from diol intermediate **9** using a known[20] method of Mitsunobu inversion at C(4) followed by protecting group interchange, then treatment of the intermediate ethyl glycoside **14** with acidic H_2O_2 (Scheme 4).

We also sought to study an AHP bearing a strongly electron-withdrawing 6-substituent, and to this end the glucuronic acid-derived glycal **15** was prepared by a known method.[21] However, we could not transform **15** to the anomeric hydroperoxide **16**, either directly or via a pseudoglycal. It appears that the destabilising effect of the 6-CO_2Me substituent on an incipient anomeric carbonium ion is decisive here. This transformation has been performed previously[22] using 85% grade H_2O_2, but this is no longer commercially available; we observed no reaction on prolonged reaction with 60% H_2O_2.



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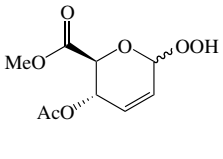

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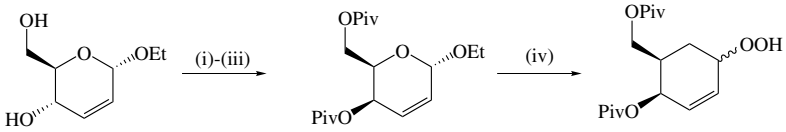
In complete contrast, the synthesis of the L-rhamnose analogue proceeded very smoothly, which we attribute to the presence of the electron-donating 6-Me group. An effective 'one pot' preparation[23] of L-rhamnal **17** from rhamnose (Scheme 5) was further improved[24] by using a non-aqueous version of the Zn–Cu couple-catalysed reductive elimination from the intermediate bromosugar to generate **17**. Acid-catalysed conversion of **17** to the desired AHP **18** did not even require the intermediacy of a pseudoglycal intermediate. In this series (cf. **1**) the acetate **18** proved quite robust; alternatively, using a four-step, but straightforward sequence, **17** could be transformed into the pivaloate **20** via the ethyl pseudoglycal **19** (Scheme 5). Both **18** and **20** were obtained very largely (ca. 9:1) as the α-anomers, which were readily separated by chromatography: for good yields of **18** and **20**, it was essential to use an Et_2O–H_2O_2–H_2SO_4 mixture.

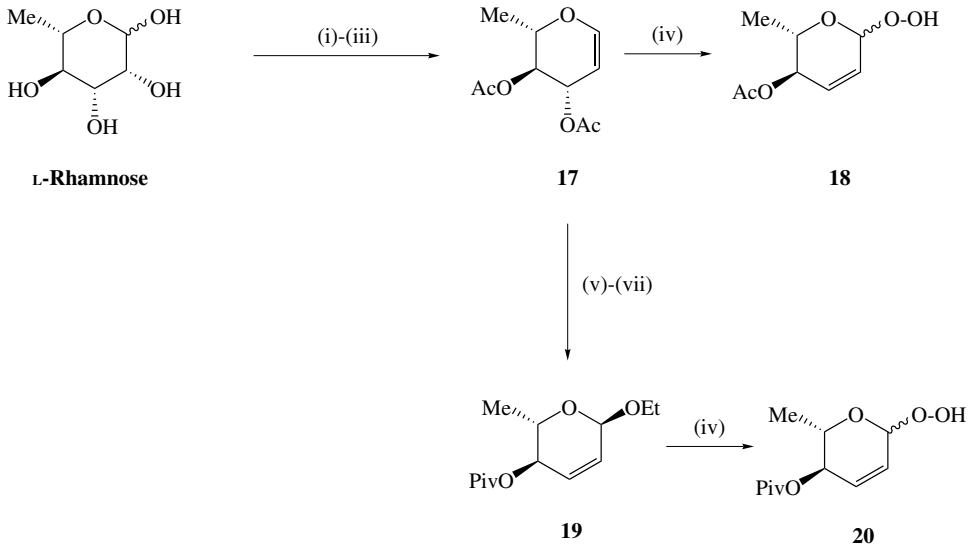
2.2. Enantioselective epoxidations

We studied a range of quinonoid substrates **4**, **5a** and **5e** to evaluate the best epoxidant, comparing mainly **1**, **13**, **18** and **20**; in the case of **4** the results for AHPs **2** and **3** have been added.[9] The quinones were prepared by literature syntheses.[12,25,26] Toluene was shown earlier to be the optimum solvent and was used exclusively here;[9] the hydroperoxides were used in 1:1 molar ratio with **4** and in 20% molar excess with **5a** and **5e**.[9] Considering first the alisamycin precursor **4** (Table 1), which gave complete reaction in a few minutes, both D-glucose derived **1** and L-rhamnose-derived **18** gave good results,



9 **14** **3**

Scheme 4. Synthesis of AHP in the D-galactose series. Reagents: (i) Ph_3P, DEAD, $PhCO_2H$, THF, 20 °C, 59%; (ii) NaOMe, MeOH; (iii) Piv-Cl, pyridine, 28% over two steps; (iv) 60% aq H_2O_2, H_2SO_4, dioxane, 43.5%, α:β, 10:1.



Scheme 5. Anomeric hydroperoxide synthesis, L-rhamnose series. Reagents: (i) Ac_2O, DMAP, CH_2Cl_2, Et_3N; (ii) HBr–AcOH, CH_2Cl_2; (iii) Zn–Cu couple, AcOH, THF, 83% over three steps; (iv) Et_2O–H_2O_2, H_2SO_4, 82%, α:β, 10:1 for **18**, 86%, α:β, 10:1 for **20**; (v) $SnCl_4$, EtOH, CH_2Cl_2, 88%; (vi) cat. K_2CO_3, Et_3N, MeOH; (vii) $Me_3C{\cdot}COCl$, pyridine, 96% over two steps.

Table 1. DBU-catalysed epoxidations of quinones with AHPs in toluene at 20 °C

Quinone	Alisamycin precursor **4**			2-Methyl naphthoquinone **5a**			2-Phenyl naphthoquinone **5e**		
Hydroperoxide	Yield (%)	Ee (%)	*T*/min	Yield (%)	Ee (%)	*T*/h	Yield (%)	Ee (%)	*T*/h
1 (D-)	55	−64[a]	5	71	+45[b]	5.0	80	+82[b]	6
2 (D-)	38	−46	5						
3 (D-)	64	−42	5						
18 (L-)	74	+55	5	32	−78	3.5	47	−37.5	25
20 (L-)	76	+22	6	74	−49	4.0			
13 (D-)	59	−30.5	5	57	+40	4.5			

Absolute configuration of each AHP in brackets.
[a] Absolute configuration of major enantiomer as in **6**.
[b] Absolute configuration of major enantiomer as in **7**.

affording access to either enantiomer predominantly, with the best ee being obtained using **1** [64% ee of the (−)-enantiomer] and the significantly better yield from **18** being offset by a slightly lower ee [55% of (+)-enantiomer]. The substitution of benzyl ether protection for esters in **2** and the inversion of C(4) in **3** offered no advantage over **1**, though reasonable ees were observed. Compared to **18**, the pivaloate **20** gave an equivalent yield (within experimental error) but a disappointing ee. As expected, the bicyclic D-glucose derived reagent **13** gave the same predominant enantiomer as **1** but with a much lower ee; it must be remembered that **13** was used as an inseparable α:β = 5:1 mixture, while other AHPs were single α-anomers.

In the case of the 2-methyl naphthoquinone **5a**, where reactions were between 50- and 300-fold slower than with **4**, AHP **18** gave the highest ee yet recorded for epoxidation in this series, 78% compared to 45% (with opposite sign) from **1**. The yield, however, was disappointing at 32%. Here the pivaloate **20** gave essentially the same yield as **1** and an almost equal but opposite ee. The bicyclic AHP **13** was slightly inferior to **1** in both yield and ee. For the 2-phenylnaphthoquinone **5e**, **1** gave an outstanding result with 80% yield and 82% ee: the reaction of **18** was much slower, for reasons that are unclear, and the yield and ee were moderate. For this substrate, both **14** and **16** reacted too slowly to be of value.

We also studied briefly the epoxidation of *trans*-chalcone, the standard substrate for the H_2O_2–polyleucine method.[3] Out of AHPs **1**, **13**, **18** and **20** only **1** would react; in a very slow reaction (4 d) a yield of 10% and an ee of 13% were obtained. Other methods[5a–c,12] are clearly superior in acyclic systems.

2.3. Molecular modelling studies

Computational methods were employed to attempt to explain the observed product enantioselectivity for the reaction of **1** with 2-methyl naphthoquinone. It was hoped that by comparing the calculated energy differences between the transition states when attack of the peroxide anion occurs from either side of the plane of the quinone system, the observed product distribution may be explained.

The reactions were modelled in silico assuming that they proceeded via a Weitz–Scheffer mechanism with attack of the peroxide anion occurring at the least hindered end of the double bond. The rationale for this assumption is outlined in a paper by Pluim and Wynberg.[27] Additional evidence for this hypothesis was shown by MOPAC[28] calculations of the LUMO of the quinone and the HOMO of the peroxide anion of **1** (see Section 4 for details). The LUMO of 2-methyl naphthoquinone is largely located on the quinone portion of the molecule and the HOMO of the attacking peroxide anion is almost entirely located on the peroxide oxygens (data not shown). Thus, it seemed reasonable that the reaction was likely to proceed via an interaction of these two molecular orbitals. The reactions were considered to be under kinetic control, and the first step (attack of the peroxide anion to the β position of the double bond) was initially taken to be the rate determining step. Kinetic control was confirmed, as the calculated heats of formation of enantiomeric products of **1** with 2-methyl naphthoquinone were very similar (data not shown). In order to investigate whether the enantioselectivity resulted from kinetic control, it was necessary to locate the transition states for each pair of reactants attacking from either face of the quinone.

Unfortunately, a literature search did not reveal a proposed transition state (TS) for the epoxidation of quinones with a peroxide anion. As a reasonable structure could not be taken from the literature, an alternative method was employed. The molecules were entered into the SYBYL 6.91[29] molecular modelling program, a constraint[30] was placed between the β-carbon and the peroxide anion (see Section 4 for details) and the system was subjected to molecular mechanics energy minimisation.[30] This partially refined structure was then inserted into MOPAC[28] and was minimised using semi-empirical quantum mechanical methods, with the distance between the β-carbon and the peroxide anion kept fixed. The output of this calculation was taken as a crude estimate of the TS. This approximate TS was refined so that the total energy gradient was very close to zero, a condition of a true TS.[31] Once refined, the TS was confirmed to be a saddle point as vibrational analysis revealed that the TS had one single negative vibration along the reaction coordinate[31] and the presence of six very small eigenvalues (less than $5\,cm^{-1}$). Two Intrinsic Reaction Coordinate (IRC) calculations confirmed that the TS did connect the reactants to the products (data not shown).

Having successfully located the TS for peroxide **11** adding to quinone **5a** when attack occurred from the *re*-face of the quinone, attempts were made to locate the TS for the reaction occurring from the *si*-face of the quinone. This was achieved in a similar manner as before and was confirmed to be a true TS by vibrational analysis and IRC calculations.

If the reaction proceeded via the proposed mechanism and under kinetic control, then the differences in heat of formation of the TS of the attack from the one face of the quinone and attack from the other face should reveal why the enantiomeric excesses were observed. We can compare the heats of formation of the TS rather than the heats of activation as the heats of formation of the starting materials are the same, independent of which side of the quinone the reaction occurs from. Disappointingly, the difference in heat of formation of the two transition states was very small and does not explain the enantioselectivity observed (Table 2).

Table 2. Heats of formation of the transition states of **1** reacting from the *re*- and *si*-faces of the 2-methyl naphthoquinone

	re-Face	*si*-Face
Heat of formation (kcal/mol)	−280.785127	−280.785040

Up to this point the first step of the reaction was taken as the rate determining step. The second step, ring closure and elimination of the alkoxide anion, was hypothesised to be not rate determining.[32] In order to investigate whether this second step was in fact rate determining, an analogous study was undertaken to locate the TS for this second step of the reaction.

The TS's were located by working from a published TS for a similar reaction.[32] The approximate TS was input into SYBYL 6.91 and various constraints[30] were applied to the system (see Section 4) to generate an approximate TS. This rough TS was refined in the same way as described above and vibrational analysis revealed one negative force constant, which led to the product epoxide and alkoxide anion, confirming that it was a true TS. A similar analysis was carried out for the case when the peroxide attacked the other face of the quinone and the TS was again confirmed by the single negative vibration, which led to the expected products. As before, there was very little difference between the two heats of formation, thus the enantiomeric excess cannot be explained by this second step of the reaction (Table 3).

Table 3. Heats of formation of the transition states of ring closure of **1** reacting from the *re*- and *si*-face of the 2-methyl naphthoquinone

	Re-Face	*Si*-Face
Heat of formation (kcal/mol)	−278.257059	−278.256986

In summary, it does not appear that the enantiomeric excess observed for this system can be explained by a transition state that involves two species, that is, the peroxide and quinone. It may be that the conjugate acid of DBU is involved in the transition state by forming an ion pair with the hydroperoxide anion. This hypothesis agrees with the findings that 'non-polar solvents gave the highest enantiomeric excesses' and 'changing the base resulted in a reduction in the yield and/or enantiomeric excesses'[9] and also the successful use of enantiopure guanidine bases for epoxidation.[8] Previous work on α,β-enones with optically active hydroperoxides has proposed that enantioselectivity has been induced through hydrogen bonded transition states that involve DBU.[33] Although the systems under investigation here are similar, they do differ in one important

respect—the quinone system places the enone functionality in a transoid configuration rather than cisoid. Thus it may be necessary to account for three species (quinone, peroxide and DBU) in the transition state to explain the enantioselectivity. Many attempts were made to locate this TS: however, they all proved unsuccessful, due to the very large problem space that exists for this type of molecular arrangement.

3. Conclusions

We have described a series of AHPs suitable for the epoxidation of some important quinones with fair to good yields and ees. With regard to the ease of formation of the AHPs, the electronic character of the carbohydrate 6-substituent is a determining factor. In the rhamnose series (6-Me), acid-catalysed hydroperoxidation at the anomeric carbon is facile, even on the glycal, while in the methyl glucuronate series it appears to be impossible on either the glycal or ethyl pseudoglycal with the strength of commercial H_2O_2 now available. The 'normal' pyranoses, glucose and galactose, show intermediate reactivity.

The situation with regard to the epoxidation results is harder to assess. Certainly the configuration of the major enantiomer obtained is determined by the absolute configuration of the AHP, in practical synthesis a very useful feature, but rationalisation of the results beyond this is difficult. While the pivaloate groups in **1** are essential to confer stability, the pivaloate **19** in the rhamnose series gave poorer ees than acetate **17**, and reacted too slowly to be useful with quinone **5e**; in yield terms, however, it offered the best results for **4** and **5a**. The bicyclic AHP **13** gave reasonable results but offered no advantage over **1**.

Molecular modelling failed to explain the observed ee for the reaction of **1** with 2-methyl naphthoquinone assuming that it proceeded via a transition state, which involved two species (peroxide and quinone). However, it was shown with fair certainty that the epoxidation is kinetically controlled and that the transition state probably intimately involves the DBU.

Further examples of the application of these AHP reagents in natural product synthesis will be presented in due course.

4. Experimental

Reactions were carried out under a nitrogen atmosphere. THF and diethyl ether (Et_2O) were distilled from benzophenone ketyl prior to use; CH_2Cl_2 was dried over CaH_2 and distilled immediately prior to use. Other solvents, of analytical grade, were used as purchased. Melting points were recorded on an Electrothermal 9100 and are uncorrected. Analytical TLC was performed using aluminium plates coated with Merck silica gel 60 F_{254}. Preparative chromatography was carried out using Fisher matrix silica gel 60 @ 760 mmHg or ICN 33–63 (60 Å) 'flash' silica gel at enhanced pressure. NMR spectra were obtained on JEOL EX270 or 400 spectrometers using the indicated solvents, operating at 270 or 400 MHz for ^1H or at 67.5 MHz for ^{13}C spectra. Chemical shifts (δ) are relative to Me_4Si and coupling constants J are quoted in hertz. IR spectra were recorded on a Thermo-Nicolet FT-IR 100 spectrometer for the physical form noted. Optical rotations were measured on a JASCO DIP-370 digital polarimeter at 20 °C (Na D-line). Mass spectra [by electron impact (EI), chemical ionisation (CI), electrospray (ES) or fast-atom bombardment (FAB)] were obtained on a Fisons analytical (VG) autospec instrument. HPLC data were recorded on a Gilson Autoinjector 234, Gilson 170 Diode Array Detector and Gilson 321 pump. For chiral HPLC, DAICEL CHIRALPAK AD or OD columns were used for the 2-substituted naphthoquinone epoxides or alisamycin precursors, respectively.

4.1. 2,3-Dideoxy-1-*O*-oxidanyl-4,6-di-*O*-pivaloyl-α-D-*erythro*-hex-2-enopyranose 1α and 2,3-dideoxy-1-*O*-oxidanyl-4,6-di-*O*-pivaloyl-β-D-*erythro*-hex-2-enopyranose 1β

Ethyl 2,3-dideoxy-4,6-di-*O*-pivaloyl-α-D-*erythro*-hex-2-enopyranoside **10**[34] (0.95 g, 2.8 mmol) in 1,4-dioxane (5 mL) was treated with 67% aq H_2O_2 (1 mL) and a catalytic amount of concd H_2SO_4, then the reaction mixture was stirred for 4 d. Partition between CH_2Cl_2 and water (10 mL each), followed by extraction of the aqueous layer with further CH_2Cl_2 (2 × 10 mL), then combination of the organic extracts, drying ($MgSO_4$) and evaporation afforded the title compound **1** and its anomer **1**β (462 mg, 50.4%, α:β = 2.2:1). This mixture was partially separable by column chromatography (PE/EtOAc 9:1 as eluent), yielding a colourless oil, a mixture of anomers (α:β = 1:1, 253 mg) and a white solid (α:β = 19:1, 209 mg), which was recrystallised from EtOAc to give pure α-hydroperoxide **1** (114 mg); mp 98–100 °C; [found C 58.9%, H 8.3%, $C_{16}H_{26}O_7$ requires C 58.2%, H 7.9%]; R_f (9:1 PE/EtOAc) 0.15; $[\alpha]_D$ +133.9 (*c* 1, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3429 (OOH), 2974 (CH), 1732 (C=O), 1481, 1283, 1152, 996; δ_H (270 MHz $CDCl_3$) 5.98–5.93 (1H, m, *H*-3), 5.71 (1H, ddd, $J_{1,2}$ 3.0, $J_{2,3}$ 10.0, $J_{2,4}$ 2.0 Hz, *H*-2), 5.48 (1H, m, *H*-1), 5.35–5.29 (1H, ddd, $J_{2,4}$ 2.0, $J_{3,4}$ 3.5, $J_{4,5}$ 9.5 Hz, *H*-4), 4.34–4.08 (3H, m, *H*-5, *H*-6, *H*-6′), 1.17 (9H, s, *OPiv*), 1.15 (9H, s, *OPiv*); δ_C (67.5 MHz, $CDCl_3$) 178.6, 177.7 (C, *OPiv*), 133.1 (CH, *C*-3), 123.0 (CH, *C*-2), 98.5 (CH, *C*-1), 67.6, 64.4 (CH, *C*-4, *C*-5), 62.3 (CH_2, *C*-6), 38.8 (C, *OPiv*), 26.9, 26.6 (CH_3, *OPiv*); CIMS *m*/*z* 348 (MNH_4^+, 18), 330 (M^+, 77), 297 (M^+-HO_2, 100), HRMS (CI): found MNH_4^+, found 348.2024. $C_{16}H_{30}NO_7$ requires 348.2022. 0.5 ppm error. Combination of the mixed fractions from a number of reactions followed by flash column chromatography (PE/EtOAc 9:1 as eluent) gave the β-anomer **1**β as a colourless oil; R_f (PE/EtOAc, 9:1) 0.19; $[\alpha]_D$ = +102.5 (*c* 1, $CHCl_3$); δ_H (270 MHz, $CDCl_3$) 9.60 (1H, br s, OO*H*), 6.15–6.07 (1H, m, *H*-3), 5.95 (1H, ddd, $J_{1,2}$ 2.5, $J_{2,3}$ 10.5, $J_{2,4}$ 1.0 Hz, *H*-2), 5.59 (1H, m, *H*-1), 5.11 (1H, m, *H*-4), 4.42–4.10 (3H, m, *H*-5, *H*-6, *H*-6′), 1.23–1.20 (18H, m, 2× *OPiv*); δ_C (67.5 MHz, $CDCl_3$) 178.5, 177.7 (C, *OPiv*), 128.7 (CH, *C*-3), 125.7 (CH, *C*-

2), 97.9 (CH, *C*-1), 73.7, 63.0 (CH, *C*-4, *C*-5), 63.9 (CH_2, *C*-6), 38.9 (C, *OPiv*), 27.0 (CH_3, *OPiv*).

4.2. 4,6-Di-*O*-benzyl-2,3-dideoxy-1-*O*-oxidanyl-α-D-*erythro*-hex-2-enopyranose 2

Ethyl 4,6-di-*O*-benzyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside[17] (400 mg, 1.1 mmol) was treated with 67% aq H_2O_2 (0.5 mL) in dioxane following the above procedure for the synthesis of hydroperoxide **1**. The product **2** was identical to that previously reported.[11]

4.3. (4a*R*,6*S*,8a*S*)-6-Ethoxy-4,4a,6,8a-tetrahydropyrano-[3,2-*d*][1,3]dioxin-2-one 11

Ethyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **8** (3.04 g, 11.8 mmol), in 1:1 MeOH/Et_3N (60 mL), together with a catalytic amount of K_2CO_3, was heated at 50 °C under N_2 for 18 h. The solvent was then filtered through Celite and the solvent removed in vacuo to give the diol **9** as a pale brown viscous oil (1.95 g), which was used without purification. A portion of **9** (504 mg, 2.89 mmol) was dissolved in pyridine (1.4 mL, 17.34 mmol) and CH_2Cl_2 (13.8 mL) under N_2 and cooled to −70 °C, then a solution of triphosgene (430 mg, 1.45 mmol) in CH_2Cl_2 (5.8 mL), was added dropwise. Once addition was complete, the reaction was allowed to warm to 20 °C over 18 h. The resultant homogenous solution was quenched with satd aq NH_4Cl and the aqueous portion was separated and extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were combined, washed with 1 M HCl (2 × 5 mL), satd aq $NaHCO_3$ (2 × 5 mL), brine (2 × 5 mL), dried (Na_2SO_4), filtered and concentrated in vacuo to give a crude cream coloured oil. Purification by flash column chromatography on silica gel (PE/EtOAc 5:1 as eluent), afforded **11** (341 mg, 59%) as a white solid, mp 79–81 °C; R_f (PE/EtOAc 1:1) 0.53; $[\alpha]_D = -17.3$ (*c* 1.02, $CHCl_3$); ν_{max} $CHCl_3$/cm^{-1} 1763 (C=O), δ_H (400 MHz, $CDCl_3$) 6.10 (1H, d, $J_{2,3}$ 10.0 Hz, H-3), 5.85 (1H, dt, $J_{1,2}$ 2.4, $J_{2,3}$ 10.0, $J_{2,4}$ 2.0 Hz, H-2), 5.07 (1H, br s, H-1), 4.62 (1H, dd, $J_{3,4}$ 1.5, $J_{4,5}$ 9.2 Hz, H-4), 4.52 (1H, dd, $J_{5,6}$ 6.0, $J_{6,6'}$ 9.8 Hz, H-6), 4.26 (1H, dd, $J_{5,6'}$ 10.7, $J_{6,6'}$ 9.8 Hz, H-6′), 4.13 (1H, ddd, $J_{5,6}$ 6.0, $J_{4,5}$ 9.2, $J_{5,6'}$ 10.7 Hz, H-5), 3.88–3.80 (1H, dq, J_{gem} 9.5, *J* 7.0 Hz, $OCH_ACH_BCH_3$), 3.62–3.54 (1H, dq, J_{gem} 9.5, *J* 7.0 Hz, $OCH_ACH_BCH_3$), 1.23 (3H, t, *J* 7 Hz, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 148.0 (C, O=CO_2), 128.8, 127.0 (CH, C-2, C-3), 95.0 (CH, C-1), 72.4, 70.3 (CH, C-5, CH_2, C-6), 65.0, 60.9 (CH_2, OCH_2CH_3, CH, C-4), 15.3 (CH_3, OCH_2 CH_3); CIMS *m*/*z* 218 (MNH_4^+, 100), 201 (MH^+, 20), 155 ($M^+-C_2H_5O$, 10); HRMS (CI): MH^+, found 201.0763. $C_9H_{13}O_5$ requires 201.0765. 0.9 ppm error.

4.4. Ethyl 4,6-*O*-(di-*tert*-butyl)silanediyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside 12

The diol **9** (510 mg, 2.93 mmol) was dissolved in CH_2Cl_2 (20 mL) under N_2 and cooled to −60 °C. 2,6-Lutidine (2.6 mL, 22.6 mmol) and di-*tert*-butylsilyl ditriflate (2.97 g, 6.74 mmol) were added at −60 °C. The reaction mixture was stirred at this temperature for 3 h, then diluted with EtOAc (25 mL) and washed with H_2O (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give a crude pale yellow oil. The product was purified by flash column chromatography on silica gel (PE/EtOAc 3:1 as eluent), yielding the title compound **12** (626 mg, 68%) as a colourless oil; R_f (PE/EtOAc 1:1) 0.80; $[\alpha]_D = +47.2$ (*c* 1.15, $CHCl_3$); ν_{max} neat/cm^{-1} 2934, 2861 (2 × O–SiR), 1473, 1392, 1306, 1057; δ_H (400 MHz, $CDCl_3$) 6.01 (1H, d, $J_{2,3}$ 10.0 Hz, H-3), 5.63 (1H, dt, $J_{1,2}$ 2.4, $J_{2,4}$ 2.4, $J_{2,3}$ 10.0 Hz, H-2), 4.93 (1H, br d, $J_{1,3}$ 1.2 Hz, H-1), 4.34 (1H, ddd, $J_{3,4}$ 1.5, $J_{2,4}$ 2.1, $J_{4,5}$ 9.0 Hz, H-4), 4.12 (1H, dd, $J_{5,6}$ 5.0, $J_{6,6'}$ 9.8 Hz, H-6), 3.86 (1H, dd, $J_{5,6'}$ 10.0, $J_{6,6'}$ 9.8 Hz, H-6′), 3.85–3.77 (2H, m, $OCH_ACH_BCH_3$, H-5), 3.57–3.49 (1H, dq, J_{gem} 9.8, *J* 7.0 Hz, $OCH_ACH_BCH_3$), 1.22 (3H, t, *J* 7.0 Hz, OCH_2CH_3), 1.05 (9H, s, C_4H_9), 0.99 (9H, s, C_4H_9); δ_C (100 MHz, $CDCl_3$) 134.4, 125.3 (CH, C-2, C-3), 94.8 (CH, C-1), 70.7, 67.4 (CH, C-5, CH_2, C-6), 67.3, 64.3 (CH_2, OCH_2CH_3, CH, C-4), 27.6, 27.2 (CH_3, CMe_3), 22.9, 20.2 (C, CMe_3), 15.5 (CH_3, OCH_2CH_3); CIMS *m*/*z* 315 (MH^+, 15), 269 ($M^+-C_2H_5O$, 100); HRMS (CI): MH^+, found 315.1992. $C_{16}H_{31}O_4Si$ requires 315.1991. 0.3 ppm error.

4.5. (4a*R*,6*R*,8a*S*)-2,2-Di(*tert*-butyl)-4,4a,6,8a-tetrahydropyrano[3,2-*d*][1,3,2]dioxasilan-6-yl hydroperoxide 13

To ethyl 4,6-*O*-(di-*tert*-butyl)silanediyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranoside **12** (105 mg, 0.33 mmol) in Et_2O–H_2O_2 (1.0 mL) at 0 °C was added concentrated H_2SO_4 (two drops). The reaction mixture was stirred for 16 h and allowed to warm to 20 °C. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and water (5 mL), then the aqueous phase was separated and washed with CH_2Cl_2 (2 × 5 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to give crude **13** as a colourless oil (88 mg, 87%). Flash column chromatography (PE/EtOAc 8:1 as eluent) afforded **13** as a colourless oil (75 mg, 75%), which by ^{1}H NMR was an inseparable 5:1 α:β anomeric mixture; R_f (PE/EtOAc 1:1) 0.71; $[\alpha]_D = +24.4$ (*c* 2.74, $CHCl_3$); ν_{max} neat/cm^{-1} 3366 (OOH), 2936, 2859 (2 × O–SiR), 1473, 1395, 1297, 1183; major anomer; δ_H (400 MHz, $CDCl_3$) 8.75 (1H, br s, OO*H*), 6.18 (1H, d, $J_{2,3}$ 10.0 Hz, H-3), 5.58 (1H, dt, $J_{1,2}$ 2.4, $J_{2,4}$ 2.4, $J_{2,3}$ 10.0 Hz, H-2), 5.44 (1H, br d, $J_{1,2}$ 1.8 Hz, H-1), 4.38 (1H, dd, $J_{2,4}$ 2.0, $J_{4,5}$ 9.0 Hz, H-4), 4.22 (1H, dd, $J_{5,6}$ 5.0, $J_{6,6'}$ 10.0 Hz, H-6), 3.92 (1H, dd, $J_{5,6'}$ 10.0, $J_{6,6'}$ 10.0 Hz, H-6′), 3.79 (1H, ddd, $J_{5,6}$ 5.0, $J_{4,5}$ 9.0, $J_{5,6'}$ 10.0 Hz, H-5), 1.05 (9H, s, C_4H_9), 0.99 (9H, s, C_4H_9); δ_C (100 MHz, $CDCl_3$) 138.2, 120.3 (CH, C-3, C-2), 98.9 (CH, C-1), 70.3, 67.9, 67.1 (CH, C-5, CH_2, C-6, C-4), 27.6, 27.2 (CH_3, CMe_3), 22.9, 20.2 (C, CMe_3); CIMS *m*/*z* 302 (M^+, 100), 285 (M^+-OH, 56), 269 (M^+-HO_2, 70); HRMS (CI): MNH_4^+, found 320.1893. $C_{14}H_{30}NO_5Si$ requires 320.1892. 0.3 ppm error.

4.6. Ethyl 2,3-dideoxy-4,6-di-*O*-pivaloyl α-D-*threo*-hex-2-enopyranoside 14

Ethyl 4,6-di-*O*-benzoyl-2,3-dideoxy-α-D-*threo*-hex-2-enopyranoside was obtained from diol **9** using a previously described[20] Mitsunobu procedure in 59% yield. To this intermediate (4.50 g, 11.8 mmol) in MeOH

(30 mL) at rt under N_2, was added sodium methoxide (1 mL, 25% solution in MeOH). The reaction was stirred at rt until deprotection was complete (2 d, TLC), then concentrated in vacuo to give a yellow residue. Purification by column chromatography (PE/EtOAc 1/1 then EtOAc as eluent) gave the diol as a yellow solid. This was dissolved in pyridine (20 mL) and cooled to 0 °C, under N_2 followed by dropwise addition, over 30 min, of pivaloyl chloride (4.0 mL, 32.7 mmol). The reaction was stirred at rt for 4 d with further pivaloyl chloride (4.0 mL) added after 2 d. On completion the reaction was concentrated in vacuo and the residue obtained dissolved in CH_2Cl_2 (30 mL), washed with water (30 mL), satd aq $CuSO_4$ solution (5 × 30 mL) and water again (30 mL), then dried ($MgSO_4$), filtered and concentrated in vacuo to give a brown oil. Purification by column chromatography (PE/EtOAc 3:2 as eluent) gave the title compound **14** (1.12 g, 27.8%) as a colourless oil; R_f (PE/EtOAc 7:1) 0.74; $[\alpha]_D = -123.8$ (*c* 0.9, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2975 (CH), 1734 (C=O), 1481, 1283, 1153, 1049; δ_H (270 MHz, $CDCl_3$) 6.06 (1H, dd, $J_{2,3}$ 10.0, $J_{3,4}$ 5.0 Hz, *H*-3), 5.98 (1H, dd, $J_{1,2}$ 3.0, $J_{2,3}$ 10.0 Hz, *H*-2), 5.03 (1H, d, $J_{1,2}$ 3.0 Hz, *H*-1), 4.94 (1H, dd, $J_{3,4}$ 5.0, $J_{4,5}$ 2.5 Hz, *H*-4), 4.35 (1H, dt, $J_{4,5}$ 2.5, $J_{5,6}$ 6.5 Hz, *H*-5), 4.26–4.10 (2H, m, *H*-6, *H*-6′), 3.83 (1H, dq, J_{gem} 9.5, *J* 7.0 Hz, $OCH_AH_BCH_3$), 3.54 (1H, dq, J_{gem} 9.5, *J* 7.0 Hz, $OCH_AH_BCH_3$), 1.22 (9H, s, *OPiv*), 1.20 (3H, t, *J* 7.0 Hz, OCH_2CH_3) 1.15 (9H, s, *OPiv*); δ_C (67.5 MHz, $CDCl_3$) 177.9, 177.5 (C, *OPiv*), 130.5 (CH, *C*-3), 125.0 (CH, *C*-2), 93.4 (CH, *C*-1), 66.8, 62.5 (CH, *C*-4, *C*-5), 63.6, 62.7 (CH_2, *C*-6, OC_2CH_3), 38.8, 38.6 (C, *OPiv*), 27.0, 26.4 (CH_3, *OPiv*), 15.1 (CH_3, OCH_2C_3); CIMS *m*/*z* 360 (MNH_4^+, 6), 297 ($M^+-C_2H_5O$, 100), 241 ($M^+-C_6H_{13}O$, 8), 195 ($M^+-C_7H_{15}O_3$, 92), HRMS (CI): MNH_4^+, found 360.2385. $C_{18}H_{34}NO_6$ requires 360.2386. 0.3 ppm error.

4.7. 2,3-Dideoxy-4,6-di-*O*-pivaloyl-D-*threo*-hex-2-enopyranosyl hydroperoxide 3

Ethyl 2,3-dideoxy-4,6-di-*O*-pivaloyl-α-D-*threo*-hex-2-enopyranoside **14** (1.07 g, 3.1 mmol) was treated with 67% aq H_2O_2 (3 mL) as described for the preparation of **1**. After 5 d the reaction was worked-up as previously described, followed by purification by flash column chromatography (PE/EtOAc 7:1 as eluent) to give the title compound **3** (454 mg, 43.5%), as a colourless oil, an inseparable mixture of anomers (α:β = 10:1); R_f (PE/EtOAc 7:1) 0.44; ν_{max} (film)/cm^{-1} 3407 (OOH), 2964 (C-H), 1725 (C=O), 1282, 1216, 1156; δ_H (270 MHz, $CDCl_3$) 6.22 (1H, ddd, $J_{1,3}$ 1.5, $J_{2,3}$ 10.0, $J_{3,4}$ 5.5 Hz, H-3α), 6.12 (1H, ddd, *J* 1.5, *J* 4.5, $J_{2,3}$ 10.0 Hz, H-3β), 5.94 (1H, dd, $J_{1,2}$ 3.0, $J_{2,3}$ 10.0 Hz, H-2α), 5.89 (1H, ddd, *J* 1.0, *J* 1.5, $J_{2,3}$ 10.0 Hz, H-2β), 5.56–5.54 (1H, m, H-1β), 5.53 (1H, dd, $J_{1,2}$ 3.0, $J_{1,3}$ 1.5 Hz, H-1α), 5.17–5.13 (1H, m, H-4β) 4.96 (1H, dd, $J_{3,4}$ 5.5, $J_{4,5}$ 2.5 Hz, H-4α), 4.40 (1H, dt, $J_{4,5}$ 2.5, $J_{5,6}$ 7.0 Hz, H-5α), 4.36–4.30 (3H, m, H-5β, H-6α, H-6β), 4.22–4.17 (1H, m, H-6′β), 4.16 (1H, dd, $J_{5,6}$ 7.0, $J_{6,6'}$ 10.5 Hz, H-6α), 1.17 (9H, s, OPiv), 1.16 (9H, s, OPiv); δ_C (67.5 MHz, $CDCl_3$) 178.3, 177.6 (C, OPiv), 128.7, 127.7 (CH, *C*-2β, *C*-3β), 128.6, 126.0 (CH, C-2α, C-3α), 99.7 (CH, C-1β), 97.8 (CH, C-1α), 70.9, 63.3 (CH, C-4β, C-5β), 67.1, 61.6 (CH, C-4α, C-5α), 62.2 (CH_2, C-6β), 61.9 (CH_2, C-6α), 38.9, 38.7 (C, OPiv), 27.0 (CH_3, OPiv); CIMS *m*/*z* 348 (MNH_4^+, 8), 330 (M^+, 66), 313 (M^+-HO, 9) 297 (M^+-HO_2, 100), 195 ($M^+-C_5H_{11}O_4$, 92); HRMS (CI): MNH_4^+, found 348.2030. $C_{16}H_{30}NO_7$ requires 348.2022. 2.3 ppm error.

4.8. (2*S*,3*R*,6*S*)-6-Hydroperoxy-2-methyl-3,6-dihydro-2*H*-pyran-3-yl acetate 18α and (2*S*,3*R*,6*R*)-6-hydroperoxy-2-methyl-3,6-dihydro-2*H*-pyran-3-yl acetate 18β

To di-*O*-acetyl-L-(+)-rhamnal **17**[23,24] (1.29 g, 6.02 mmol) in Et_2O–H_2O_2 [6.0 mL, prepared by extracting 50% aq H_2O_2 (5 mL) into Et_2O (2 × 10 mL); CARE!][35] at 0 °C was added concentrated H_2SO_4 (two drops, cat.). The reaction mixture was stirred overnight with slow warming to 20 °C. The reaction mixture was diluted with CH_2Cl_2 (20 mL) and water (20 mL), then the aqueous phase was separated and washed with CH_2Cl_2 (2 × 15 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to give a very pale yellow oil (929 mg, 82%), which was an α:β= 10:1 mixture of anomers by NMR. Separation by flash chromatography (PE/EtOAc 4:1 as eluent) afforded pure **18**α and **18**β. α-Anomer **18**α: R_f (PE/EtOAc 1:1) 0.38; $[\alpha]_D = -138.5$ (*c* 0.84, $CHCl_3$); ν_{max} $CHCl_3$/cm^{-1} 3379 (OOH), 2983 (CH), 1742 (C=O), 1449, 1374, 1238, 1197, 1098; CIMS *m*/*z* 188 (M^+, 100), 155 (M^+-HO_2, 60); HRMS (CI): MNH_4^+, found 206.2156. $C_8H_{16}NO_5$ requires 206.2157. 0.5 ppm error. δ_H (400 MHz, $CDCl_3$) 8.57 (1H, br s, OO*H*), 6.00 (1H, d, $J_{2,3}$ 10.0 Hz, H-3), 5.72 (1H, dt, $J_{1,2}$ 2.7, $J_{2,3}$ 10.0, $J_{2,4}$ 2.0 Hz, H-2), 5.48 (1H, br s, H-1), 5.08 (1H, dq, $J_{1,4}$ 1.4, $J_{2,4}$ 2.0, $J_{3,4}$ 1.6, $J_{4,5}$ 9.2 Hz, H-4), 3.97 (1H, dq, $J_{4,5}$ 9.2, $J_{5,Me}$ 6.2 Hz, H-5), 2.10 (3H, s, OAc), 1.28 (3H, d, $J_{5,Me}$ 6.2, Me); δ_C (100 MHz, $CDCl_3$) 170.5 (C=O, OAc), 133.4, 122.9 (=CH, C-3, C-2), 98.6 (CH, C-1), 70.3, 65.6 (CH, C-5, C-4), 21.0 (CH_3, OAc); 17.8 (Me). β-Anomer **18**β: R_f (PE/EtOAc 1:1) 0.39; $[\alpha]_D = -116.5$ (*c* 0.84, $CHCl_3$); ν_{max} $CHCl_3$/cm^{-1} 3379 (OOH), 2983 (CH), 1742 (C=O), 1449, 1374, 1238, 1197, 1098; δ_H (400 MHz, $CDCl_3$) 8.60 (1H, br s, OO*H*), 6.05 (1H, ddd, $J_{1,3}$ 1.6, $J_{3,4}$ 3.5, $J_{2,3}$ 10.0 Hz, H-3), 5.87 (1H, dt, $J_{1,2}$ 1.6, $J_{2,3}$ 10.0, $J_{2,4}$ 1.8 Hz, H-2), 5.60 (1H, br d, $J_{1,2}$ 1.6 Hz, H-1), 5.02 (1H, m, H-4), 3.99 (1H, dq, $J_{4,5}$ 5.4, $J_{5,Me}$ 6.5 Hz, H-5), 2.09 (3H, s, OAc), 1.36 (3H, d, $J_{5,Me}$ 6.5 Hz, Me); δ_C (100 MHz, $CDCl_3$) 170.6 (C=O, OAc), 129.9, 126.0 (=CH, C-3, C-2), 98.7 (CH, C-1), 70.8, 68.2 (CH, C-5, C-4), 20.6 (CH_3, OAc); 18.2 (Me). CIMS *m*/*z* 188 (M^+, 100), 155 (M^+-HO_2, 60); HRMS (CI): MNH_4^+, found 206.2156. $C_8H_{16}NO_5$ requires 206.2157. 0.5 ppm error.

4.9. Ethyl-4-*O*-pivaloyl-2,3,6-trideoxy-α,β-L-erythro-hex-2-enopyranoside 19

To a solution of di-*O*-acetyl-L-(+)-rhamnal **17** (530 mg, 2.47 mmol) in CH_2Cl_2 (10.6 mL) containing dry EtOH (0.3 mL, 5.14 mmol) was added a solution of $SnCl_4$ in CH_2Cl_2 (22.7 μL, 1.0 M; 5 mol%). The resulting mixture was stirred at rt for 20 min, quenched with satd aq $NaHCO_3$ (~2.6 mL) and then extracted (3 × 8.0 mL) with CH_2Cl_2. The organic phases were combined, washed

with brine (~2.6 mL), dried ($MgSO_4$) and evaporated to furnish a crude brown syrup as a mixture of anomers α:β = 5.9:1 by ^{1}H NMR (438 mg, 88%). The crude material [2.3 g, 11.5 mmol, R_f 0.54 (PE/EtOAc 1:1)] had spectroscopic data in accordance with literature values[36] and was progressed without further purification; the compound in 1:1 MeOH/Et_3N (16.0 mL) along with a spatula of K_2CO_3 under N_2, was heated at 50 °C for 6 h. The solvent was then removed in vacuo to give a pale brown oil. This was immediately taken up in pyridine (10 mL) under N_2 and cooled to 0 °C, then pivaloyl chloride (2.4 mL, 19.6 mmol) was added dropwise. The reaction mixture was stirred at rt for 24 h then diluted with water (15 mL) and extracted with EtOAc (3 × 15 mL). The organic phases were combined, washed with satd aq $CuSO_4$ solution (5 × 15 mL), water (2 × 15 mL), satd aq $NaHCO_3$ (2 × 15 mL), water again (2 × 15 mL), dried ($MgSO_4$), filtered and concentrated in vacuo to give the title compound **19** as a crude brownish orange oil. This was purified by flash column chromatography (PE/EtOAc 3:1 as eluent) furnishing **19** as an orange oil (2.68 g, 96%) R_f (PE/EtOAc 1:1) 0.74; $[\alpha]_D = -124.7$ (*c* 1.06, $CHCl_3$); ν_{max} neat/cm^{-1} 1733 (C=O), 1480, 1280, 1156, 1058; δ_H (400 MHz, $CDCl_3$) 5.78–5.82 (2H, m, H-2,3), 5.01 (1H, d, $J_{4,5}$ 9.5 Hz, H-4), 4.95 (1H, br s, H-1), 4.01–3.94 (1H, dq, $J_{5,Me}$ 6.4, $J_{4,5}$ 9.2 Hz, H-5), 3.86-3.77 (1H, dq, J_{gem} 9.5, J 7.0 Hz, OCH_AH_B-CH_3), 3.57–3.49 (1H, dq, J_{gem} 9.5, J 7.0 Hz, OCH_A-H_BCH_3), 1.24–1.19 (6H, m, OCH_2CH_3 + $CHCH_3$), 1.17 (9H, OPiv); δ_C (100 MHz, $CDCl_3$) 178.0 (C, OPiv), 130.0, 128.6 (CH, C-2, C-3), 94.4 (CH, C-1), 70.7, 64.9 (CH, C-4, C-5), 64.2 (CH_2, OCH_2CH_3), 38.9 (C, OPiv), 27.1 (CH_3, OPiv), 18.1 (Me), 15.5 (CH_3, OCH_2CH_3); CIMS *m*/*z* 197 ($M^+-C_2H_5O$, 100). HRMS (CI): MNH_4^+, found 260.1862. $C_{13}H_{26}NO_4$ requires 260.1858. 1.5 ppm error.

4.10. (2*S*,3*R*,6*R*)-6-Hydroperoxy-2-methyl-3,6-dihydro-2*H*-pyran-3-yl pivalate 20α, (2*S*,3*R*,6*S*)-6-hydroperoxy-2-methyl-3,6-dihydro-2*H*-pyran-3-yl pivalate 20β

To ethyl-4-*O*-pivaloyl-2,3,6-trideoxy-α-L-erythro-hex-2-enopyranoside **19** (1.01 g, 4.17 mmol) in Et_2O–H_2O_2 (6.0 mL) at 0 °C was added concentrated H_2SO_4 (two drops). The reaction mixture was stirred overnight slowly warming to 20 °C. The reaction mixture was diluted with CH_2Cl_2 (15 mL) and water (15 mL). The aqueous phase was separated and washed with CH_2Cl_2 (2 × 10 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to give a colourless oil (825 mg, 86%). Compounds **20**α and **20**β were obtained as a 10:1 mixture of anomers, respectively, by ^{1}HNMR. The crude mixture of hydroperoxides was partially separable by flash column chromatography (PE/EtOAc 8:1 as eluent), yielding pure α-anomer **20**α as a colourless oil (367 mg, 38%), which crystallised on standing in the freezer, as well as a mixture of anomers α:β = 10:1 (400 mg, 52%); α-anomer **20**α: R_f (PE/EtOAc 1:1) 0.52; $[\alpha]_D = -159.6$ (*c* 1.01, $CHCl_3$); ν_{max} neat/cm^{-1} 3379 (OOH), 2983 (CH), 1742 (C=O), 1449, 1374, 1238, 1197, 1098; δ_H (400 MHz, $CDCl_3$) 8.67 (1H, br s, OO*H*), 5.96 (1H, d, $J_{2,3}$ 10.0 Hz, H-3), 5.72 (1H, dt, $J_{1,2}$ 2.8, $J_{2,3}$ 10.0, $J_{2,4}$ 2.1 Hz, H-2), 5.49 (1H, br s, H-1), 5.05 (1H, dt, $J_{2,4}$ 1.8, $J_{3,4}$ 1.5, $J_{4,5}$ 9.2 Hz, H-4), 3.98 (1H, dq, $J_{4,5}$ 9.2, $J_{5,Me}$ 6.4 Hz, H-5), 1.26 (3H, d, $J_{5,Me}$ 6.4 Hz, Me), 1.21 (9H, s, OPiv); δ_C (100 MHz, $CDCl_3$) 178.0 (C=O, OPiv), 133.8, 122.9 (=CH, C-3, C-2), 98.8 (CH, C-1), 70.1, 65.8 (CH, C-5, C-4), 39.0 (C, OPiv), 27.2 (CH_3, OPiv), 18.0 (Me); CIMS *m*/*z* 230 (M^+, 72), 213 (M^+-OH, 85), 197 (M^+-HO_2, 100); HRMS (CI): MNH_4^+, found 248.1498. $C_{11}H_{22}NO_5$ requires 248.1492. 2.4 ppm error.

4.11. 2-(5-Cyclohexylpenta-2′*E*,4′*E*-dienamido)-5,6-epoxy-1,4-benzoquinone 6:[37] general procedure

To a solution of hydroperoxide (see Table 1, 0.14 mmol) in toluene (20 mL) at room temperature was added DBU (20 mg, 0.14 mmol). The mixture was stirred for 10 min, then 2-(5-cyclohexylpenta-2′*E*,4′*E*-dienamido)-1,4-benzoquinone **4** (40 mg, 0.14 mmol) in toluene (20 mL) was added. The reaction was stirred until completion (see Table 1), deemed to be the point when the solution no longer produced a yellow colour on a TLC plate. Water (5 mL) was then added to quench the reaction. Following addition of water and transfer to a separating funnel, the two layers were separated and the aqueous phase washed with CH_2Cl_2 (2 × 30 mL). The organic phases were combined, dried ($MgSO_4$), filtered and concentrated in vacuo to give a brown residue. Purification by flash column chromatography (CH_2Cl_2 as eluent) gave the title compound **6** (for yields see Table 1) as a pale yellow solid; mp 158–159 °C (lit.[37] mp 159–160 °C); R_f (PE/EtOAc 7:3) 0.82; δ_H (270 MHz, $CDCl_3$) 7.85 (1H, br s, N*H*), 7.61 (1H, d, $J_{3,5}$ 2.5 Hz, H-3), 7.32 (1H, m, vinyl-H), 6.22–6.09 (2H, m, vinyl-H), 5.91 (1H, d, $J_{2',3'}$ 15.0 Hz, H-2′), 3.91 (1H, d, $J_{5,6}$ 3.5 Hz, H-6), 3.82 (1H, dd, $J_{3,5}$ 2.5, $J_{5,6}$ 3.5 Hz, H-5), 2.10 (1H, m, cy-H), 1.76–1.65 (4H, m, cy-H), 1.21 (6H, m, cy-H); δ_C (67.5 MHz, $CDCl_3$) 191.1, 188.2 (C, C-1, C-4), 165.0 (C, C-1′), 152.4 (C, C-2), 146.0, 125.4, 122.4, 120.0, 115.2 (CH, vinyl), 53.8, 52.5 (CH, C-5, C-6), 41.2 (CH, cy), 32.1, 25.9, 25.7 (CH_2, cy). The data were consistent with the literature values.[37] Ee values (Table 1) were determined both by polarimetry and by HPLC analysis using a Daicel AD column eluted with *n*-hexane/EtOH mixtures and UV detection.

4.12. 2-Substituted-2,3-epoxy-1,4-naphthoquinones 7a and 7e:[15] general procedure

To a solution of hydroperoxide (see Table 1, 0.28 mmol) in toluene (20 mL) at 20 °C, was added DBU (35 mg, 0.23 mmol). The mixture was stirred for 10 min then the appropriate 2-substituted-1,4-naphthoquinone (0.23 mmol) in toluene (20 mL) was added. The reaction was stirred until completion (see Table 1) then water (5 mL) was added to quench the reaction. Work-up, purification and chiral analysis were the same as above for 2-(5-cyclohexylpenta-2′*E*,4′*E*-dienamido)-5,6-epoxy-1,4-benzoquinone **6**.

4.13. 2-Methyl-2,3-epoxy-1,4-naphthoquinone 7a

2-Methyl-1,4-naphthoquinone **5a**[25] was treated with several hydroperoxides (see Table 1) as described above to

yield the title compound **7a** in the yields shown, as a yellow solid; mp 95–96 °C (lit.[38] mp 96–97 °C); R_f (PE/EtOAc 9:1) 0.72; δ_H (270 MHz, $CDCl_3$) 8.03–7.89 (2H, m, Ar–*H*), 7.77–7.69 (2H, m, Ar–*H*), 3.85 (1H, s, *H*-3), 1.72 (3H, s, CH_3).

4.14. 2-Phenyl-2,3-epoxy-1,4-naphthoquinone 7e

2-Phenyl-1,4-naphthoquinone **5e**[26] (54 mg) was treated with several hydroperoxides (see Table 1) as described above to yield the title compound **7e** in the yields shown, as a yellow solid; mp 61–62 °C (lit.[38] mp 62–63 °C); R_f (PE/EtOAc 9:1) 0.77; δ_H (270 MHz, $CDCl_3$) 8.12–7.98 (2H, m, Ar–*H*), 7.79–7.72 (2H, m, Ar–*H*), 7.52–7.36 (5H, m, Ph–*H*), 3.96 (1H, s, *H*-3).

4.15. Computational methods

All calculations were performed on a PC running RedHat Linux 7.3.[39] Molecular mechanics energy minimisations were performed using the default settings in SYBYL 6.91, expect that Gasteiger–Hückel charges were accounted for and 100,000 iterations were used.[29] Constraints were used to help locate the transition states and default settings were employed. For identifying the approximate first transition state (peroxide attacking quinone), a constraint of 2 Å was chosen between the β-carbon of the quinone and the peroxide anion. For the generation of the approximate second TS (formation of epoxide via ring closure and elimination of alkoxide), two distance constraint of 1.9 Å were placed between the terminal peroxide oxygen and the carbons at either end of the double bond. An angle constraint was applied between the carbon of the double bond, terminal peroxide oxygen and the adjacent oxygen of 146° and the whole system then underwent energy minimisation.[30] Input files for MOPAC calculations (atom types and connectivity) were obtained using SYBYL 6.91.[29] Semi-empirical calculations were carried out in the gas phase using MOPAC with the AM1 Hamiltonian.[28] Molecules were modelled in vacuo as MOPAC does not model toluene, a solvent with a low dielectric constant,[40] very well. MOPAC 7 is freely available from internet sources.[41] All structures were optimised using the eigenvector following algorithm. For each molecule and transition state, the vibrational spectrum was produced by a FORCE calculation. Both ground states and transition states (TS) were confirmed by the presence of six eigenvalues that were very small (less than $\sim 5\,cm^{-1}$). A TS was further characterised by one, and only one, negative force constant corresponding to atomic motion along the reaction coordinate.[31] It was also necessary to show that a proposed TS connects the desired reactant(s) to the product(s). This was achieved by performing two intrinsic reaction coordinate (IRC) calculations. The first IRC began with an initial perturbation of the atomic coordinates in the direction of the single negative frequency and the second IRC calculation with a negative perturbation of the atomic coordinates along the same normal coordinate. By joining the results of the two calculations together it was easy to tell if the TS does indeed link reactants to products.

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