Efficient one-step approach to annulated tetrahydrofurans: supporting the search for new potent CCR2 receptor antagonists

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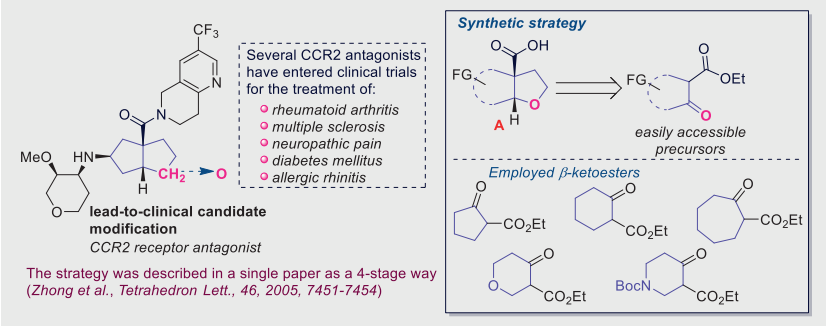
Background and synthetic strategy

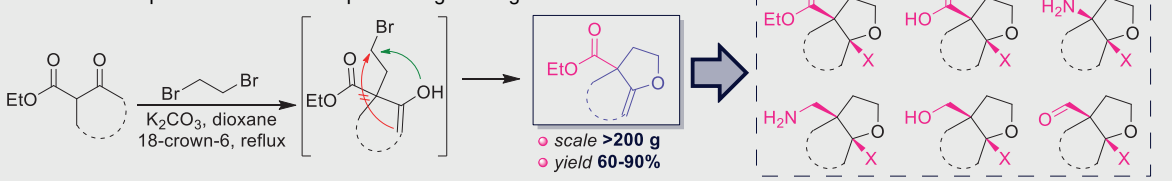
Oxygen-rich low molecular 3D frameworks with the restricted conformation are valuable tools for medicinal chemistry:
• a shift from a carbon backbone to the oxygen containing counterpart **(CH_2→O)** decreases lipophilicity, thus empowering those fragments to be implemented into a drug scaffold and resulting in both pronounced target affinity and bioavailability

A remarkable example on the issue is development of a selective CCR2 receptor antagonist by *Janssen:*
• there is significant ongoing effort directed towards the optimization of CCR2 antagonists;
• the possibility of modifying the cyclopentane cycle with a change in the structure of the scaffold has not been studied.

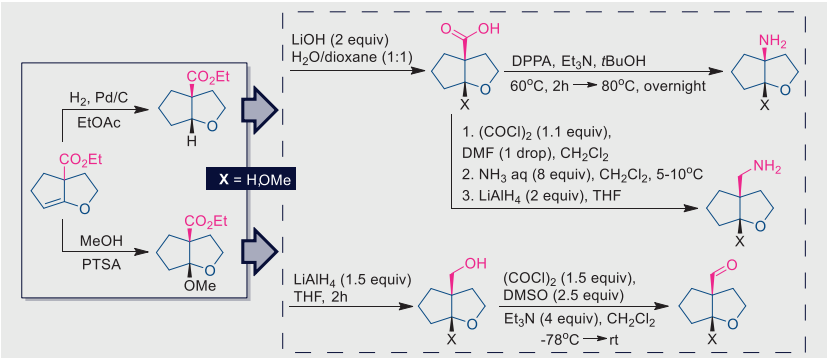


Synthetic results

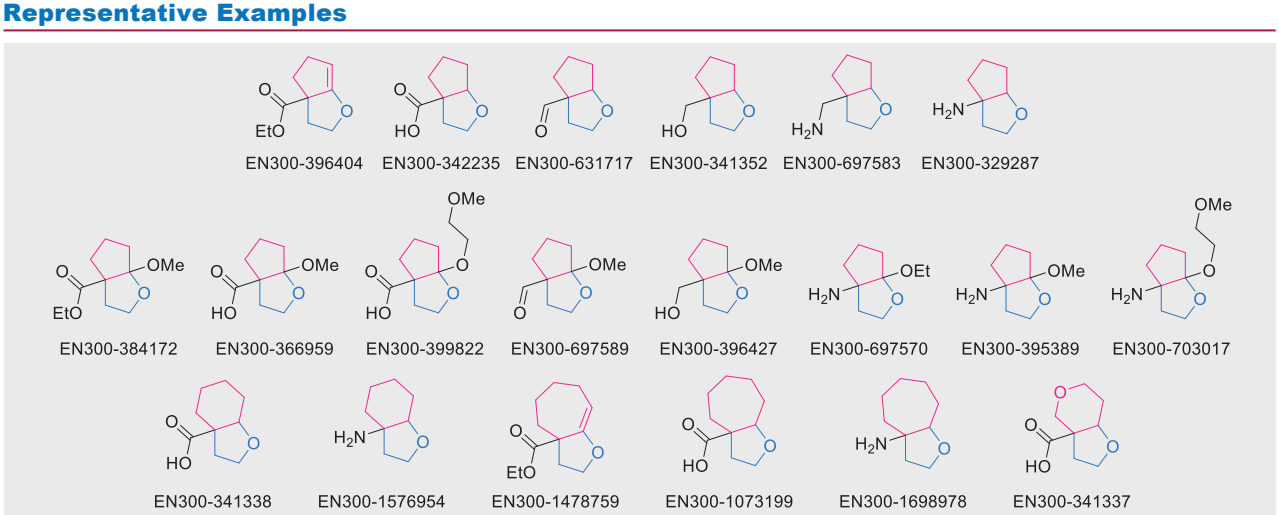
A CONCEPT OF THE WORK: to develop a flexible method for the synthesis of **type A** bifunctional compounds for the subsequent design of targeted libraries.



Research outlines:
• multigram scale (>200 g from 1 synthetic run) method for the synthesis of bicyclic fused tetrahydrofuranes with various sizes and natures of the adjacent rings;
• highly reactive vinyl alcohol moiety allowing its conversion to the corresponding cyclic acetals immediately under solvolytic conditions;
• the building blocks can significantly impact the lead optimization approaches *via* increasing the toolbox of synthetic chemists.



Representative Examples



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