Bioinspired Synthesis of Tetraponerines and Analogues Thereof

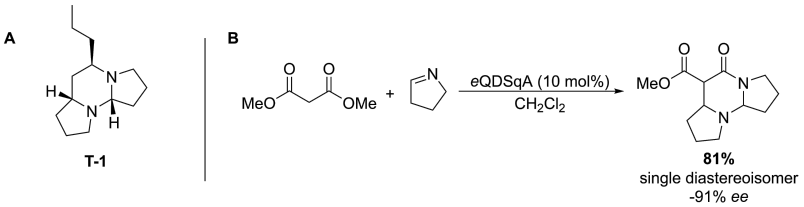
F. Kölblin[1], J. W. Rackl[1], T. Egger[1], H. Wennemers[1]*

[1]Laboratory of Organic Chemistry, D-CHAB, ETH Zürich, Vladimir-Prelog-Weg 3, 8093 Zürich

Tetraponerines are natural alkaloids that occur in the smear venom of *Tetraponera* ants. Eight different members (T-1 to T-8) have been identified, with T-8 being the most abundant.[1] All consist of a tricyclic aminal with a linear alkyl substituent (Figure 1). Tetraponerines inhibit non-competitively the nicotinic acetylcholine-receptor and thereby paralyze their enemy.[1]

The Wennemers group has developed stereoselective (thio)acetate and (thio)malonate addition reactions by utilizing malonic acid-derived thioesters. These (thio)acetate equivalents react in the presence of catalytic amounts of cinchona alkaloid derivatives with a variety of different electrophiles, including aldehydes, nitroolefins, and imines.[2]

Herein, we present the stereoselective addition of malonates to cyclic imines that yields the tricyclic core of tetraponerines (Figure 2). This organocatalytic addition reaction proceeds with high stereoselectivity (>90% *ee*). The synthesis of tetraponerines requires only four steps and is, thus, the shortest stereoselective synthesis of tetraponerines known to date. [3],[4]



A: Structure of Tetraponerine T-1; B: Stereoselective addition of dimethyl malonate to Δ1-pyrroline as the key step.

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