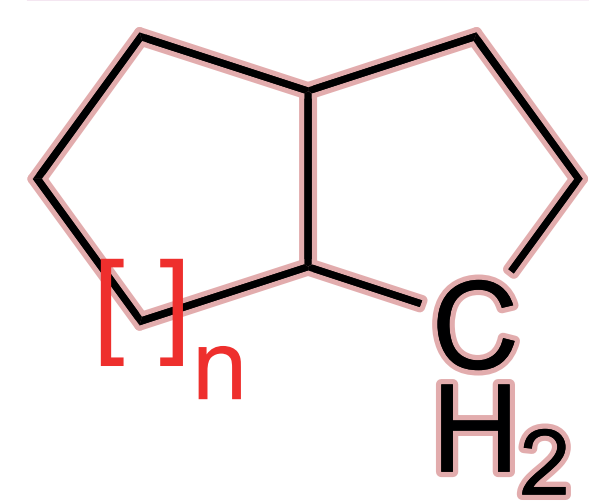


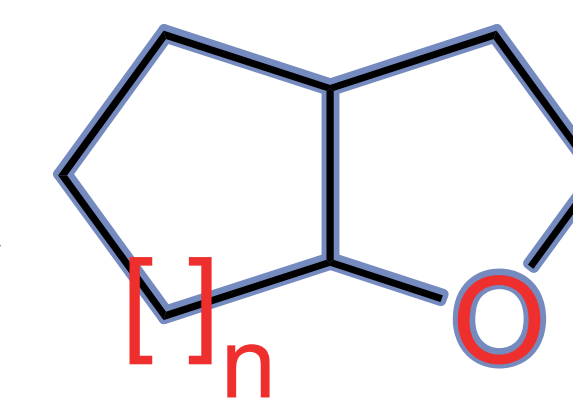
Functionalized bicyclic tetrahydrofurans: practical approach to CCR2 antagonist precursors

V. Turcheniuk, A. Kapeliukha, E. Ostapchuk, S. Bondarenko, A. Hanopolskyi, S. Ryabukhin, D. Volochnyuk

Background and synthetic strategy

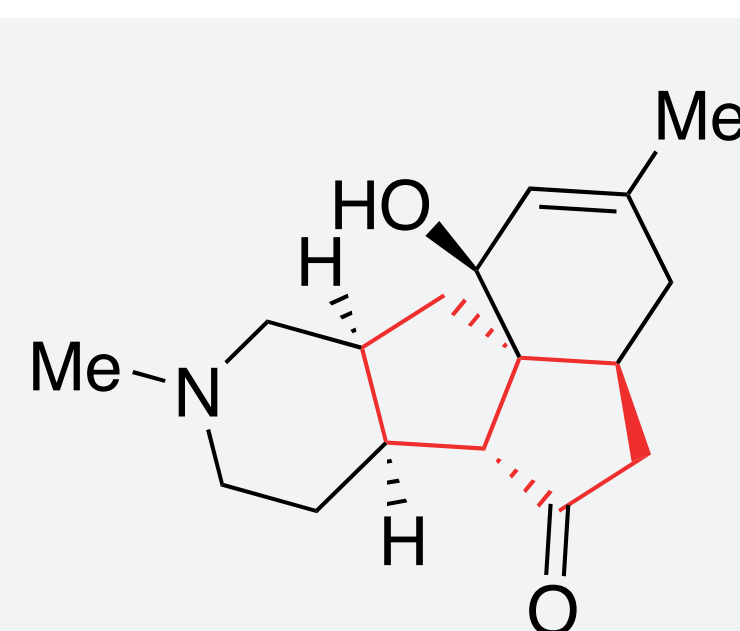


a shift from a carbon backbone to the oxygen-containing counterpart ($\text{CH}_2 \rightarrow \text{O}$) **decreases lipophilicity**, thus empowering those fragments to be implemented into a drug scaffold and resulting in both pronounced target affinity and bioavailability

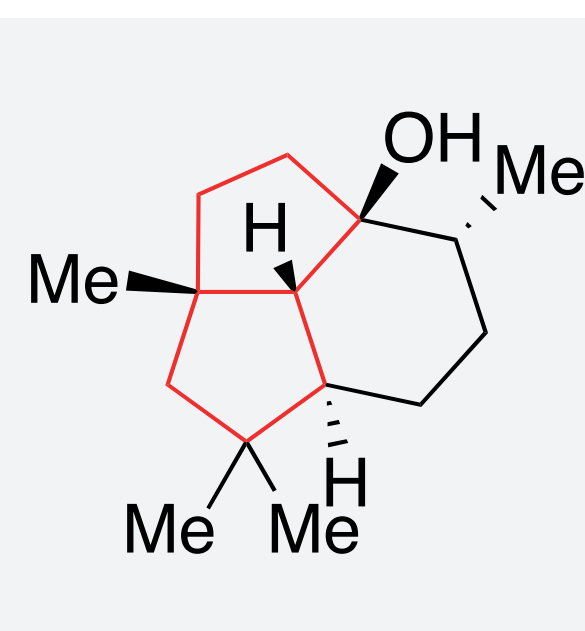


• **diquinane** is a conspicuous structure unit existing in the carbon frameworks of a wide range of natural products

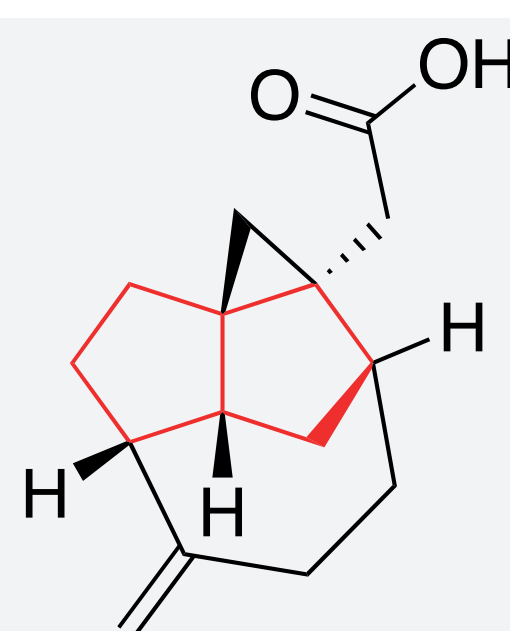
• **functionalized bicyclic THFs** are underrepresented versatile BB with a great potential to address unmet needs in drug discovery



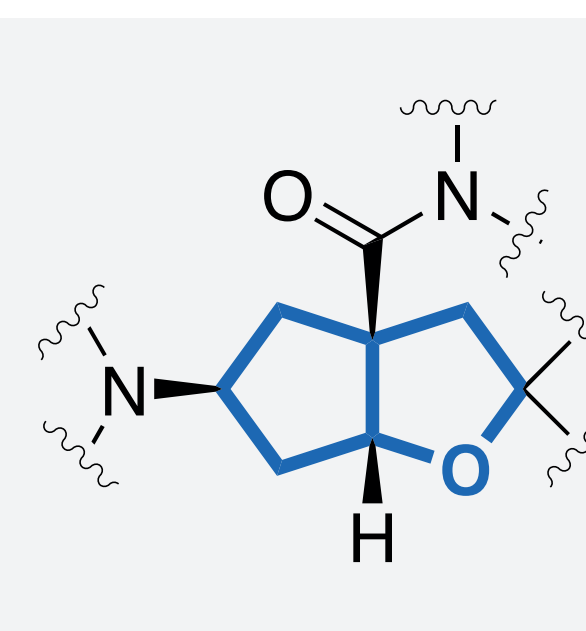
paniculatin



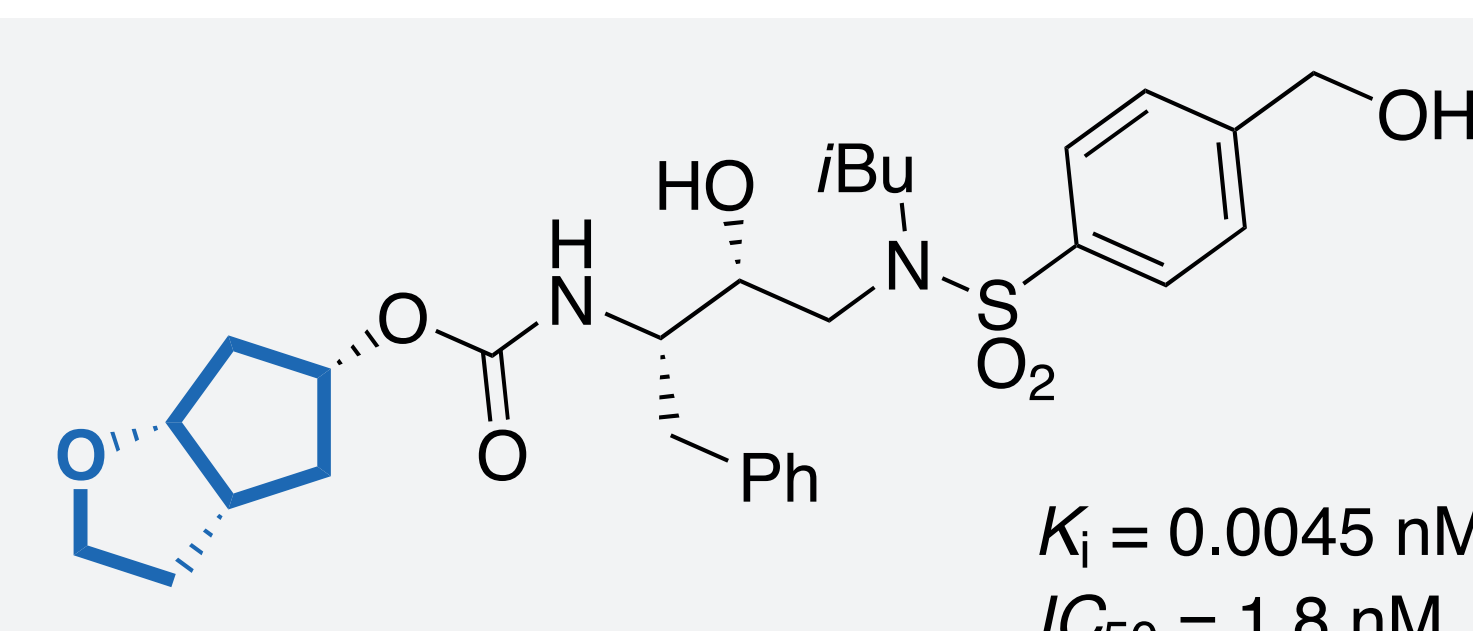
presilphiperfolane-1-ol



(+)-echinopine A



the principal core of CCR2 inhibitors



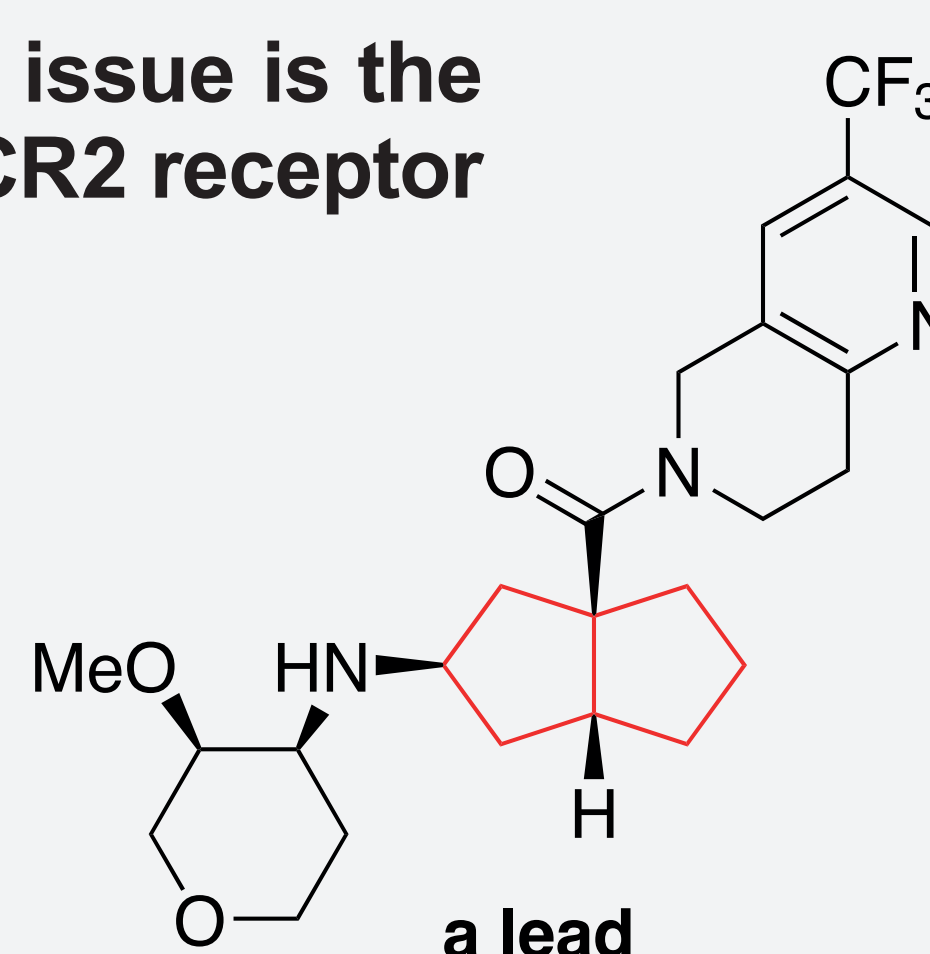
HIV1 protease inhibitor

$K_i = 0.0045 \text{ nM}$
 $IC_{50} = 1.8 \text{ nM}$

A remarkable example on the issue is the development of a selective CCR2 receptor antagonist by Janssen

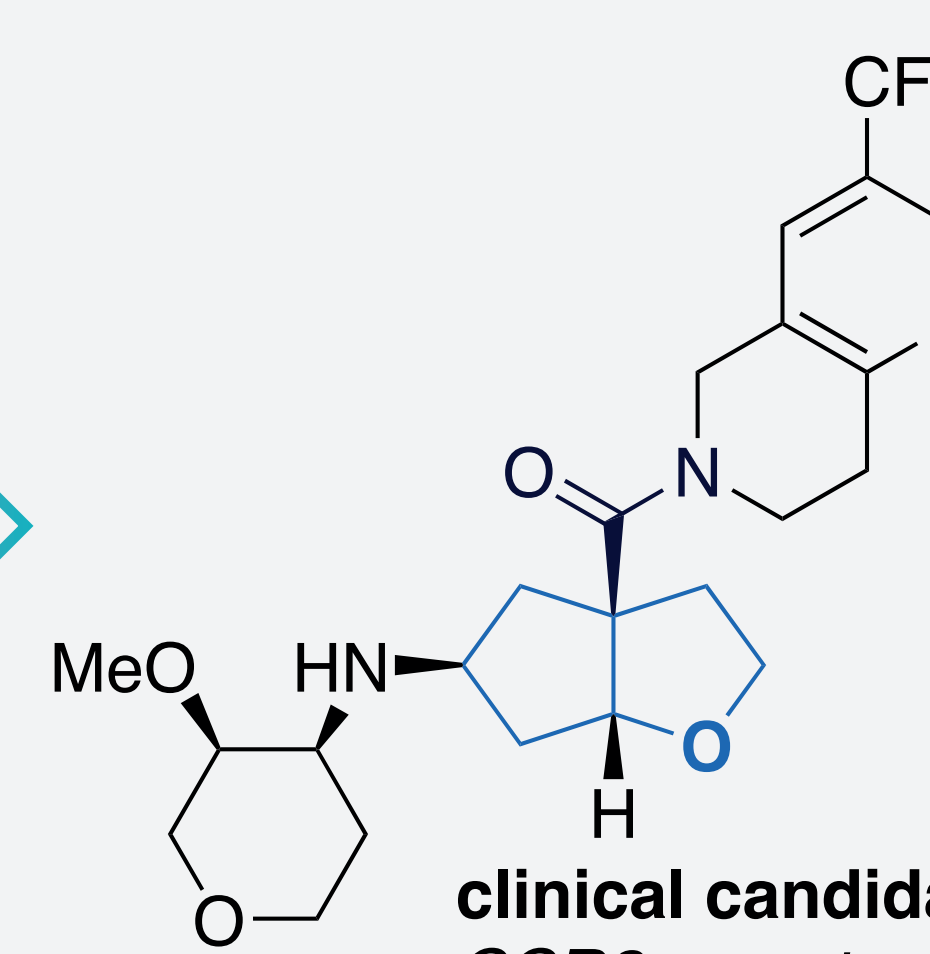
NB!

synthetic pathways for the synthesis of fused THFs suffer from **limited scope and/or scalability**



a lead

$\text{CH}_2 \rightarrow \text{O}$
ISOSTERIC SHIFT



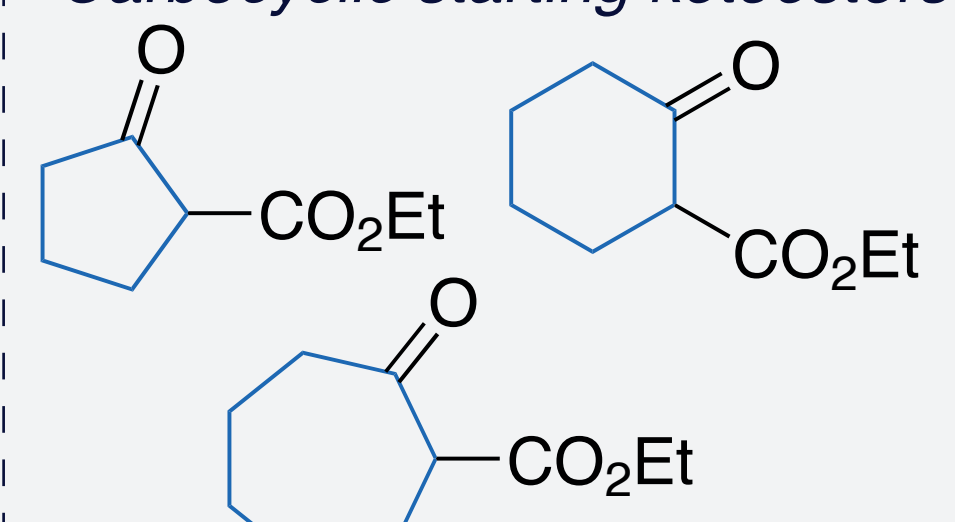
clinical candidate
CCR2 receptor antagonist

Possible cure against:

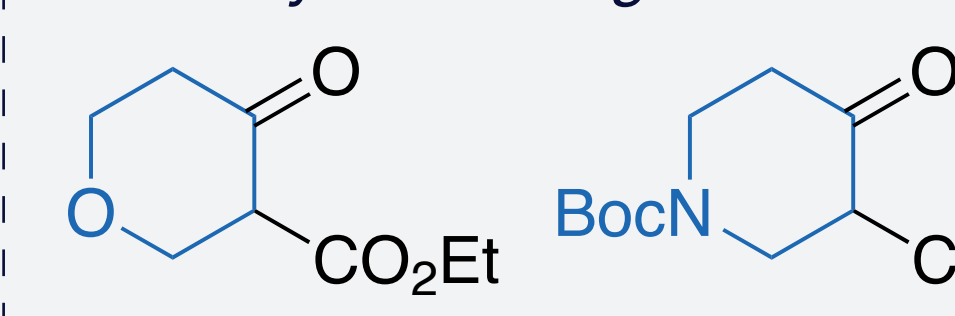
- rheumatoid arthritis
- multiple sclerosis
- neuropathic pain
- diabetes mellitus
- allergic rhinitis
- obesity
- asthma

Synthetic results

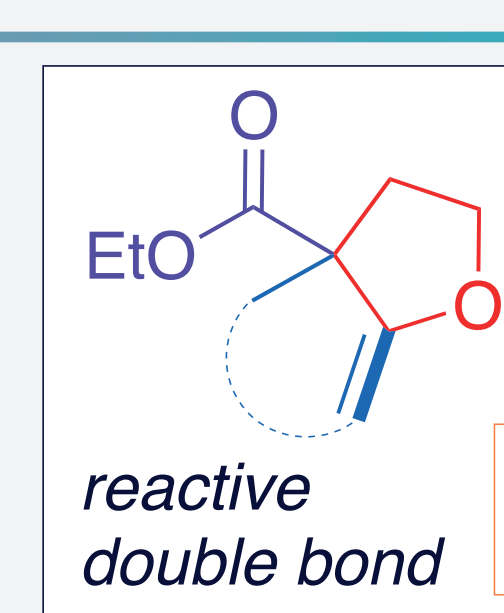
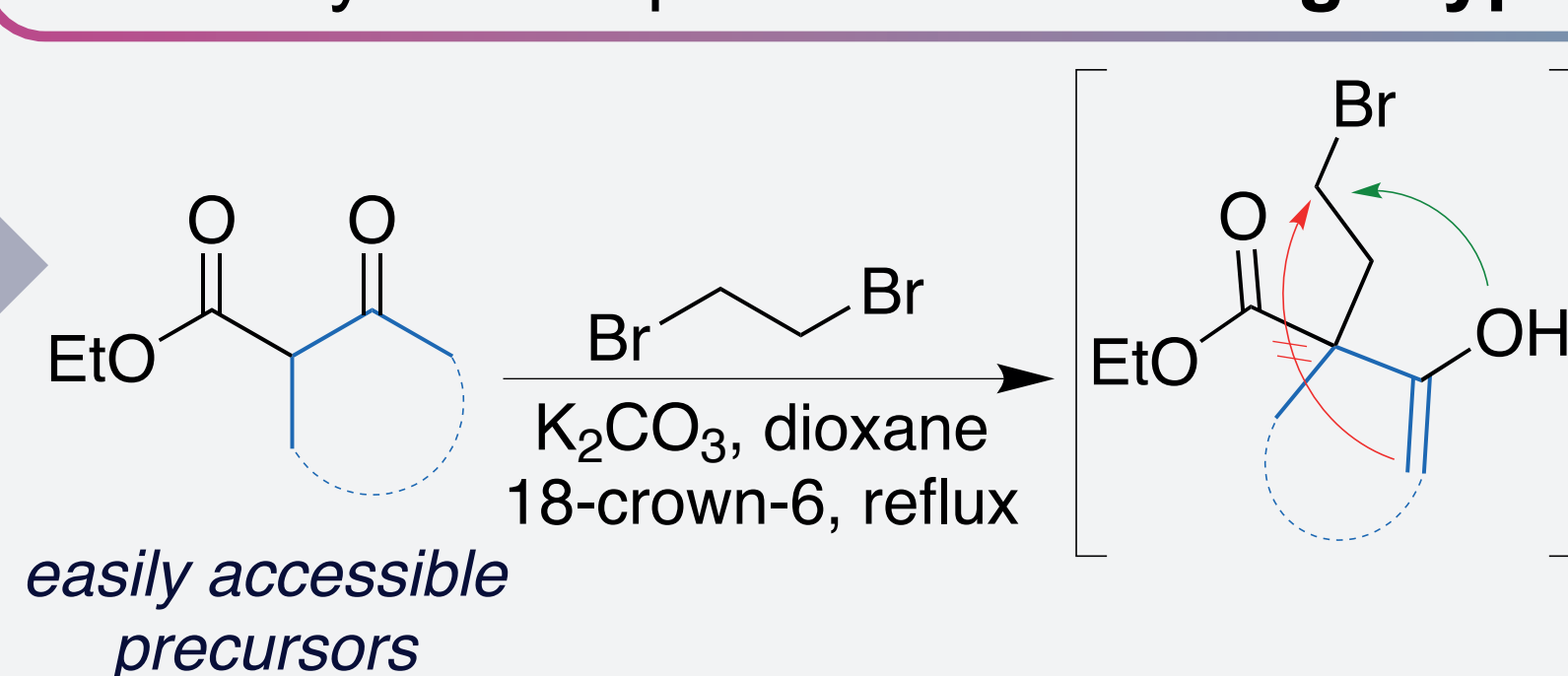
Carbocyclic starting ketoesters



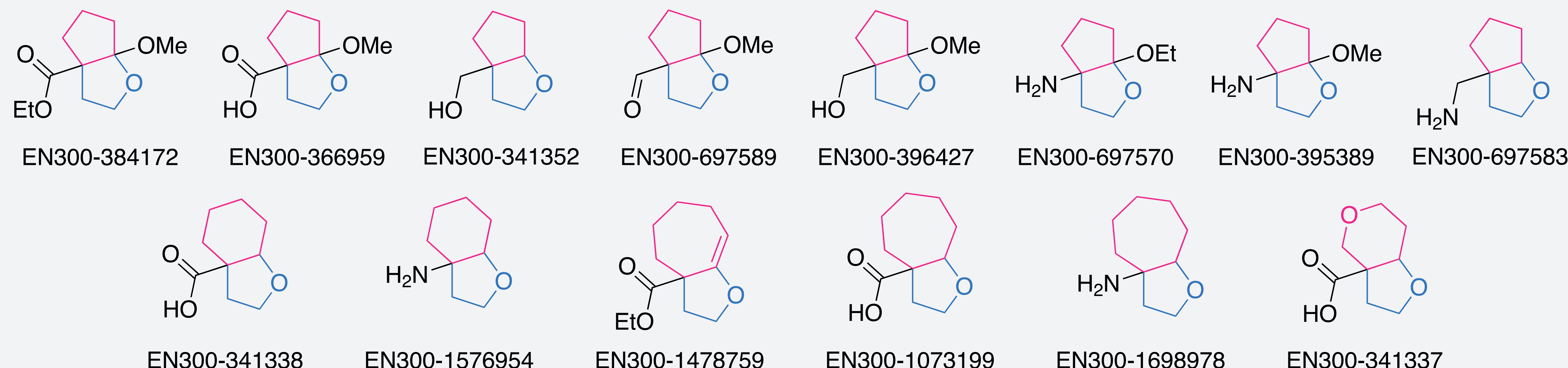
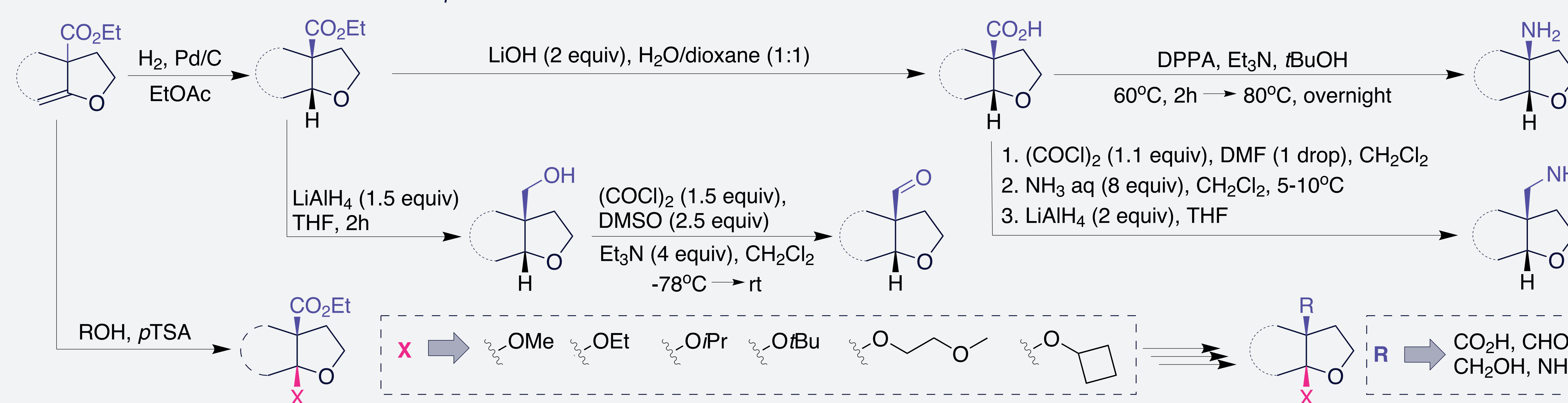
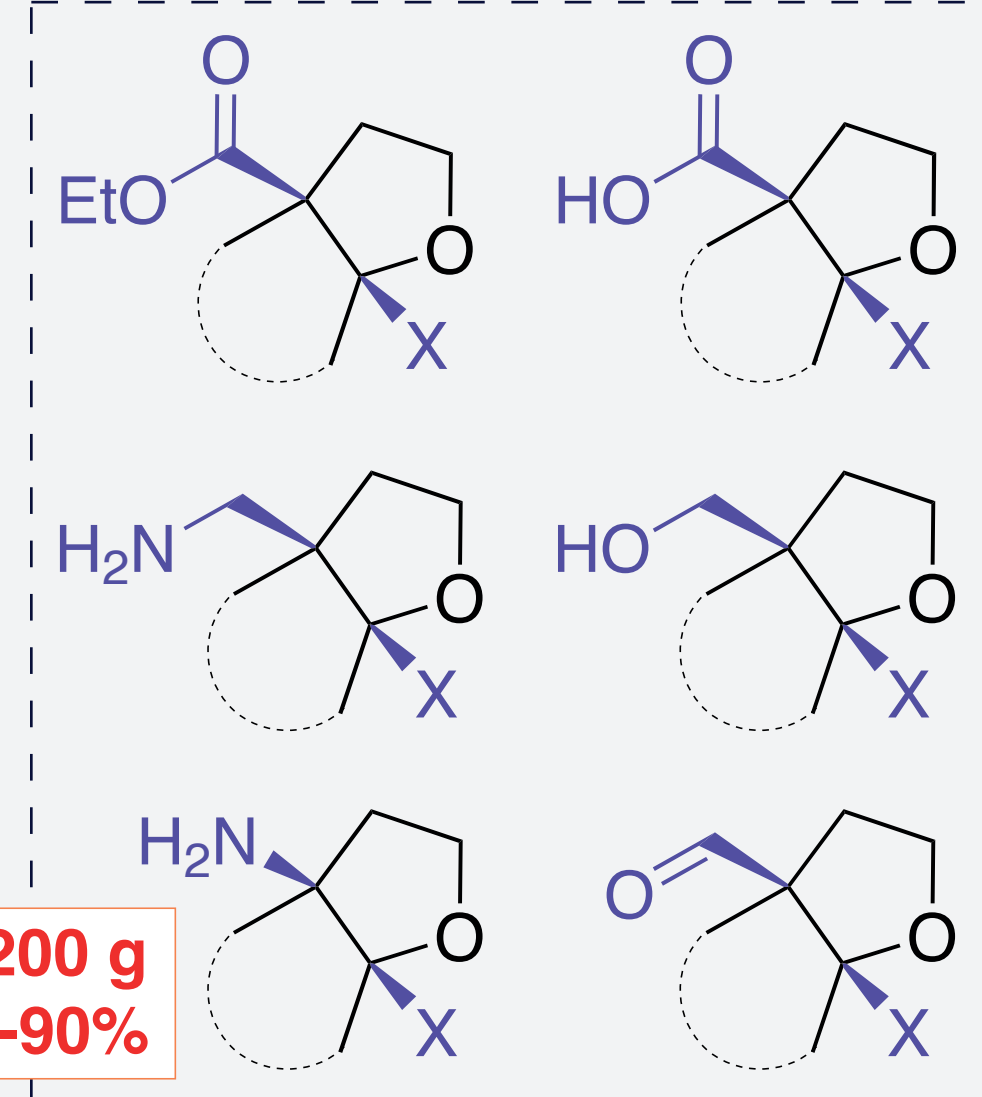
Heterocyclic starting ketoesters



- **multigram (>200 g from 1 synthetic run)** method for the synthesis of fused THFs with various sizes and natures of the adjacent rings
- [3+3]-adducts exhibit **highly reactive vinyl alcohol moiety**, which forms cyclic acetals immediately under solvolytic conditions
- the bicyclic compounds **can undergo typical FG interconversions**



scale >200 g
yield 60-90%



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