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Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: https://www.tandfonline.com/loi/lsyc20

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To cite this article: Chiranjeevi Kalavakuntla, Vijaya Babu Kummari & Jhillu Singh Yadav (2019): An alternative total synthesis of diplodialide-B, Synthetic Communications, DOI: 10.1080/00397911.2019.1663541

To link to this article: https://doi.org/10.1080/00397911.2019.1663541

SYNTHETIC COMMUNICATIONS®
https://doi.org/10.1080/00397911.2019.1663541

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An alternative total synthesis of diplodialide-B

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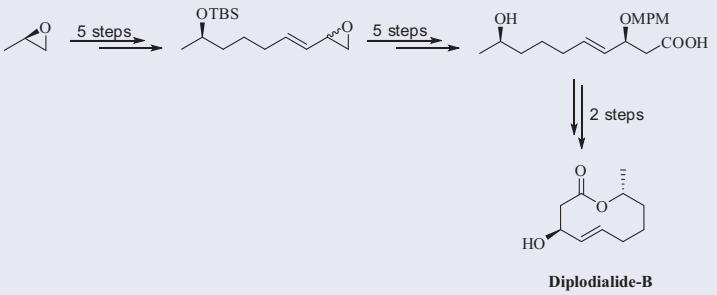
ABSTRACT

In this paper, an enantioselective synthesis of diplodialide-B has been described. To accomplish this target, a combination of regioselective ring opening of the chiral epoxide, Jacobsen hydrolytic kinetic resolution and Yamaguchi macrolactonization were used as the key steps.

GRAPHICAL ABSTRACT



Diplodialide-B

ARTICLE HISTORY
Received 29 June 2019

KEYWORDS
Diplodialide-B; Jacobsen hydrolytic kinetic resolution; (R)-propylene oxide; stereoselective synthesis; Yamaguchi macrolactonization

Introduction

Naturally occurring 10-membered ring lactones, commonly known as decanolides, have attracted considerable attention from synthetic organic chemists as well as bioorganic chemists, because of their interesting structural features and various biological activities such as plant growth inhibition and anti-feedant, anti-fungal and anti-bacterial activities.

Diplodialides A (**1a**), B (**1b**), C (**1c**), and D (**1d**) (Figure 1) are the naturally occurring ten-membered monocyclic ring lactones, which were isolated from the plant pathogenic fungus *Diplodiapinea* (IFO 6472) by Wada and Ishida[1,2]. The absolute stereochemistry of diplodialides (9 R)-**1a**, (3S,9R)-**1b**, and (3 R,9R)-**1c** was determined by Wada and Ishida[3].

Due to the promising biological activity and the impressive structural features, diplodialides appeared to be attractive targets for total synthesis. To date, several approaches to the synthesis of diplodialides have been reported[4]. As a part of our interest in the

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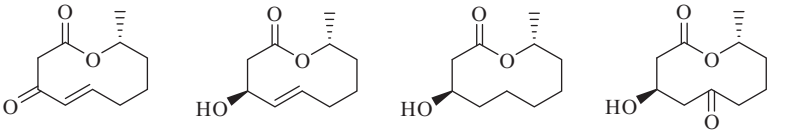
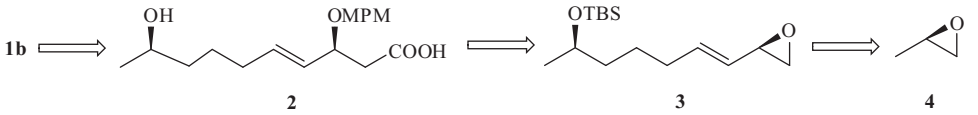


Figure 1. Structure of diplodialides.



Scheme 1. Retrosynthetic analysis of diplodialide-B (**1b**).

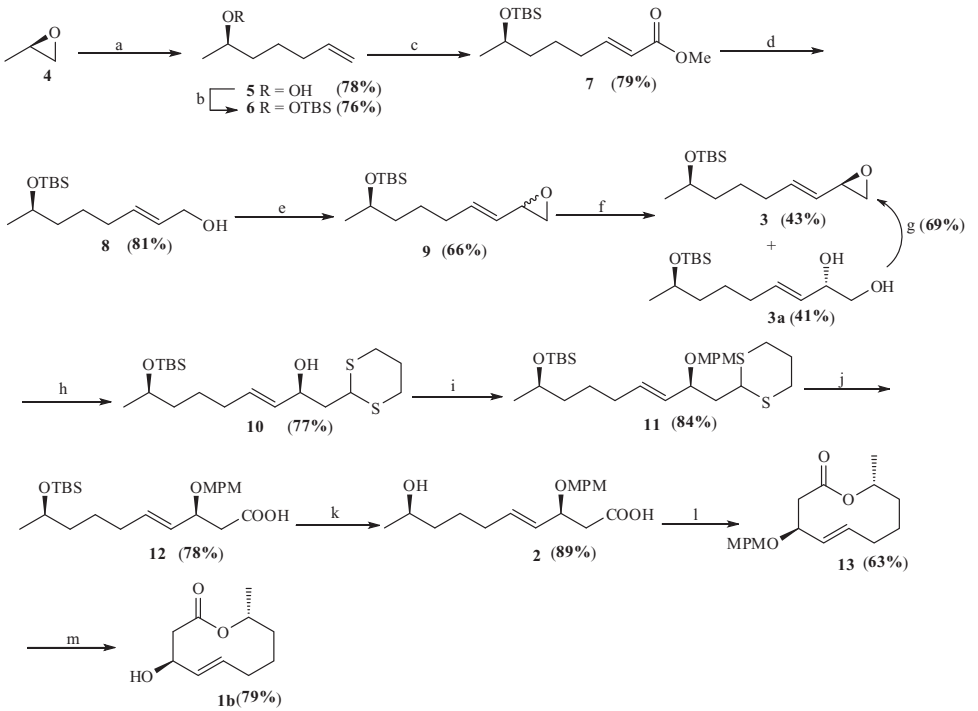
total synthesis of macrolides, herein, we report an efficient and alternate route to the total synthesis of diplodialide-B starting from (R)-Propylene oxide. In our approach, Jacobsen hydrolytic kinetic resolution and Yamaguchi macrolactonisation have been utilized as the key steps.

Results and discussion

Retrosynthetic analysis of the target molecule has been depicted in Scheme 1. Target molecule could be obtained from hydroxy-acid **2** using Yamaguchi macrolactonisation conditions followed by deprotection of 4-methoxybenzyl ether. While compound **2** could be accessed from chiral epoxide **3**. Compound **3** could be synthesized from known chiral epoxide **4** (Scheme 1).

Synthesis of diplodialide-B (**2**) began with known epoxide **4** (Scheme 2)[5]. Regioselective ring opening of chiral epoxide **4** with Grignard reagent in dry ether at −78 °C gave secondary alcohol **5** in 78% yield, which on subsequent masking of the hydroxyl group in **5** with TBSCl in CH_2Cl_2 in the presence of imidazole afforded silyl ether **6** in 76% yield. Next the double bond in silyl ether **6** was subjected to Ozonolysis to give corresponding aldehyde, which upon subsequent Wittig olefination with (methoxycarbonylmethylene)triphenyl phosphorane in benzene under reflux yielded desired (*E*) α,β-unsaturated ester **7** in 79% yield. The E-geometry of the double bond was confirmed by coupling constant between the respective olefin protons ($J = 15.6$ Hz). Further, selective reduction of the ester **7** with DIBAL-H in CH_2Cl_2 gave allylic alcohol **8** in 81% yield. Swern Oxidation of the alcohol **8** gave the corresponding aldehyde, which on subsequent treatment with trimethylsulfonium iodide,[6] NaH and DMSO in THF afforded the corresponding epoxide **9** as a diastereomeric mixture in 66% yield. Later, hydrolytic kinetic resolution[7] of the epoxide **9** using Jacobsen reagent (*R,R*)-(+)-*N,N′*-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane diaminocobalt (II) afforded chiral epoxide **3** and diol **3a,** which was easily separated by column chromatography.

Diol **3a** was recycled to **3** by a three-step sequence. Thus, **3a** was mono-benzoylated ($BzCl/Et_3N/CH_2Cl_2/0$ °C-rt) followed by tosylation of the secondary hydroxyl ($TsCl/Et_3N/CH_2Cl_2/0$ °C-rt) to give the diprotected compound. which, on further reaction with K_2CO_3 in methanol furnished the desired epoxide **3** with **69**% yield (for 3 steps).



Scheme 2. Synthesis of diplodialide-B (**1b**). *Reagents and conditions*: (a) homoallyl bromide, Mg, dry ether, −78 °C, 2 h; (b) TBSCl, Imidazole, CH_2Cl_2, rt, 4 h; (c) (i) O_3, CH_2Cl_2, −78 °C, 30 min; (ii) $Ph_3P=CHCOOMe$, Benzene, reflux, 2 h; (d) DIBAL-H, CH_2Cl_2, −78 °C, 2 h; (e) (i) $(COCl)_2$, DMSO, −78 °C, Et_3N, CH_2Cl_2, (ii) Trimethylsulfonium iodide, DMSO, NaH, THF, 75 °C to −5 °C, 4 h.; (f) (*R*,*R*)-salen-Co-(OAc) (0.5 mol %), distd H_2O (0.55 equiv.), 0 °C, 13 h; (g) (i) BzCl, Et_3N, CH_2Cl_2, 0 °C-rt, 3 h (ii) p-TsCl, Et_3N, CH_2Cl_2, 0 °C-rt, 2 h; (iii) K_2CO_3, MeOH, 0 °C-rt, 1 h; (h) 1,3-dithiane, *n*-BuLi, dry THF, 4 °C, 3 h; (i) PMBBr, NaH, THF, 25 °C, 8 h; (j) $CaCO_3$, MeI, CH_3CN:H_2O (9:1), rt, 19 h; (ii) NaH_2PO_4, $NaClO_2$, MeCN, H_2O, 2-methyl-2-butene, rt, 3 h; (k) TBAF, THF, 0 °C to rt, 3 h; (l) (i) 2,4,6-trichlorobenzoyl chloride, Et_3N, dry THF, rt, 2 h; (ii) DMAP, toluene, 90 °C, 10 h; (m) DDQ, CH_2Cl_2:H_2O (19:1), rt, 3 h.

Next, Regioselective ring opening of chiral epoxide **3** in the presence of an anion derived from 1,3-dithane yielded compound **10** in 77% yield, which on subsequent protection with PMB-Br, NaH in dry THF gave **11** in 84% yield. Hydrolysis of the dithane group in **11** afforded aldehyde, which was converted into acid **12** by using NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene in CH_3CN:H_2O (1:1) (Pinnick's oxidation) at room temperature with **78**% yield[4f]. Desilylation of the acid **12** with TBAF in dry THF afforded the hydroxy-acid **2** in **89**% yield.

Next, hydroxy-acid **2** was subjected to macrolactonisation under Yamaguchi high dilution conditions[8] using 2,4,6-trichlorobenzoyl chloride and Et_3N in dry THF to afford the lactone **13** in 63% yield. Finally, PMB ether was deprotected using DDQ in CH_2Cl_2:H_2O (19:1) for 3 h to afford the diplodialide-B (**1b**) in 79% yield. The spectral and analytical data of synthetic diplodialide B (**1b**) were in good agreement with the reported values in the literature.[3] Thus, we accomplished the total synthesis of diplodialide-B in an enantioselective way.

Experimental section

Diplodialide-B (1b)

To a solution of **13** (0.1 g, 0.32 mmol) in aq. CH_2Cl_2 (2 mL, 19:1), DDQ (0.11 g, 0.49 mmol) was added and stirred at room temperature for 3 h. The reaction mixture was quenched with sat. $NaHCO_3$ solution (1 mL), filtered and washed with CH_2Cl_2 (10 mL). The filtrate was washed with water (3 mL), brine (3 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (60–120 Silica gel, 18% EtOAc in pet. ether) to furnish **1b** (47 mg, 79%) as colorless sirup. $[\alpha]_D^{28} = -40.1$ (*c* 0.6, $CHCl_3$); (Lit $[\alpha]_D^{28} = -37.3$ (*c* 0.93, $CHCl_3$)) ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.51 (m, 1 H), 5.42 (m, 1 H, H-5), 4.79–4.68 (m, 1 H), 4.51–4.41 (m, 1 H), 2.70 (dd, 1 H, $J = 7.3$, 15.7 Hz), 2.37 (dd, 1 H, $J = 3.7$, 7.3 Hz), 2.03 (m, 2 H), 1.88–1.44 (m, 4 H), 1.33 (bs, 1 H, –OH), 1.20 (d, 3 H, $J = 6.8$ Hz); ^{13}C NMR ($CDCl_3$, 300 MHz): δ 169.0, 132.1, 128.4, 72.2, 67.0, 44.4, 35.6, 33.4, 27.3, 21.0; IR (Neat): 3551, 1726, 1233, 1158, 971 cm^{-1}. HRMS *m/z* $[M + Na]^+$: calculated for $C_{10}H_{16}O_3Na$, 207.0997; found: 207.0991.

Conclusions

In conclusion, a stereoselective total synthesis of diplodialide-B was accomplished in 12 steps with an overall yield of 3.97%. A combination of Jacobsen's hydrolytic kinetic resolution, regioselective ring opening of epoxide and Yamaguchi macrolactonisation were used as the key steps.

Full experimental details, spectral data of the products, ^{1}H NMR and ^{13}C NMR of all the new compounds can be found via the Supplementary Content section of this article's Web page.

Acknowledgments

The authors are thankful to CSIR-Indian Institute of Chemical Technology, Hyderabad and CSIR, New Delhi for constant encouragement in providing laboratory facilities and analytical data.

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