# A Cross-Metathesis Approach to the Synthesis of Key Precursor of the Macrolide Core of Rhizoxin D[1]

Srinivas Padakanti,[a,b] Bukkapattanam R. Sreekanth,[a] Velisoju Mahendar,[a] Manojit Pal,[a] Khagga Mukkanti,[b] Javed Iqbal,[a] Parthasarathi Das*[a]

[a] Discovery Research, Dr. Reddy's Laboratories Ltd., Bollaram Road, Miyapur, Hyderabad 500049, AP, India
Fax +91(40)23045438; E-mail: parthasarathi@drreddys.com

[b] Chemistry Division, Institute of Science & Technology, JNT University, Kukatpally, Hyderabad 500072, AP, India

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**Abstract:** The synthesis of key precursor **5** of the macrolide core of rhizoxin D has been achieved by cross metathesis between two olefinic fragments **6** and **7**. Both the olefinic fragments are easily synthesized in a diastereoselective manner from the common precursor 1-benzyloxy-2-methylhex-5-ene-3-ol (**8**).

**Keywords:** rhizoxin D, Keck allylation, Crimmins aldol, Takai olefination, cross metathesis

Rhizoxin (**1**) is a 16-membered macrolide isolated from the fungus *Rhizopus chinensis* by Iwasaki and co-workers (Figure 1).[2] In addition to antibiotic and antifungal activity, it has been shown to possess potent antitumor activity,[3] including activity against vincristine and adriamycin resistant cells.[4] The discovery of rhizoxin was soon followed by the isolation of several close structural analogues including rhizoxin D (**2**), which is believed to be a biogenetic precursor of **1**. Studies have shown that this desepoxy derivative possesses bioactivity and antitumor activity equivalent to those of rhizoxin, demonstrating that the epoxide moieties are not needed for in vitro activity.[5] It seems probable that in vivo hydrolysis of the epoxides may be responsible to some degree for the very short half-life of rhizoxin in the body, making compound **2** an intriguing potential therapeutic agent. The interesting biological activity and challenging macrolide structure prompted several groups to undertake the synthesis of this molecule.[6,7] Olefin cross metathesis has became a viable synthetic strategy for the synthesis of highly functionalized alkenes[8] and also applied for total synthesis of complex natural products.[9] In an approach to the synthesis of rhizoxin D and its structural analogues, herein we report the synthesis of the key precursor of its macrolide core using cross-metathesis reaction[10] as the key step.

Our retrosynthesis analysis of rhizoxin D is based on the synthesis of the corresponding macrolide **3** which appeared to be a suitable precursor on which the side chain of rhizoxin D could be easily introduced by the following established synthetic procedures (Scheme 1).[6b] Macrolide **3** can be achieved via intramolecular Stille coupling on **4**, which can be obtained from primary alcohol **5**. Whereas compound **5** can be assembled by following a cross-metathesis approach between **6** and **7**. Both the olefinic fragments **6** and **7**[11] can be synthesized from the common precursor **8** in a diastereoselective manner.

As depicted in Scheme 2 our synthesis commenced with addition of allyltributyltin[12] to the known aldehyde **9** in the presence of $SnCl_4$ resulting in alcohol **8** in 92% yield and with 36:1 diastereoselctivity. The TBDPS protection of the allylalcohol followed by oxidative cleavage of the terminal olefin by using $OsO_4$–$NaIO_4$ in the presence of 2,6 lutidine afforded aldehyde **11**.

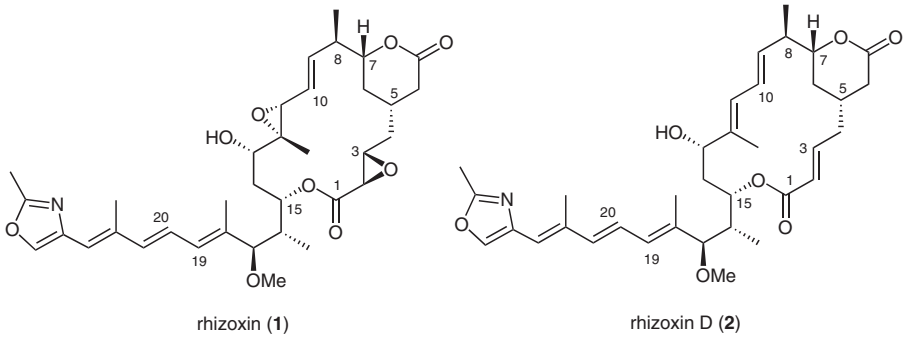


**Figure 1**

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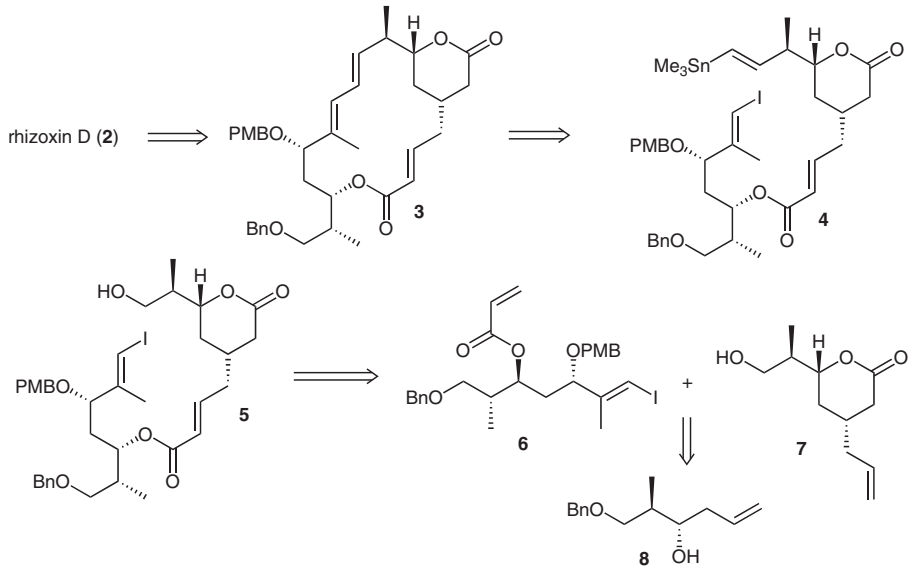
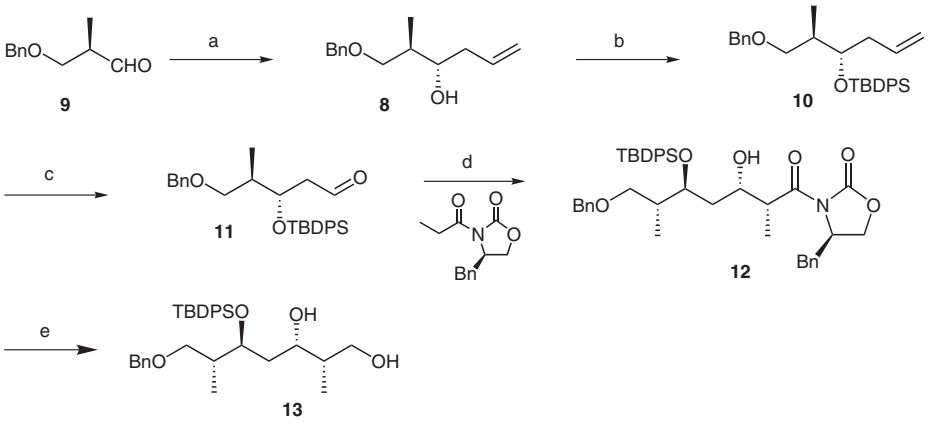



**Scheme 1** Retrosynthesis for macrolide

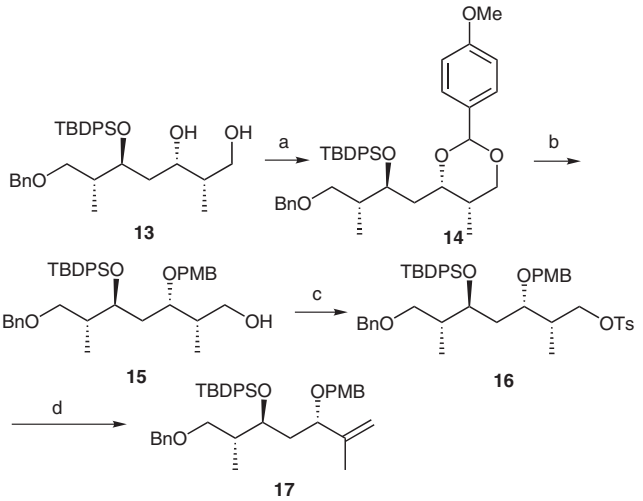



**Scheme 2** *Reagents and conditions*: (a) allyl tributyltin, $SnCl_4$, $CH_2Cl_2$, –90 to 0 °C, 1 h, 92%; (b) TBDPSCl, imidazole, DMF, r.t., 10 h, 95%; (c) $OsO_4$, $NaIO_4$, 2,6-lutidine, THF–$H_2O$ (3:1), r.t., 5 h, 85%; (d) $TiCl_4$, (–)-sparteine, $CH_2Cl_2$, –78 to 0 °C, 2 h, 90%; (e) $NaBH_4$, THF–$H_2O$ r.t., 4 h, 90%.

Introduction of the C13 stereocenter with the desired stereochemistry was carried out by using Crimmins' aldol protocol.[13] Addition of the titanium enolate derived from acyloxazolidinone to aldehyde **11** resulted in the formation of *syn*-aldol product **12** in 85% yield and excellent diastereoselectivity (≥96%). A reductive removal of the chiral auxiliary with sodium borohydride in THF[14] gave alcohol **13**.

Protection of 1,3-diol **13** with 4-methoxybenzaldehyde dimethyl acetal afforded the corresponding acetal **14** in good yield. Regioselective cleavage[15] of the acetal group of **14** using DIBAL-H in $CH_2Cl_2$ and protection of the resulting alcohol **15** with tosyl chloride in pyridine resulted in **16**.

Subsequently, compound **16** was converted to the corresponding terminal olefin **17**[16] by heating with NaI and DBU in 1,2-dimethoxyethane (Scheme 3). The stereochemistry and the *anti* relationship between the C13 and




**Scheme 3** *Reagents and conditions*: (a) $(MeO)_2CHC_6H_4OMe$, CSA, $CH_2Cl_2$, r.t., 16 h, 85%; (b) DIBAL-H, $CH_2Cl_2$, 0 °C, 2 h, 90%; (c) TsCl, pyridine, r.t., 3 h, 93%; (d) NaI, DBU,1,2-dimethoxyethane, 85 °C, 2.5 h, 96%.



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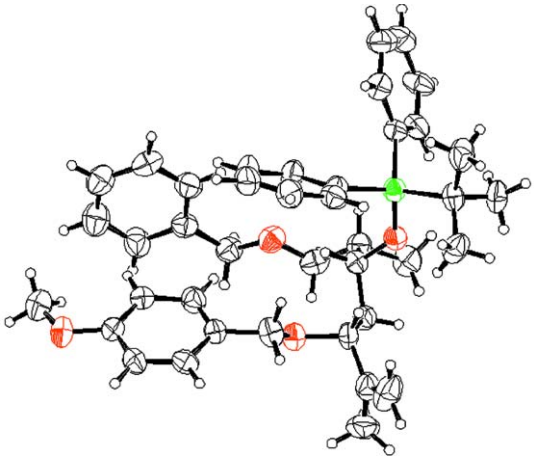
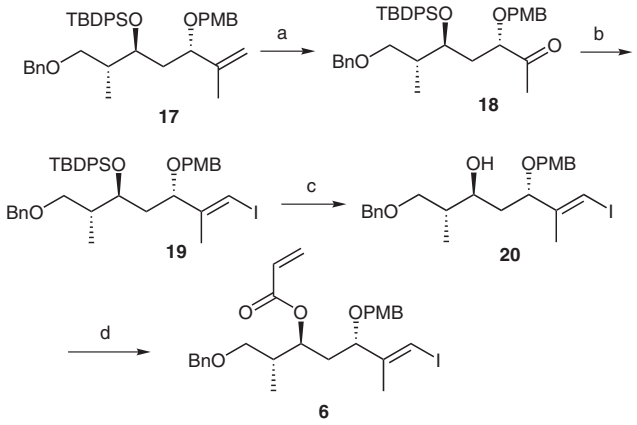


**Figure 2** ORTEP diagram of fragment **17**

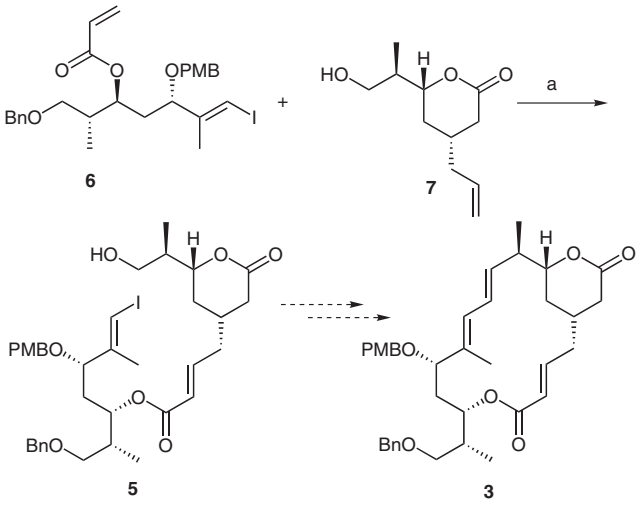



**Scheme 4** *Reagents and conditions*: (a) $OsO_4$, $NaIO_4$, 2,6-lutidine, THF–$H_2O$ (3:1), r.t., 4 h, 85%; (b) $CrCl_2/CHI_3$, THF, r.t., 70 h, 50%; (c) TBAF, THF, r.t., 12 h, 86%; (d) acryloyl chloride, $Et_3N$, $CH_2Cl_2$, r.t., 2.5 h, 92%.

C15 alcohols were established by single crystal X-ray diffraction analysis (Figure 2).[17]

Oxidative cleavage of terminal olefin with $OsO_4$–$NaIO_4$ in the presence of NMO was followed by Takai olefination[18] ($CrCl_2/CHI_3$) and resulted in olefin **19**. Deprotection of the *tert*-butyldiphenylsilyl ether of **19** provided compound **20**, which on acryloylation afforded compound **6**[19] ready for cross methathesis (Scheme 4).

We finally conducted the most crucial bond formation by subjecting **6** and **7** to Grubbs second-generation catalyst which led to the desired key intermediate **5**[20] in good yield (Scheme 5). Among the noteworthy features of this synthesis is the high yield of the cross-metathesis reaction and comptability of the vinyl iodide group with these reaction conditions. By following the protocol of Mitchell and co-workers,[6f] conversion of the primary alcohol group into the vinyl stannane present on the δ-lactone moiety and subsequent Stille coupling could give the macrolide core **3** of rhizoxin D.




**Scheme 5** *Reagents and conditions*: (a) Grubbs II catalyst, DCE, 85 °C, 24 h, 80%.

In conclusion, we have accomplished the synthesis of a key precursor **5** to the macrolide core of rhizoxin D from fragments **6** and **7** by using a cross-metathesis approach. The most interesting features of the synthesis are that both the olefinic partners required for cross metathesis were synthesized from the common intermediate 1-benzyloxy-2-methylhex-5-en-3-ol. This flexible approach has provided us with a robust route towards the total synthesis of rhizoxin D and structural analogues for biological studies, which are currently under way in our laboratory.

## Acknowledgment

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(17) **Crystal Data for Fragment 17**
$C_{40}H_{50}O_4Si_1$, $M$ = 622.92, monoclinic, space group $P2_1$, $a$ = 14.79 (2) Å, $b$ = 9.29 (1) Å, $c$ = 15.09 (2) Å, $b$ = 102.33 (2)°, $V$ = 2026 (4) Å$^3$, $Z$ = 2, $D_c$ = 1.021 g cm$^{-3}$, reflections collected = 20735, unique reflections = 4637, [$R_{int}$ = 0.0682], final $R$ indices [$I > 2s(I)$]: $R_1$ = 0.065, $wR_2$ = 0.114, CCDC-662327 contains the supplementary crystallographic data for this letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk./data_request/cif.

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(19) **Spectral Data for 6**
$[\alpha]_D^{23}$ –21.6 (*c* 0.5, $CHCl_3$). IR (neat): 2918, 1722, 1614, 1514 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, 3 H, *J* = 6.8 Hz), 1.72 (ddd, 1 H, *J* = 14.0, 10.4, 3.6 Hz), 1.77 (d, 3 H, *J* = 1.2 Hz), 1.89 (ddd, 1 H, *J* = 12.0, 9.6, 2.4 Hz), 2.14 (ddd, 1 H, *J* = 11.6, 6.4, 4.8 Hz), 3.29 (dd, 1 H, *J* = 9.2, 6.4 Hz), 3.46 (dd, 1 H, *J* = 10.0, 6.4 Hz), 3.78 (s, 3 H), 3.82 (dd, 1 H, *J* = 9.2, 4.0 Hz), 4.11 (d, 1 H, *J* = 10.8, Hz), 4.30 (d, 1 H, *J* = 10.8 Hz), 4.46 (m, 2 H), 5.29 (ddd, 1 H, *J* = 7.2, 4.8, 2.4 Hz), 5.79 (dd, 1 H, *J* = 10.4, 1.6 Hz), 6.05 (dd, 1 H, *J* = 17.2, 10.4 Hz), 6.20 (s, 1 H), 6.34 (dd, 1 H, *J* = 17.2, 1.2 Hz), 6.83 (d, 2 H, *J* = 8.8 Hz), 7.22 (d, 2 H, *J* = 8.4 Hz), 7.28 (m, 5 H). $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 13.0, 19.1, 35.7, 37.3, 55.2, 70.3, 71.9, 72.6, 72.9, 79.2, 80.0, 113.8, 127.4, 127.5, 128.3, 129.4, 129.6, 130.0, 130.5, 138.4, 148.0, 159.1, 165.5. ESI-HRMS: *m/z* calcd for $C_{27}H_{33}IO_5Na$ [M + Na]$^+$: 587.1270; found: 587.1277.

(20) **Synthetic Procedure and Spectroscopic Data of 5**
A mixture of a solution of **6** (0.035 g, 0.06 mmol) and **7** (0.024 g, 0.123 mmol) in DCE (0.3 mL) was treated with Grubbs second-generation catalyst (5.25 mg, 0.0056 mmol) and the dark purple solution stirred at reflux temperature for 48 h. The reaction mixture was then loaded directly on top of a wet column packed with $SiO_2$ and purified by flash chromatography (EtOAc–hexane, 1:3) to afford the product **5** (0.036 g, 80%) as light brown oil; $[\alpha]_D^{23}$ –22.0 (*c* 0.1, $CHCl_3$). IR (neat): 3468, 2924, 1712, 1414, 1247 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, 3 H, *J* = 6.8 Hz), 0.97 (d, 3 H, *J* = 7.2 Hz), 1.42 (m, 1 H), 1.72 (m, 1 H), 1.77 (s, 3 H), 1.88 (m, 2 H), 2.18 (m, 6 H), 2.71 (dd, 1 H, *J* = 12.0, 2.0 Hz), 3.30 (dd, 1 H, *J* = 9.2, 6.4 Hz), 3.45 (dd, 1 H, *J* = 9.6, 6.4 Hz), 3.62 (dd, 1 H, *J* = 10.4, 5.2 Hz), 3.71 (dd, 1 H, *J* = 10.8, 7.6 Hz), 3.78 (s, 3 H), 3.82 (dd, 1 H, *J* = 8.8, 4.4 Hz), 4.12 (m, 2 H), 4.30 (d, 1 H, *J* = 10.8), 4.57 (s, 2 H), 5.26 (ddd, 1 H, *J* = 7.2, 4.8, 2.8 Hz), 5.81 (d, 1 H, *J* = 15.6 Hz), 6.20 (s, 1 H), 6.79 (m, 1 H), 6.83 (d, 2 H, *J* = 8.4 Hz), 7.21 (d, 2 H, *J* = 8.8 Hz), 7.38 (m, 5 H). $^{13}$C NMR (50 MHz, $CDCl_3$): δ = 10.4, 12.4, 19.0, 30.9, 32.0, 35.4, 35.9, 37.2, 38.5, 39.6, 55.1, 63.9, 70.2, 71.9, 72.6, 72.8, 79.3, 80.0, 80.2, 113.7, 123.9, 127.4, 128.2, 129.2, 129.5, 129.9, 138.3, 144.5, 147.8, 159.0, 165.4, 170.9. ESI-HRMS: *m/z* calcd for $C_{36}H_{47}IO_8Na$ [M + Na]$^+$: 757.2213; found: 757.2210.

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