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Total synthesis of (+)-cladospolide D

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ABSTRACT

The asymmetric total synthesis of cladospolide D, a natural 12-membered macrolide antibiotic, has been accomplished in 12-steps. Sharpless asymmetric dihydroxylation, Grubb's cross metathesis, and Shiina lactonization have been employed as the key reactions for the installation of the desired stereocenter and the construction of the macrolactone framework.

1. Introduction

In 2001, Omura et al. have isolated a new 12-membered γ-oxo-lactone, namely cladospolide D **1**, along with two known cladospolides A **2** and B **3** from the fermentation broth of *Cladosporium* sp. FT-0012.[1] Species belonging to the genus Cladosporium have also produced a family of other fungal secondary metabolites, cladospolides A–C **2–4** and *iso*-cladospolide B **5**, which are plant-growth regulators (Fig. 1).[2] Unlike these members, cladospolide D exhibited antimicrobial properties with IC_{50} values of 0.1 and 29 μg/mL against *Mucor recemosus* and *Pyricularia oryzae*, respectively. Although, the initial structural determination of cladospolide D was carried out during the isolation, the absolute and relative stereochemistry as well the stereochemical assignment of the C2–C3 double bond were correctly determined only after studies on its total synthesis independently by Hou et al.[3] and O'Doherty et al.[4] Later, Kaliappan and Si et al. also achieved the total synthesis of naturally occurring (+)-cladospolide D.[5] In continuation of our research program on the total synthesis of bioactive natural macrolides,[6] in particular the cladospolides,[7] we herein report the asymmetric total synthesis of (+)-cladospolide D **1**.

A retrosynthetic analysis suggests TBS-protected alkenol **7** could be a suitable starting material. Cladospolide D **1** could be prepared by Shiina lactonization of hydroxy acid **6**, which in turn could be obtained from alkenol **7** involving Sharpless asymmetric dihydroxylation for the installation of the C5-hydroxyl group and Grubbs olefin metathesis to obtain the desired C2–C3 olefin functionality of the target molecule. The above reaction sequence has not been utilized previously for the synthesis of cladospolide D (Scheme 1).

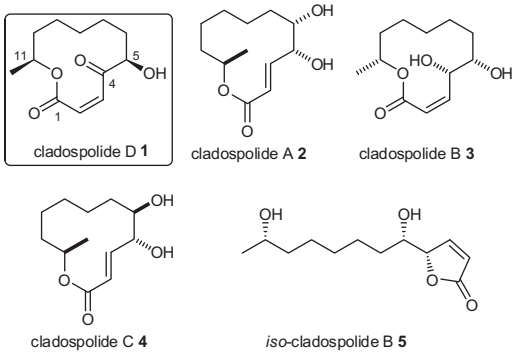
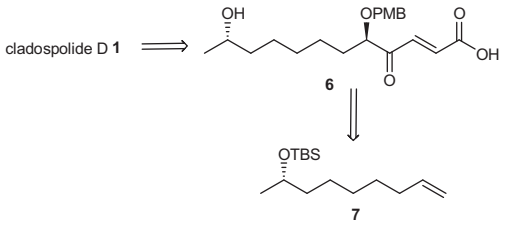


Figure 1. Structures of cladospolides A–D and *iso*-cladospolide.



Scheme 1. Retrosynthetic analysis of cladospolide D **1**.

2. Results and discussion

As shown in Scheme 2, the synthesis of cladospolide D **1** began from the known alkenyl *tert*-butyldimethylsilyl ether **7**, which was obtained readily in two-steps from (*S*)-propylene oxide following

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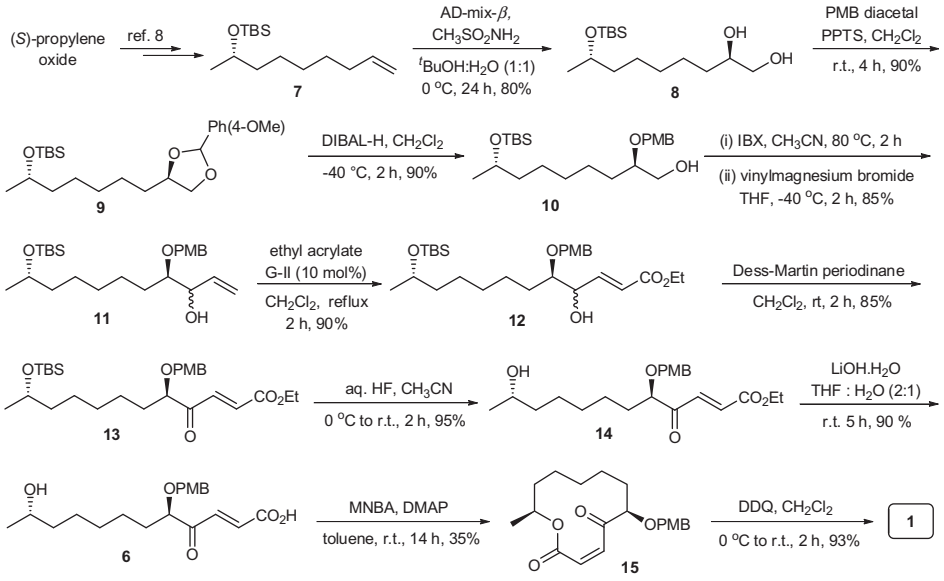

Scheme 2. Synthesis of (+)-cladospolide D **1**.

the literature.[8] Sharpless asymmetric dihydroxylation[9] of alkene **7** with AD-mix-β, $CH_3SO_2NH_2$ and *t*BuOH/H_2O (1:1) gave diol **8** in 80% yield as a separable diastereomeric mixture (95:5). Diol **8** was protected as its *para*-methoxybenzylidene acetal **9** in 90% yield, which was subsequently subjected to reductive opening under DIBAL-H in CH_2Cl_2 at −78 °C to provide the primary alcohol **10** in 81% yield. Primary alcohol **10** was oxidized using IBX in CH_3-CN to give the aldehyde, which upon treatment with vinylmagnesium bromide afforded allylic alcohol **11** as a diastereomeric mixture. To obtain the desired α,β-unsaturated ester, allylic alcohol **11** was subjected to a cross-metathesis reaction with ethyl acrylate using Grubb's second-generation catalyst (G-II),[10] which provided **12** in 90% yield. The hydroxyl group of **12** was oxidized under Dess–Martin periodinane conditions to yield keto-ester **13** in 85% yield. Toward macrolactonization, deprotection of *tert*-butyldimethyl silyl (TBS) was carried out under aq HF in CH_3CN to obtain hydroxy keto-ester **14** in 95% yield. Hydrolysis of the ester group of **14** using LiOH in THF/H_2O gave the hydroxyl acid **6** (90%), a key precursor for macrolactonization. Treatment of **6** under Shiina lactonization[11] with 2-methyl-6-nitrobenzoic anhydride (MNBA) in the presence of DMAP in toluene provided keto-lactone **15** in 35% yield. Finally, DDQ-mediated deprotection of the *para*-methoxy benzyl group of **15** provided the target molecule, cladospolide D, in 93% yield. The spectroscopic data (IR, ^1H and ^{13}C NMR) of **1** were identical and the specific rotation observed for **1**, $[\alpha]_D^{20}$ = +55.5 (*c* 0.8, CH_3OH), is comparable with the reported data {lit: $[\alpha]_D$ = +56.0 (*c* 1.00, CH_3OH)}.[1]

3. Conclusion

In conclusion, the chemistry described herein defines an asymmetric approach for the construction of natural cladospolide D based on a Shiina lactonization strategy involving Sharpless asymmetric dihydroxylation and Grubb's olefin cross metathesis reactions as key steps.

4. Experimental

4.1. General

All reagents and solvents were of reagent grade and used without further purification unless otherwise stated. All of the reactions were performed under N_2 in flame or oven dried glassware with magnetic stirring. Reactions were monitored by thin-layer chromatography carried out on silica plates (silica gel 60 F254, Merck) using UV-light and anisaldehyde or potassium permanganate or β-naphthol for visualization. Column chromatography was performed on silica gel (60–120 mesh) using hexanes and ethyl acetate as eluents. Evaporation of the solvents was conducted under reduced pressure at temperatures less than 45 °C. IR spectra were recorded on Perkin–Elmer 683, Nicolet Nexus 670 spectrometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on a 300 MHz, 500 MHz and 600 MHz NMR spectrometer. Chemical shifts δ and coupling constants *J* are given in ppm (parts per million) and Hz (hertz) respectively. Chemical shifts are reported relative to a residual solvent as an internal standard for ^1H and ^{13}C ($CDCl_3$: δ 7.26 ppm for ^1H and 77.0 ppm for ^{13}C). Mass spectra were obtained on Finnigan MAT1020B, micromass VG 70–70H or LC/MSD trapSL spectrometer operating at 70 eV using direct inlet system. Optical rotations were measured on an Anton Paar MLP 200 modular circular digital polarimeter by using a 2-mL cell with a path length of 1 dm.

4.1.1. (2*R*,8*S*)-8-((*tert*-Butyldimethylsilyl)oxy)nonane-1,2-diol 8

To a 500 mL round bottom flask, were added 85 mL of *t*BuOH, 85 mL of H_2O and AD-mix-β (27.3 g, 1.4 g/mmol) and methane sulfonamide (2.6 g, 19.5 mmol). The mixture was stirred at room temperature for 5 min, then cooled to 0 °C. To this cooled solution, was added compound **7** (5 g, 19.5 mmol) and stirred for 24 h at 0 °C. The reaction was quenched with saturated sodium sulfite at room temperature. The mixture was diluted with EtOAc (50 mL) and after separation of the layers, the aqueous layer was further extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine solution (40 mL) and dried over Na_2SO_4. The crude mixture was purified by column chromatography (silica gel, 20% → 30% EtOAc in hexanes) to give compound **8** (4.37 g, 80% yield) as a clear colorless oil. $[\alpha]_D^{25}$ = +4.4 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 3.84–3.51 (m, 3H), 3.37 (dt, *J* = 37.7, 18.8 Hz, 1H), 2.27–2.03 (m, 2H), 1.59–1.14 (m, 10H), 1.07 (d, *J* = 6.1 Hz, 3H), 0.84 (s, 9H), 0.00 (s, 3H), −0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 72.3, 68.64, 66.9, 39.6, 33.2, 29.7, 25.9, 25.6, 23.8, 21.9, 18.2, −4.4, −4.7; IR (KBr): 3365, 2932, 2858, 1464, 1374, 1253, 1134, 1066, 835, 774 cm^{-1}; MS (ESI): *m*/*z* 313 $(M+Na)^+$; HRMS (ESI): *m*/*z* calcd for $C_{15}H_{34}NaO_3Si$ $(M+Na)^+$: 313.2168, found: 313.2181.