SYNTHESIS OF THE AB RING SYSTEM OF CLIFEDNAMIDE

Moritz Sinast[a], Inga Loke[a], Guillaume Bentzinger[a], Julia Holz[a], Aruna Raja[b], Aman Bhasin[b], Florenz Sasse[b], Andreas Köhn[c,*], Rainer Schobert[d], and Sabine Laschat[a,*]

[a]Institut für Organische Chemie, Universität Stuttgart, 70569 Stuttgart, Germany
[b]Abteilung Chemische Biologie, Helmholtz-Zentrum für Infektionsforschung, 38124 Braunschweig, Germany
[c]Institut für Theoretisch Chemie, Universität Stuttgart, 70569 Stuttgart, Germany
[d]Lehrstuhl für Organische Chemie, Universität Bayreuth, 95447 Bayreuth, Germany

A synthesis leading to the functionalized AB ring system of clifednamide, member of macrocyclic tetramic acid lactams, was developed. The key steps of this approach employed an intramolecular Diels-Alder reaction and an Ireland-Claisen rearrangement.

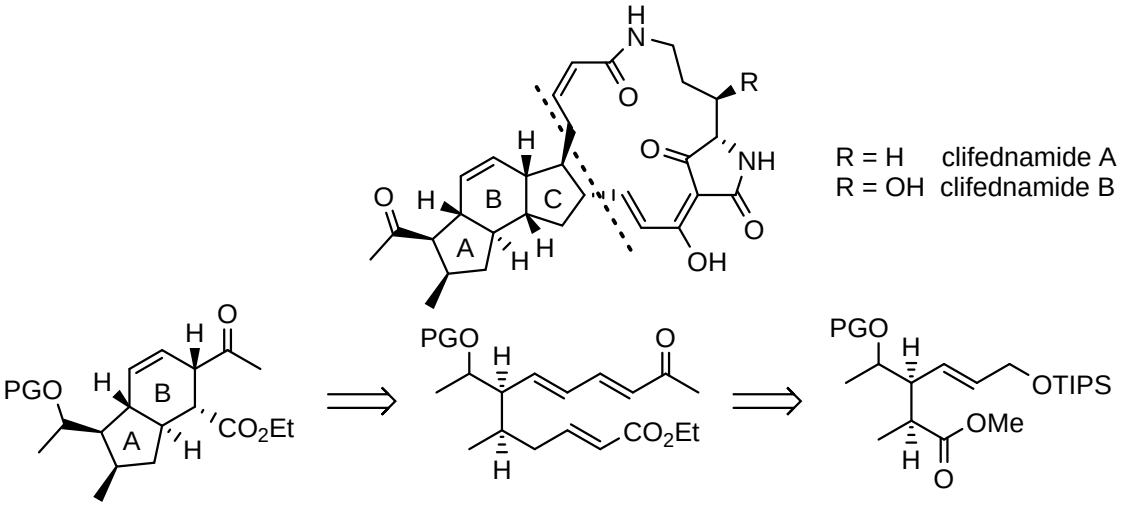

Figure 1: Retrosynthetic approach to the AB ring system of clifednamide

The synthesis started from di-*O*-isopropylidene-D-mannitol to obtain the precursor for the Ireland-Claisen reaction. This sigmatropic rearrangement takes place diastereoselectively, with the enone moiety being protected as allyl silyl ether, which was confirmed by deuteration experiments. The desired triene system could be synthesized in 8 further steps. The subsequent thermal intramolecular Diels-Alder reaction led stereoselectively to only one relative configuration for the ethyl hexahydro-1*H*-indene-carboxylate. Quantum-chemical calculations verified the selectivity of the intramolecular Diels-Alder reaction regardless of the steric demand of the protecting group. Finally, the AB ring was synthesized in an overall yield of 1.3% in 17 steps.[1]

[1] I. Loke, G. Bentzinger, J. Holz, A. Raja, A. Bhasin, F. Sasse, A. Köhn, R. Schobert, S. Laschat, *Org Biomol Chem* **2016**, *14*, 884–894.