

## THE ENANTIOSELECTIVE TOTAL SYNTHESIS OF THE ANTITUMOR MACROLIDE NATURAL PRODUCT RHIZOXIN D

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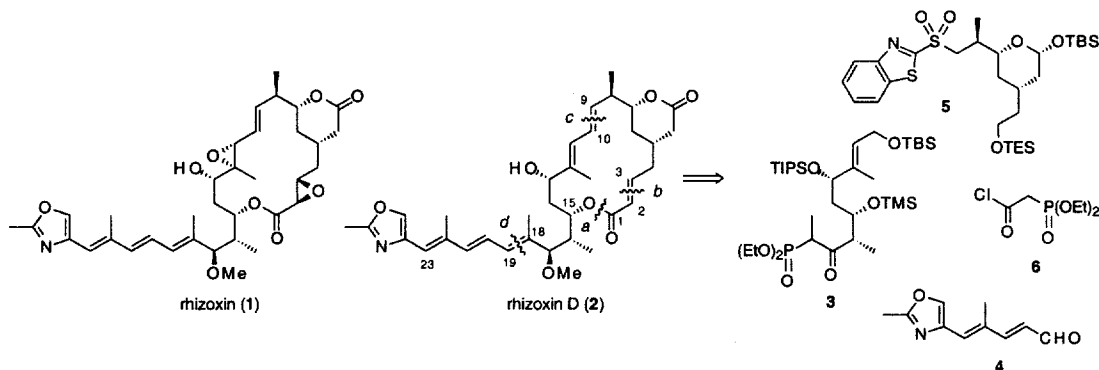
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**Abstract:** A convergent, enantioselective total synthesis of rhizoxin D (didesepoxy-rhizoxin), a potent antitumor natural product, was achieved via three critical olefinations, including a Horner-Emmons macrocyclization. © 1999 Elsevier Science Ltd. All rights reserved.

In the mid-1980's, Iwasaki and coworkers discovered an exciting new family of 16-membered macrolactones known as the rhizoxins from the fungus *Rhizopus chinensis*.<sup>2</sup> The subsequent discovery that these compounds possess remarkable antitumor and antifungal activity has prompted considerable interest in these natural products,<sup>3</sup> and rhizoxin (**1**, Scheme I) has undergone extensive clinical studies as a potential chemotherapeutic agent.<sup>4</sup> A minor component isolated in 1986 was found to be the didesepoxy analog of rhizoxin (rhizoxin D, **2**),<sup>5</sup> and **2** is thought to be the biogenetic precursor to **1**. Although rhizoxin D possesses biological activity equivalent to **1** and may thus be able to circumvent some of the clinical shortcomings of rhizoxin,<sup>6</sup> it has been less studied primarily because of the limited quantity of **2** available.<sup>7</sup> Not surprisingly, there has been substantial interest in the synthesis of the rhizoxins,<sup>8</sup> including two recently completed syntheses of **2**.<sup>9</sup> We wish to communicate our efforts, which have culminated in the total synthesis of rhizoxin D.<sup>10</sup>

Scheme I

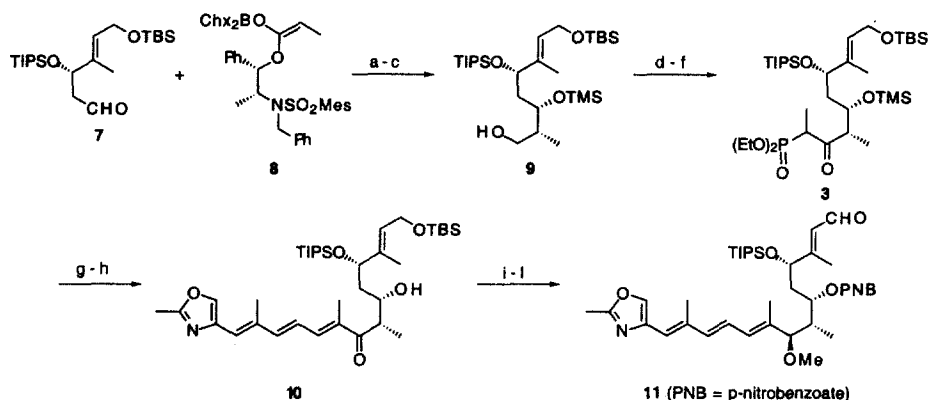


We chose to disconnect the molecule about the macrolide linkage (*a*), the C2-C3 olefin (*b*), the C9-C10 olefin (*c*) and the C18-C19 olefin (*d*), leading to the initial synthetic targets **3-6**. Our original plan was to complete the synthesis via one of the known macrolactonization methods, a strategy that ultimately proved unsuccessful.<sup>11</sup> This necessitated the development of the strategy detailed below. In our initial efforts, we set the C15 stereocenter in the unnatural *R* configuration predicated on a subsequent inversion using the Mitsunobu macrolactonization protocol, with inversion via protection deemed a suitable backup plan.<sup>10</sup> In practice that proved to be unsatisfactory, and thus the revised synthesis began with an *anti*-aldol addition to **7** (Scheme II).<sup>12</sup> While numerous *anti*-aldol procedures were explored, success was ultimately achieved through the norephedrine-based methodology of Masamune.<sup>13</sup> Thus, addition of **8** allowed installation of both the C15 and C16 stereocenters with excellent diastereoselectivity (90% de) and in good yield. Silylation and reductive cleavage of the auxiliary then provided **9**.

Installation of the triene portion of the oxazole also proved to be a challenging task. We explored the construction of virtually every bond from C18 to C23 before we were satisfied that a Horner-Emmons reaction

uniting C18 and C19 represented our best option. Dess Martin oxidation of **9** followed by conversion to the  $\beta$ -ketophosphonate gave us the requisite precursor, and addition to aldehyde **4** afforded the desired triene.<sup>14</sup> Removal of the TMS protecting group was remarkably difficult, as significant isomerization about the C22-C23 olefin was typically observed, and fairly specialized fluorosilicic acid conditions were required.<sup>15</sup> Once alcohol **10** was in hand, an intramolecular Tishchenko reaction with *p*-nitrobenzaldehyde was used to install the C17 stereocenter.<sup>16</sup> Methylation of the allylic alcohol was followed by selective desilylation and oxidation to generate **11**.<sup>17</sup>

Scheme II



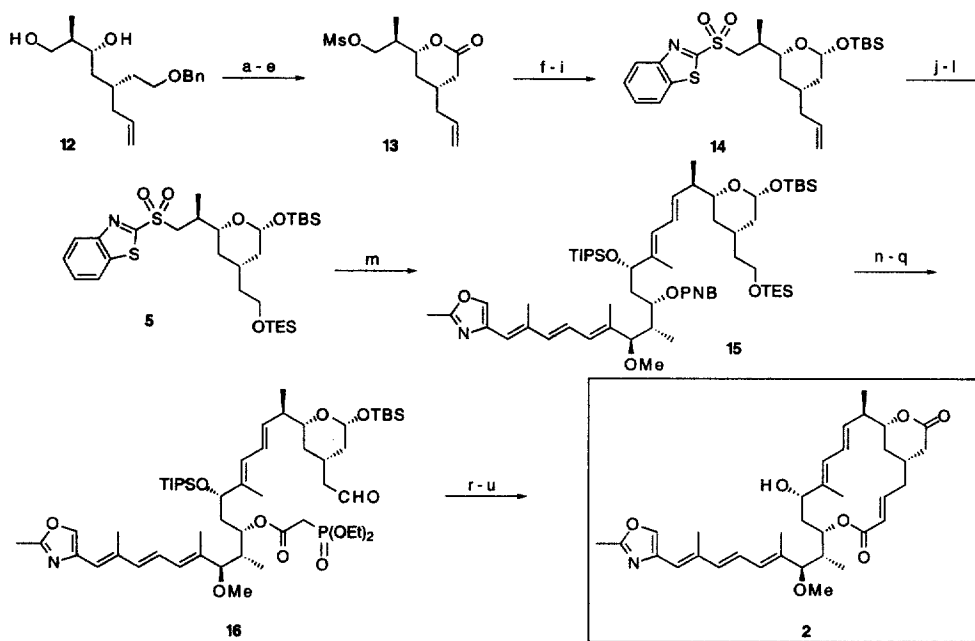
a)  $\text{NEt}_3$  (81 %); b)  $\text{TMSCl}$ , imid. (86 %); c) DIBAL (100 %); d) Dess-Martin oxid. (90 %); e) 2-lithioethyldiethylphosphonate (100 %); f) Dess-Martin oxid. (96 %); g) **4**,  $\text{Ba}(\text{OH})_2 \cdot \text{H}_2\text{O}$  (85 %); h)  $\text{H}_2\text{SiF}_6$ , *i*-PrOH  $-40^\circ\text{C}$  (86 %); i) *p*-nitrobenzaldehyde,  $\text{SmI}_2$  (83 %); j) MeI,  $\text{Ag}_2\text{O}$ , ultrasound (77 %); k)  $\text{H}_2\text{SiF}_6$ , 4:1  $\text{CH}_3\text{CN}/t\text{-BuOH}$  (94 %); l) Dess-Martin oxid. (82 %)

Our unsuccessful bid to perform a Mitsunobu or any standard macrolactonization demanded that we revise our synthesis of the right hand portion of rhizoxin as well. Specifically, we needed to facilitate a Horner-Emmons macrocyclization, and experience told us that we also needed the  $\delta$ -lactone to be closed in a masked form.<sup>11</sup> Previously prepared **12** (Scheme III)<sup>10</sup> was converted to mesylate **13** in a straightforward manner. We discovered that the use of standard Julia couplings in the synthesis of the rhizoxin skeleton was not fruitful, and were thus intrigued by the prospects of utilizing the one-pot modification of this olefination reaction.<sup>18</sup> Toward this end, displacement of mesylate **13** with the sodium salt of 2-mercaptobenzothiazole and molybdenum oxidation supplied the sulfone. The  $\delta$ -lactone was then masked as acetal **14** and the C3 terminus was converted to the corresponding TES ether **5**.<sup>19</sup> Deprotonation and coupling with aldehyde **11** then gave **15** as a single isomer in one step and in good overall yield.<sup>20</sup>

With the C3-C26 backbone of our target completed, we turned to the functionalization of **15** to prepare for macrocyclization. The PNB ester was reductively removed and replaced with a diethylphosphonoacetyl group at C15 via **6**.<sup>21</sup> Selective cleavage of the TES ether was accomplished using fluorosilicic acid, and Dess Martin oxidation yielded macrolide precursor **16**. We found the barium hydroxide-mediated Horner-Emmons conditions to be the best method for effecting the cyclization of **16**,<sup>14</sup> the macrolide could then be selectively deprotected to the hemiacetal. TPAP oxidation and TBAF deprotection finally afforded rhizoxin D, which was identical in all respects to data provided for the natural product.

**Acknowledgements:** Helpful discussions regarding the Julia olefination with Professor Philip Kocienski and Dr. Richard Brown are gratefully acknowledged, as are the invaluable experimental details for the preparation of dicyclohexylboron triflate communicated to us by Professor Ian Paterson. We wish to thank the National Science Foundation (predoctoral fellowship to JAL and NSF CHE-9502507), Eastman Kodak (predoctoral fellowship to DPP), the Research Corporation (Cottrell Scholar Award to JWJ) and the University of California Cancer Research Coordinating Committee for funding this endeavor, and Professors Andrew Kende and David Williams for their generosity in sending us NMR spectra for rhizoxin D.

## Scheme III

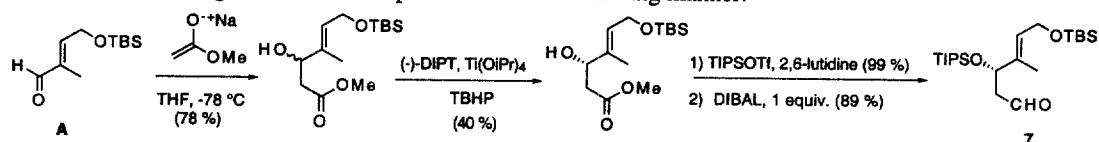


a) TIPSCL, imid. (95 %); b) Na/NH<sub>3</sub> (98 %); c) Ag<sub>2</sub>CO<sub>3</sub>/celite (86 %); d) HF, CH<sub>3</sub>CN (95 %); e) MsCl, NEt<sub>3</sub> (96 %); f) ArSNa (94 %); g) Mo(VI), H<sub>2</sub>O<sub>2</sub> (91 %); h) DIBAL (80 %); i) TBSCl, imid. (85 %); j) OsO<sub>4</sub>, NMO; NaIO<sub>4</sub> (87 %); k) NaBH<sub>4</sub> (88 %); l) TESCL, *i*-Pr<sub>2</sub>NEt (96 %); m) **11**, LiHMDS (2.3 equiv.), -78 °C → rt (79 %); n) DIBAL (90 %); o) **6**, pyr. (92 %); p) H<sub>2</sub>SiF<sub>6</sub>, *i*-PrOH, -40 °C (88 %); q) Dess-Martin oxid. (78 %); r) Ba(OH)<sub>2</sub>·H<sub>2</sub>O (49 %); s) HF·pyr. (80 %); t) TPAP, NMO (61 %); u) TBAF (73 %)

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- See, for example, Onozawa, C.; Shimamura, M.; Iwasaki, S.; Oikawa, T. *Jpn. J. Cancer Res.* **1997**, *88*, 1125 and references cited. The palmitate ester of rhizoxin (RS-1541) has also been studied (see, for example Kurihara, A.; Shibayama, Y.; Kasuya, A.; Ikeda, M.; Hisaoka, M. *J. Drug Target.* **1998**, *5*, 491).
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10. For our initial efforts in this area, see: (a) Lafontaine, J. A.; Leahy, J. W. *Tetrahedron Lett.* **1995**, *36*, 6029. (b) Provencal, D. P.; Gardelli, C.; Lafontaine, J. A.; Leahy, J. W. *Tetrahedron Lett.* **1995**, *36*, 6033.
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12. While **7** could be prepared in a manner analogous to our previous work,<sup>10</sup> the material could be efficiently generated on large scale from compound **A**<sup>10</sup> in the following manner:



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17. Key analytical data for **11**:<sup>22</sup>  $[\alpha]_{D}^{23} + 40.5$  (c 0.38,  $\text{CH}_2\text{Cl}_2$ ); IR (thin film) 2942, 1723, 1677, 1529, 1276, 1103  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR:  $\delta$  0.96 (m, 2H), 1.05 (d, 3H,  $J = 7.0$  Hz), 1.55 (s, 3H), 1.87 (s, 3H), 1.91 (m, 1H), 2.07 (m, 1H), 2.09 (s, 3H), 2.24 (m, 1H), 2.47 (s, 3H), 3.18 (s, 3H), 3.29 (d, 1H,  $J = 8.0$  Hz), 4.27 (t, 1H,  $J = 6.2$  Hz), 5.09 (dd, 1H,  $J = 3.8, 9.3$  Hz), 5.87 (d, 1H,  $J = 7.8$  Hz), 6.09 (d, 1H,  $J = 10.4$  Hz), 6.26 (s, 1H), 6.36 (d, 1H,  $J = 15.2$  Hz), 6.59 (dd, 1H,  $J = 10.8, 15.1$  Hz), 7.55 (s, 1H), 8.11 (dt, 2H,  $J = 2.0, 8.9$  Hz), 8.28 (dt, 2H,  $J = 2.0, 8.9$  Hz), 9.68 (d, 1H,  $J = 7.8$  Hz);  $^{13}\text{C}$  NMR:  $\delta$  10.2, 12.2, 12.5, 13.8, 14.3, 17.87, 17.92, 22.6, 31.5, 35.6, 39.1, 56.2, 73.7, 75.7, 88.6, 120.7, 123.6, 123.9, 126.4, 129.2, 130.3, 135.7, 135.9, 136.7, 137.7, 138.6, 150.5, 160.8, 162.8, 163.6, 190.7. Anal. Calcd for  $\text{C}_{39}\text{H}_{56}\text{N}_2\text{O}_8\text{Si}$ : C, 66.07; H, 7.96; N, 3.95. Found: C, 65.74; H, 8.33; N, 3.67.
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19. Key analytical data for **5**:<sup>22</sup>  $[\alpha]_{D}^{23} + 3.68$  (c 0.38,  $\text{CH}_2\text{Cl}_2$ ); IR (thin film): 2953, 1472, 1330, 1150;  $^1\text{H}$  NMR:  $\delta$  0.06 (s, 6H), 0.58 (q, 6H,  $J = 7.9$  Hz), 0.87 (s, 9H), 0.94 (t, 9H,  $J = 7.9$  Hz), 0.90-1.04 (m, 2H), 1.15 (d, 3H,  $J = 7.0$  Hz), 1.46 (m, 3H), 1.76 (m, 1H), 1.79 (d, 1H,  $J = 14.0$  Hz), 2.46 (m, 1H), 3.40 (dd, 1H,  $J = 7.5, 14.4$  Hz), 3.54 (d, 1H,  $J = 12.7$  Hz), 3.63 (t, 2H,  $J = 6.5$  Hz), 3.79 (dd, 1H,  $J = 4.9, 14.4$  Hz), 4.69 (dd, 1H,  $J = 2.0, 9.0$  Hz), 7.59 (dt, 1H,  $J = 1.2, 7.2$  Hz), 7.64 (dt, 1H,  $J = 1.2, 7.2$  Hz), 8.01 (d, 1H,  $J = 7.7$  Hz), 8.20 (d, 1H,  $J = 7.7$  Hz);  $^{13}\text{C}$  NMR:  $\delta$  -5.1, -3.9, 4.3, 6.7, 14.7, 18.0, 25.7, 30.7, 32.8, 33.3, 39.3, 40.4, 58.1, 59.9, 76.6, 97.0, 122.3, 125.4, 127.6, 127.9, 136.7, 152.7, 166.4. Anal. Calcd. for  $\text{C}_{29}\text{H}_{51}\text{NO}_5\text{S}_2\text{Si}_2$ : C, 56.73; H, 8.37; N, 2.28. Found: C, 56.80; H, 8.32; N, 2.13.
20. Key analytical data for **15**:<sup>22</sup>  $[\alpha]_{D}^{23} + 41.2$  (c 0.17,  $\text{CH}_2\text{Cl}_2$ ); IR (thin film): 2954, 2866, 1724, 1530, 1276, 1085;  $^1\text{H}$  NMR:  $\delta$  0.09 (s, 3H), 0.11 (s, 3H), 0.58 (q, 6H,  $J = 7.9$  Hz), 0.88 (s, 9H), 0.89 (m, 9H), 0.95 (m, 2H), 1.03 (d, 3H,  $J = 6.9$  Hz), 1.04 (m, 3H), 1.26 - 1.29 (m, 3H), 1.43 - 1.52 (m, 3H), 1.66 (s, 3H), 1.71 (m, 2H), 1.79 (m, 2H), 1.88 (s, 3H), 1.96 (m, 1H), 2.14 (s, 3H), 2.22 (m, 1H), 2.47 (s, 3H), 3.04 (dd, 1H,  $J = 8.1, 9.2$  Hz), 3.17 (s, 3H), 3.28 (d, 1H,  $J = 8.3$  Hz), 3.64 (t, 2H,  $J = 6.4$  Hz), 4.63 (dd, 1H,  $J = 1.4, 9.0$  Hz), 5.08 (dd, 1H,  $J = 2.7, 9.9$  Hz), 5.47 (dd, 1H,  $J = 7.6, 15.0$  Hz), 5.79 (d, 1H,  $J = 10.9$  Hz), 5.88 (dd, 1H,  $J = 10.2, 15.0$  Hz), 6.10 (d, 1H,  $J = 10.7$  Hz), 6.26 (s, 1H), 6.36 (d, 1H,  $J = 15.1$  Hz), 6.60 (dd, 1H,  $J = 11.1, 15.3$  Hz), 7.55 (s, 1H), 8.11 (d, 2H,  $J = 8.6$  Hz), 8.25 (d, 2H,  $J = 8.6$  Hz);  $^{13}\text{C}$  NMR:  $\delta$  -5.2, -4.0, 4.4, 6.8, 10.5, 11.7, 12.0, 12.4, 13.8, 14.4, 16.2, 18.0, 18.1, 25.8, 30.7, 34.7, 35.1, 35.6, 39.1, 39.5, 40.4, 42.0, 56.2, 60.0, 74.4, 76.4, 79.0, 89.0, 97.1, 120.6, 123.4, 124.2, 125.3, 125.9, 129.3, 130.5, 135.9, 136.0, 136.2, 136.7, 136.9, 137.56, 137.65, 138.7, 150.3, 160.9, 163.8. HRMS (FAB)  $m/z$  calcd. for  $\text{C}_{61}\text{H}_{102}\text{N}_2\text{O}_{10}\text{Si}_3$  ( $M^+$ ): 1106.6842. Found: 1106.6849.
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22. All  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$  on a Bruker AMX system at 500 MHz and 125 MHz respectively, using tetramethylsilane as an internal standard. Optical rotations were recorded at room temperature on a Perkin Elmer 241 polarimeter using a sodium lamp ( $\lambda$  589). Infrared spectra were recorded on a Perkin Elmer 1600 FTIR as solutions in  $\text{CDCl}_3$ . Elemental analytical data were obtained from MHW Laboratories, Phoenix, AZ. High resolution mass spectra were obtained from the University of California College of Chemistry Microanalytical Facility.