# Synthesis, identification, and chemoenzymatic functionalisation of inhibitors of sterol transport proteins

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Sterol transport proteins (STPs) all bind and transport sterols, and their mis-regulation has been associated with lipid storage disorders, atherosclerosis, and a wide range of cancers.[1] Crucially, very few STP inhibitors have been reported, often with little or no selectivity annotations, and the majority of these target a small fraction of STPs, highlighting a significant gap in the field. The pseudo-natural product (PNP) strategy was applied by fusing the *cis*-decalin scaffold as found in cholic acid with natural product fragments resulting in novel analogues. Additional analogues were accessed from the resulting PNPs using a "complexity-to-diversity" approach to give ring-distorted products. Through the biological screening of the analogues against a panel of different STPs, the complex and three-dimensional spirooxepinoindole was identified as a privileged scaffold for the STPs. With careful optimisation of the scaffold the selectivity could be directed towards a single transporter, as showcased by the development of (−)-asteroxin-1 as a potent and selective new chemotype Aster-A inhibitor.[2] Late-stage chemoenzymatic functionalisation of (−)-asteroxin-1 and its late intermediates was performed achieving both enzyme- and substrate-dependent selectivity and oxidation sites not easily accessible by classical chemical means.

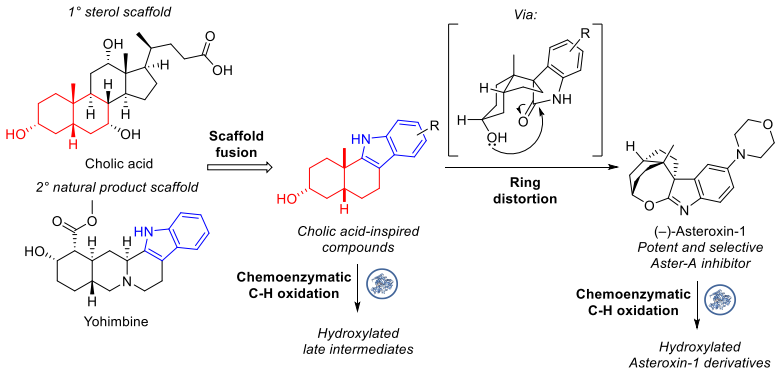


**Figure 1.** Identification of (–)-asteroxin-1 and its chemoenzymatic functionalisation.

1 U. Soffientini, A. Graham, *Clin. Sci.*, **2016**, *130*, 1843.
2 F. S. Bro, L. Depta, N. J. Dekker, H. P. Bryce-Rogers, M. L. Madsen, K. F. Præstegaard, T. Petersson, T. Whitmarsh-Everiss, M. Kubus, L. Laraia, *ACS Cent. Sci*, **2025**, *in press*, DOI: 10.1021/acscentsci.4c01657.