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The first stereo selective total synthesis of (3*R*),(5*R*)-5-hydroxy-de-*O*-methyllasiodiplodin and its epimer via a RCM protocol

J. S. Yadav *, Saibal Das, J. Satyanarayana Reddy, N. Thrimurtulu, A. R. Prasad

Organic Division-1, Indian Institute of Chemical Technology (CSIR), Tarnaka, Hyderabad 500 607, India

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ABSTRACT

The first total synthesis of (3*R*),(5*R*)-5-hydroxy-de-*O*-methyllasiodiplodin and its epimer is reported from malic acid. The adopted approach is highly convergent and stereoselective. The strategy utilizes *syn* selective reduction and ring-closing metathesis as key steps.

Lasiodiplodin and its family are identified to be very efficient inhibitors of prostaglandin biosynthesis, and exhibit significant anti-leukemic and potato micro-tuber inducing activities.[1] The hydroxyl-lasiodiplodins were isolated from the mycelium extracts of a fungus where Lasiodiplodia theobromae IFO 31059, and their structures were acknowledged as (3*R*),(5*R*)-5-hydroxy-de-*O*-methyllasiodiplodin **(1)**, (3*R*),(4*S*)-4-hydroxylasiodiplodin **(3)** and (3*R*),(6*R*)-6-hydroxy-de-*O*-methyllasiodiplodin **(4)**[2] which was found to implement strong potato micro-tuber inducing activity in the growth of higher plants and produces various organic metabolites[3] where earlier reports also revealed the presence of some biologically active compounds from IFO 31059 namely jasmonic acid, mellein, theobroxide, and 5-hydroxy lasiodiplodins[3] (**2a**/**2b**) (Fig. 1). And lately it has also been reported to show antimicrobial activities.[4]

Considering the growing importance of this family of compounds and our ongoing interest in the total synthesis of biologically active natural products, herein we report the first total synthesis of (3*R*),(5*R*)-5-hydroxy-de-*O*-methyllasiodiplodin **(1)** and (3*R*),(5*S*)-5-hydroxy-de-*O*-methyllasiodiplodin **(2)**, its epimer. The strategy involves *syn*-stereoselective 1,3-asymmetric reduction and ring-closing metathesis as the key steps, utilizing a very common and inexpensive starting material, L-malic acid (Scheme 1).

Accordingly, (3*R*),(5*R*)-5-hydroxy-de-*O*-methyllasiodiplodin (**1**) and (3*R*),(5*S*)-5-hydroxy-de-*O*-methyllasiodiplodin (**2**) were prepared from **5**, which was obtained using classical chemistry from L-malic acid.[5] Compound **5** was then transformed into its Weinreb amide **6** in 90% excellent yield, under the conditions defined by Williams et al.,[6] after which it was treated with homoallylmagnesium bromide to afford the corresponding homoallylic ketone **7**[7] in 78% yield. Compound **7** was then subjected to *syn* selective 1,3-asymmetric reduction following the method of Mori et al. using $LiAlH_4$–LiI[8] in ether, *anti*:*syn* diols were obtained in the ratio of 30(**8**):70(**9**) with 92% yield. Both the isomers were easily separated and taken forward towards the desired target (Scheme 2).

Secondary alcohols **8** and **9**, thus obtained were protected to its benzyl ethers **10** and **11**, respectively to undergo acid-catalyzed hydrolysis in aqueous methanol, to furnish the corresponding diols **12** and **13** in excellent yields. Then chemoselective tosylation of terminal alcohols provided the mono-tosylated compounds, which upon treatment with LAH[9] furnished the required secondary alcohols **14** and **15** in 70–73% yield to be utilized for esterification (Scheme 3).

Having both the intermediate alcohols **14**[10] and **15**[11] in hand for synthesizing **1** and **2**, respectively, we then focused our interest towards the synthesis of required intermediate **20** (Scheme 4) starting from readily available 2,4,6-trihydroxy benzoic acid, which furnished compound **16** in good yields (75%) under classical

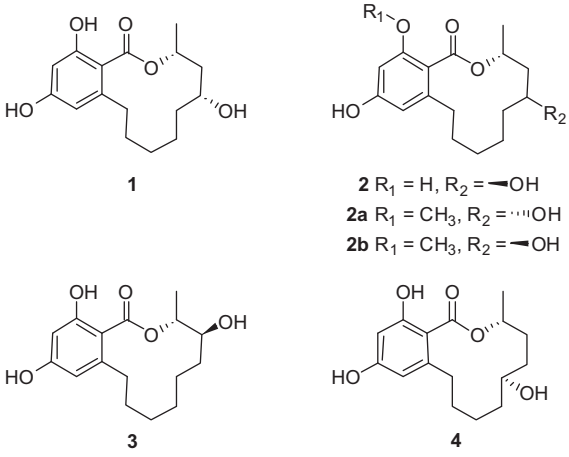

Figure 1. Molecules from Lasiodiplodin family.

* Corresponding author. Tel.: +91 40 2716 3030; fax: +91 40 2716 0387.
E-mail addresses: yadavpub@iict.res.in, saibal.sky007@gmail.com (J.S. Yadav).

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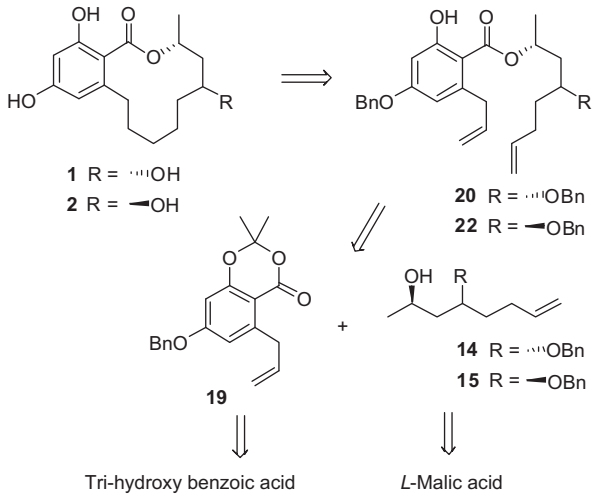
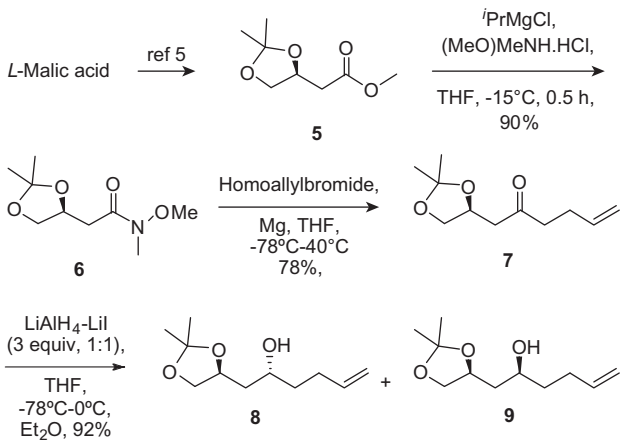
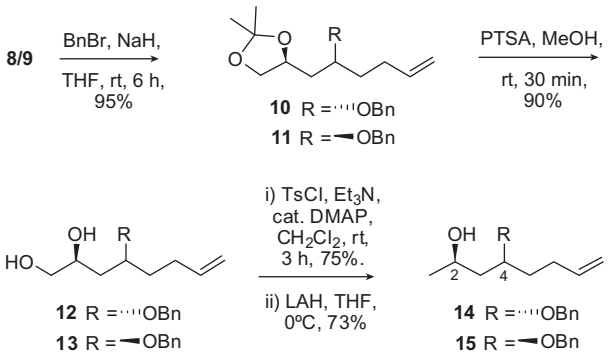


Scheme 1. Retro synthesis of 5-hydroxy-de-*O*-methyllasioplodins.

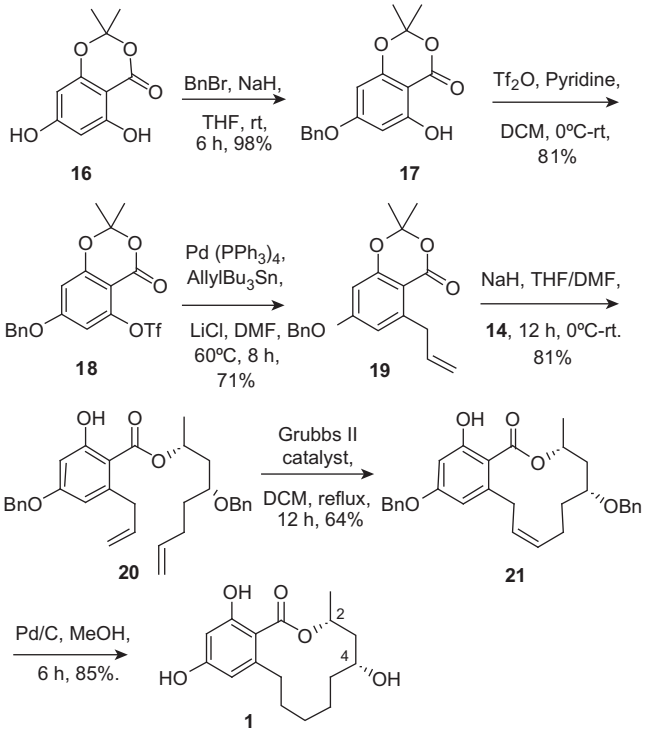


Scheme 2.

reaction conditions.[12] Selective O-benzylation of **16** produced **17** under mild conditions with an excellent yield of 98%. The aromatic alcohol **17** was then treated with Tf_2O to obtain **18**[13] in 81% yield, which upon Pd-catalyzed Stille coupling[14] with allylstannane in the presence of LiCl yielded the desired product **19** in 71% yield. Compound **19** was then treated with formerly prepared alcohol **14**, which was deprotonated in situ with NaH to obtain the alkoxide anion for the esterification to afford the required diene[12] **20** in



Scheme 3.

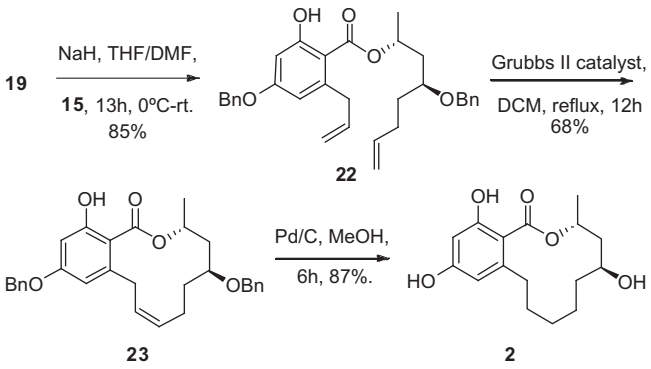


Scheme 4.

81% yield. Then diene **20** was engaged for the key RCM reaction with 5 mol % Grubb's II catalyst under high dilution conditions[15] (0.001 M in DCM) to afford the cyclic ester **21** in 64% yield, which was further reacted with Pd/C in methanol to deliver the desired compound **1** in 85% yield, wherein, benzyl deprotection along with the reduction of the olefin was accomplished in single step. The spectral data of thus synthesized compound **1**[16] was in agreement with the natural product[2] and was further confirmed by NOE experiment by irradiation of proton present at position 2, also validating the **14** as *anti*-diol and **15** as *syn*-diol at 2 and 4 positions.

It is noteworthy that the crucial esterification[12] of alcohols **14** and **15** to furnish the desired dienes **20** and **22**, respectively, which were obtained using diluted solution of compound **19** in dry THF/DMF (1:1) with moderate yield.

Once esterification furnished compound **22**, was then treated with 5 mol % Grubb's II catalyst under high diluted conditions (0.001 M in DCM)[15] to afford the lactone **23** in 68% yield, which upon treatment with palladium on carbon provided the desired compound **2**[17] in 87% yield (Scheme 5).



Scheme 5.

In summary, we have demonstrated for the first time a simple and concise total synthesis of (3*R*),(5*R*)-5-hydroxy-de-*O*-methyllasiodiplodin **1** and its epimer **2** employing ring-closing metathesis strategy, wherein L-malic acid was engaged as the common and inexpensive starting material towards the access of both the desired compound.

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10. *Spectral data* (**14**): (2*R*,4*R*)-4-(benzyloxy)oct-7-en-2-ol, a light yellow syrup. $[\alpha]_D^{25} = -18.2$ (*c* 0.9, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz): δ 7.32–7.22 (m, 5H), 5.84–5.69 (m, 1H), 5.03–4.91 (m, 2H), 4.52 (s, 2H), 4.12–4.0 (m, 1H), 3.72–3.63 (m, 1H), 2.1 (q, 2H, *J* = 6.8, 14.3 Hz), 1.85–1.50 (m, 4H), 1.15 (d, 3H, *J* = 6.3 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.2, 128.4, 127.9, 127.7, 114.7, 76.5, 71.1, 64.6, 41.3, 32.6, 29.6, 23.6. IR (neat): *v* 3440, 3072, 2929, 2858, 1738, 1641, 1461, 1253, 1084 cm^{-1}. MS (LCMS): *m/z* 257 $[M+23]^+$.
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16. *Spectral data* (**1**): (3*R*),(5*R*)-5-hydroxy-de-*O*-methyllasiodiplodin, white powder (mp: 150–155 °C). $[\alpha]_D^{25} = +19.1$ (*c* 1.1, MeOH); ^1H NMR (CD_3OD, 300 MHz): δ 6.18 (d, 1H, *J* = 2.45 Hz), 6.12 (d, 1H, *J* = 2.6 Hz) 5.24–5.04 (m, 1H), 4.05–3.94 (m, 1H), 3.78–3.60 (m, 1H), 2.31–2.18 (m, 1H), 2.12–1.95 (m, 1H), 1.85–1.44 (m, 7H) 1.35 (d, 3H, *J* = 6.04). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.1, 166.6, 163.8, 150.1, 112.2, 105.0, 101.9, 73.3, 70.7, 62.2, 41.9, 35.7, 35.1, 33.0, 29.1, 21.7, 19.5. IR (neat): *v* 3432, 2926, 2856, 1640, 1459, 1259, 1169, 1024 cm^{-1}. MS (LCMS): *m/z* 295 $[M+1]^+$.
17. *Spectral data* (**2**): (3*R*),(5*S*)-5-hydroxy-de-*O*-methyllasiodiplodin, white powder (mp: 130–135 °C). $[\alpha]_D^{25} = +15$ (*c* 0.3, MeOH); ^1H NMR ($CDCl_3$, 200 MHz): δ 11.79 (s, 1H), 6.27 (d, 1H, *J* = 2.6 Hz), 6.22 (d, 1H, *J* = 2.64 Hz) 5.56–5.45 (m, 1H), 4.04–3.95 (m, 1H), 3.43–3.32 (m, 1H), 2.42–2.19 (m, 3H), 1.98–1.88 (dd, 1H, *J* = 5.2, 15.8 Hz), 1.82–1.45 (m, 7H) 1.36 (d, 3H, *J* = 6.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.6, 165.3, 160.0, 148.9, 110.5, 105.4, 101.3, 69.6, 68.9, 38.4, 33.0, 31.8, 25.9, 20.9, 20.0. IR (neat): *v* 3432, 2926, 2856, 1640, 1459, 1259, 1169, 1024 cm^{-1}. MS (LCMS): *m/z* 295 $[M+1]^+$.