Concise Asymmetric Synthesis of (–)-Bilobalide
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Introduction
- Bilobalide (1) is widely ingested (1 million US adults in 2012), but poorly understood.
- It antagonizes gamma-aminobutyric acid A receptors (GABA_As) and rescues cognitive deficits in mouse models of Down syndrome.
- PTX is an antagonist of GABA_A; however, it is non-convulsive whereas PTX is convulsive at low dose.

Retrosynthetic Analysis
- Previous syntheses required 8–11 redox manipulations
- This work (2019): 11 total steps, 4 redox steps
- Removal of O-atom reduces synthetic complexity, but requires late-stage [O].
- Radical reactions form the hindered cyclopentene core.
- Oxidation states are embedded in a symmetrical building block.

Asymmetric Synthesis of (–)-Bilobalide

Optimization of Mukaiyama Hydration

Optimization of Oxetane Formation

Late-Stage 'Inside-Out' Oxidation

Conclusions and Future Directions

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