

Total synthesis of (+)-chloriolide†

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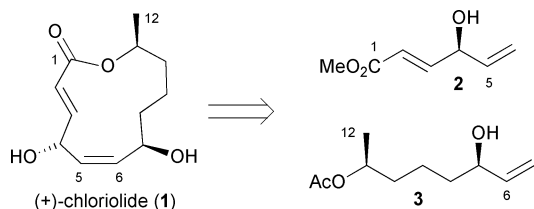
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The first total synthesis of (+)-chloriolide, a 12-membered macrolide from *Chloridium virescens* (var. *chlamydosporum*), was accomplished in a longest linear sequence of 20 steps from commercial materials in 7% overall yield.

Chloriolide (**1**), a 12-membered macrolide, was isolated together with the known bioactive macrolides radicicol¹ and pochonin B² from solid-substrate fermentation cultures of *Chloridium virescens* (var. *chlamydosporum*) in 2006 by Gloer and co-workers.³ The endophytic fungus, encountered as a colonist of a decaying hardwood branch, was considered to be fungicolous and therefore was examined for its ability to produce bioactive metabolites.^{4,5} Unlike the closest known structural analogs, patulolides A–C⁶ and cladospolides A–D,⁷ that have been reported to exhibit significant antifungal and antibacterial activity, chloriolide was fully inactive in antifungal and antibacterial assays.³ Following the widely accepted opinion that secondary metabolites of fungi are intentionally produced to provide the producer an advantage,⁸ chloriolide was considered an attractive target for synthesis, not only because of its novel structure, but because a chemical synthesis would allow to reveal and further evaluate the biological activity. The gross structure and relative configuration of the natural product were secured by X-ray crystallographic analysis; its absolute configuration was defined by applying the modified Mosher method on a rearrangement product.³ A somewhat unique structural feature of chloriolide (**1**) is the (2*E*,5*Z*)-4,7-dihydroxy-2,5-dienoate subunit (C1–C7) that presents a particular challenge for total synthesis due to the high lability already mentioned by Gloer and co-workers.^{3,9} In this communication, we report the first total synthesis of (+)-chloriolide (**1**).

We envisioned constructing **1** *via* the assembly of two simple allylic alcohol fragments (**2** and **3**) and using a macrolactonization to close the 12-membered ring (Scheme 1). The ring-closure



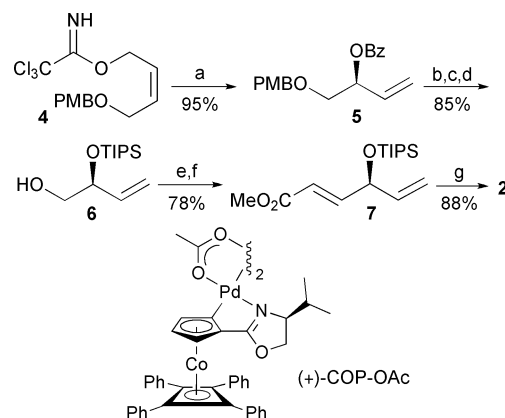
Scheme 1 Retrosynthetic disconnection of chloriolide (**1**).

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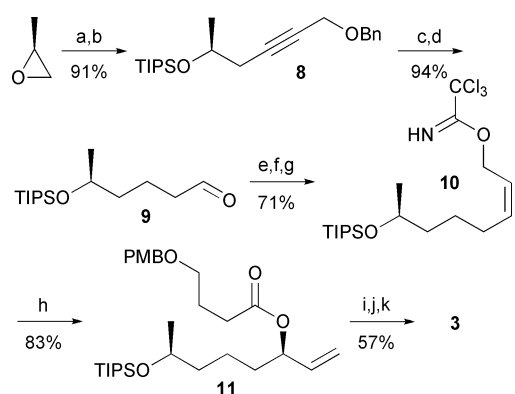
proved to be quite challenging. Our preceding strategies for closing the ring by formation of the C2–C3 bond *via* intramolecular Horner-Wadsworth-Emmons olefination or the C5–C6 bond *via* ring-closing metathesis (RCM) either showed markedly reduced feasibility or totally failed.¹⁰ The preparation of each of the two fragments required the asymmetric construction of an allylic alcohol moiety. Application of the asymmetric esterification developed by Overman^{11,12} was expected to provide both stereogenic centres (C4 and C7) with predictable stereochemical outcome using catalyst control.

The synthesis of allylic alcohol **2** began with the reaction of readily available trichloroacetimidate **4**¹¹ and benzoic acid in the presence of palladacycle (+)-COP-OAc (1 mol%).¹³ The Overman esterification provided (*S*)-allylic ester **5** in 95% yield and 96% ee after 16 h in CH₂Cl₂ at 23 °C (Scheme 2).¹¹ Unfortunately, (*S*)-1-hydroxybut-3-en-2-yl benzoate, which was obtained from **5** by simple removal of the *p*-methoxybenzyl (PMB) group, failed to undergo direct oxidation to the corresponding aldehyde, using all standard oxidants we surveyed. As a result, removal of the benzoate group, subsequent silylation to form the triisopropylsilyl (TIPS) ether, and oxidative cleavage of the *p*-methoxybenzyl ether provided primary alcohol **6** in 85% overall yield. Then, clean oxidation of this intermediate could be realized by exposing **6** to *o*-iodoxybenzoic acid (IBX) in EtOAc at 80 °C.¹⁴ The resulting aldehyde was directly converted into ester **7** through Wittig reaction with methyl (triphenylphosphoranylidene)acetate (*E/Z* > 95/5). Finally, HF-mediated removal of the TIPS protective group gave rise to fragment **2**.



Scheme 2 Synthesis of fragment **2**. Reagents and conditions: (a) PhCOOH, (+)-COP-OAc (1 mol%), 23 °C, CH₂Cl₂, 95%, 96% ee; (b) K₂CO₃, 23 °C, MeOH, 89%; (c) TIPSCl, Im, 23 °C, DMF, 96%; (d) DDQ, 23 °C, pH 7 buffer–CH₂Cl₂, 99%; (e) IBX, 80 °C, EtOAc; (f) Ph₃P=CHCOOMe, 23 °C, CH₂Cl₂, 78% (over two steps); (g) HF, 23 °C, MeCN–H₂O, 88%.

The required fragment **3** was readily obtained starting from commercially available (*S*)-propylene oxide as summarized in Scheme 3. Exposing the oxirane to lithiated benzyl propargyl ether in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ led to the expected epoxide opening,¹⁵ and the resulting alcohol was reacted with TIPSCl and imidazole in DMF to yield TIPS ether **8**. At this stage, the TIPS protective group was chosen because it proved compatible with later transformations, in particular with the catalyst-controlled creation of the C7 stereogenic centre. Complete hydrogenation of alkyne **8** over Pd/C and Swern oxidation¹⁶ of the resulting alcohol then provided aldehyde **9** in 94% overall yield. Olefination with methyl (diphenylphosphono)acetate under Ando conditions¹⁷ gave the corresponding *Z*-olefin in 75% yield after separation of the minor *E*-isomer by silica gel chromatography. The ester was reduced with DIBAL-H, and then the *Z*-configured allylic alcohol was converted into trichloroacetimidate **10**. The imidate was subsequently reacted with 4-(*p*-methoxybenzyloxy)butyric acid¹⁸ in the presence of (+)-COP-OAc (5 mol%) to create the stereogenic centre at C7. Under catalyst control, protected ester **11** was produced in excellent diastereoselectivity (>99:1). Our decision to introduce the 4-(*p*-methoxybenzyloxy)butyryl ester was driven by the desire to form the acetate-containing fragment

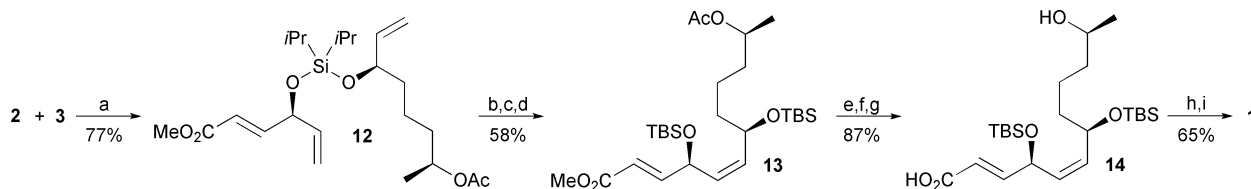


Scheme 3 Synthesis of fragment **3**. *Reagents and conditions:* (a) i) $\text{BnOCH}_2\text{C}\equiv\text{CH}$, $n\text{BuLi}$; ii) $\text{BF}_3 \cdot \text{OEt}_2$; iii) (*S*)-(-)-propylene oxide, -78°C , THF, 93%; (b) TIPS-Cl, Im, 23°C , DMF, 98%; (c) H_2 , Pd/C (5 mol%), 23°C , EtOH, quant.; (d) i) $(\text{COCl})_2$, DMSO, -78°C ; ii) NEt_3 , -78°C to rt, CH_2Cl_2 , 94%; (e) i) methyl (diphenylphosphono)acetate, NaH, 0°C , THF; ii) **9**, -78°C to -20°C , THF, 75%; (f) DIBAL-H, -78°C , THF, 97%; (g) CCl_3CN , DBU (10 mol%), 23°C , CH_2Cl_2 , 97%; (h) $\text{PMBO}(\text{CH}_2)_3\text{COOH}$, (+)-COP-OAc (5 mol%), 23°C , CH_2Cl_2 , 83%, d.r. >99:1; (i) HF, 23°C , $\text{MeCN}-\text{H}_2\text{O}$, 79%; (j) Ac_2O , 23°C , pyridine, 83%; (k) i) DDQ, 23°C , pH 7 buffer- CH_2Cl_2 ; ii) KOtBu (15 mol%), 23°C , THF, 87%.

3 with a minimum of protective group manipulations. This ester, which to the best of our knowledge has not been used before as protective group in synthesis,¹⁹ was expected to undergo selective removal by oxidation and lactonization in the presence of other esters and alkene moieties. As anticipated, cleavage of the TIPS group of **11** and subsequent treatment with Ac_2O in pyridine gave a diester intermediate that was selectively transformed into acetate **3** upon sequential exposure to DDQ and KOtBu in an overall yield of 57%.

To complete the synthesis of (+)-chloriolide (**1**), we now needed to construct the C5–C6 double bond with *Z*-configuration. To this end, a silyl-tethered RCM²⁰ was ideally suited to connect the two fragments **2** and **3**.²¹ By use of a high-yielding one-pot protocol,²² allylic alcohol **2** was covalently tethered to **3** through a diisopropylsilyl linker to generate disiloxane **12** in 77% yield (Scheme 4). The subsequent RCM proceeded smoothly in 86% yield. Desilylation produced the corresponding *Z*-diol, which was then converted into bis-silyl ether **13**. Further experiments indicated that the simultaneous protection of the free hydroxy groups as *tert*-butyldimethylsilyl (TBS) ethers was essential for the effective completion of the synthesis. Interestingly, the desilylated product of the RCM performed significantly worse in the later macrolactonization step. In line with the above-mentioned lability of the 4,7-dihydroxy-2,5-dienoate subunit, exposure of ester **13** to a range of standard saponification conditions either resulted in no reaction or gave rise to a series of uncharacterizable products. In this respect, we were delighted to find that key intermediate **14** was readily accessed through reduction with DIBAL-H at -78°C in CH_2Cl_2 to give the diol followed by chemoselective oxidation. The delicate oxidative transformation could be realized in two steps by first exposing the diol to MnO_2 in CH_2Cl_2 ,²³ which upon further oxidation with buffered NaClO_2 ²⁴ gave acid **14** in 87% yield. Macrolactonization using the protocol of Yamaguchi²⁵ afforded the 12-membered macrocycle in 65% yield. Finally, the silyl groups were removed quantitatively by treatment with HF, thus completing the total synthesis of (+)-chloriolide (**1**). The spectroscopic data of synthetic chloriolide agreed perfectly with those reported for the natural product³ as did the optical rotation: $[\alpha]_D^{20} +101$ (c 0.21, CH_2Cl_2) [lit.³ $[\alpha]_D^{25} +107$ (c 0.2, CH_2Cl_2)].

In summary, an expedient asymmetric synthesis of chloriolide (**1**) was accomplished in a longest linear sequence of 20 steps from commercial materials in 7% overall yield (88% average yield per step). The sequence features the catalytic asymmetric construction of allylic esters through Overman esterification, the first use of an oxidatively cleavable ester as hydroxyl protecting group, and a silyl-tethered RCM to form a *Z*-alkene. Investigations into



Scheme 4 Synthesis of chloriolide (**1**). *Reagents and conditions:* (a) **2**, $(i\text{Pr})_2\text{SiCl}_2$, 23°C , pyridine, then **3**, 77%; (b) Grubbs-II (5 mol%), 80°C , toluene, 86%; (c) HF, 23°C , $\text{MeCN}-\text{H}_2\text{O}$, 85%; (d) TBSCl, Im, 23°C , DMF, 80%; (e) DIBAL-H, -78°C , CH_2Cl_2 , quant.; (f) MnO_2 , 23°C , CH_2Cl_2 ; (g) NaClO_2 , 2-methyl-2-butene, NaH_2PO_4 , $t\text{BuOH}-\text{H}_2\text{O}$, 87% (over two steps); (h) i) 2,4,6-trichlorobenzoyl chloride, NEt_3 , 23°C , THF; ii) DMAP, 23°C , benzene, 65%; (i) HF, 23°C , $\text{MeCN}-\text{H}_2\text{O}$, quant.

the biological activity of chloriolide are currently underway; the modular nature of the route should enable rapid access to a variety of new analogs for structure–activity relationships.

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