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Stereoselective synthesis of the C1–C10 fragment of rhizoxin D☆

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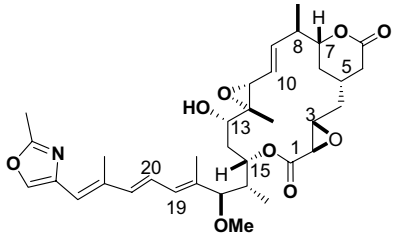
Abstract—A novel approach towards the synthesis of the C1–C10 fragment of the biologically active antimitotic agent rhizoxin D is described. The synthesis involves a stereoselective Michael addition reaction of lithium diallyl cuprate with an α,β-unsaturated six membered lactone.

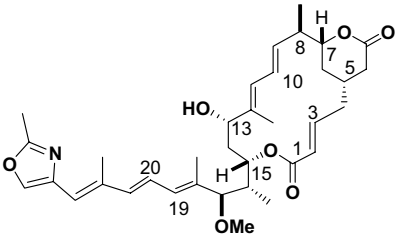
Rhizoxin (**1**, Fig. 1), a 16-membered macrolide **2** is known to be an anti-tumour and tubulin-interactive antimitotic agent and was isolated by Iwasaki et al.[1] from the fungus *Rhizopus chinensis*. Later a biogenetic precursor, that is, a didesepoxy analogue of rhizoxin, namely rhizoxin D, (**2**, Fig. 1) was isolated from the same fungus.[2] This has superior therapeutic properties over rhizoxin because of the absence of epoxides at C2–C3 and C11–C12 which leads to a shorter half-life of rhizoxin in the body. Due to its significant biological activity and highly functionalized macrolide structure rhizoxin D continues to be an attractive target for synthetic organic chemists.

Due to our interest in the development of novel approaches towards the synthesis of macrolides[3] we became interested in the synthesis of rhizoxin D and a retrosynthetic strategy is outlined in Scheme 1. Disconnection of the ester linkage of the macrolide core **2** at C1–C15 and the C10–C11 bond leads to key fragment **3.** Crucial steps in the synthesis of fragment **3** could be the cross metathesis of lactone **4** with *t*-butyl acrylate and a Takai reaction. Compound **4** may be accessed via the acrylic ester of alcohol **6** by RCM followed by Michael addition using allylic cuprate. Alcohol **6** may be generated by allylation of aldehyde **7**.

Initially we planned to synthesize compound **3** from the known aldehyde **8**[4] according to the reaction sequence shown in Scheme 2. Thus allylation of (*R*)-3-benzyloxy-2-methylpropanal **8** afforded the corresponding alcohol **9** in 93% yield, which was converted to the desired *syn* stereoisomer **10** using a Mitsunobu inversion.[5] Subsequently, esterificaton of **10** with acryloyl chloride followed by a Grubbs' RCM (first generation catalyst) afforded **11**.[6] The 1,4-Michael addition of compound **11** using lithium diallyl cuprate afforded product **12**[7] with 100% diastereomeric excess. Deprotection of the hydroxyl group with boron trichloride afforded alcohol **13**,[5b] which was found to possess the undesired configuration



Rhizoxin (1)



Rhizoxin D (2)

Figure 1.

Keywords: Rhizoxin; Stereoselective Michael addition.
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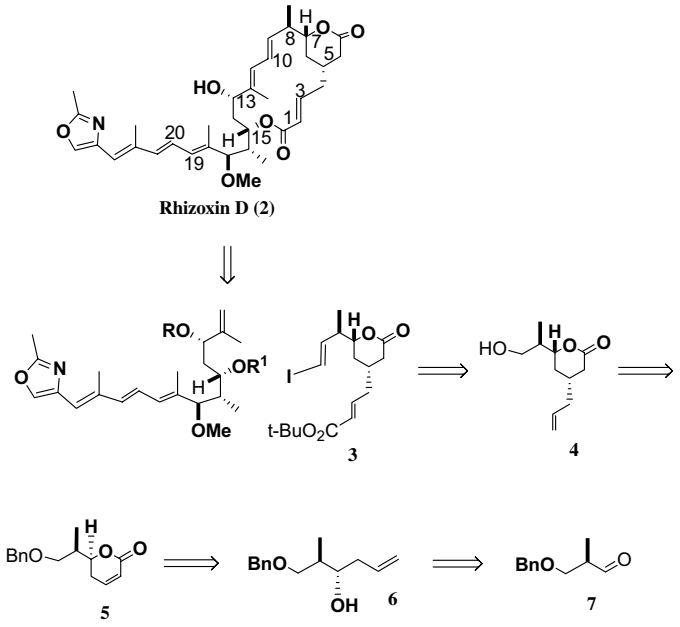
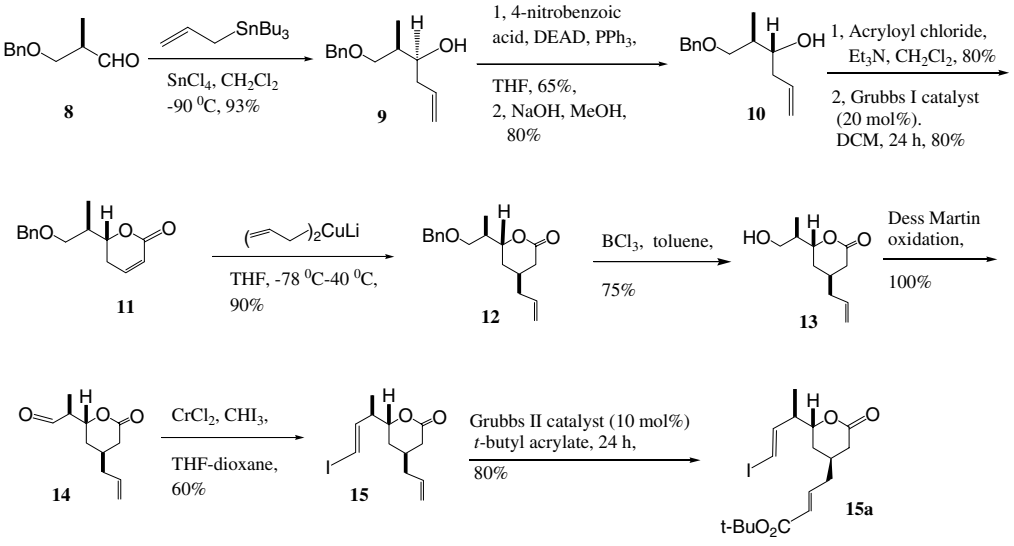


Scheme 1.

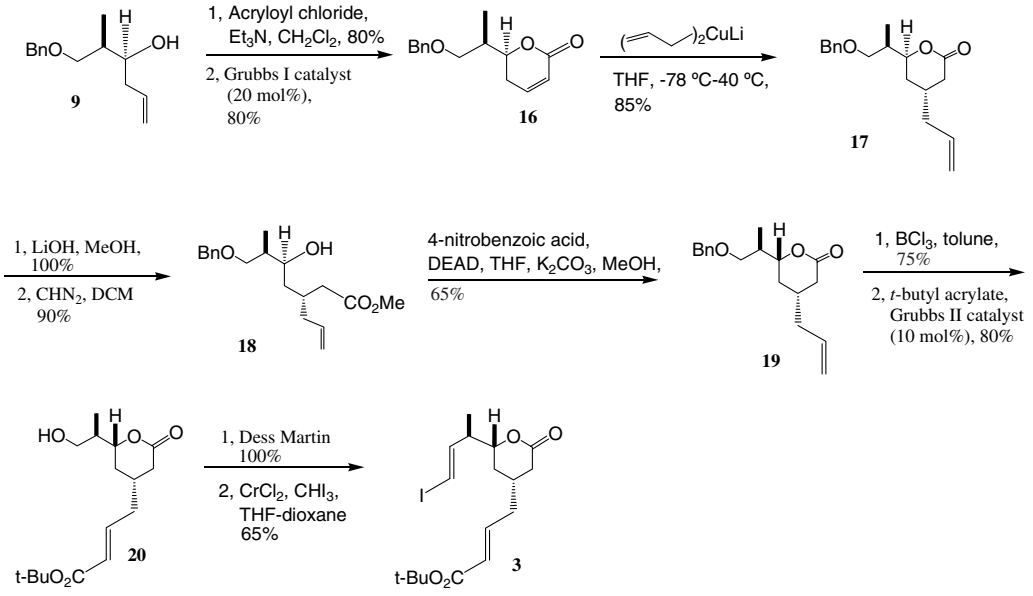


Scheme 2.

at the C-5 chiral centre of rhizoxin D as revealed by the literature data.[8] However, we decided to continue our synthetic work according to Scheme 2 as we were also interested in isolating the unnatural C5 diastereomer of rhizoxin D in order to study its chemical and biological properties. Thus alcohol **13** was oxidized to aldehyde **14**[9] which was converted to **15** using a Takai olefination[10] ($CrCl_2/CHI_3$) followed by a Grubbs' cross metathesis[11] reaction with *t*-butyl acrylate to afford **15a**[12] in good yield.

Since **15a** was found to be the undesired isomer, we revisited our strategy, the Michael addition of compound **11** being of particular interest. It is known[6] that the C7 stereocentre of lactone **11** plays a key role in controlling the stereochemistry of the Michael addition. Accordingly we changed our strategy as illustrated in Scheme 3.

Esterification of **9** with acryloyl chloride followed by Grubbs' RCM afforded lactone **16**, which upon Michael addition with lithium diallyl cuprate furnished **17** having the desired configuration at C5. We then installed the desired configuration at C7 by opening lactone **17** by hydrolysis followed by methylation of the resulting acid with diazomethane to give **18**. A Mitsunobu inversion on **18** followed by selective cleavage of the 4-nitrobenzoic ester using K_2CO_3 in methanol[13] afforded lactone **19** with the correct stereochemistry at C-5. Debenzylation of **19** and Grubbs' cross metathesis with *t*-butyl acrylate afforded **20** which was transformed into the desired key intermediate **3**[14] by the route outlined in Scheme 3.



Scheme 3.

In summary, we have accomplished the synthesis of the C1–C10 fragment of rhizoxin D in ten steps. Further work towards the total synthesis of rhizoxin D by employing fragment **3** is in progress.

Acknowledgements

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12. *Spectral data of compound* **15a**: $[\alpha]_D^{23}$ +1.8 (*c* 0.5, $CHCl_3$); IR (neat) 1730, 1710, 1152 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (d, 3H, $J = 6.7$ Hz, CH_3-8), 1.49 (s, 9H), 1.55 (m, 1H, Hax-6), 1.81 (m, 1H, Heq-6), 2.01 (m, 1H, Heq-5a), 2.21 (m, 1H, 1H-5), 2.29 (m, 2H, H-4), 2.50 (m, 1H, H-8), 2.55 (dd, 1H, $J = 10.7$, 3.2 Hz, Hax-5a), 4.14 (m, 1H, H-7), 5.79 (d, 1H, $J = 15.5$ Hz, H-2), 6.21 (dd, 1H, $J = 14.5$, 0.8 Hz, H-10), 6.46 (dd, 1H, $J = 14.5$, 8.3 Hz, H-9), 6.73 (d, 1H, $J = 15.5$ Hz, H-3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.0 (CH_3-8), 28.1 (–$(CH_3)_3$), 28.2 (C-5), 29.7 (C-6), 35.1 (C-5a), 37.7 (C-4), 44.9 (C-8), 76.3 (O–C), 78.7 (C-10), 80.6 (C-7), 125.9 (C-2), 142.8 (C-3), 145.4 (C-9), 165.0 (CO), 170.8 (CO); MS (ESI) 438 (M+NH_4^+); HRMS calcd. for $C_{17}H_{29}NO_4I$ (M+NH_4^+) 438.1141, found 438.1126.
13. After completion of the reaction, the mixture was treated with 2 N hydrochloric acid to give the lactone.
14. *Spectral data of compound* **3**: $[\alpha]_D^{23}$ +6.5 (*c* 1.0, $CHCl_3$); IR (neat) 1729, 1710, 1152 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.11 (d, 3H, $J = 6.7$ Hz, CH_3-8), 1.19 (td, 1H, $J = 14.2$, 13.9 Hz, Hax-6), 1.41 (s, 9H, *O-t*-Bu), 1.90 (dddd, 1H, $J = 20.1$, 13.4, 4.8, 3.2 Hz, Heq-6), 2.11 (m, 1H, Heq-5a), 2.13 (m, 1H, H-5), 2.22 (m, 2H, H-4), 2.50 (m, 1H, H-8), 2.70 (dd, 1H, $J = 11.8$, 1.6 Hz, Hax-5a), 4.14 (ddd, 1H, $J = 14.5$, 9.1, 2.6 Hz, H-7), 5.80 (d, 1H, $J = 15.5$ Hz, H-2), 6.20 (d, 1H, $J = 15.0$ Hz, H-10), 6.49 (dd, 1H, $J = 14.5$, 8.0 Hz, H-9), 6.84 (dt, 1H, $J = 15.3$, 7.2 Hz, H-3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.6 (CH_3-8), 28.1 (–$(CH_3)_3$), 29.6 (C-5), 30.9 (C-6), 35.9 (C-5a), 38.4 (C-4), 45.1 (C 8), 76.3 (O–C), 77.6 (C-10), 82.1 (C-7), 125.8 (C-2), 142.7 (C-3), 145.8 (C-9), 165.2 (CO), 170.8 (CO); MS (ESI) 438 (M+NH_4^+); HRMS calcd. for $C_{17}H_{29}NO_4I$ (M+NH_4^+) 438.1141, found 438.1129.