Biocatalytic and Stereoselective Synthesis
Chiral Oxygenated Heterocycles

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BACKGROUND
The Flavours and Fragrances industry is a rapidly growing multi-billion dollar global industry, mainly driven by expanding markets in middle-to-low income countries, including South Africa. Heterocyclic compounds are among the key targets in this industry and also the pharmaceutical industry. This includes the commercially available fragrances namely, Rhubafuran (1) Florol (2) and Jessemal (3) as shown on figure 1, whose key feature is that they are heterocycles (tetrahydrofuran or tetrahydropyran) with several chiral centres.

Figure 1. Examples of oxygenated heterocyclic compounds in commercial fragrances

PROBLEM STATEMENT
Fragrant molecules with more than one chiral center are complex because one isomer can be pleasant or more potent than the other where others may be harmful hence, the increasing interest of formulating fragrant molecules that are enantiomerically enriched with most pleasant stereoisomer and minimizing potential toxicological hazards.

METHODS
We envisioned that chiral tetrahydrofurans and tetrahydropyrans could be synthesised from 1,2,4-triols or 1,3,5-triols via a mild stereoselective cyclodehydration which our research group has already demonstrated that it does not lead to scrambling or loss of stereochemistry. To incorporate biocatalysis early in the synthetic scheme we identified hydroxyepoxide 8 as the key target for enzymatic resolution (Scheme 1 and 2).

RESULTS

Scheme 2 lipase acetylation of 8

Scheme 1. Synthesis of a key hydroxyepoxide 8 intermediate, tetrahydrofurans 10 and tetrahydropyrans 15

CONCLUSION
Different oxidation ways were tried to form 7 which resulted in poor yields and decomposition. Early results on the lipase acetylation of 8 using porcine pancreas lipase (PPL) are poor (22% after 90 h), but other enzymes are yet to be explored. Cyclisation of 8 to form 10 was obtained in good yield. 15 will be obtained via cyclisation after opening oxirane ring 12.

References:

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