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De Novo Asymmetric Synthesis of Cladospolide B–D: Structural Reassignment of Cladospolide D via the Synthesis of its Enantiomer

Yalan Xing and George A. O'Doherty*

Department of Chemistry, West Virginia University, Morgantown, West Virginia 26506 george.odoherty@mail.wvu.edu

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ABSTRACT



The enantioselective synthesis of cladospolide B, C, and (*ent*)-cladospolide D has been achieved in 11-15 steps from 1-nonyne. The route relies upon an alkyne zipper reaction to relay an ynone and dienoate functional groups across a nine carbon fragment, which enables a highly enantioselective Noyori ynone reduction and a diastereo- and regioselective Sharpless dihydroxylation of a dienoate. In addition to being a flexible approach to three members of the cladospolide natural products, this route for the first time correctly established the structure for cladospolide D.

The cladospolides (A–D) are a family of 12-membered macrolactones, isolated from various Cladosporium species, and possess a range of biological activities (Figure 1).¹ Although fungal metabolites, the cladospolides appear to act as plant pheromones.^{1b,c} For instance, cladospolides A–C inhibit the shoot elongation in rice seedlings.^{1c} Interestingly, cladospolides A and B have the opposite effect on the root growth of lettuce seedlings.^{1b} More detailed mechanisms of action studies have suggested that cladospolide C acts via the inhibition of gibberellin biosynthesis.^{1c} Of the cladospolides, cladospolide D possesses the most interesting activity with IC₅₀ values of 0.1 and 29 µg/mL against *Mucor racemosus* and *Pyricularia oryzae*, respectively.^{1d}

The absolute and relative stereochemistry for the cladospolides A, B, and C have been confirmed by several total syntheses from known chiral starting materials.² For instance, cladospolides A–C have been prepared by Banwell from 1-hepten-2-ol and *cis*-2,3-dihydroxychlorobenzene which can be prepared in optically pure form via enzymatic resolution and biotransformation,^{2j,3} whereas others have chosen carbohydrate starting materials.² In contrast, at the start of this investigation, the absolute and relative stereochemistry of cladospolide D has not been determined.^{1d,4} In addition, the stereochemical assignment of the C2/C3 double bond was in doubt being solely based on a 13.5 Hz vicinal coupling constant

 ⁽a) Hirota, A.; Isogai, A.; Sakai, H. Agric. Biol. Chem. 1981, 45, 799. (b) Hirota, A.; Sakai, H.; Isogai, A. Agric. Biol. Chem. 1985, 49, 731.
 (c) Fujii, Y.; Fukuda, A.; Hamasaki, T.; Ichimoto, I.; Nakajima, H. Phytochemistry 1995, 40, 1443. (d) Zhang, H.; Tomoda, H.; Tabata, N.; Miura, H.; Namikoshi, M.; Yamaguchi, Y.; Masuma, R.; Omura, S. J. Antibiot. 2001, 54, 635. (e) Hirota, A.; Sakai, H.; Isogai, A.; Kitano, Y.; Ashida, T.; Hirota, H.; Takahashi, T. Agric. Biol. Chem. 1985, 49, 903. (f) Hirota, H.; Hirota, A.; Sakai, H.; Isogai, A.; Takahashi, T. Bull. Chem. Soc. Jpn. 1985, 58, 2147. (g) Smith, C. J.; Abbanat, D.; Bernan, V. S.; Maiese, W. M.; Greenstein, M.; Jompa, J.; Tahir, A.; Ireland, C. M. J. Nat. Prod. 2000, 63, 142.

⁽²⁾ For the synthesis of cladospolide A, see: (a) Banwell, M. G.; Loong, D. T. J. Org. Biomol. Chem. 2004, 2, 2050. (b) Banwell, M. G.; Jolliffe, K. A.; Loong, D. T. J.; McRae, K. J.; Vounatsos, F. J. Chem. Soc., Perkin Trans. 1 2002, 22. (c) Solladie, G.; Almario, A. Tetrahedron: Asymmetry 1995, 6, 559. (d) Solladie, G.; Almario, A. Pure Appl. Chem. 1994, 66, 2159. (e) Ichimoto, I.; Sato, M.; Kirihata, M.; Ueda, H. Chem. Express 1987, 2, 495. (f) Maemoto, S.; Mori, K. Chem. Lett. 1987, 109. (g) Mori, K.; Maemoto, S. Liebigs Ann. Chem. 1987, 863. For the synthesis of cladospolide B, see: (h) Pandey, S. K.; Kumar, P. Tetrahedron Lett. 2005, 46, 6625. (i) Austin, K. A. B.; Banwell, M. G.; Loong, D. T. J.; Rae, A. D.; Willis, A. C. Org. Biomol. Chem. 2005, 3, 1081. For the synthesis of cladospolide C: (j) Banwell, M. G.; Loong, D. T. J.; Willis, A. C. Aust. J. Chem. 2005, 58, 511. (k) Chou, C.-Y.; Hou, D.-R. J. Org. Chem. 2006, 71, 9887. (l) Sharma, G. V. M.; Reddy, K. L.; Reddy, J. J. Tetrahedron Lett. 2006, 47, 6537.

⁽³⁾ Hudlicky, T.; Gonzalez, D.; Gibson, D. T. Aldrichimica Acta 1999, 32, 35.

⁽⁴⁾ As this manuscript was being completed, a report of a synthesis and stereochemical assignment for cladospolide D appeared, see: Lu, K.-J.; Chen, C.-H.; Hou, D.-R. *Tetrahedron* **2009**, *65*, 225. This assignment unfortunately must be considered erroneous, vide infra.



Figure 1. Cladospolides and Grahamimycin A.

for the purported *trans*-enoate carbon/carbon double bond.^{1d}

Drawn by the structural and biological similarities between cladospolides and grahamimycin A(Figure 1),⁵ we became interested in the de novo synthesis of the cladospolides.⁶ In particular, we were interested in the synthesis and stereo-chemical assignment of cladospolide D. Herein, we report the de novo synthesis of cladospolides B-D. The approach features the use of the alkyne zipper reaction to remotely link an alkyne functional group across nine carbon atoms, which enables a Noyori asymmetric ynone reduction and a Sharpless regio- and stereoselective dienoate dihydroxylation.

As part of our efforts for the use of asymmetric catalysis for the enantioselective synthesis of antimicrobial lactones, we were interested in an enantioselective synthesis of cladospolide D. Because of the ambiguity associated with the cladospolide D structure, we initially targeted the reduced natural products cladospolides B and C along with their C4/C5 bisepimers **1** and **2** (Scheme 1). Thus, a selective oxidation of the allylic alcohol from one of these four diastereomers was likely to give



Scheme 2. De Novo Synthesis of Dienoate 5



cladospolide D along with its double bond isomer. Retrosynthetically, we envisioned that cladospolides B and C as well as the bisepimers 1 and 2 could come from the diastereo- and regioselective dihydroxylation⁷ and subsequent lactonization of dienoate 5. In turn, dienoate 5 could come from the carboxylation and diene conjugation of hydroxyalkyne 6, which could be prepared from the Noyori asymmetric reduction/alkyne zipper isomerization of ynone 7. Finally, ynone 7 could be prepared from commercially available 1-nonyne 8.

To access synthetically useful quantities of dienoate 5, an efficient seven-step approach was developed (Scheme 2). The route featured an alkyne zipper reaction⁸ and the Ph₃P promoted ynoate to dienoate isomerization, developed by Trost.⁹ Treatment of the lithium acetylide of 8 with acetylaldehyde gave good yield (80%) of a racemic propargylic alcohol (rac)-9, which when oxidized with MnO₂ gave the ynone 7. Exposure of the ynone 7 to our modified Noyori conditions¹⁰ provided an excellent yield (85%) of propargyl alcohol 9 with high enantiomeric purity (>96% ee). Exposure of 9 to the KAPA reagent readily isomerized it to the terminal undecynol 6 in good yield (85%) and with no loss of enantiomeric purity (>96% ee).¹¹ The secondary alcohol in 6 was cleanly protected as a TBS-ether (TBSCI/imid. in DMF, 97%), and the terminal alkyne was carboxylated (n-BuLi/ClCO₂Et, 83%) to give ynoate 10. Exposure of

(6) Hunter, T. J.; O'Doherty, G. A. Org. Lett. 2002, 4, 4447-4450.

(7) The regioselectivity of the asymmetric dihydroxylation of dienoates has been studied by Sharpless and our group. See: (a) Berker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345. (b) Zhang, Y.; O'Doherty, G. A. *Tetrahedron* **2005**, *61*, 6337–6351.

(8) (a) Brown, C. A.; Yamashita, A. J. Am. Chem. Soc. 1975, 97, 891–892.
(b) Kimmel, T.; Becker, D. J. Org. Chem. 1984, 49, 2494–2496.
(c) Hoye, R. C.; Baigorria, A. S.; Danielson, M. E.; Pragman, A. A.; Rajapakse, H. A. J. Org. Chem. 1999, 64, 2450–2453.

(9) (a) Rychnovsky, S. D.; Kim, J. J. Org. Chem. 1994, 59, 2659–2660.
(b) Trost, B.; Kazmaier, U. J. Am. Chem. Soc. 1992, 114, 7933–7935.

(10) Li, M.; Scott, J. G.; O'Doherty, G. A. Tetrahedron Lett. 2004, 45, 1005–1009.

(11) Trost, B. M.; Horne, D. B.; Woltering, M. J. Chem.-Eur. J. 2006, 12, 6607.

⁽⁵⁾ Gurusiddaiah, S.; Ronald, R. C. Antimicrob. Agents Chemother. 1981, 19, 153–165.



alkynoate **10** to the Rychnovsky variant of the Trost isomerization (Ph₃P/PhOH) cleanly gave *E*,*E*-dienoate **5** in excellent yield (90%) and stereoselectivity.

We next turned to the oxidative assembly of the macrolactone natural product cladospolide C and its double bond isomer 4,5bis-*epi*-cladospolide B **1** (Scheme 3). The sequence began with the use of the Sharpless protocol for the regio- and stereoselective dihydroxylation of dienoate **5** to provide diol **3**.⁷ Acidcatalyzed acetonide diol protection/TBS deprotection of **3** followed by base-promoted ester hydrolysis gave good yields of the hydroxy acid **11** (74%). Unfortunately, the seco-acid **11** only gave polymeric products with exposure to the Keck-DCC protocol for macrocyclization.¹² In contrast, when the Yamaguchi conditions¹³ were used, good yields of a separable mixture of macrolactones **12** and **13** were formed in a 6:1 ratio. Acidcatalyzed deprotection of the two acetonides **12** and **13** with TFA gave good yields of cladospolide C (80%)¹⁴ and 4,5-bis*epi*-cladospolide **1** (78%), respectively.

Following a nearly identical protocol, dienoate **5** was converted into the macrolactone natural product cladospolide B and its double bond isomer 4,5-bis-*epi*-cladospolide C **2** (Scheme 4). Simply switching the (DHQD)₂PHAL ligand to (DHQ)₂PHAL in the Sharpless dihydroxylation gave the diastereomeric diol **4** in the same yield and regioselectivity but opposite diastereoselectivity. Similarly, acid-catalyzed acetonide diol protection/TBS deprotection of **4** followed by base-promoted ester hydrolysis gave the hydroxy acid **14** (70%).

Scheme 4. Synthesis of Cladospolide B and 4,5-bis-*epi*-Cladospolide C 2



Exposure of **14** to the Yamaguchi conditions yielded a 6:1 mixture of macrolactones **15** and **16**. The lactones **15** and **16** were separated and deprotected with TFA to give cladospolide B $(81\%)^{14}$ and 4,5-bis-*epi*-cladospolide C **2** (82%), respectively.

With the required four stereoisomeric macrolactone diols with defined stereochemistry, we turned our attention to the synthesis and structural proof of cladospolide D. This began with the investigation of the selective oxidation of the allylic alcohol in cladospolide C (Scheme 5). In our grahamimycin A synthesis, we had previously found that the enone functionality could be installed by a stoichiometric TEMPO

Scheme 5. Synthesis of Purported Cladospolide D



⁽¹²⁾ Keck, G. E.; Murry, J. A. J. Org. Chem. 1991, 56, 6606-6611.

⁽¹³⁾ Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. Bull. Chem. Soc. Jpn. **1979**, *52*, 1989–1993.

⁽¹⁴⁾ The ⁱH and ¹³C NMR spectral data, optical rotation, and mp match the reported data for cladospolide B and C, although it should be noted that Banwell reports the opposite value for cladospolide B. See Supporting Information section E.

⁽¹⁵⁾ The enantiomer of structure 22 was incorrectly assigned as cladospolide D by Hou et al. See ref 4.

Scheme 6. Synthesis of Cladospolide D



oxidation of the allylic alcohol in colletodiol, without the need for selective protection.⁶ Unfortunately, when we applied these same conditions to cladospolide C, no simple oxidation products were detected. Thus, we turned to a selective protection/oxidation/deprotection sequence.

Mono-TBS protection of cladospolide C occurred when exposed to TBSCl/imid. in CH₂Cl₂ (90%) to give a separable mixture of regioisomers but with poor regioselectivity (17 to **18** in a 1:2 ratio). Dess-Martin oxidation of minor product **17** cleanly gave an enone, which after TBS deprotection (5 mol % HF/CH₃CN) gave **19**, one of the two possible diastereomers of the purported cladospolide D structure. Similar mono-TBS protection of diol 2 occurred when exposed to TBSCI/imid. in CH_2Cl_2 (90%), to give a separable mixture of regioisomers, with better regioselectivity (20 to 21 in a 2:1 ratio). Dess-Martin oxidation and TBS deprotection (5 mol % HF/CH₃CN) of 20 gave 22, which is the other possible diastereomer of the purported cladospolide D structure. To our surprise, comparison of the ¹H NMR and ¹³C NMR spectra of synthetic 19 and 22 with that reported for cladospolide D clearly indicated that these two isomers were different structures than cladospolide D.15 Particularly diagnostic details were coupling constants and chemical shifts for the α . β -enone protons.

Thus, we turned to the synthesis of the two diastereomers of the *cis*-double bond isomer of the cladospolide D, which



initially began with 4,5-bis-*epi*-cladospolide B **1** and cladospolide B (Scheme 6). As before, mono-TBS protection of diol **1** was unselective, yielding a separable mixture of alcohols **23** and **24** with the desired product isolated as the minor isomer. Oxidation of the allylic alcohol **23** gave a good yield of enone **25** (95%), which was deprotected with 5 mol % HF/CH₃CN (86%) to give one of the two possible *cis*diastereomers of the purported cladospolide D structure. Similarly, the monoprotection of cladospolide B was unselective to give an inseparable mixture of regioisomers **27**/ **28**, which when oxidized gave a poor yield of the *cis*-enone **29**. To our delight, upon exposure of **29** to 5 mol % HF/ CH₃CN, TBS deprotection occurred to give γ -keto-enoate **30**, with which ¹H NMR and ¹³C NMR matched the reported data for cladospolide D (vide infra).^{1d}

With the knowledge of the structure of the desired target molecule, we next sought an improved synthesis (Scheme 7). This brought us back to the *trans*-enone **31**, which was made from the Dess-Martin oxidation of **20**. Interestingly, when **31** was treated with HF/Py (instead of 5 mol % HF/ CH₃CN), a clean double bond isomerization occurred to give the previous prepared *cis*-isomer **29**. As before, TBS deprotection with 5 mol % HF/CH₃CN occurred to give γ -ketoenoate **30**. Synthetic **30** material was spectroscopically (¹H NMR, ¹³C NMR, IR and MS; see page S107 in the Supporting Information) identical with natural cladospolide D, although the optical rotation was opposite in sign ([α]_D -58 vs + 56 in MeOH). Thus, structure **30** must be the enantiomer of cladospolide D, and the structure should be revised to the *cis*-isomer as shown in Figure 1.

In conclusion, a short and enantioselective synthesis of cladospolide B, cladospolide C, and (ent)-cladospolide D has been developed along with the synthesis of all the possible stereoisomers of cladospolide D. Because the Noyori reduction for 7 can produce either enantiomer of 9, this synthesis is also a formal synthesis of the natural stereoisomer of cladospolide D. This de novo asymmetric approach installs all the stereocenters in the cladospolides using two catalytic asymmetric reactions (Noyori reduction and Sharpless asymmetric dihydroxylation). The overall route to this class of natural products was achieved in less steps and greater overall efficiency than the previous routes from chiral starting materials and is amenable for the preparation of either enantiomer. In addition, this study for the first time correctly establishes the absolute and relative stereochemistry of cladospolide D and serves as a correction of the originally assigned natural product structure. Further studies on the use of this de novo asymmetric sequence for the preparation of other macrolactone antibiotics as well as cladospolide analogues will be reported in due course.

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Supporting Information Available: Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.