Total Synthesis

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The Total Synthesis of Chlorotonil A**

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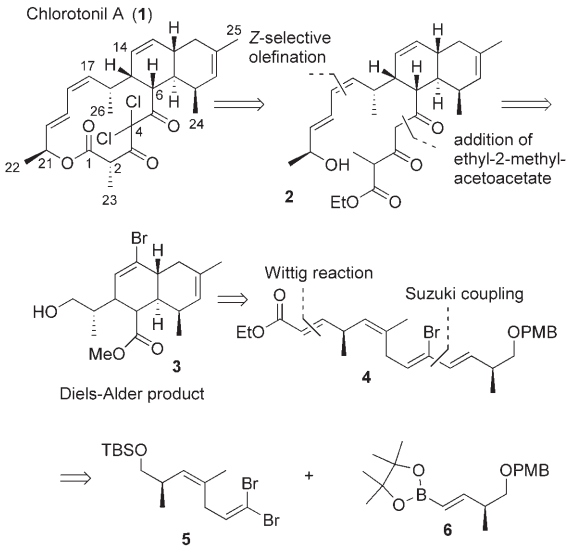
This work is dedicated to Professor Ekkehard Winterfeldt on the occasion of his 75th birthday

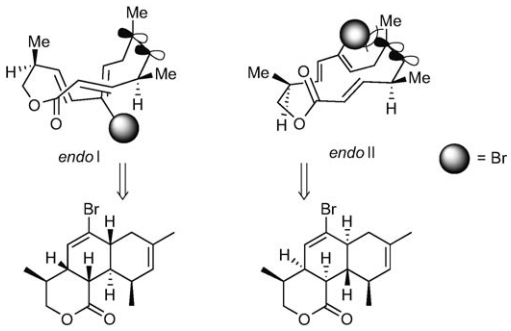
Myxobacteria are a particularly rich source of structurally novel metabolites with a broad range of biological functions. In 2004 researchers at the Helmholtz Centre for Infection Research (formerly GBF) isolated chlorotonil from the myxobacterium *Sorangium cellulosum*.[1] Its structure, which was determined by NMR studies and X-ray crystallography,[2] features an unprecedented motif in which a CCl_2 unit in a 14-membered macrolide framework is flanked by two carbonyl groups. This highly unusual and intriguing molecular architecture together with promising first biological data[3] rendered chlorotonil a highly attractive synthetic target. Herein, we report the first total synthesis of chlorotonil A (**1**) employing a biomimetic and highly stereocontrolled route which also established the absolute configuration of chlorotonil unambiguously.

Our retrosynthetic analysis identified fragment **3** to be the pivotal intermediate, which could be extended into hydroxy ester **2** through a *Z*-selective olefination[4] reaction and addition of ethyl-2-methyl acetoacetate (Scheme 1). We envisioned that the configuration at C2 could be set by taking advantage of the different acidities of axial and equatorial hydrogens on the macrolactone. In agreement with the X-ray structure of chlorotonil A (**1**) the methyl group in the axial orientation at C2 is coplanar with the adjacent π orbitals; consequently the proton at C2 not conjugated to the carbonyl groups.

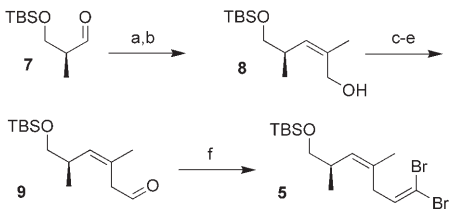
Unsaturated ester **4**, in turn, should be generated through an *anti*-selective Suzuki coupling between dibromoolefin **5** and vinyl boronate **6**. To obtain the desired *endo* product in the Diels–Alder reaction we took advantage of the discriminating effect of the vinyl bromide substituent, which had been successfully applied in total syntheses published by the research groups led by Evans and Roush.[5] In our case the bromine substituent would disfavor the *endo*-II transition state owing to electronic and steric repulsion of the C9–C10 double bond (Scheme 2). Dibromoolefin **5** was obtained in six steps from the TBS-protected aldehyde **7** derived from the Roche ester[6] (Scheme 3). A Still–Gennari reaction[7] followed by DIBAL-H reduction afforded allyl alcohol **8**,[8]



Scheme 1. Retrosynthetic analysis of chlorotonil A (**1**). TBS = *tert*-butyldimethylsilyl, PMB = *para*-methoxybenzyl.



Scheme 2. Comparison of *endo* transition states.



Scheme 3. Synthesis of **5**: a) $(CF_3CH_2O)_2P(O)CH(CH_3)CO_2CH_3$, [18]crown-6, KHMDS, THF, −40 to −78 °C, 85%; b) DIBAL-H, CH_2Cl_2, −78 °C, 87%; c) LiCl, 2,6-lutidine, CF_3SO_2Cl, DMF, 79%; d) NaCN, DMF, 0 °C, 96% based on recovered starting material; e) DIBAL-H, CH_2Cl_2, −78 °C, EtOH, 81%; f) CBr_4, PPh_3, Zn, CH_2Cl_2, RT, 91%. KHMDS = potassium bis(trimethylsilyl)amide, DIBAL-H = diisobutylaluminum hydride, DMF = *N*,*N*-dimethylformamide.

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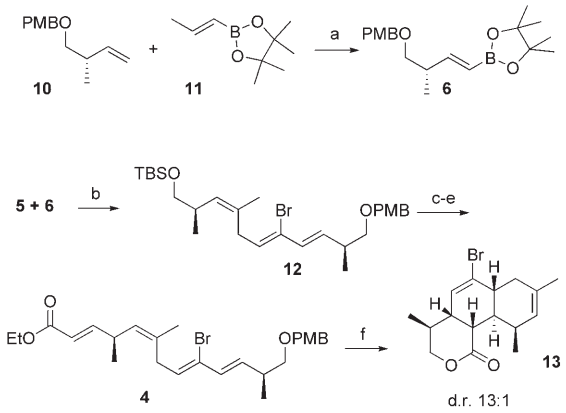
which was homologated to aldehyde **9** in three steps.[9] Notably, no isomerization to the α,β-unsaturated nitrile or aldehyde was observed. Corey–Fuchs homologation then gave the desired dibromoolefin **5** in high yields.[10]

The synthesis of compound **6** utilized a cross-metathesis reaction between olefin **10**[11] and vinyl boronate **11**[12] as the final transformation (Scheme 4) and delivered the desired boronic ester **6** in good yield and *E*/*Z* selectivity (*E*/*Z* > 50:1).



Scheme 4. Synthesis of **13**: a) Grubbs 2nd generation catalyst, CH_2Cl_2, reflux, 81%, *E*/*Z* > 50:1; b) [Pd(PPh$_3$)$_4$], TlOEt, H_2O/THF, RT, 76%; c) HF·pyridine, THF/pyridine (1:1), RT, 96%; d) Dess–Martin periodinane, CH_2Cl_2, RT, 82%; e) PPh_3=$CHCO_2Et$, CH_2Cl_2, RT, 89%; f) BF_3·Et_2O, toluene, 85 °C, 58%.

Elaboration of ester **4** commenced with the coupling of boronic ester **6** and dibromoolefin **5** according to Suzuki's protocol (Scheme 4).[13] After the cross-coupling reaction the TBS group of **12** was removed by treatment with HF·pyridine, and the resulting free hydroxy group was subsequently oxidized and the carbon chain was extended through a Wittig olefination. Gratifyingly, the pivotal Diels–Alder reaction could be effected by treatment with BF_3·Et_2O (RT→85 °C, 3 h). To our delight, these reaction conditions led to simultaneous removal of the PMB group, transesterification, and Diels–Alder reaction, yielding **13** in very good diastereoselectivity (d.r. 13:1). The configuration of this crucial intermediate was assigned unambiguously by X-ray crystallography to be the desired *endo* product (Figure 1). The bromine substituent that dictated the *endo* selectivity could be removed later using sodium mercury alloy in methanol (Scheme 7).

To further assess the directing effect of the bromine substituent, we prepared the dehalogenated tetraene **14** from compound **4** by treatment with sodium–mercury alloy and subjected the resulting Diels–Alder substrate to the reaction conditions used before (Scheme 5). Analysis of the complex mixture of products revealed a 3:1:1 ratio of the desired *endo* product **15** together with *endo* II product **17** and *exo* product **16** in 49% combined yield. This result clearly showed the importance of the bromine substituent for obtaining useful selectivity and the advantage of halogen-directed Diels–Alder reaction over standard Diels–Alder routes.

For extension of fragment **13** careful optimization of reaction conditions was required (Scheme 7). First, the

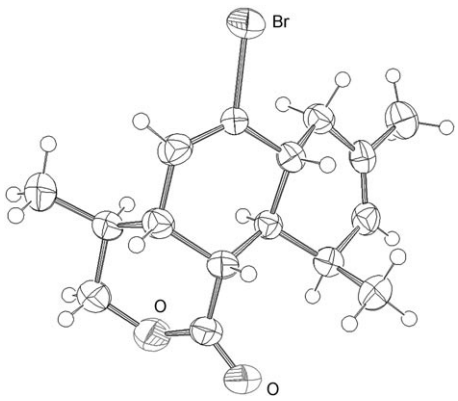
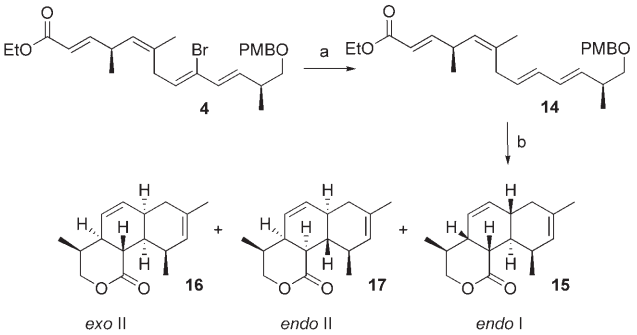


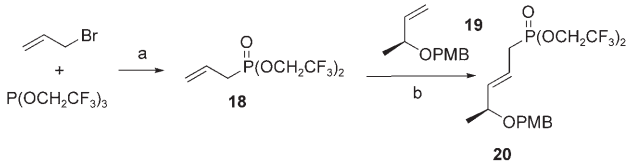
Figure 1. X-ray crystal structure of compound **13** (ellipsoids at the 50% probability level).[14]



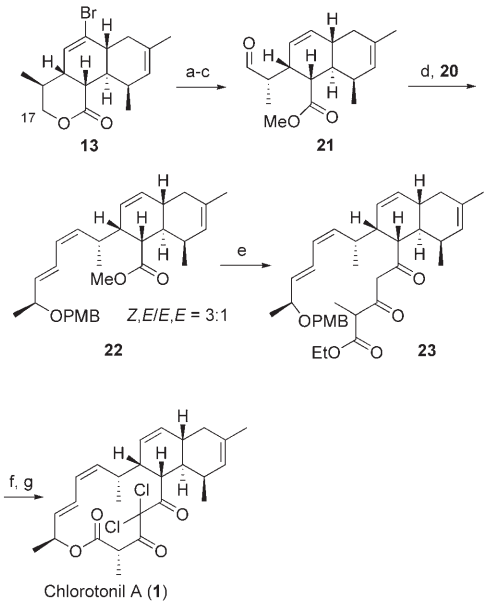
Scheme 5. a) Na/Hg (5%), MeOH, RT, 2 h, 61%; b) BF_3·Et_2O, toluene, 85 °C, 49%, **15**/**16**/**17** = 3:1:1.

lactone opening could be achieved by employing KOH/MeOH, and the resulting acid was then immediately transformed into its methyl ester by adding diazomethane. The liberated primary C17 hydroxy group was subsequently oxidized to give aldehyde **21**. For its extension to **22**, the novel allyl phosphonate reagent **20** was envisioned, which was generated through a cross-metathesis reaction between allyl phosphonate **18** and olefin **19** (Scheme 6). It should be pointed out that the anion generated from phosphonate **20** did not eliminate the allylic OPMB group as one might expect. Optimization of reaction conditions identified KHMDS in Et_2O to provide the best yields and selectivities.

Finally, addition of the dianion generated from ethyl-2-methylacetoacetate led to intermediate **23** (Scheme 7). Having recognized that BF_3·Et_2O could efficiently cleave PMB ethers and would lead to concomitant lactonization, we treated **23** with BF_3·Et_2O at room temperature. After 20 min



Scheme 6. a) Bu_4NI (cat.), 180 °C, neat, 61%; b) Grubbs 2nd generation catalyst, CH_2Cl_2, 64%.



Scheme 7. Synthesis of chlorotonil A (**1**): a) Na/Hg, MeOH, RT, 92%; b) KOH, MeOH then diazomethane, RT, 97%; c) Dess–Martin periodinane, CH_2Cl_2, RT, 79%; d) KHMDS, **20**, Et_2O, −80°C, 55%; e) NaH, *n*BuLi, ethyl-2-methylacetoacetate, THF, −78°C to RT; f) $BF_3{\cdot}EtO_2$, toluene, RT, 47% for two steps; g) NCS, 2,6-lutidine, CH_2Cl_2, RT, 65%. NCS = *N*-chlorosuccinimide.

the starting material had been consumed, and a new compound was isolated which could be identified as the dehalogenated analogue of chlorotonil. Gratifyingly, the new compound was generated as a single isomer, and the configuration could be assigned by comparing the NMR spectra of this synthetic intermediate to those of the compound obtained by dehalogenation of the natural product. Finally, the halogenation was performed employing NCS[15] to complet the total synthesis of chlorotonil. Comparison of the optical rotation of synthetic chlorotonil to that of an authentic sample confirmed the absolute configuration of the natural product as that described here.[16]

In summary, we have reported the first total synthesis of chlorotonil A (**1**) by a highly stereoselective and modular route which should be readily amenable to the preparation of analogues. Notable features of our synthetic route include a halogen-directed Diels–Alder reaction in conjunction with a one-pot esterification and PMP removal, and a novel olefination for the rapid construction of one side chain. A conformation-based selective acidification relying on the different acidities of the axial and equatorial positiond in the macrocyclic lactone was exploited for the stereoselective construction of the chiral center in α position to the lactone. Additionally, this example serves as an extension of the halogen-directed Diels–Alder approach and adds to the picture of general applicability of this strategy.

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[16] Synthetic chlorotonil: $[\alpha]_D^{25} = -180.9$ ($c = 1.05$, $CHCl_3$); authentic chlorotonil: $[\alpha]_D^{22} = -159.5$ ($c = 1.05$, $CHCl_3$).