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Stereoselective synthesis of (3*R*,6*S*)-6-hydroxylasiodiplodin

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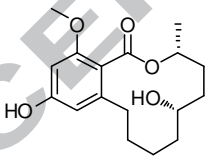
ABSTRACT

The first stereoselective synthesis of polyketide natural product (3*R*,6*S*)-6-hydroxylasiodiplodin (**1**) has been described starting from commonly available starting materials D-mannitol and 2,4,6-trihydroxybenzoic acid. The key reactions involved are Keck asymmetric allylation, Stille coupling, De Brabander's esterification and Ring - closing metathesis (RCM) reaction. The total synthesis was achieved in 19.3% overall yield making the route significant.

Introduction

Resorcylic acid lactones (RALs) are an important class of natural products with a wide range of biological activities[1] and majority of these lactones are 14-membered. However, 12-membered RALs (RAL_{12}) have also been known since the first isolation of lasiodiplodin and de-O-methyl-lasiodiplodin in 1971,[2] followed by resorcylide in1978.[3] Since then, nearly about thirty RAL_{12} have been isolated from various sources. Lasiodiplodins show broad spectrum of biological activities such as proliferation function of primary osteoblasts (OBs) *in vitro*,[4] inhibition of prostaglandin biosynthesis,[5] potent anti-leukemic activity,[6] cytotoxic,[7] potent nonsteroidal antagonist of the mineralocorticoid receptor (MR),[8] anti-microbial activity,[9] potato micro-tuber inducing activities,[10] plant-gowth inhibitor[2] and also act as a Hill reaction inhibitor.[11] Recently, this family of compounds have been reported to exhibit α-glucosidase inhibitory activity.[12] Compound (3*R*,6*S*)-6-hydroxylasiodiplodin **1** (Figure 1) was isolated by Takahashi and co-workers from *Lasiodiplodia theobromae*[13] which is a common pathogenic fungus found in tropic and subtropical region. The structure of **1** was determined by means of spectroscopic analyses, modified Mosher's method and chemical conversion.[13] The compound **1** showed in particular potato micro tuber inducing activity at a concentration of 10^{-4}M.



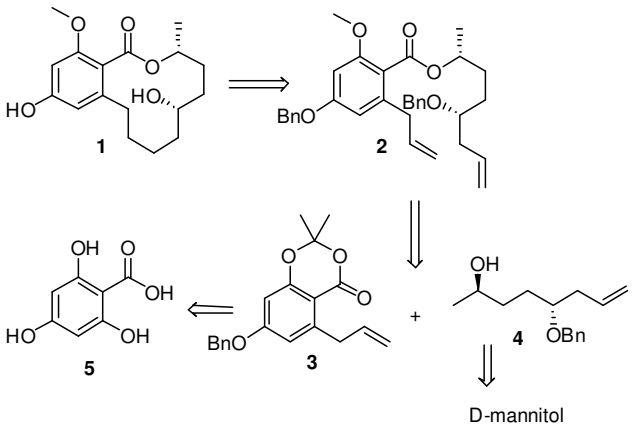


Figure 1: Structure of (3*R*,6*S*)-6-hydroxylasiodiplodin (**1**)

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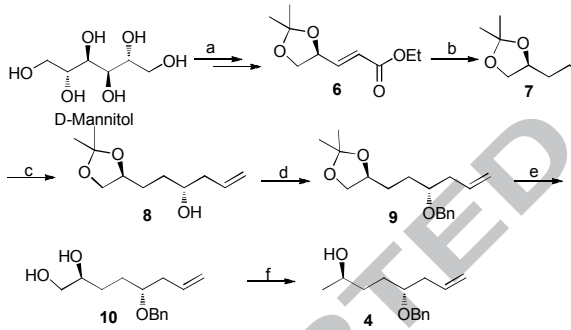
Our continued interest in the synthesis of bioactive natural products[14] coupled with interesting biological activities of these classes of compounds prompted us to synthesize 1. Herein, we report the first stereoselective total synthesis of (3*R*,6*S*)-6-hydoxylasiodiplodin (**1**) using Keck asymmetric allylation, Stille coupling, De Brabander's esterification and RCM reaction from D-mannitol and 2,4,6-trihydroxybenzoic acid.

Results and Discussion:

Our retrosynthetic analysis is depicted in Scheme 1. Accordingly, **1** could be achieved under RCM reaction condition with compound **2** which in turn could be visualized to be obtained by the coupling of lactone **3** and the secondary alcohol **4**. Lactone **3** and alcohol **4** could be obtained from 2,4,6- trihydroxybenzoic acid (**5**) and D-mannitol respectively using general reaction protocols.

Scheme 1: Retrosynthetic analysis of compound **1**

'The total synthesis began with first synthesizing the aliphatic subunit **4** from cheap and commercially available D-mannitol.' (Scheme 2). The known α,β-unsaturated ester **6** was prepared from D-mannitol using well known literature procedure.[15] The double bond as well as the ester were reduced with $NaBH_4$/LiCl to give saturated alcohol **7** in 82% yield.[16] The primary alcohol **7** was efficiently oxidized with IBX (2-Iodoxybenzoic acid) in DMSO/THF at ambient temperature to provide the expected aldehyde, which upon treatment under Keck asymmetric allylation conditions {allyl tributyltin, (*S*)-BINOL, [(*S*)-(-)-1,1'-Bi (2-naphthol)] $Ti(O^iPr_4)$, 4Å MS, dry CH_2Cl_2, -78 °C to -20 °C} furnished the desired homo allylic alcohol **8** in 79% over two steps.[17] The absolute stereochemistry of the newly generated stereogenic center in compound **8** bearing the hydroxyl group was determined by preparing the (*S*) and (*R*)-MTPA esters [prepared by using MTPA (Methoxytrifluoromethylphenylaceticacid) with DCC as the coupling reagent] by modified Mosher's method[18] and was found to have *R* configuration by studying their ^{1}H NMR spectra (Figure 2) .The negative chemical shift difference to the left side of the MTPA plane and the positive chemical shift to the right side of the MTPA plane indicated that the hydroxyl stereochemistry has *R* configuration.



Scheme 2: Reagents and conditions: a) ref. 15 b) $NaBH_4$:LiCl (1:1), THF:EtOH (1:1), 0 °C to rt, 48 h, 82%; c) (1) IBX, DMSO/THF, 20 °C, 4 h; (2) (*S*)-BINOL, $Ti(O^iPr_4)$, , 4 Å molecular sieves, allyl tributyltin, CH_2Cl_2, -78 °C then -20 °C , 79% over two steps; d) NaH, BnBr, THF, 0 °C to rt, 6 h, 89%; e) 60% AcOH in water, rt, overnight, 87%; f) (1) *p*-TsCl, Et_3N, n-Bu_2SnO, CH_2Cl_2, 0 °C to rt, 30 min; (2) $LiAlH_4$, THF, 0 °C to rt, 30 min, 74% over two steps.

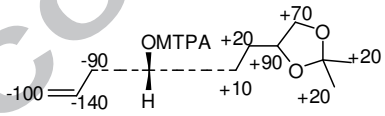
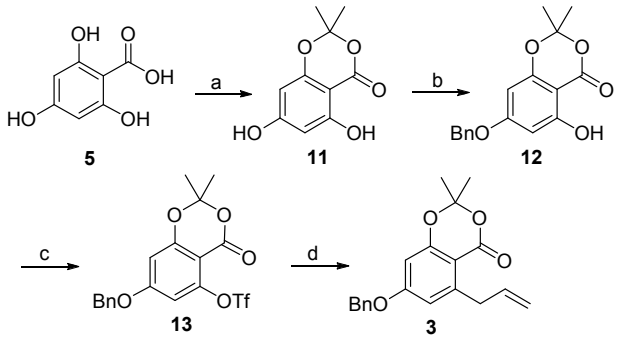


Figure 2: Determination of absolute configuration and Δδ values for the (*S*) and (*R*) –MTPA ester derivatives of **8** ($\Delta\delta=\delta_S-\delta_R$) x 10^3.

The homoallylic alcohol **8** was then protected as its benzyl ether using benzyl bromide in the presence of NaH in THF to afford the corresponding benzyl ether **9** in 89% yield (≥98 *dr* based on HPLC).[19] The isopropylidine protection was removed using 60% AcOH in water to afford the desired 1,2-diol **10** in 87% yield. A regioselective tosylation of the primary hydroxyl group in **10** was achieved through dibutylstanylene acetal[20] and subsequent reduction with $LiAlH_4$ gave alcohol **4** in 74% yield over two steps.

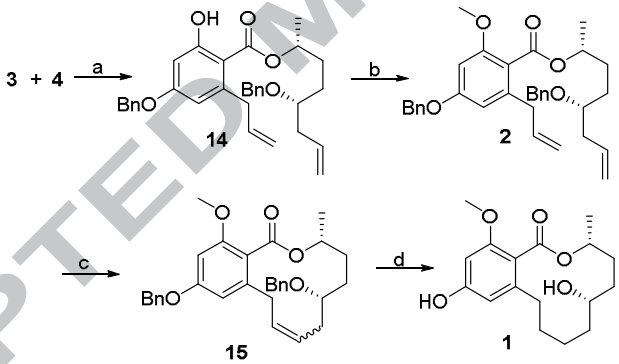
The aromatic coupling partner (**3**) was prepared starting from readily available 2,4,6-trihyroxybenzoic acid monohydrate (**5**) , which was converted into its corresponding acetonide protected compound **11** using Danishefsky's modified protocol[21] (trifluoroacetic acid (TFA), trifluoroacetic anhydride (TFAA) and acetone) in 60% yield (Scheme 3). Regioselective protection of 4-hydroxy group

as its benzyl ether was achieved under Mitsunobu conditions [PPh_3 and DIAD (Diisopropyl azodicarboxylate)] to obtain compound **12** in 88% yield.[22] Compound **12** was converted into its corresponding triflate **13** using trifluoromethanesulfonic anhydride in the presence of pyridine in 92% yield[23] which was then subjected to Pd-catalysed Stille coupling with allylstannane in the presence of LiCl gave the compound **3** in 72% yield.[24]



Scheme 3: Reagents and conditions: a) TFA, TFAA, acetone, 0 °C to rt, 48 h, 60%; b) PPh_3, DIAD, BnOH, THF, 0 °C to rt, 3 h, 88%; c) Tf_2O, pyridine, CH_2Cl_2, 0 °C to rt, 4 h, 92%; d) allyltributyltin, LiCl, $Pd(PPh_3)_4$, DMF, 60 °C, 8 h, 72%.

After successfully synthesizing the two fragments **3** and **4**, we next focused to couple them to form an entire frame work. Accordingly, compounds **3** and **4** were subjected to De Brabander's esterification conditions[25] (NaH, THF, 0 °C - r.t.) for to the formation of the desired ester **14** in 84% yield (Scheme 4). Free *ortho*-phenolic group present in **14** was methylated using dimethyl sulphate and K_2CO_3 in acetone to obtain compound **2** in 92% yield.[26] Then, diene **2** was treated with 5 mol% of Grubbs second generation catalyst under dilute conditions to give the required lactone **15** as a mixture of an *E*/*Z* in 83% yield. The newly formed double bond after RCM, would be of no importance as it would be saturated in the later stage of the synthesis. Finally, deprotection of the two benzyl groups as well as the saturation of the double bond in compound **15** was achieved using Pd/C to provide the target compound **1** in 81% yield. The spectral data (^1H, ^{13}C and MS) and optical rotation of the thus synthesized target compound were in good agreement with the reported values of the natural product **1**. The optical rotation of **1** showed +10.0 (c = 0.1, MeOH) compared to reported value +12 (c = 0.1, MeOH).[13, 27]



Scheme 4: Reagents and conditions: a) NaH, THF, 0 °C to rt, 6 h, 84%; b) K_2CO_3, $(CH_3)_2SO_4$, Dry acetone, reflux, 6 h, 92%; c) Grubbs II catalyst (5 mol%), CH_2Cl_2, reflux, 4 h, 83%; d) 10% Pd/C, EtOAc, 6 h, 81%.

In conclusion, we have successfully accomplished the first stereoselective synthesis of (3*R*,6*S*)-6-hydroxylasiodiplodin (**1**) by employing Keck asymmetric allylation, Stille coupling, De Brabander's esterification and RCM reaction in 9 longest linear steps with an overall yield of 19.3% starting from **6**. The facile reaction protocol opens up the scope of the current synthesis in larger quantities for screening purposes and biological studies.

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Supporting Information:
Supplementary data associated with this article can be found, in the online version.

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27 **(3*R*,6*S*)-6-hydoxylasiodiplodin (1):** Mp = 230-234; $[\alpha]_D^{27}$ = +10.0 (c = 0.1, MeOH); IR (KBr): 3371, 3132, 2951, 1677, 1604, 1467, 1435, 1348, 1271, 1167, 1081, 845 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 1.15-1.06 (m, 2H), 1.22 (d, J = 6.1 Hz, 3H), 1.28-1.24 (m, 1H), 1.66-1.42 (m, 6H), 1.98-1.91 (m, 1H), 2.41-2.32 (m, 1H), 2.49-2.45 (m, 1H), 3.62-3.55 (m, 1H), 3.69 (s, 3H), 4.34 (d, J = 4.5 Hz, 1H), 5.16-5.06 (m, 1H), 6.22 (br s, 1H), 6.26 (br s, 1H), 9.69 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 18.8, 22.6, 28.4, 29.3, 29.4, 29.8, 32.3, 55.7, 68.7, 71.3, 97.0, 107.8, 116.1, 141.8, 157.4, 159.2, 167.9; MS (ESI): m/z = 309 $(M+H)^+$; HRMS (ESI): calcd. for $C_{17}H_{25}O_5$ $(M+H)^+$ 309.1696, found 309.1689.

Graphical Abstract

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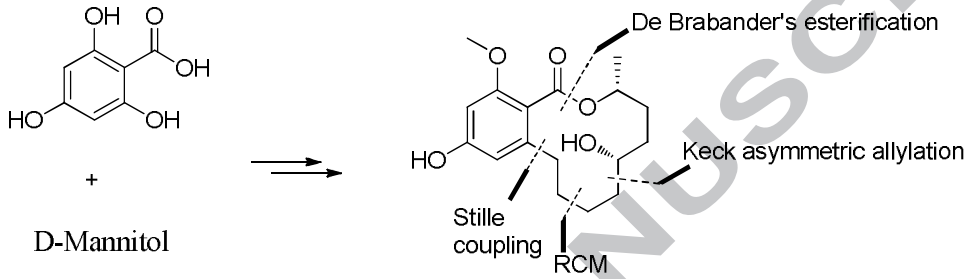
Sheshurao Bujaranipalli and Saibal Das*



HIGHTLIGHTS

- First stereoselective synthesis of natural product (3*R*,6*S*)-6-hydroxylasiodiplodin has been achieved.
- The total synthesis was achieved in 19.3% overall yield
- Commonly available starting materials D-mannitol and 2,4,6-trihydroxybenzoic acid have been utilized.