Pergamon

Tetrahedron Letters, Vol. 37, No. 19, pp. 3291-3294, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00578-3

Synthetic Studies on the Rhizoxins. II. An Approach to the C_{10}-C_{26} Subunit Using "Substrate Directed" Allylstannane Additions to Aldehydes.

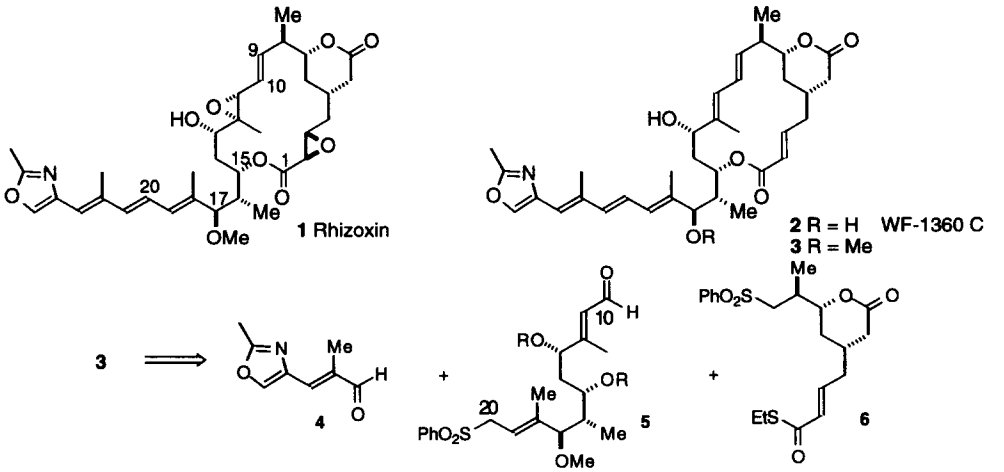
Gary E. Keck*, Kenneth A. Savin, Michael A. Weglarz, and Erik N. K. Cressman

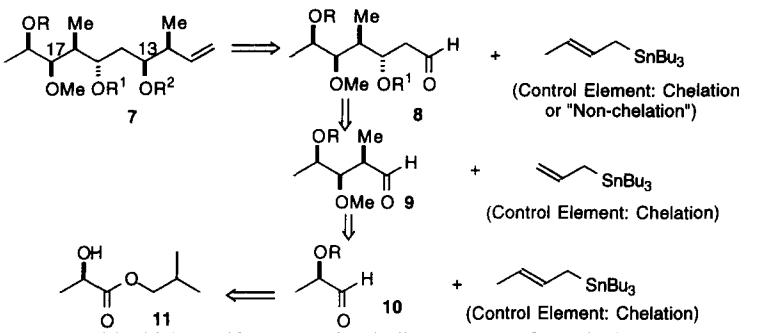
Department of Chemistry, University of Utah, Salt Lake City, Utah 84112.

Abstract: The construction of a C_{10}-C_{26} fragment of the 16-membered antitumor macrolide rhizoxin has been achieved in an efficient manner. The central portion of this molecule has been prepared in enantiopure form via an iterative allylstannylation protocol starting with the ester of (*R*)-lactic acid. The oxazole portion of rhizoxin was attached via a samarium diiodide modified Julia coupling to generate the requisite all *E* triene.

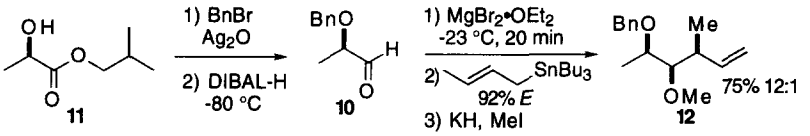
Rhizoxin (**1**), a 16-membered macrolide, and several close structural analogs have been isolated from *Rhizopus chinesis*, the pathogen of rice seedling blight.[1] Rhizoxin has been found to exhibit antimitotic activity in many eukariotic cells by inhibition of microtubule polymerization,[2] and subsequently has been found to be active against vincristine- and adriamycin-resistant tumor cell lines *in vitro* and *in vivo*.[3] Rhizoxin showed greater cytotoxicity in cultured tumor cells than did vincristine; however, its toxicity in animal experiments appears lower than that of vincristine.[3] The potent biological activity, potential as a chemotherapeutic agent, and unique structure of rhizoxin have prompted us to undertake the total synthesis of this class of compounds.

Analog **3** (unfortunately not assigned a name or number, but occasionally referred to as "pre-rhizoxin") has activity very similar to rhizoxin itself, and it has been demonstrated that bis-epoxidation of an advanced macrocyclic intermediate enroute to **3** can be conducted to yield rhizoxin (**1**).[4a, b] We have therefore chosen analogs **2** and **3** as targets for total synthesis.[4] A previous report from this laboratory has described the synthesis of a potential C_1-C9 fragment, and other groups have reported routes to this subunit as well.[5] We describe herein one approach to the C_{10}-C_{26} subunit which utilizes a sequence based on iterative allylstannane additions to aldehydes, using the retrosynthetic analysis described below.



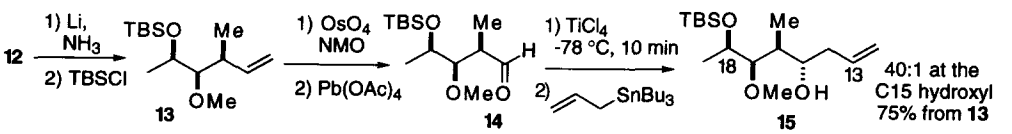


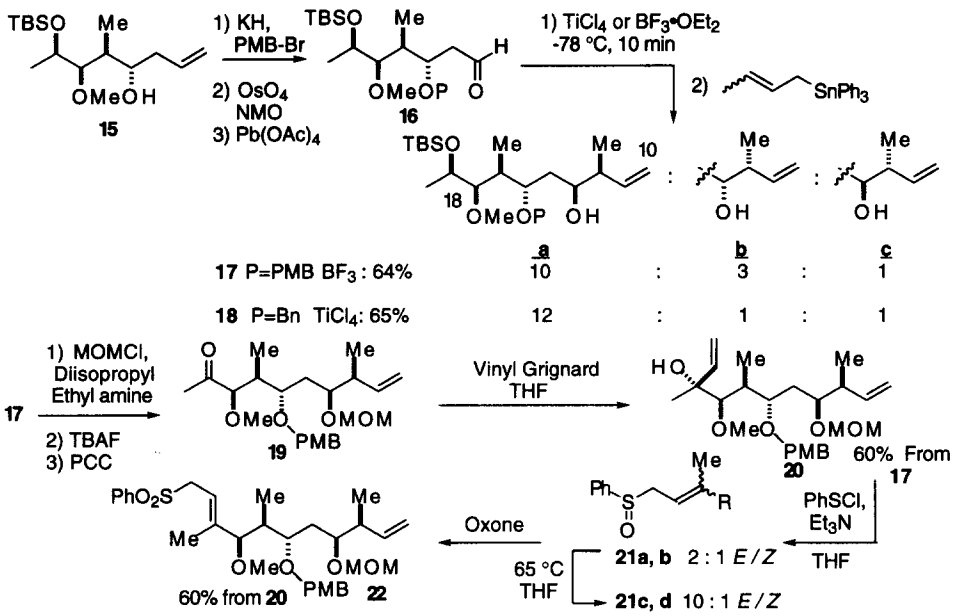
The route began with aldehyde **10** (prepared as indicated below from the isobutylester of (*R*)-lactic acid), which was subjected to reaction with *E*-crotyltri-*n*-butylstannane following complexation with $MgBr_2$. As expected, essentially complete diastereofacial selectivity is realized under these conditions via chelation control,[6] and the bond construction was predominantly (>12 : 1) *syn*. After methylation (KH, MeI) of the hydroxyl, the benzyl ether was removed and the resulting alcohol was protected as the TBS ether.[7] Oxidative cleavage of the olefin to aldehyde **14** was followed by a second "chelation controlled" addition, this with allyltri-*n*-butylstannane and $TiCl_4$ as Lewis acid, to yield **15**. The high level of diastereoselectivity (40 : 1) associated with this process is clearly due to mutually reinforcing steric effects in the titanium chelate derived from **9**, since neither the α or β stereocenters alone in substrates similar to **9** lead to significant levels of asymmetric induction with the parent (unsubstituted) allylstannane.[8] The alcohol in **15** was then protected as



either a benzyl ($PhCH_2$-Br, KH, 92%) or 4-methoxy benzyl (PMB-Br, KH, 89%) ether. Following oxidative cleavage of the olefin to the corresponding aldehyde, additions of crotyltriphenylstannane were examined under conditions appropriate for either chelation or "non-chelation" reactions, both of which are expected to yield the same product.[9] The benzyl protected substrate **16**, with $TiCl_4$ as Lewis acid, afforded **18** as the major product along with small amounts of two other diastereomers (ratio 12 : 1 : 1) whose structures were not determined. Use of $TiCl_4$ with the PMB derivative was precluded due to decomposition of this material in the presence of $TiCl_4$; however, the PMB derivative with BF_3•OEt_2 as Lewis acid afforded mainly **17** along with two other diastereomers (ratio 10 : 3 : 1). Either the benzyl substrate **18** or the PMB derivative **17** could in principle be deployed in the subsequent reactions; we proceeded with the PMB derivative **17** even though it was formed with lower stereoselectivity.

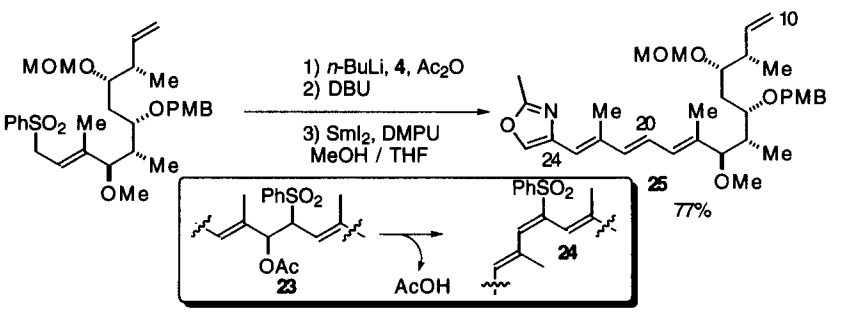
Alcohol **17** was easily transformed to the ketone **19**; however, at this point a variety of Wittig or Horner-Emmons chain extensions to afford the *E* trisubstituted olefin failed due to a pronounced lack of reactivity for the α-methoxy ketone. Thus an indirect method for accomplishing this transformation was pursued. Reaction of **19** with vinylmagnesium bromide in THF afforded **20** as a single stereoisomer, presumably as the result of another chelation directed process,[10] which was then processed *via* Evans-Mislow sulfenate rearrangement.[11] Thus, treatment of alcohol **20** with PhSCl and NEt_3 (initially at -78 °C with warming to ambient temperature) afforded after workup a 2 : 1 (*E*/*Z*) mixture of allylic sulfoxides **21a-b**, each as a single epimer at sulfur. Heating this mixture to 65 °C in THF gave a 10 : 1 (*E*/*Z*) mixture, each as a 1 : 1 mixture of epimers at sulfur (**21c-d**). Oxidation with oxone removed this stereocenter and afforded the desired sulfone **22**.





Reaction of the lithio derivative (*n*-BuLi) of sulfone **22** with the oxazole aldehyde **4**, followed by quenching with acetic anhydride, afforded acetate **23**. Processing **23** according to the modified Julia-Lythgoe olefination developed for this specific application then yielded **25**.[12, 13]

The results described illustrate a linear iterative approach toward the synthesis of the C_{10}-C_{26} fragment of rhizoxin **25**. The remaining challenges include elaboration of the C_{10} terminus to prepare for a second Julia-Lythgoe coupling to a C_1-C_9 subunit and effecting the macrolactonization. Investigations of these remaining challenges are being actively pursued.



Acknowledgment: Financial support by the National Institutes of Health (through NIH Grant GM 28961) is gratefully acknowledged. We also thank Mr. Greg Lundquist for assistance with some of the early steps in this route.

References and Notes:

1. a) Iwasaki, S.; Kobayashi, H.; Furukawa, J.; Namikoshi, M.; Okuda, S.; Sato, Z.; Matsuda, I.; Noda, T. *J. Antibiot.* **1984**, *37*, 354. b) Kiyoto, S.; Kawai, Y.; KawaKita, T.; Kino, E.; Okuhara, M.; Uchida, I.; Tanaka, H.; Hashimoto, M.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot.* **1986**, *39*, 762.
2. a) Takahashi, M.; Iwasaki, S.; Kobayashi, H.; Okuda, S.; Murai, T.; Sato, Y.; Haraguchi-Hiraoka, T.; Nagano, H. *J. Antibiot.* **1987**, *40*, 66. b) Takahashi, M.; Iwasaki, S.; Kobayashi, H.; Okuda, S.; Murai, T.; Sato, Y. *Biochemica et. Biophysica Acta.* **1987**, *926*, 215. c) Iwasaki, S. *Novel Microbial*

Products for Medicine and Agriculture, Society for Industrial Microbiology. Demain, G. A.; Somkuti, Hunter-Cevera, J. C.; Rossmoore, H. W. Ed. **1989**, Chapter 10; page 79.

3. Tsuruo, T.; Oh-hara, T.; Iida, H.; Tsukagoshi, S.; Sato, Z.; Matsuda, I.; Iwasaki, S.; Okuda, S.; Shimizu, F.; Sasagawa, K.; Fukami, M.; Fukuda, K.; Arakawa, M. *Cancer Research*, **1986**, *46*, 381.
4. For total syntheses of rhizoxin, see: a) Nakada, M.; Kobayashi, S.; Iwasaki, S.; Ohno, M. *Tetrahedron Lett.* **1993**, *34*, 1035. b) Nakada, M.; Kobayashi, Shibasaki, M.; S.; Iwasaki, S.; Ohno, M. *Tetrahedron Lett.* **1993**, *34*, 1039. c) Kende, A. S.; Blass, B. E.; Henry, J. R. *Tetrahedron Lett.* **1995**, *36*, 4741.
5. For previous synthetic studies on rhizoxin, 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. c) Keck, G. E.; Park, M.; Krishnamurthy, D. *J. Org. Chem.* **1993**, *58*, 3787. d) Rama Rao, A. V.; Bhanu, M. N.; Sharma, G. V. M. *Tetrahedron Lett.* **1993**, *34*, 707. e) Rama Rao, A. V.; Sharma, G. V. M.; Bhanu, M. N. *Tetrahedron Lett.* **1992**, *33*, 3907. f) Boger, D. L.; Curran, T. T. *J. Org. Chem.* **1992**, *57*, 2235. g) Kobayashi, S.; Nakada, M.; Ohno, M. *Pure Appl. Chem.* **1992**, *64*, 1121.
6. a) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 1879. b) Keck, G. E.; Savin, K. A.; Cressman, E. N. K.; Abbott, D. E. *J. Org. Chem.* **1994**, *59*, 7889.
7. a) It was not possible to effect reaction of the aldehyde derived from the benzyl substrate **12** with allyltri-*n*-butylstannane with a high degree of stereoselectivity. In this case, use of 1.0 equiv. of Lewis acid ($TiCl_4$ or $MgBr_2$) did not promote reaction at all; with 2.0 equiv. reaction was observed, but without significant stereoselectivity. It seems likely that the first equivalent of Lewis acid is irreversibly sequestered by formation of a 5-ring chelate between the benzyl and methyl ethers in this case, thus preventing the desired chelation between the aldehyde oxygen and the methyl ether moieties. Use of the TBS silyl ether precludes the undesired sense of complexation. b) Keck, G. E.; Andrus, M. B.; Castellino, S. *J. Am. Chem. Soc.* **1989**, *111*, 8136. c) Keck, G. E.; Castellino, S. *Tetrahedron Lett.* **1987**, *28*, 281. d) Keck, G. E.; Castellino, S.; Andrus, M. B. Selectivities in Lewis Acid Promoted Reactions; Schinzer, D., Ed.; NATO ASI Series; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1989; Chapter 5.
8. a) In this case the β-alkoxy substituent is methoxy, which leads to little 1, 3 asymmetric induction in "chelation controlled" reactions, in contrast to more sterically demanding groups such as benzyl.[8b] In such cases (e.g. benzyl) the C_3 substituent adopts an axial position in the 6-ring chelate. It seems likely that the ether oxygen is essentially planar (sp^2 hybridized) in such chelates and that the preference for an axial C_3 substituent is due to allylic strain. b) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett.* **1984**, *25*, 1883. c) Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5478.
9. For descriptions of "chelation" vs "non-chelation" controlled reactions and 1,3 asymmetric induction, see: a) Reetz, M. T.; Harms, K.; Reif, W. *Tetrahedron Lett.* **1988**, *29*, 5881. b) Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556. c) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron* **1984**, *40*, 4327. d) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462.
10. For a closely related example, see: Nicolaou, K. C.; Claremon, D. A.; Barnette, W. E. *J. Am. Chem. Soc.* **1980**, *102*, 6611.
11. a) Jones-Hertzog, D. K.; Jorgensen, W. L. *J. Org. Chem.* **1995**, *60*, 6682. b) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147.
12. Keck, G. E.; Savin, K. A.; Weglarz, M. A. *J. Org. Chem.* **1995**, *60*, 3194.
13. Spectral data for compound **25**: 500 MHz ^1H NMR; 7.54 (s, 1 H), 7.24 (d, J = 8.3 Hz, 2 H), 6.86 (d, J = 8.3 Hz, 2 H), 5.55 (dd, J = 15.1, 11.2 Hz, 1 H), 6.37 (d, J = 15.1 Hz, 1 H), 6.25 (s, 1 H), 6.09 (d, J = 10.7 Hz, 1 H), 5.91 (m, 1 H), 5.08-5.00 (m, 2 H), 4.56 (d, J = 6.8 Hz, 1 H), 4.47 (d, J = 11.2 Hz, 1 H), 4.39 (d, J = 6.8 Hz, 1 H), 4.29 (d, J = 10.7 Hz, 1 H), 3.79 (s, 3 H), 3.61 (m, 1 H), 3.42 (m, 1 H), 3.31 (d, J = 8.3 Hz, 1 H), 3.27 (s, 3 H), 3.19 (s, 3 H), 2.49 (m, 1 H), 2.46 (s, 3 H), 2.14 (s, 3 H), 1.75 (s, 3 H), 1.58 (m, 1 H), 1.50 (dd, J = 13.7, 10.7 Hz, 1 H), 1.39 (dd, J = 14.7, 9.8 Hz, 1 H), 0.98 (d, J = 7.3 Hz, 3 H), 0.95 (d, J = 6.8 Hz, 3 H). 125 MHz ^{13}C NMR; 160.9, 159.1, 140.5, 138.7, 137.2, 137.0, 135.9, 131.1, 129.3, 124.2, 120.2, 114.4, 113.7, 96.8, 88.7, 79.5, 76.5, 70.7, 56.3, 55.6, 55.3, 53.4, 41.1, 37.5, 32.3, 14.8, 14.4, 13.9, 12.1, 10.0.

(*Received in USA* 9 *February* 1996; *revised* 10 *March* 1996; *accepted* 11 *March* 1996)