

Total Synthesis of Hectochlorin

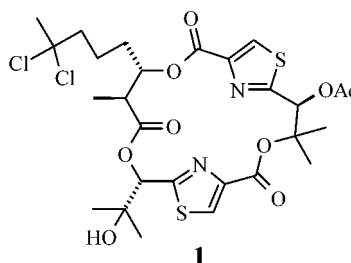
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ABSTRACT



Hectochlorin (**1**) is a marine natural product with significant fungicidal activity. A synthesis effort was initiated to develop a flexible route to hectochlorin which would allow access to analogues with potentially improved activity and/or attributes relative to the natural product. A successful total synthesis of hectochlorin is described.

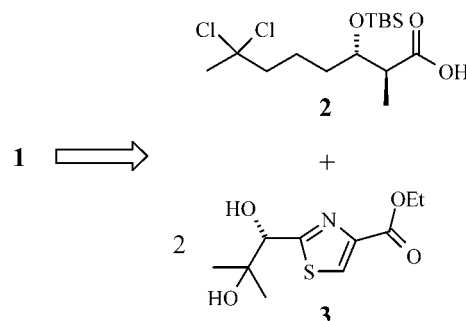
Hectochlorin (**1**) is a novel, natural fungicide isolated from *Lyngbya majuscula*, a cyanobacterium collected in Hector Bay, Jamaica. It has recently been fully characterized,¹ and it was found to be active against a number of pathogens in our crop disease screens. A synthesis program was initiated to develop a convergent route to hectochlorin and its analogues. A successful total synthesis of hectochlorin is described herein.

Retrosynthetically, hectochlorin disconnects to two less complex subunits: the aldol subunit, **2**, and the thiazole subunit, **3** (Scheme 1). The synthesis of (2*R*,3*S*)-**2** is published,² and an analogous approach incorporating inversion of the hydroxy group is all that is necessary to access (2*S*,3*S*)-**2**. The thiazole segments in hectochlorin can both be derived from subunit **3**. The forward synthesis requires the generation and coupling of two suitably protected thiazole precursors to give a bis-thiazole, introduction of the aldol subunit, and finally cyclization to afford hectochlorin.

The thiazole subunit **3** was prepared in two steps from 2-bromo-4-carboethoxythiazole (**4**, Scheme 2).³ A Negishi reaction was used to install the isobutylene group in **5**,⁴ and a Sharpless catalytic asymmetric dihydroxylation of the alkene provided the vicinal diol **3**.⁵ The *S* configuration of the asymmetric center in **3** was assigned on the basis of a modified Mosher's ester analysis.⁶

The next task was to differentially protect **3** to give two thiazole coupling precursors. A *p*-methoxybenzylidene acetal

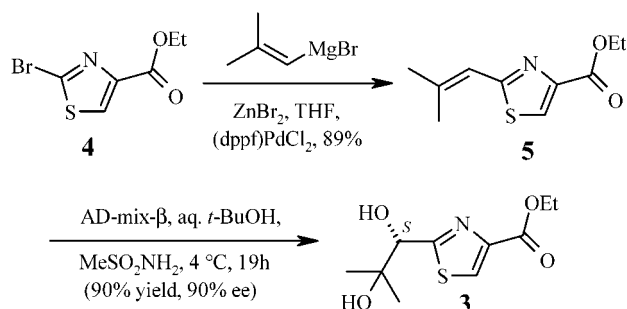
Scheme 1. Retrosynthesis of Hectochlorin



(1) Structure and Absolute Stereochemistry of Hectochlorin, a Potent Stimulator of Actin Assembly. Marquez, B. L.; Watts, K. S.; Yokochi, A.; Roberts, M. A.; Verdier-Pinard, P.; Jimenez, J. I.; Hamel, E.; Scheuer, P. J.; Gerwick, W. H. Submitted.

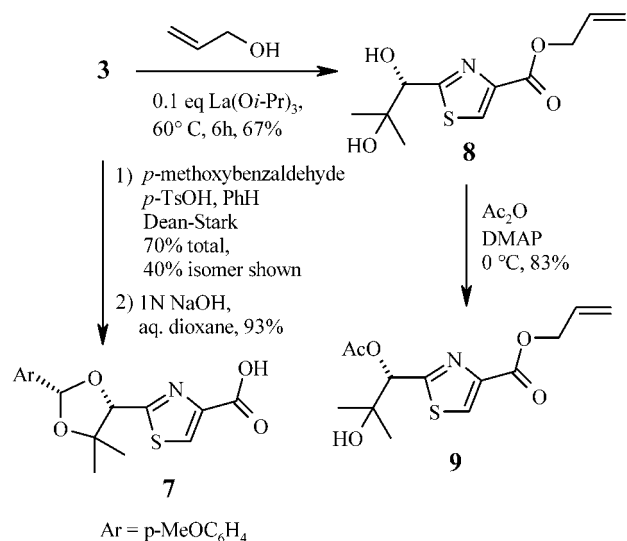
(2) Sone, H.; Kondo, T.; Kiryu, M.; Ishiwata, H.; Ojika, M.; Yamada, K. *J. Org. Chem.* **1995**, *60*, 4774–4781.

Scheme 2



was chosen to protect the diol because it could be removed using neutral conditions which would not concomitantly remove the secondary acetate. The ethyl ester was then hydrolyzed in high yield to provide the carboxylic acid coupling precursor **7** (Scheme 3).

Scheme 3



For the tertiary alcohol coupling piece, the ethyl ester in **3** was transesterified to the allyl ester **8** using lanthanum(III) isopropoxide as the catalyst.⁷ The allyl ester is the protecting group of choice for the acid, as it will be removed late in the synthesis using mild conditions which should be compatible with the other esters in the molecule. The acetate was then installed selectively on the secondary alcohol, leaving the tertiary alcohol of **9** available for coupling to the acid in **7**.

(3) Kelly, T. R.; Lang, F. J. *Org. Chem.* **1996**, *61*, 4623–4633.

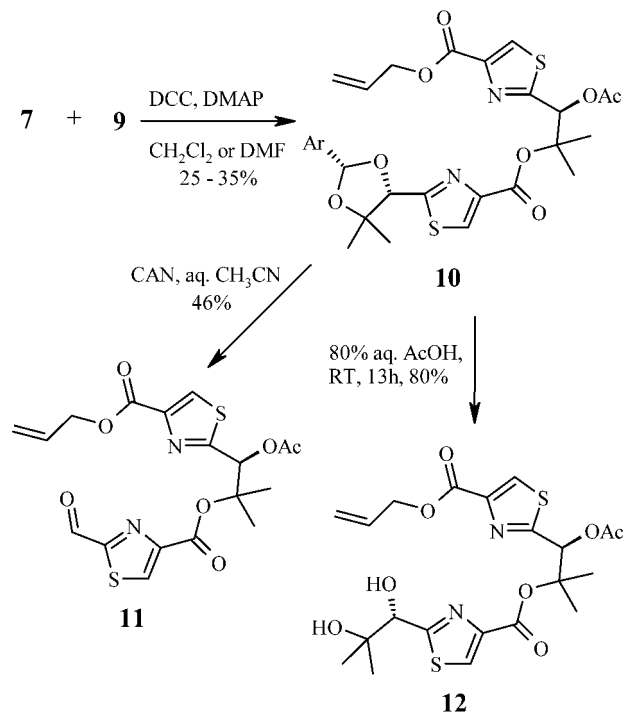
(4) Campbell, J. B., Jr.; Firor, J. W.; Davenport, T. W. *Synth. Commun.* **1989**, *19*, 2265–2272.

(5) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.

(6) Ohtani, I.; Takenori, K.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096. A detailed description of the modified Mosher analysis of **3** is included in the Supporting Information.

(7) Okano, T.; Miyamoto, K.; Kiji, J. *Chem. Lett.* **1995**, 246.

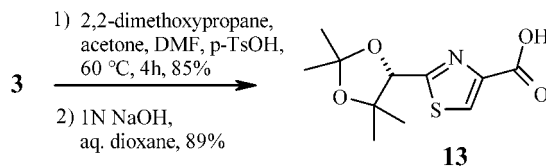
Scheme 4



The coupling of **7** and **9** was performed using dicyclohexylcarbodiimide (DCC) with a catalytic amount of 4-(dimethylamino)pyridine (DMAP), giving the coupled product **10** in low yield (Scheme 4). Treatment of **10** with CAN not only removed the benzylidene acetal but oxidatively cleaved the resulting diol to give the aldehyde **11**. As it turned out, the benzylidene acetal could be removed from the coupled product under acidic conditions to give diol **12** in good yield without adversely affecting the acetate.

Armed with the information that acidic conditions would not harm the acetate, an isopropylidene acetal was chosen to replace the benzylidene acetal. It was hoped that replacement of the acid-labile stereocenter present in the benzylidene acetal with an achiral acetone would simplify the isolation of coupled products and possibly boost the yield. The isopropylidene acetal was installed in **3** under standard conditions (Scheme 5). The ethyl ester was then removed to

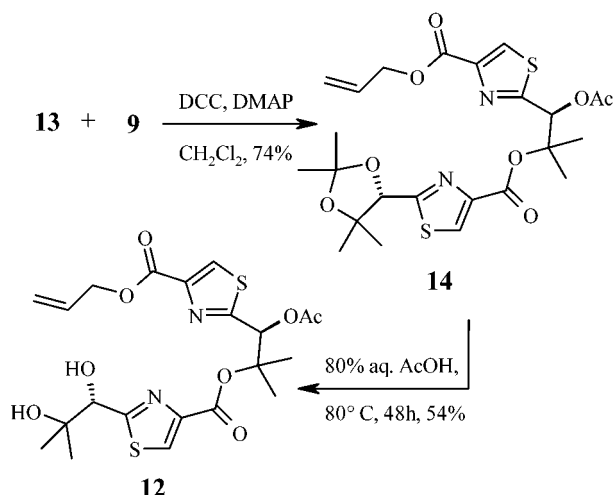
Scheme 5



provide the new carboxylic acid coupling partner **13**.

Although use of the isopropylidene acetal protecting group in place of the benzylidene acetal led to a higher yield of coupled product (**14**, Scheme 6), removal of the isopropyl-

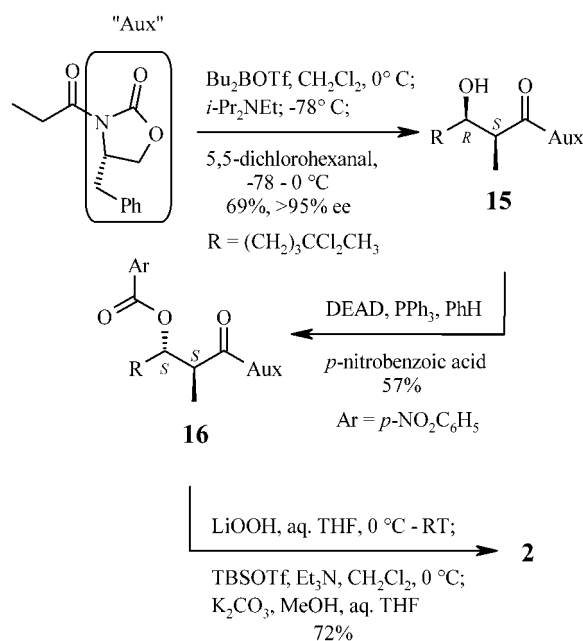
Scheme 6



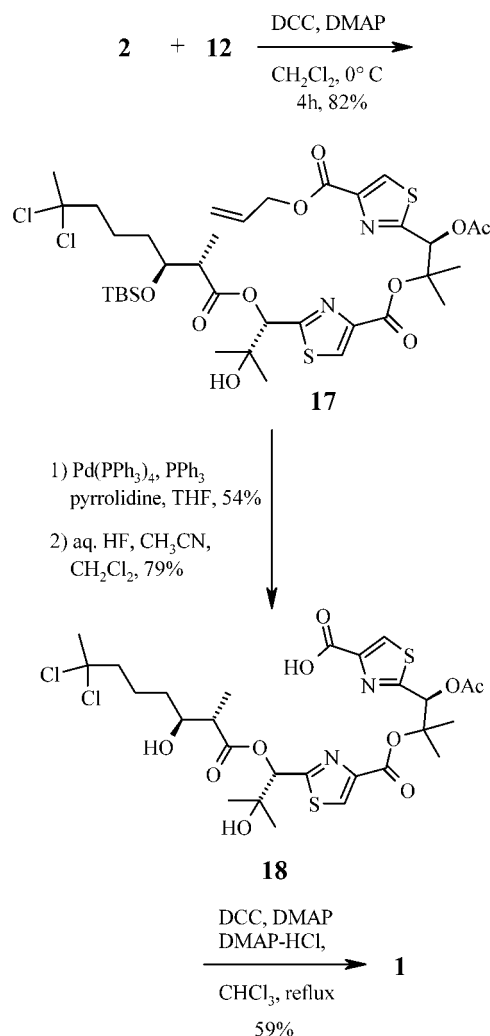
lidene acetal required much more forcing conditions than did removal of the benzylidene acetal. However, the two-step yield for the sequence using the isopropylidene acetal (40%) was significantly higher than that for the sequence utilizing the benzylidene acetal ($\sim 24\%$), so the former route was utilized to make several hundred milligrams of **12** for coupling to aldol subunits.

The preparation of the aldol subunit **2** is shown in Scheme 7. 5,5-Dichlorohexanal^{2,8} was reacted with the boron enolate of (*S*)-(+)-4-benzyl-3-propionyl-2-oxazolidinone in an Evans asymmetric aldol reaction⁹ resulting in a 69% yield of (2*S*,3*R*)-**15** in $>95\%$ de.¹⁰ The secondary hydroxy group in **15** was inverted using Mitsunobu conditions to give a 57%

Scheme 7



Scheme 8



yield of the inverted *p*-nitrobenzoate ester **16**.¹¹ Conditions for hydrolysis of the chiral auxiliary also effected removal of the *p*-nitrobenzoate ester. The secondary alcohol was then protected as its *tert*-butyldimethylsilyl (TBS) ether. Silylation of the free acid also occurred, so the reaction mixture was subjected to potassium carbonate in methanol in order to remove the resulting silyl ester. This sequence was performed in one pot, providing the desired aldol coupling piece **2** in 72% yield.

Coupling of aldol subunit **2** with the bis-thiazole diol **12** to produce the linear triester **17** proceeded smoothly using the same DCC/DMAP conditions employed earlier in the synthesis (Scheme 8). The allyl ester and TBS protecting groups were removed under standard conditions, and the

(8) Villieras, J.; Perriot, P.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1979**, 765–768.

(9) Evans, D. A.; Rieger, D. L.; Jones, T. K.; Kaldor, S. W. *J. Org. Chem.* **1990**, 55, 6260–6268.

(10) The de for **15** could be estimated from the 600 MHz ¹H NMR of the mixture.

(11) The success of the inversion was confirmed by comparing coupling constants of key protons in inverted benzoate **16** to those of the noninverted benzoate prepared directly from **15**. Details are provided in the Supporting Information.

seco-acid **18** was subjected to Keck macrolactonization conditions.¹² The use of DMAP·HCl as a buffer in this reaction was critical to its success.¹³ Hectochlorin was isolated in 59% yield and was spectroscopically identical to natural hectochlorin. The optical rotation for the synthetic material ($[\alpha]^{20}_{\text{D}} = -12.5$) was slightly less than that of the natural product ($[\alpha]^{20}_{\text{D}} = -14.9$) which most likely reflects the fact that some of the antipode is present.

Hectochlorin is a fungicidal natural product which demonstrated activity on pathogens in crop disease screens. A synthetic route to hectochlorin was devised and carried out, and this methodology has been applied to the synthesis of

analogues. The synthesis and activity of these analogues will be reported in due course.

Acknowledgment. The authors would like to thank Professor Bill Gerwick and Dr. Brian Marquez for supplying initial samples of and spectroscopic data for hectochlorin.

Supporting Information Available: Experimental procedures and characterization of compounds **3**, **13**, **9**, **12**, **2**, **17**, and **1**. Additionally, a detailed description of the modified Mosher ester analysis of **3**, NMR data supporting the inversion of (2*S*,3*R*)-**16** to (2*S*,3*S*)-**16**, and a ¹H NMR comparison of natural and synthetic hectochlorin. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(12) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001–7031.

(13) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394–2395.