Structure Investigations of (*ent*)-Cladospolide D by De Novo Synthesis and Kinetic and Thermodynamic Isomerization

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Abstract: The de novo asymmetric synthesis of cladospolides B and C and (*ent*)-cladospolide D has been achieved from achiral non-1-yne. The 11–13-step route relies upon a Noyori reduction and a KAPA promoted alkyne zipper reaction to relay an achiral functionality across a nine-carbon fragment and to enable the installation of a dienoate functionality. A diastereo- and regioselective Sharpless dihydroxylation of a dienoate installed the remaining stereochemistry. The de novo asymmetric route allowed for the asymmetric synthesis of three members of the cladospolide natural products and correctly established the structure for cladospolide D.

Key words: cladospolides B–D, asymmetric synthesis, natural product synthesis, *E/Z*-alkene isomerization

In an interesting synergistic relationship between parasite and host, the *Cladosporium* species produce secondary metabolites that can regulate the host plant's growth.[1] This growth regulation is believed to occur via the inhibition of gibberellin biosynthesis.[1c] Structurally these fungal products/plant pheromones are made up of a group of diastereomeric twelve-membered macrolactone diols, which differ in stereochemistry at the C4/C5 diol and C2/C3 double bond stereochemistry (Figure 1).[1] These stereochemical differences affect the biological activity. For instance, cladospolides A–C inhibit the shoot elongation in rice seedlings,[1c] whereas, cladospolides A and B have the opposite effect on the root growth of lettuce seedlings.[1b]

These three natural products, cladospolides A–C,[2–4] are produced by the same and related organisms and it was initially suggested that they should share the same C11 carbinol stereochemistry, which biosynthetically would be formed earliest in the fatty acid biosynthetic pathway. The relative stereochemistry for the cladospolides A–C have been confirmed by several total syntheses, although it should be noted that questions remain around cladospolide B, where the different signs of rotation were found for the same absolute stereoisomer for synthetic cladospolide B by Banwell and us.[2–4]

In contrast to the plant pheromone activity of cladospolide A–C, cladospolide D possesses antimicrobial activity with IC_{50} values of 0.1 and 29 μg/mL against *M. racemosus* and *P. oryzae*, respectively.[1d] Until our work, the absolute and relative stereochemistry of cladospolide D had not been correctly determined.[5] At issue was the stereochemical assignment of the C2–C3 double bond, which was solely based on a 13.5 Hz vicinal coupling constant for the purported *trans*-enoate C=C bond.[1d]

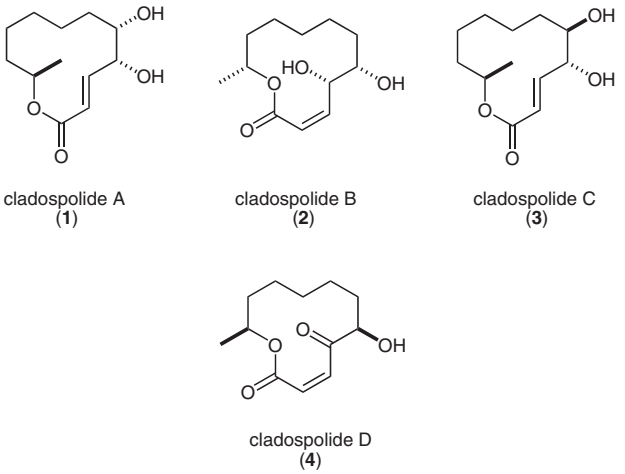

Figure 1 Cladospolides A–D

Using asymmetric synthesis of all the possible diastereomers and the comparison of optical rotation data, we assigned the absolute and relative stereochemistry for cladospolide D (Figure 2).[3c] This work resulted in a correction of the initially assigned C2–C3 double bond stereochemistry, which the first synthesis of cladospolide D, by Hou, initially confirmed the structure as *E*-isomer **6**.[5] Unfortunately, this synthetic study missed a facile *E/Z*-double bond isomerization and, thus, they actually prepared the *Z*-isomer of cladospolide D (**4**), although they reported it as (*E*)-cladospolide D (**6**). Herein, we report the full account of our synthetic studies toward the successful synthesis of cladospolide B/C and the (*ent*)-cladospolide D, which includes our study of the *E/Z*-double

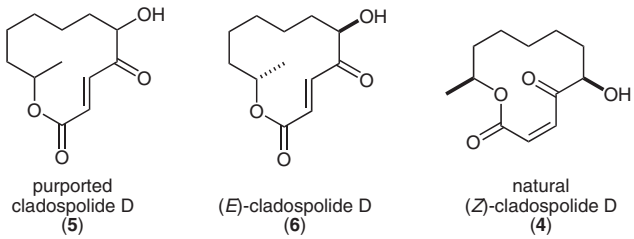

Figure 2 (*E/Z*)-Cladospolide D

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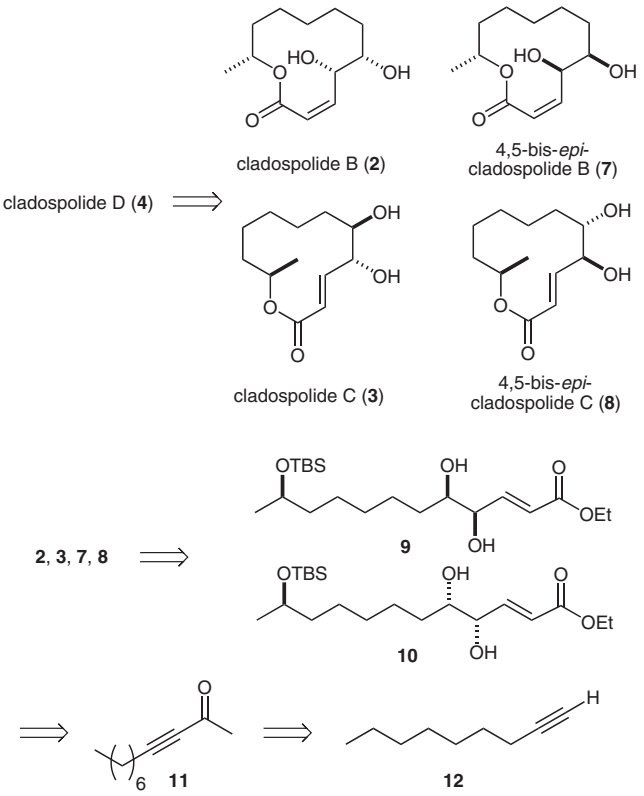
bond isomerization of cladospolides and their diastereomers.

At the outset of this project, we had reservations regarding the assignment of double bond stereochemistry for purported cladospolide D (**5**). Accordingly, our retrosynthetic analysis (Scheme 1) envisioned that (*Z*)-cladospolide D (**4**) could be prepared from cladospolide B (**2**) or its bis-epimer **7**. Similarly, (*E*)-cladospolide D (**6**) could be prepared from cladospolide C (**3**) or its bis-epimer **8**. In turn, cladospolides B and C (**2** and **3**) and their bis-epimers **7** and **8** could come from the lactonization reactions of diols **9** and **10**. Diols **9** and **10** could come from the diastereoselective and regioselective dihydroxylation,[6] diene conjugation,[7] alkyne zipper isomerization,[8] and Noyori asymmetric reduction of ynone **11**,[9] which could be prepared from commercially available non-1-yne (**12**).



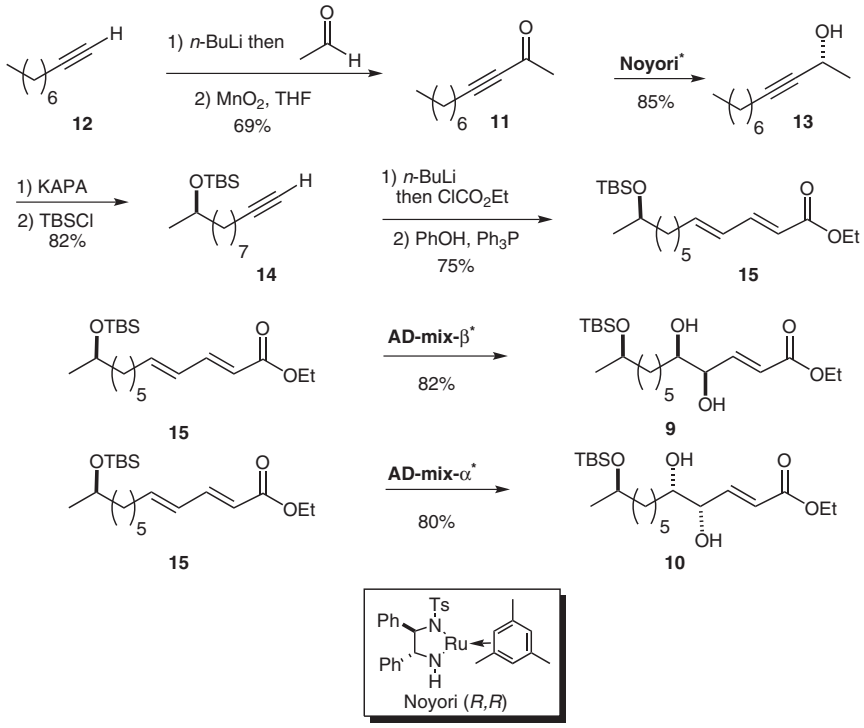
Scheme 1 Retrosynthetic analysis

Lithiation of commercially available non-1-yne (**12**) and alkylation with acetaldehyde gave racemic propargylic alcohol *rac*-**13** (69%, two steps). Propargylic oxidation of *rac*-**13** with manganese dioxide gave the ynone **11**. Exposure of the ynone **11** to our modified Noyori conditions[9] provided an excellent yield (85%) of propargyl alcohol **13** with high enantiomeric purity (>96% ee). Exposure of **13** to potassium 3-aminopropylamine reagent (KAPA) readily isomerized it to the terminal undecynol,[8] which was protected as its *tert*-butyldimethylsilyl ether (TBSCl/imidazole, DMF) in good overall yield (82%) and with no loss of enantiomeric purity (>96% ee).[10] The terminal alkyne **14** was carboxylated (*n*-BuLi/$ClCO_2Et$, 83%) to give an ynoate, which by means of the Rychnovsky variant of the Trost ynoate to dienoate isomerization (Ph_3P/PhOH) was cleanly converted into (*E*,*E*)-dienoate **15** in good yields (90%) and stereoselectivity.[7] Dienoate **15** was subjected to Sharpless asymmetric dihydroxylation conditions [2% OsO_4, 4% $(DHQD)_2PHAL$] to give diol **9** in approximately 82% yield and as a single diastereomer.[6] Similarly, dienoate **15** was dihydroxylated with the pseudoenantiomeric reagent [2% OsO_4, 4% $(DHQ)_2PHAL$] to give diol **10** in approximately 80% yield and as a single diastereomer (Scheme 2).

With all the sp^3 stereocenters established for the cladospolides, we turned to the assembly of the macrocycle (Scheme 3). To our delight this occurred with a small amount of double bond isomerization. Thus exposing diol **9** to acid-catalyzed acetonide formation/TBS deprotection conditions gave the desired seco-acid, which when exposed to the Yamaguchi lactonization conditions[11] gave a 6:1 mixture of cladospolide C (**3**) (36%) and its double bond isomer **7** (6%), after trifluoroacetic acid promoted acetonide deprotection. Following a virtually identical macrocyclization protocol, diol **10** was converted into a similar mixture of cladospolide B (**2**) (6%) and its double bond isomer **8** (34%).

With the construction of the required four stereoisomeric macrolactone diols, 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 (**3**) (Scheme 4). Unfortunately, several oxidants (e.g., MnO_2 and Dess–Martin periodinane) lead to oxidative diol cleavage to give a dialdehyde product. In our grahamimycin A synthesis, we had previously found that the enone functionality could be installed by a stoichiometric 2,2,6,6-tetramethylpiperidin-1-yloxy (TEMPO) oxidation of the allylic alcohol in colletodiol, without the need for selective protection.[6c] Unfortunately, when we applied these same conditions to the cladospolides, only products of double oxidation were obtained. For instance, when we exposed cladospolide C (**3**) and its *C*-4,5-bis-epimer **8** to the catalytic TEMPO oxidation conditions [TEMPO (1 mol%), trichloroisocyanuric acid (1 equiv)][12] only diketone **16** was observed. When only one equivalent of co-oxidant was used [TEMPO (1 mol%), trichloroisocyanuric acid (0.33 equiv)] low yields of **16** and starting material were observed. Similarly, cladospolide B (**2**) and its *C*-4,5-bis-epimer **7** reacted under the TEMPO oxidation conditions to give diketone **17**. Thus, we turned to a selective protection/oxidation/deprotection sequence.

Because the absolute stereochemistry of cladospolide D was not known and we had our doubts about the assigned olefin geometry, we decided to perform the protection/oxidation/deprotection sequence on both cladospolide B (**2**) and C (**3**) as well as their 4,5-bis-epimers **7** and **8**. Due to the exploratory nature of these studies, no effort was made to maximize the regioselectivity in the protection step. Rather a regio-unselective TBS-protection was chosen for simplicity's sake (i.e., no bis-protection was ob-

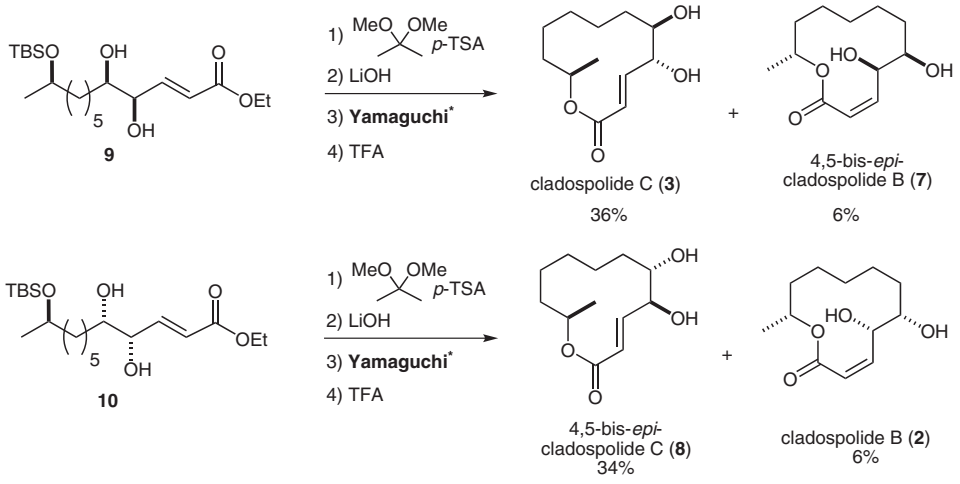


Scheme 2 Synthesis of diols. *Reagents and conditions*: Noyori* = Noyori (*R*,*R*) (0.2 mol%), HCO_2H/Et_3N (5:4); AC-mix-β* = 1% OsO_4, 5% $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*-BuOH–H_2O (1:1); AD-mix-α* = 1% OsO_4, 5% $(DHQ)_2PHAL$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*-BuOH–H_2O (1:1).

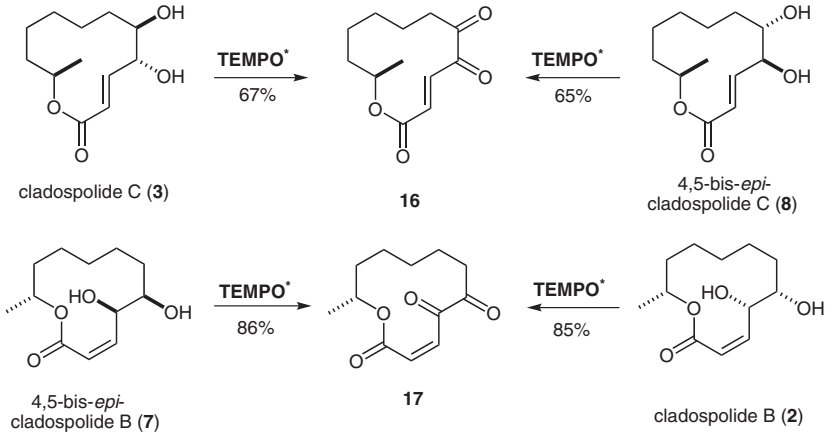
served and the minor regioisomer could be recycled). This, in turn, helped with the assignment of the regioisomers.

Exposure of cladospolide C (**3**) to the three-step TBS monoprotection/Dess–Martin oxidation/hydrogen fluoride deprotection gave a 27% yield of enone **18** (Scheme 5). Cladospolide B (**2**) and its 4,5-bis-epimer **7** gave the corresponding enones **21** and **20**, respectively, with similar yields for this three-step sequence. The low yield for these sequences was due to the poor regioselectivity (1:2 against) in the TBS-protection step. In contrast, when the 4,5-bis-epimer **8** was exposed to the same three-step sequence a higher yield of enone **19** was obtained due to improved regioselectivity in the TBS protection (2:1).[13] Of the four enones produced, only **21** had spectral data that matched cladospolide D,[1d] although the rotation was opposite in sign. The spectral data for this *Z*-enone also matched the data report by Hou for his synthetic cladospolide D, although it was assigned as the enantiomer of the *E*-isomer **19** (**6**). Therefore, we concluded that a hidden alkene isomerization reaction must have occurred during the Hou synthesis.

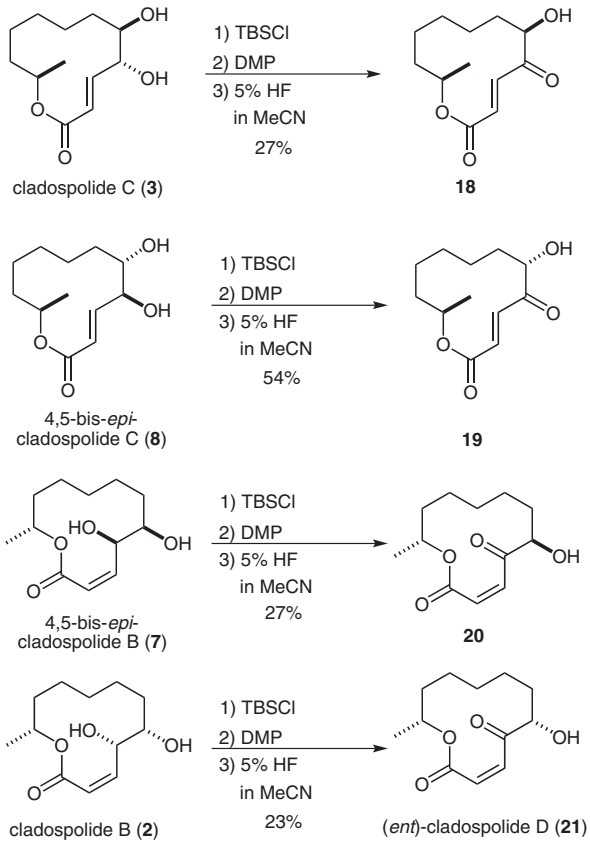
Consequently, we decided to investigate the isomerization of the olefin **19**. When enone **19** was irradiated with UV light (300 nm) with and without iodine, a 1:1 ratio of **19** and (*ent*)-cladospolide D (**21**) was found along with a sig-



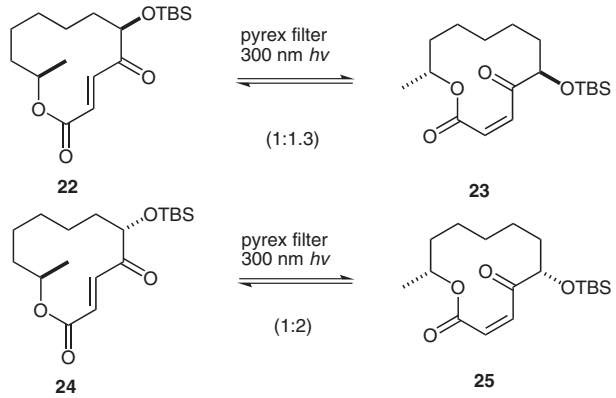
Scheme 3 Synthesis of cladospolide B and C and isomers. *Reagents and conditions*: Yamaguchi* = 2,4,6-trichlorobenzoyl chloride, DMAP.



Scheme 4 Diol oxidations. *Reagents and conditions*: TEMPO* = TEMPO, trichloroisocyanuric acid.



Scheme 5 Synthesis of cladospolide D and diastereomers



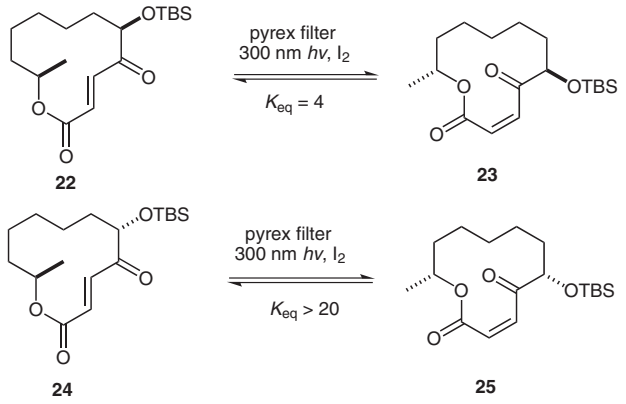
Scheme 6 Photoequilibration

nificant amount of photodegradation products. While this isomerization explained the problem with Hou's assignment of cladospolide D, the photochemical isomerization reaction was not clean enough to be consistent with his reported yield. Similarly byproducts were also observed, when we explored the photoisomerization of **18** and **20**. However, much cleaner isomerization reactions were observed for the TBS-protected enones, **22**, **23**, **24**, and **25** (Scheme 6).

When we irradiated benzene-d_6 solutions of pure **22** and **23** for 24 hours with 300-nm light through a Pyrex filter, a photoequilibrium (*Z*/*E*, 1.3:1) was established with the *Z*-isomer **23** being slightly favored. When we irradiated benzene-d_6 solutions of **24** and **25** under identical conditions a photoequilibrium (*Z*/*E*, 2:1) was established, which slightly favored the *Z*-isomer **25** (Scheme 6).

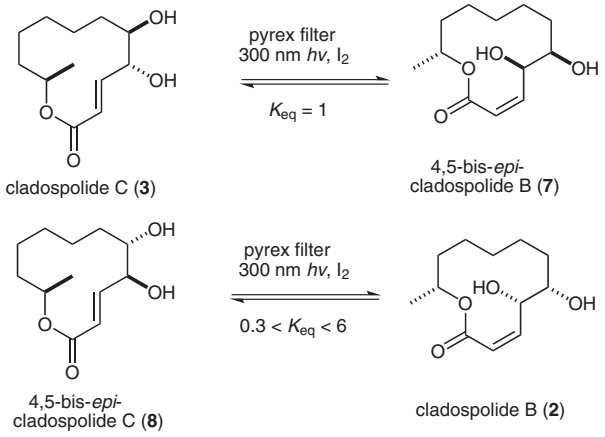
The photoisomerization gave photoequilibria and not true K_{eq}, hence, we decided to isomerize the enones under iodine radical conditions. We exposed pure benzene-d_6 solutions of **22** and **23** to a catalytic amount of iodine under thermal and photochemical conditions (Scheme 7). Under these conditions, both solutions rapidly (<1 h) reached equilibrium (K_{eq} = 4, *Z*/*E*) with the *Z*-isomer being more stable. When we turned to the *E*/*Z*-isomers of the natural cladospolide D diastereomer, we found a much greater difference in stability. When the same isomerization was preformed with pure solutions of **24** and **25** the equilibrium was reached much more quickly and the equilibrium achieved was in even greater preference for the *Z*-isomer **25** (K_{eq} >20, *Z*/*E*). Therefore, we concluded that the driving force and barrier to isomerization of the cladospolide D diastereomer **25** is quite strong.

For comparison, we decided to study the double bond isomerization between cladospolide C (**3**) and its 4,5-bis-epimer **8** using the same equilibration condition (Scheme 8). This study showed that no strong thermodynamic preference for the *Z*-isomers could be found. For



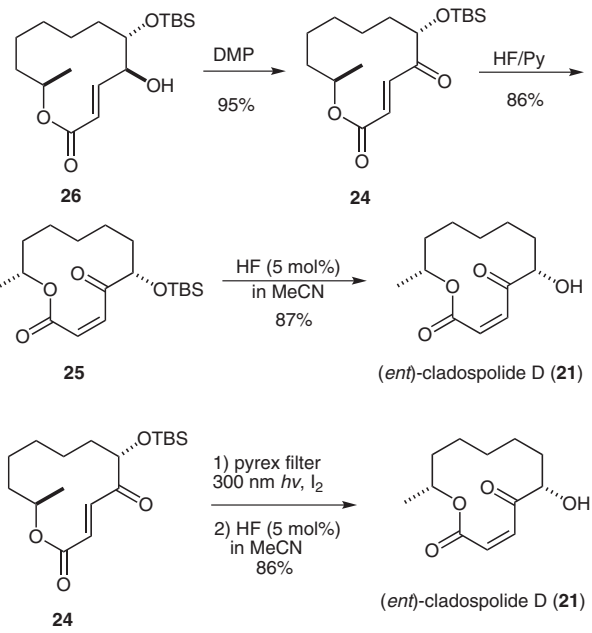
Scheme 7 Photochemical equilibrium

example, when cladospolide C (**3**) and its double bond isomer **7** were isomerized under radical iodine conditions (24 h irradiation with I_2), we found equal amounts of **3** and **7** ($K_{eq} = 1$). In contrast, we were not able to reach to full equilibrium for the isomerization of 4,5-bis-*epi*-cladospolide C (**8**) to cladospolide B (**2**), but we could bracket the equilibrium constant to be between 0.3 and 6 (Scheme 8), suggesting that the C4 carbonyl in cladospolide D has a strong effect on the *E*/*Z*-stability.



Scheme 8 Photochemical equilibrium

With the knowledge of the structure of the desired target molecule, we next sought an improved synthesis of cladospolide D (Scheme 9). We returned to the *trans*-diol **8**, which could be regioselectively protected to give **26** in good yield. Dess–Martin oxidation of **26** cleanly gave enone **24**. At this stage photochemical isomerization of **24** cleanly gave the previously prepared *Z*-isomer **25** in near quantitative yield (>95%). Interestingly, when **24** was treated with the conditions used by Hou (HF/Py), instead of our preferred conditions (5% HF/MeCN), clean double bond isomerization occurred to give **25**. As before, TBS-deprotection with 5% hydrogen fluoride in acetonitrile occurred to give γ-keto-enoate **21**. Synthetic **21** material was spectroscopically (^{1}H NMR, ^{13}C NMR, IR, and MS) identical with natural cladospolide D, although the optical rotation was opposite in sign ($[\alpha]_D$ –58 vs +56 in MeOH). Hence, structure **21** must be the enantiomer of cladospolide D and the structure should be revised to structure **4** as shown in Figure 1.



Scheme 9 Improved approaches to cladospolide D

In conclusion, a short and enantioselective synthesis of (*ent*)-cladospolide D has been developed, which clears up any ambiguities with its structural assignment. This structural proof involved the synthesis of all the possible stereoisomers of cladospolide D as well as another two members of this family of natural products, cladospolides B and C. This de novo asymmetric approach used two remote catalytic asymmetric reactions (Noyori reduction and Sharpless asymmetric dihydroxylation) to establish its asymmetry, therefore, this synthesis is also a formal synthesis of the natural stereoisomer of cladospolide D. This de novo route to the cladospolides compares favorably (i.e., fewer steps and greater overall efficiency) to the previous routes from chiral starting materials. In addition, this route enabled the study of the C2–C3 alkene isomerization that was of central importance to the structural proof of cladospolide D.

^{1}H and ^{13}C NMR spectra were recorded on 600 M or 270 M NMR spectrometers. Chemical shifts are reported relative to $CDCl_3$ (δ = 7.26) or CD_3OD (δ = 3.31) for ^{1}H, and $CDCl_3$ (δ = 77.0) or CD_3OD (δ = 49.15) for ^{13}C. Optical rotations were measured with a digital polarimeter in the solvent specified. IR spectra were obtained on a FT-IR spectrophotometer. Melting points are uncorrected. R_f values were obtained by elution of TLC plate in the stated solvent ratios (v/v). Toluene, Et_2O, THF, CH_2Cl_2, and Et_3N were dried by passing through activated alumina column with argon gas pressure. Commercial reagents were used without purification unless otherwise noted. Air and/or moisture-sensitive reactions were carried out under an atmosphere of argon using oven/flamed-dried glassware and standard syringe/septa techniques. Only new procedures are reported in this experimental section.

(*R*,*E*)-12-Methyloxacyclododec-3-ene-2,5,6-trione (16)

From diol **3**: A soln of diol **3** (6 mg, 0.026 mmol) and trichloroisocyanuric acid (6.1 mg, 0.026 mmol) in Et_2O (0.3 mL) was stirred at –30 °C, then TEMPO was added in one portion. The mixture was stirred for 60 min and then quenched with sat. Na_2CO_3. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Chromatography (silica gel) gave **16** (3.8 mg, 67%) as a colorless oil.

From diol **8**: A soln of diol **8** (12 mg, 0.052 mmol) and trichloroisocyanuric acid (12.3 mg, 0.053 mmol) in Et_2O (0.5 mL) was stirred at –30 °C, then TEMPO was added in one portion. The mixture was stirred for 60 min and then quenched with sat. Na_2CO_3. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Chromatography (silica gel) gave **16** (7.6 mg, 65%) as a colorless oil.

R_f = 0.67 (hexane–EtOAc, 7:3). ^{1}H spectra shows a mixture of diketone **16** and its hydride.

$[\alpha]_D^{20}$ –2 (*c* 0.1, MeOH).

IR (thin film): 3373, 2934, 1715, 1134, 1040, 987, 706 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = peaks associated with the diketone: 6.87 (d, *J* = 15.6 Hz, 1 H), 6.36 (d, *J* = 15.6 Hz, 1 H), 5.05 (m, 1 H), 3.05 (ddd, *J* = 13.2, 7.8, 3.0 Hz, 1 H), 2.36 (ddd, *J* = 13.2, 12.0, 3.0 Hz, 1 H), 1.41 (d, *J* = 7.8 Hz, 3 H); peaks associated with the hydrate: 7.00 (s, 2 H), 4.60 (m, 1 H), 4.14 (s, 1 H), 3.73 (s, 1 H), 2.69 (m, 1 H), 2.54 (m, 1 H), 1.41 (d, *J* = 6.6 Hz, 3 H), peaks associated with the mixture: 1.67–1.54 (m).

^{13}C NMR (150 MHz, CD_3Cl): δ = diketone **16**: 204.2, 195.6, 164.9, 136.6, 136.0, 75.5, 39.5, 34.8, 24.8, 23.4, 21.8, 20.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{17}O_4$: 225.1121; found: 225.1122.

(*R*,*Z*)-12-Methyloxacyclododec-3-ene-2,5,6-trione (17)

From diol **7**: A soln of diol **7** (6 mg, 0.026 mmol) and trichloroisocyanuric acid (6.0 mg, 0.026 mmol) in Et_2O (0.3 mL) was stirred at –30 °C, then TEMPO was added in one portion. The mixture was stirred for 40 min and then quenched with sat. Na_2CO_3. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Chromatography (silica gel) gave **17** (5.0 mg, 86%) as a colorless oil.

From diol **2**: A soln of diol **2** (15 mg, 0.066 mmol) and trichloroisocyanuric acid (15.3 mg, 0.066 mmol) in Et_2O (0.6 mL) was stirred at –30 °C, then TEMPO was added in one portion. The mixture was stirred for 40 min and then quenched with sat. Na_2CO_3. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. Chromatography (silica gel) gave **17** (12 mg, 85%) as a colorless oil.

R_f = 0.34 (hexane–EtOAc, 9:1).

$[\alpha]_D^{25}$ +2 (*c* 0.5, CH_2Cl_2).

IR (thin film): 2931, 1710, 1377, 1284, 995 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.49 (d, *J* = 12.6 Hz, 1 H), 6.29 (d, *J* = 12.6 Hz, 1 H), 5.02 (dqd, *J* = 6.0, 6.0, 2.4 Hz, 1 H), 3.13 (ddd, *J* = 15.6, 10.2, 2.4 Hz, 1 H), 2.44 (ddd, *J* = 15.6, 9.6, 2.4 Hz, 1 H), 1.98 (m, 1 H), 1.83 (m, 1 H), 1.59–1.61 (m, 6 H), 1.18 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (150 MHz, CD_3Cl): δ = 199.1, 190.4, 163.8, 135.7, 129.6, 73.2, 34.6, 31.6, 26.5, 21.4, 21.0, 19.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{17}O_4$: 225.1121; found: 225.1122.

(6*S*,12*R*,*Z*)-6-Hydroxy-12-methyloxacyclododec-3-ene-2,5-dione [(*ent*)-Cladospolide D, 21]

To a soln of **24** (1.0 mg) in benzene-d_6 (3.0 mL), I_2 (0.1 mg) was added, the soln was irradiated with 300-nm UV light through a Pyrex filter for 20 min; chromatography gave double bond isomer **25** (0.95 mg, 95%). To a plastic flask was added **25** (5 mg, 0.015 mmol), MeCN (0.1 mL), and 5% HF in MeCN (17 μL) at r.t. The mixture was stirred for 2 h and then Et_2O was added to dilute the soln. The mixture was washed with $NaHCO_3$, extracted with EtOAc, dried (Na_2SO_4), and evaporated under reduced pressure to leave the crude product, which was then purified using flash chromatography (silica gel) to give **21** (3 mg, 87%) as a colorless oil; R_f = 0.36 (30% Et_2O–hexane).

$[\alpha]_D^{25}$ –57 (*c* 0.1, CH_2Cl_2).

IR (thin film): 3467, 2936, 1720, 1224, 1167, 1083 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.40 (d, *J* = 13.2 Hz, 1 H), 6.31 (d, *J* = 13.2 Hz, 1 H), 5.22 (dqd, *J* = 9.0, 6.0, 6.0 Hz, 1 H), 4.66 (ddd, *J* = 8.4, 6.0, 5.4 Hz, 1 H), 3.16 (d, *J* = 6.0 Hz, 1 H), 1.95 (m, 1 H), 1.72–1.18 (m, 9 H), 1.30 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (150 MHz, CD_3Cl): δ = 203.5, 165.4, 133.3, 130.9, 73.5, 71.5, 33.2, 31.1, 23.0, 21.6, 21.5, 20.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{19}O_4$: 227.1278; found: 227.1278.

Photoequilibration of TBS-Protected (*E*)-5-bis-Cladospolide D 22 and TBS-Protected (*Z*)-5-bis-Cladospolide D 23

A soln of **22** (1.5 mg) in benzene-d_6 (3.5 mL) was irradiated with 300-nm UV light through a Pyrex filter. After 24 h, a photoequilibrium (**23**/**22**, 1.3:1) was established with the *Z*-isomer **23** slightly favored; **22** and **23** could be separated by chromatography.

Pure **23** (1.0 mg) was irradiated in benzene-d_6 (3.0 mL) soln with 300-nm UV light through a Pyrex filter, the same photoequilibrium (**23**/**22**, 1.3:1) was established with the *Z*-isomer **23** slightly favored; **22** and **23** could be separated by chromatography.

(*E*)-*O*-(*tert*-Butyldimethylsilyl)-5-bis-cladospolide D (22)

R_f = 0.33 (10% Et_2O–hexane).

$[\alpha]_D^{25}$ –12 (*c* 0.5, CH_2Cl_2).

IR (thin film): 2931, 2858, 1721, 1463, 1251, 1078, 838, 779 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 16.8 Hz, 1 H), 6.90 (d, *J* = 16.8 Hz, 1 H), 4.89 (dqd, *J* = 7.8, 6.0, 4.8 Hz, 1 H), 4.41 (dd, *J* = 6.0, 4.2 Hz, 1 H), 1.78–1.15 (m, 10 H), 1.34 (d, *J* = 6.0 Hz, 3 H), 0.91 (s, 9 H), 0.10 (s, 3 H), 0.07 (s, 3 H).

^{13}C NMR (150 MHz, CD_3Cl): δ = 200.8, 166.8, 138.2, 131.3, 79.2, 75.3, 35.1, 34.1, 27.7, 25.8, 23.9, 20.6, 18.1, –4.79, –5.25.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{32}O_4SiNa$: 363.1962; found: 363.1964.

(*Z*)-*O*-(*tert*-Butyldimethylsilyl)-5-bis-cladospolide D (23)

R_f = 0.50 (10% Et_2O–hexane).

$[\alpha]_D^{25}$ +18 (*c* 0.4, CH_2Cl_2).

IR (thin film): 2932, 2857, 1717, 1464, 1285, 1098, 838, 778 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.78 (d, *J* = 12.6 Hz, 1 H), 5.95 (d, *J* = 12.6 Hz, 1 H), 4.87 (dqd, *J* = 9.0, 6.0, 3.0 Hz, 1 H), 4.14 (dd, *J* = 9.6, 3.0 Hz, 1 H), 1.84–1.24 (m, 10 H), 1.25 (d, *J* = 6.0 Hz, 3 H), 0.91 (s, 9 H), 0.09 (s, 6 H).

^{13}C NMR (150 MHz, CD_3Cl): δ = 204.3, 164.5, 140.4, 125.9, 78.8, 73.9, 31.9, 31.3, 27.1, 25.7, 20.7, 19.5, 19.3, 18.0, –4.80, –5.13.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{32}O_4SiNa$: 363.1962; found: 363.1964.

Iodine-Promoted Photochemical Equilibration of TBS-Protected (*E*)-5-bis-Cladospolide D 22 and TBS-Protected (*Z*)-5-bis-Cladospolide D 23

To a soln of **22** (1.5 mg) in benzene-d_6 (3.5 mL), I_2 (0.1 mg) was added, the soln was irradiated with 300-nm UV light through a Pyrex filter. After 50 min, a photochemical equilibrium (K_{eq} = 4, **23/22**) was established with the *Z*-isomer **23** favored; **22** and **23** could be separated by chromatography.

To a soln of **23** (1.0 mg) in benzene-d_6 (3.0 mL), I_2 (0.1 mg) was added, the soln was irradiated with 300-nm UV light through a Pyrex filter. After 50 min, the same photochemical equilibrium (K_{eq} = 4, **23/22**) was established with the *Z*-isomer **23** favored; **22** and **23** could be separated by chromatography.

Photoequilibration of TBS-Protected (*E*)-Cladospolide D 24 and TBS-Protected (*Z*)-Cladospolide D 25

A soln of **24** (1.0 mg) in benzene-d_6 (3.0 mL) was irradiated with 300-nm UV light through a Pyrex filter. After 24 h, a photoequilibrium (**24/25**, 1:2) was established with the *Z*-isomer **25** slightly favored; **24** and **25** could be separated by chromatography.

When pure **25** (1.0 mg) was irradiated in benzene-d_6 (3.0 mL) soln with 300 nm UV light through a Pyrex filter, the same photo equilibrium (**24/25**, 1:2) was established with the *Z*-isomer **25** slightly favored; **24** and **25** could be separated by chromatography.

(*E*)-*O*-(*tert*-Butyldimethylsilyl)cladospolide D (24)

R_f = 0.64 (10% Et_2O–hexane).

$[\alpha]_D^{25}$ +31 (*c* 0.4, CH_2Cl_2).

IR (thin film): 2932, 2858, 1723, 1464, 1254, 1095, 847, 779 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 16.8 Hz, 1 H), 6.93 (d, *J* = 16.8 Hz, 1 H), 4.63 (qdd, *J* = 6.0, 6.0, 6.0 Hz, 1 H), 4.34 (dd, *J* = 6.0, 1.6 Hz, 1 H), 1.90–1.06 (m, 10 H), 1.34 (d, *J* = 6.0 Hz, 3 H), 0.92 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H).

^{13}C NMR (150 MHz, CD_3Cl): δ = 201.3, 167.5, 134.2, 132.0, 77.2, 74.9, 34.8, 34.2, 27.9, 25.7, 24.1, 21.4, 20.6, 18.1, –4.91, –4.90.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{33}O_4Si$: 341.2143; found: 341.2144.

(*Z*)-*O*-(*tert*-Butyldimethylsilyl)cladospolide D (25)

R_f = 0.37 (10% Et_2O–hexane).

$[\alpha]_D^{25}$ –80 (*c* 0.5, CH_2Cl_2).

IR (thin film): 2931, 2860, 1726, 1464, 1251, 1164, 1119, 839, 778 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 6.73 (d, *J* = 12.6 Hz, 1 H), 6.23 (d, *J* = 12.6 Hz, 1 H), 4.91 (dqd, *J* = 9.6, 6.0, 3.0 Hz, 1 H), 4.32 (dd, *J* = 7.8, 4.2 Hz, 1 H), 1.93–1.26 (m, 10 H), 1.27 (d, *J* = 6.0 Hz, 3 H), 0.93 (s, 9 H), 0.11 (s, 3 H), 0.09 (s, 3 H).

^{13}C NMR (150 MHz, CD_3Cl): δ = 203.2, 166.3, 133.6, 130.6, 76.4, 73.9, 33.3, 330.5, 26.3, 25.8, 22.1, 21.2, 20.0, 18.1, –4.91, –5.07.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{33}O_4Si$: 341.2143; found: 341.2144.

Iodine-Promoted Photochemical Equilibration of TBS-Protected (*E*)-Cladospolide D 24 and TBS-Protected (*Z*)-Gladospolide D 25

To a soln of **24** (1.0 mg) in benzene-d_6 (3.0 mL), I_2 (0.1 mg) was added, the soln was irradiated with 300-nm UV light through a Pyrex filter. After 20 min, a photochemical equilibrium (K_{eq} > 20, **25/24**) was established with the *Z*-isomer **25** favored.

To the other soln of **25** (1.0 mg) in benzene-d_6 (3.0 mL), I_2 (0.1 mg) was added, the soln was irradiated with 300-nm UV light through a Pyrex filter. After 20 min, the same photochemical equilibrium (K_{eq} > 20, **25/24**) was established with the *Z*-isomer **25** favored.

Iodine-Promoted Photochemical Equilibration of Cladospolide C (3) and 4,5-bis-*epi*-Cladospolide B (7)

To a soln of **3** (1.0 mg) in benzene-d_6 (3.0 mL), I_2 (0.1 mg) was added, the soln was irradiated with 300-nm UV light through a Pyrex filter. After 24 h, a photochemical equilibrium (K_{eq} = 1, **3/7**) was established; **3** and **7** were separated by chromatography (silica gel, 50% Et_2O–hexane).

To the other soln of **7** (1.0 mg) in benzene-d_6 (3.0 mL), I_2 (0.1 mg) was added; the soln was irradiated with 300-nm UV light through a Pyrex filter. After 24 h, the same photochemical equilibrium (K_{eq} = 1, **3/7**) was established; **3** and **7** were separated by chromatography (silica gel, 50% Et_2O–hexane).

Cladospolide C (3)

Mp 91–92 °C; R_f = 0.27 (50% Et_2O–hexane).

$[\alpha]_D^{25}$ +53 (*c* 0.4, MeOH).

IR (thin film): 3415, 2940, 2864, 1705, 1650, 1460, 1258, 1035 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 6.81 (dd, *J* = 15.6, 9.0 Hz, 1 H), 6.05 (d, *J* = 15.6 Hz, 1 H), 4.98 (dqd, *J* = 8.4, 6.0, 1.8 Hz, 1 H), 3.98 (dd, *J* = 8.4, 7.8 Hz, 1 H), 3.57 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1 H), 1.30 (d, *J* = 6.0 Hz, 3 H) 1.69–1.11 (m, 10 H).

^{13}C NMR (150 MHz, CD_3Cl): δ = 166.7, 145.3, 124.5, 77.5, 76.5, 74.3, 33.9, 32.1, 27.3, 24.5, 24.1, 20.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{21}O_4$: 229.1434; found: 229.1435.

4,5-bis-*epi*-Cladospolide B (7)

R_f = 0.33 (50% Et_2O–hexane).

$[\alpha]_D^{25}$ –1 (*c* 0.2, MeOH).

IR (thin film): 3272, 2943, 2862, 1710, 1461, 1278, 1050 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 6.12 (dd, *J* = 12.0, 8.4 Hz, 1 H), 6.05 (dd, *J* = 12.0, 1.2 Hz, 1 H), 5.10 (qdd, *J* = 6.0, 5.4, 3.0 Hz, 1 H), 4.97 (ddd, *J* = 8.4, 4.8, 1.2 Hz, 1 H), 3.87 (ddd, *J* = 9.0, 4.8, 3.0 Hz, 1 H), 2.04–1.35 (m, 10 H), 1.25 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (150 MHz, CD_3Cl): δ = 166.7, 145.3, 124.5, 77.5, 76.5, 74.3, 33.9, 32.1, 27.3, 24.5, 24.1, 20.8.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{21}O_4$: 229.1434; found: 229.1435.

Isomerization of Cladospolide B (2) and 4,5-bis-*epi*-Cladospolide C (8)

To a soln of **8** (1.0 mg) in benzene-d_6 (3.0 mL), I_2 (0.1 mg) was added; the soln was irradiated with 300-nm UV light through a Pyrex filter. After 24 h, a photochemical equilibrium (K_{eq} = 0.3, **2/8**) was established; **8** and **2** were separated by chromatography (silica gel, 50% Et_2O–hexane).

To the other soln of **2** (1.0 mg) in benzene-d_6 (3.0 mL), I_2 (0.1 mg) was added; the soln was irradiated with 300 nm UV light through a Pyrex filter. After 24 h, a photochemical equilibrium (K_{eq} = 6, **2/8**) was established; **8** and **2** were separated by chromatography (silica gel, 50% Et_2O–hexane).

4,5-bis-*epi*-Cladospolide C (8)

R_f = 0.41 (50% Et_2O–hexane).

$[\alpha]_D^{25}$ –13 (*c* 0.1, MeOH).

IR (thin film): 3396, 2937, 2870, 1711, 1464, 1247, 1028 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 6.94 (dd, *J* = 15.6, 6.0 Hz, 1 H), 6.12 (dd, *J* = 15.6, 1.2 Hz, 1 H), 4.96 (dqd, *J* = 6.6, 6.0, 3.0 Hz, 1

H), 4.12 (ddd, *J* = 7.2, 6.0, 1.2 Hz, 1 H), 3.32 (ddd, *J* = 9.6, 7.8, 1.8 Hz, 1 H), 1.74–1.20 (m, 10 H), 1.28 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (150 MHz, CD_3Cl): δ = 167.2, 146.9, 122.5, 78.0, 77.8, 73.1, 33.2, 32.6, 28.3, 25.0, 22.8, 19.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{20}O_4Na$: 251.1254; found: 251.1254.

Cladospolide B (2)

Mp 108–109 °C; R_f = 0.57 (50% Et_2O–hexane).

$[\alpha]_D^{25}$ +24 (*c* 0.1, MeOH).

IR (thin film): 3345, 2934, 2865, 1707, 1461, 1280, 1046 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.23 (dd, *J* = 12.0, 8.4 Hz, 1 H), 5.77 (dd, *J* = 12.0, 1.2 Hz, 1 H), 5.26 (ddd, *J* = 8.4, 4.2, 1.2 Hz, 1 H), 4.88 (dqd, *J* = 10.2, 6.0, 1.8 Hz, 1 H), 3.77 (ddd, *J* = 9.0, 4.2, 2.4 Hz, 1 H), 1.84–1.35 (m, 10 H), 1.28 (d, *J* = 6.0 Hz, 3 H).

^{13}C NMR (150 MHz, CD_3Cl): δ = 165.8, 148.5, 121.9, 74.4, 73.9, 67.5, 32.0, 30.6, 25.7, 24.1, 21.3, 19.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{21}O_4$: 229.1434; found: 229.1435.

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References

(1) (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.

(3) For the synthesis of cladospolide B, see: (a) Pandey, S. K.; Kumar, P. *Tetrahedron Lett.* **2005**, *46*, 6625. (b) Austin, K. A. B.; Banwell, M. G.; Loong, D. T. J.; Rae, A. D.; Willis, A. C. *Org. Biomol. Chem.* **2005**, *3*, 1081. (c) Xing, Y.; O'Doherty, G. A. *Org. Lett.* **2009**, *11*, 1107.

(4) For the synthesis of cladospolide C, see ref. 3c and: (a) Banwell, M. G.; Loong, D. T. J.; Willis, A. C. *Aust. J. Chem.* **2005**, *58*, 511. (b) Chou, C.-Y.; Hou, D.-R. *J. Org. Chem.* **2006**, *71*, 9887. (c) Sharma, G. V. M.; Reddy, K. L.; Reddy, J. J. *Tetrahedron Lett.* **2006**, *47*, 6537. (d) Reddy, C. R.; Rao, N. N. *Tetrahedron Lett.* **2009**, *50*, 2478.

(5) For the synthesis of cladospolide D, see ref. 3c and: Lu, K.-J.; Chen, C.-H.; Hou, D.-R. *Tetrahedron* **2009**, *65*, 225.

(6) 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. For synthetic application of this, see: (c) Hunter, T. J.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 4447. (d) Guo, H.; Mortensen, M. S.; O'Doherty, G. A. *Org. Lett.* **2008**, *10*, 3149. (e) Ahmed, M. d. M.; Mortensen, M. S.; O'Doherty, G. A. *J. Org. Chem.* **2006**, *71*, 7741. (f) Ahmed, M. d. M.; O'Doherty, G. A. *Tetrahedron Lett.* **2005**, *46*, 3015. (g) Ahmed, M. d. M.; Berry, B. P.; Hunter, T. J.; Tomcik, D. J.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 745.

(7) (a) Rychnovsky, S. D.; Kim, J. *J. Org. Chem.* **1994**, *59*, 2659. (b) Trost, B.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933. For synthetic application of this, see: (c) Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 3987.

(8) (a) Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891. (b) Kimmel, T.; Becker, D. *J. Org. Chem.* **1984**, *49*, 2494. For synthetic application of this, see: (c) Hoye, R. C.; Baigorria, A. S.; Danielson, M. E.; Pragman, A. A.; Rajapakse, H. A. *J. Org. Chem.* **1999**, *64*, 2450. (d) Li, M.; O'Doherty, G. A. *Org. Lett.* **2006**, *8*, 6087.

(9) For the Noyori reduction of ynones see: (a) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521. (b) Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40*, 40. For its use in synthesis, see: (c) Guo, H.; O'Doherty, G. A. *Org. Lett.* **2005**, *7*, 3921.

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

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

(12) (a) Luca, L. D.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2001**, *3*, 3041. (b) Ahmed, M. d. M.; Cui, H.; O'Doherty, G. A. *J. Org. Chem.* **2006**, *71*, 6686.

(13) The double bond stereochemistry for four potential diastereomers of cladospolide D **18**–**21** were conclusively assigned by examination of the C2/C3 H–H coupling constants (for the *E*-isomers, **18**, *J* = 16.2 Hz; **19**, *J* = 16.2 Hz; and for the *Z*-isomers **20**, *J* = 13.2 Hz and **21**, *J* = 13.2 Hz).