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A Route to Potent, Selective, and Biased Salvinorin Chemical Space
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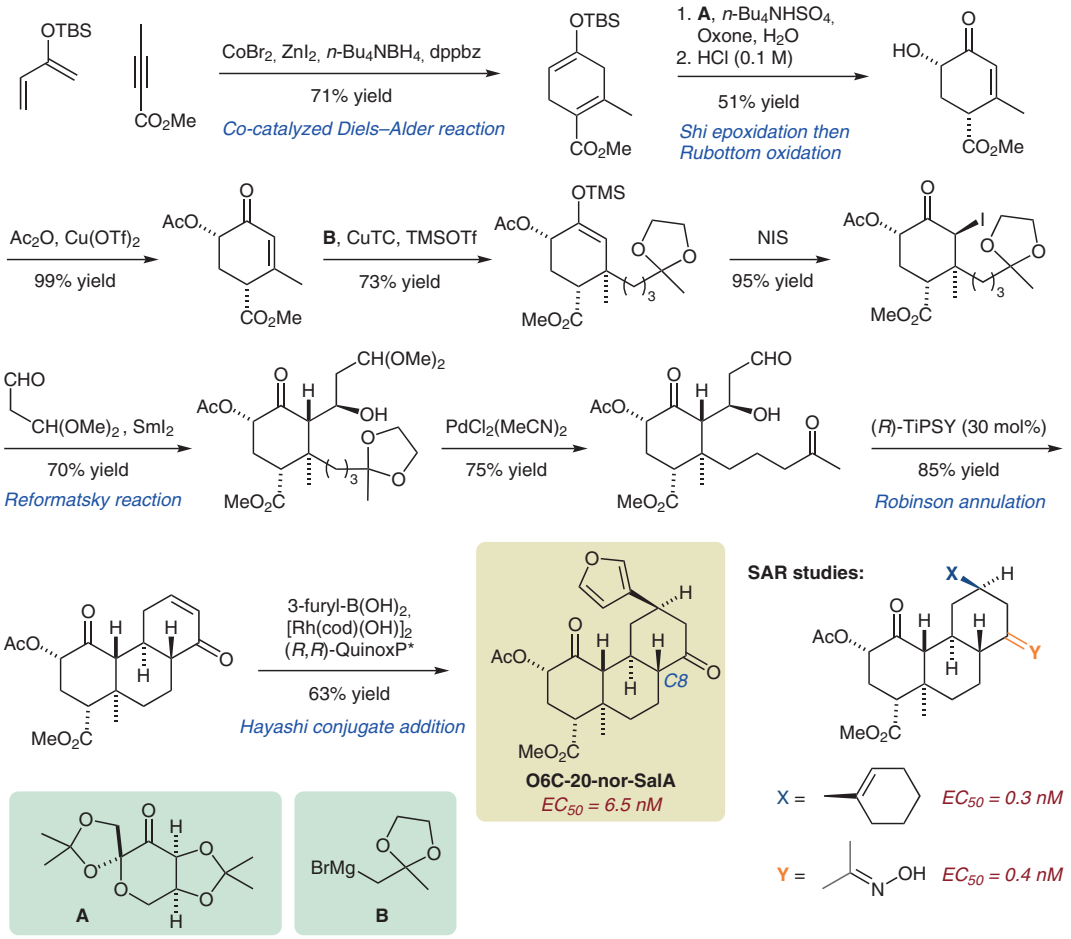
Stereoselective Robinson Annulation Enables Access to Potent and Selective Salvinorin Analogs



Significance: Salvinorin A is the main psychotropic compound of *Salvia divinorum*, a hallucinogenic plant from traditional Mazatec shamanic origin. It exhibits potent and selective KOR (kappa-opioid receptor) agonism and has been subject of extensive synthetic and semisynthetic campaigns. **O6C-20-nor-SalA** is a Salvinorin A analog that was shown to be resistant to C8 epimerization and a promising scaffold. Here, the authors report an asymmetric synthesis to this scaffold and the synthesis of 29 other bioactive analogs from a common intermediate.

Comment: The synthesis of Salvinorin A analogs was started from a cobalt-catalyzed Diels–Alder reaction between two electronically matched partners. A stereoselective samarium iodide-promoted Reformatsky reaction allows for the installation of the key β-hydroxy aldehyde intermediate. Finally, a challenging Robinson annulation, effected from the enolization of an unactivated ketone in the presence of an unstable electrophile, furnished the desired scaffold. Diverse Salvinorin A analogs were synthesized, including some with picomolar activity.

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Key words
Salvinorin
Reformatsky reaction
Robinson annulation
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Synfact of the Month