Bioinspired Synthesis of Tetraponerines and Analogues Thereof

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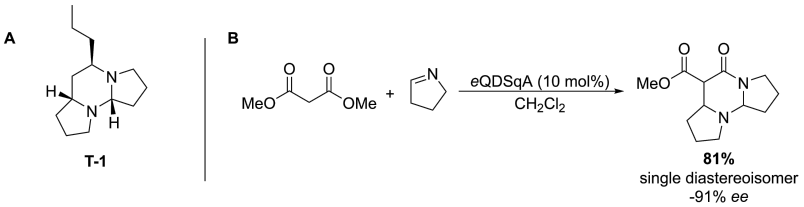
Tetraponerines are natural alkaloids that occur in the smear venom of *Tetraponera* ants. Eight different members (T-1 to T-8) have been identified, with T-8 being the most abundant.[1] All consist of a tricyclic aminal with a linear alkyl substituent (Figure 1). Tetraponerines inhibit non-competitively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

[1] W. R. Kem, K. Wildeboer, S. LeFrancois, M. Raja, W. Marszalec, J.-C. Braekman, *Cell. Mol. Neurobiol.* **2004**, *24*, 535–551.
[2]a) J. Lubkoll, H. Wennemers, *Angew. Chem. Int. Ed. Engl.* **2007**, b) *46*, 6841 – 6844; P. Clerici, H. Wennemers, *Org. Biomol*. *Chem.* **2012**, *10*, 110 – 113; c) A. Bahlinger, S. P. Fritz, H. Wennemers, *Angew. Chem. Int. Ed* **2014**, *53*, 8779 – 8783; d) J. Saadi, H. Wennemers, *Nature Chem.* **2016**, *8*, 276–280.
[3] M. Plehiers, S. Heilporn, D. Ekelmans, S. Leclercq, M. Sangermano, J. C. Braekman, D. Daloze, *Can. J. Chem.* **2000**, *78*, 1030–1034.
[4] a) P. Macours, J.C. Braekman, D. Daloze, *Tetrahedron* **1995**, *51*, 1415-1428. b) R. Stragies, S. Blechert, *J. Am. Chem. Soc.* **2000**, *122*, 9584–9591. c) E. Airiau, N. Girard, M. Pizzeti, J. Salvadori, M. Taddei, A. Mann, *J. Org. Chem.* **2010**, *75*, 8670–8673. d) I. Bosque, J. C. González-Gómez, A. Guijarro, F. Foubelo, M. Yus, *J. Org. Chem.* **2012**, *77*, 10340–10346. e) S. G. Davies, A. M. Fletcher, I. T. T. Houlsby, P. M. Roberts, J. E. Thomson, *J. Org. Chem.* **2017**, *82*, 6689–6702.