

The Total Synthesis of Chlorotonil A via Intramolecular Diels-Alder Reaction

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Chlorotonil A (**1**) (Figure 1) was isolated from myxobacterium *Sorangium cellulosum* by Höfle *et al.* at the HZI (Helmholtz Centre for Infection Research, Braunschweig, Germany) in 2004.^[1] Its structure was determined by NMR studies and X-ray analysis. The biological potential of Chlorotonil A is currently being evaluated. Its structural features, in conjunction with its potentially valuable biological activity in secondary metabolism, make it an attractive target for total synthesis.

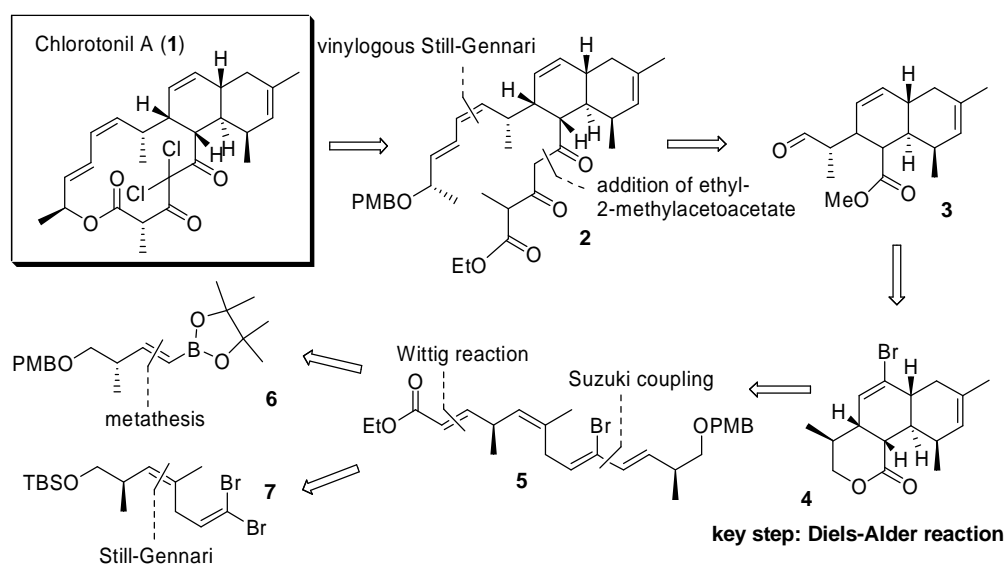


Figure 1 Retrosynthetic analysis of Chlorotonil A (**1**)

We started our synthesis by building up fragment **6** and **7** which are then coupled via Suzuki-Miyaura reaction^[2] (Figure 1). After deprotection, oxidation and Wittig olefination a transannular Diels-Alder reaction, the key step of our synthesis, yields intermediate **4** in a diastereomeric ratio of 13:1. Molecule **4** is debrominated employing Na/Hg couple and lactone opening is performed with KOH in methanol. The resulting acid is transformed into the methyl ester using diazomethane and the aldehyde function is generated with Dess-Martin reagent. We were able to extend the side chains of methyl ester **3** via a vinylogous Still-Gennari reaction^[3] and addition of ethyl-2-methylacetoacetate to the methyl ester. Treatment of molecule **2** with $\text{BF}_3 \cdot \text{OEt}_2$ led to the formation of the lactone. The last step of the synthesis is the chlorination with NCS yielding Chlorotonil A after 21 linear steps in an overall yield of 1.5 %.

[1] Unpublished natural product.

[2] S.A. Frank, W.R. Roush, *J. Org. Chem.* **2002**, *67*, 4316.

[3] S.R. Chemler, D.S. Coffey, W.R. Roush, *Tetrahedron Lett.* **1999**, *40*, 1269.