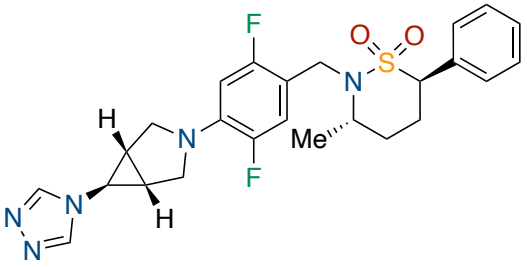
GDC-0022

Background:

- Retinoic acid receptor-related orphan receptor γ (RORc) is a transcription factor involved in the production and regulation of the pro-inflammatory cytokine interleukin (IL)-17
- RORc plays a role in multiple inflammatory pathways including regulation of IL-2211, granulocyte macrophage colonystimulating factor (GM-CSF)12, ofinnate lymphoid cells (ILCs)13,14, and γδT cells
- RORc is a potential target for the treatment of inflammatory and autoimmune diseases such as psoriasis and rheumatoid arthritis

Genentech
A Member of the Roche Group



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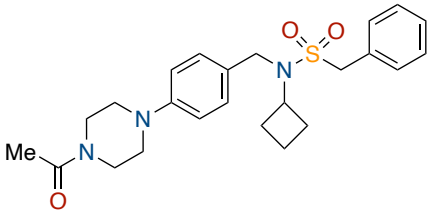
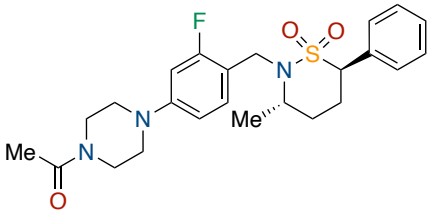
RORc Inhibitors: Lead Candidates



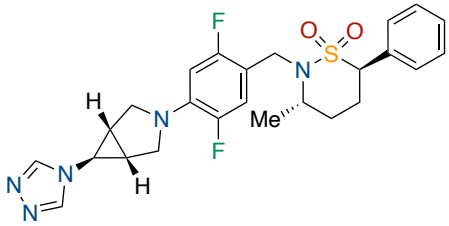
RORc EC_{50} = 130 nM
HLM CL_{hep} = 19 mL/min/kg

Improved potency

and ADME properties



GNE-3500
RORc EC_{50} = 47 nM
HLM CL_{hep} = 10 mL/min/kg



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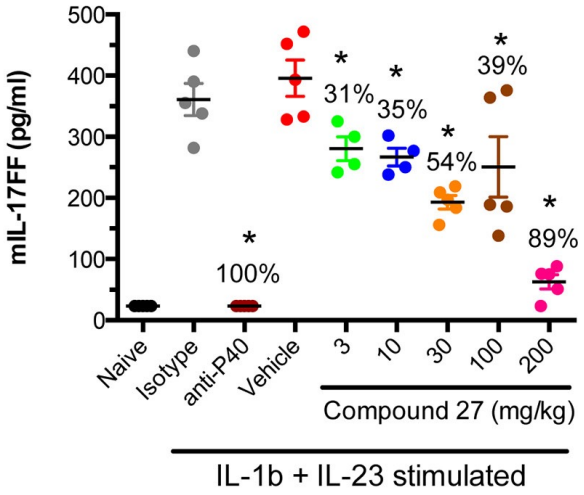
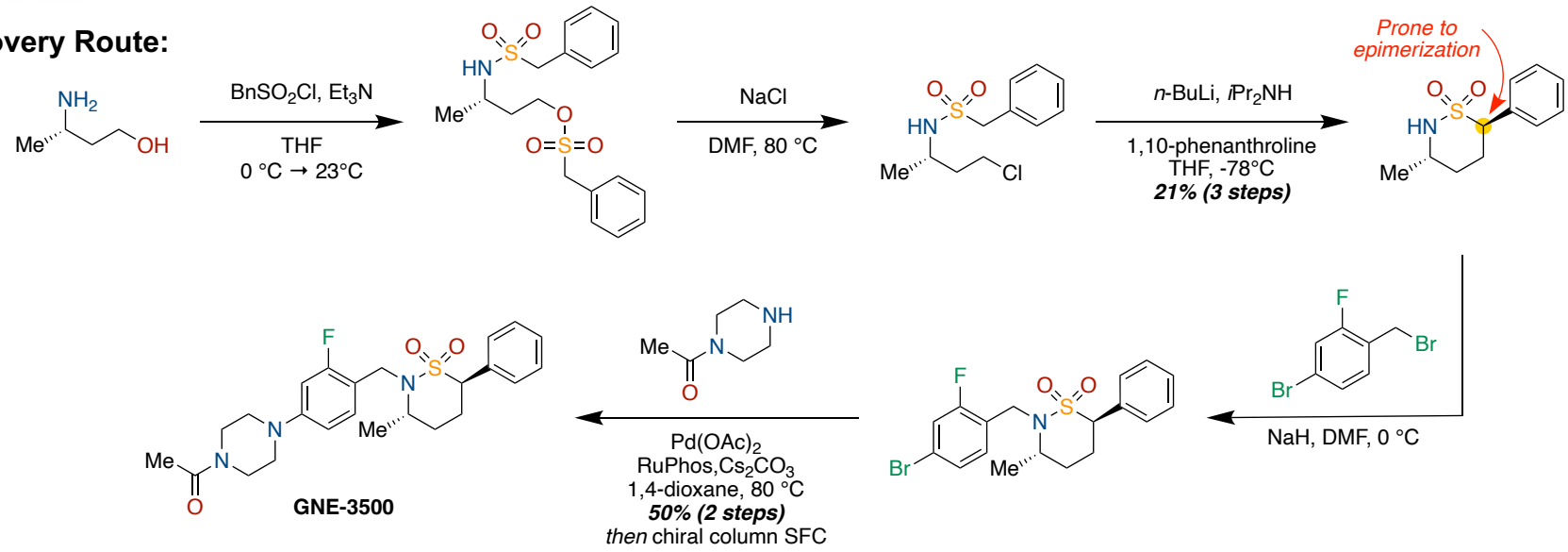


RORc inhibition reduces attenuates (IL)-17 production in a murine model

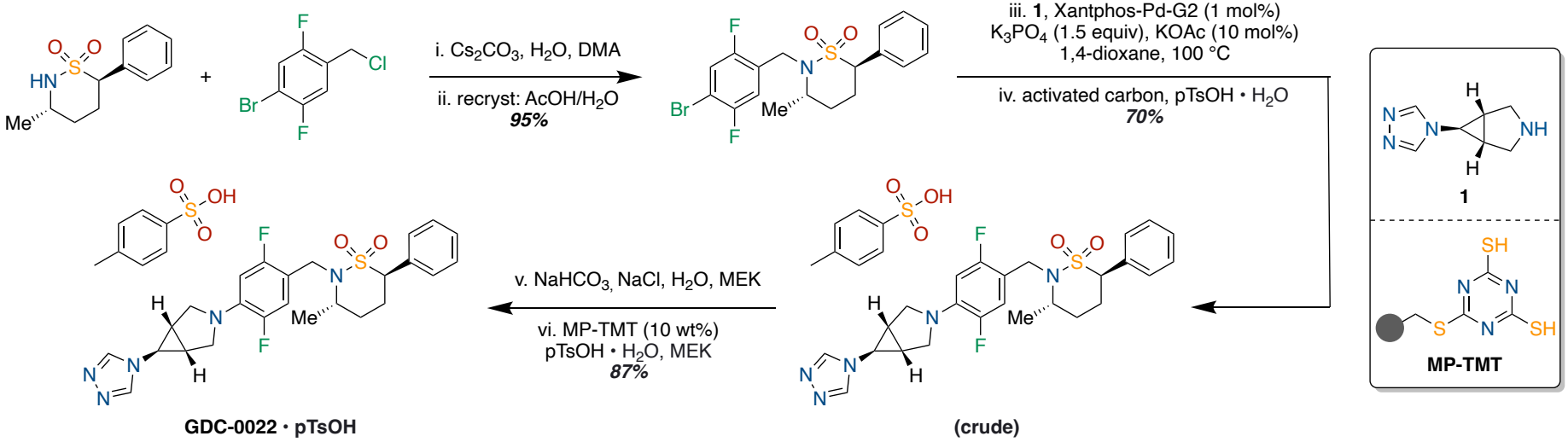
Fauber, B. P. *J. Med. Chem.* **2015**, *58* (13), 5308–5322. https://doi.org/10.1021/acs.jmedchem.5b00597
Sirois, L. E. *Org. Process Res. Dev.* **2020**, *24* (4), 567–578. https://doi.org/10.1021/acs.oprd.0c00012

Discovery Route:



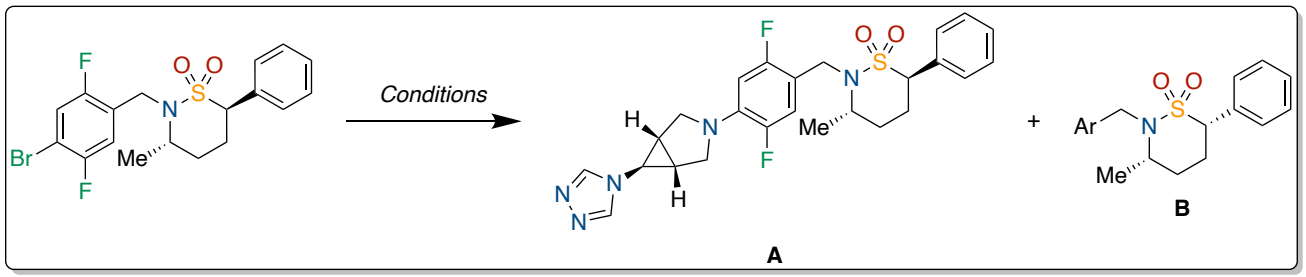
Fauber, B. P. *J. Med. Chem.* **2015**, *58* (13), 5308–5322. https://doi.org/10.1021/acs.jmedchem.5b00597

Process Route:



Sirois, L. E. *Org. Process Res. Dev.* **2020**, *24* (4), 567–578. https://doi.org/10.1021/acs.oprd.0c00012

GDC-0022

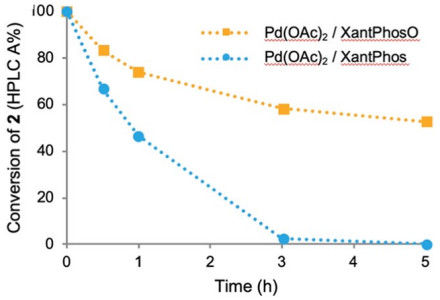


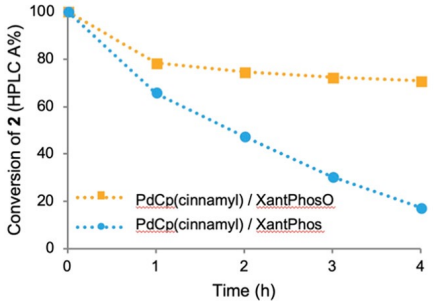
Conditions	Conversion (A%)	B (A%)
a. $Pd(OAc)_2$ (10 mol%) XantPhos (20 mol%), $CsCO_3$ (5 equiv)	25-40*	Up to 12*
b. XantPhos-Pd-G2 (1 mol%) K_3PO_4 (1.5 equiv)	69	4
c. XantPhos-Pd-G2 (1 mol%) K_3PO_4 (1.5 equiv), KOAc (10 mol%)	93	4

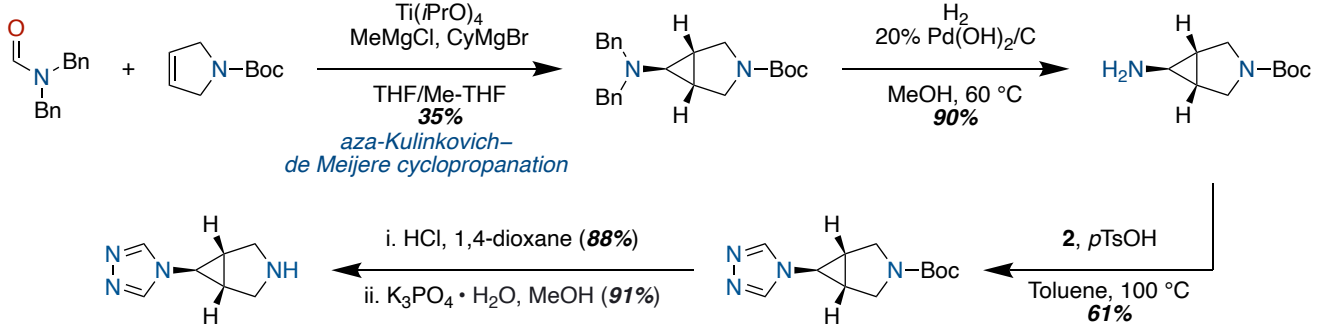
*Isolated yield

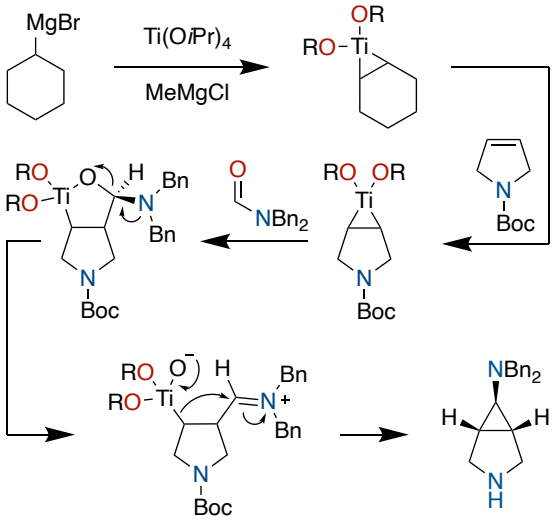
*Although condition **b** provide a cleaner reaction profile, addition of KOAc is necessary for adequate turnover with low catalyst loading!*

Reaction progress kinetic analysis (RPKA) suggested catalyst deactivation or product inhibition. Ligand oxidation to a bisphosphine monoxide was shown to be a potential mode of catalyst deactivation.









Sirois, L. E. *Org. Process Res. Dev.* **2018**, *22* (6), 728–735. https://doi.org/10.1021/acs.oprd.8b00101