Synthetic Studies on the Rhizoxins. 1. Two Stereoselective Routes to a Functionalized C_1–C_9 Subunit

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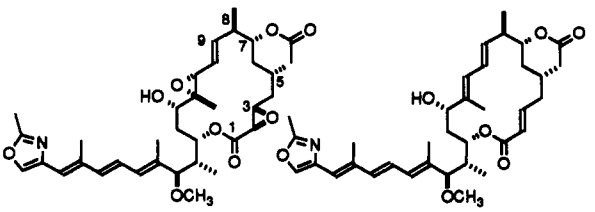
Summary: Two syntheses of a potential C_1–C_9 subunit of rhizoxin are described. In the first, chelation-controlled allylstannane addition to optically pure aldehyde **3**, conversion to unsaturated ester **7**, and stereoselective intramolecular Michael addition is used to establish the relative stereochemistry at C_7 and C_8 (rhizoxin numbering). In the second, an Evans aldol condensation is used to control absolute and relative stereochemistry at these centers. Both approaches use thermodynamic control to establish the correct stereochemistry at C_5.

The rhizoxin family of antibiotics, exemplified by rhizoxin itself (**1**) and the close structural analogue **2**, represent very promising lead compounds with potent *in vitro* cytotoxic activity and demonstrated *in vivo* antitumor activity.[1] The mechanism of action is thought to be similar

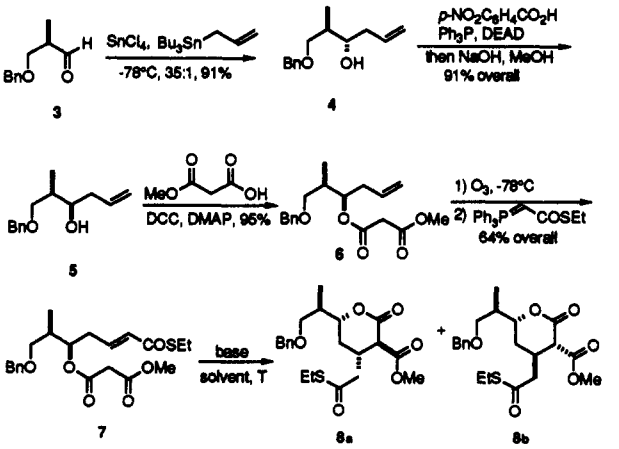


Rhizoxin 1 2

to, but distinct from, that of the clinically effective dimeric vinca alkaloids vincristine and vinblastine[2] and to involve rather specific pathways for inhibition of tubulin polymerization. Significantly, rhizoxin is effective against adriamycin and vincristine resistant cell lines and has been claimed to be both more potent and less toxic than vincristine.[3] The significant therapeutic potential of these compounds (and, possibly, structurally simplified analogues[4]) has encouraged us to undertake a major synthetic effort in this area.

Since rhizoxin (**1**) and its deoxygenated cogener (**2**) cooccur in the same fermentation, it seemed likely that **2** could be the biosynthetic precursor of **1** and that **2** (or a close relative lacking the triene–oxazole moiety) might be stereoselectively oxidized to **1** due to conformational constraints imposed by the densely functionalized 16-membered macrocyclic lactone moiety present in **2**. Thus, the total synthesis of **2** was chosen as one of our initial goals. We record herein a synthetic approach to a potential C_1–C_9 subunit of these materials.

The first synthetic approach to a C_1–C_9 fragment began with the known[5] addition of allyltrichlorostannane to aldehyde **3**, which afforded homoallylic alcohol **4** in 91% yield and with 35:1 diastereoselectivity. Our initial intent



was to process **4** directly to **6** *via* Mitsunobu esterification;[6] however, the reaction with methyl malonate was unexpectedly found to yield a mixture of diastereomers (3:1). Therefore an indirect approach was necessary. Mitsunobu esterification of **4** with *p*-nitrobenzoic acid, followed by hydrolysis (NaOH, MeOH, 91% overall), afforded alcohol **5**, which was esterified with methyl malonate (DCC, DMAP) to afford **6** in 95% yield. Ozonolysis, followed by Wittig chain extension with [carbothioethoxymethylidene]-triphenylphosphorane[7] then gave the *trans* unsaturated thiol ester **7** (64% overall). Intramolecular Michael reaction was then easily effected (cesium carbonate, acetonitrile, 0 °C) to give a mixture of two diastereomers, **8a** and **8b**, in which **8a** predominated (>8:1 ratio[8]).

Several features of this reaction proved to be noteworthy; the most salient experimental data are summarized in Table I. Most dramatic is the dependence of diastereoselectivity on the base employed, with **8a** favored to a substantial and synthetically useful level with cesium carbonate, while **8b** predominated (and to a similar extent) when sodium hydride was used. Changing solvent from

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(4) Kato, Y.; Ogawa, Y.; Imada, T.; Iwasaki, S. *J. Antibiot.* **1991**, *44*, 66.

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(8) This product ratio varied slightly from run to run, in the range of 8:1 to 10:1.

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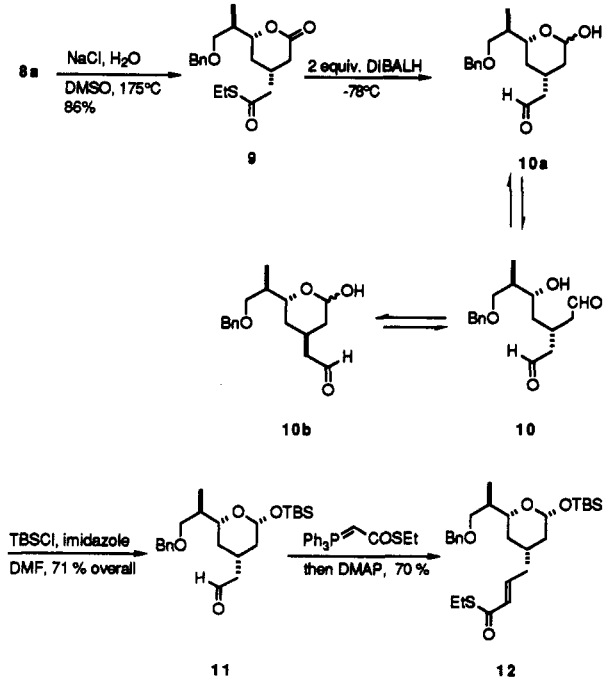
Table I. Diastereoselectivity of Intramolecular Michael Addition[a]

		reaction condns/ratios (8a:8b)			
base	solvent	25 °C (4 h)	25 °C (12 h)	45 °C (4 h)	65 °C (12 h)
Cs_2CO_3	CH_3CN	8:1	8:1	9.6:1	11:1[b]
	C_6H_6	8:1	8:1	*c*	*c*
NaH	CH_3CN	1:8	1:8	*c*	*c*
	C_6H_6	1:8	1:8	*c*	1:2.4[b]

[a] Product ratios were determined by HPLC analysis. [b] These products were also isolated and analyzed by NMR spectroscopy. [c] Accurate product ratios could not be obtained in these experiments due to the formation of unidentified side products.

acetonitrile to benzene had little effect on the ratio of products. Moreover, when a mixture enriched in **8b** (ca. 10:1, obtained from the NaH cyclization conditions) was subjected to exposure to cesium carbonate in acetonitrile at room temperature, the ratio of **8b** to **8a** was unchanged. The ratio was also unchanged upon warming to 45 °C and observed to decrease (to *ca.* 5:1, some decomposition also noted) upon heating at 65 °C for 24 h, but did *not* reverse to favor **8a**.[9] Thus, *both 8a and 8b appear to be the products of kinetic control* under the two different sets of reaction conditions, although a *small* amount of equilibration (favoring **8a**) may contribute to the overall predominance of **8a** using cesium carbonate. For the purposes of the present synthesis both **8a** and **8b** can be processed to afford **12** (*vide infra*), but the stereoselective formation of either diastereomer by choice of reaction conditions is unusual and could prove very useful in other contexts.

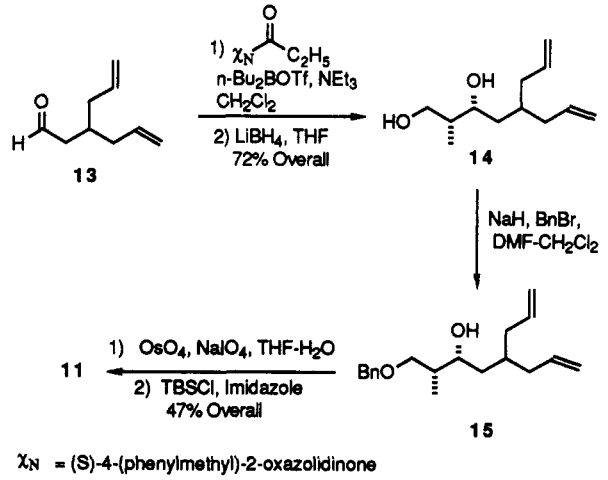


(9) It seems likely that the microscopic reverse of the pathway leading from 7 to 8 is not accessible due to kinetic and essentially irreversible deprotonation of 8 at the β-dicarbonyl position.

Key to the planning of both routes described herein was the expectation that C_5 stereochemistry could be established based on simple thermodynamic considerations, *via* equilibration between lactols **10a** (C_5 and C_7 substituents both equatorial) and **10b** (one of these substituents axial).

Methyl ester cleavage of **8** with concomitant decarboxylation afforded lactone **9** (86%) which was reduced with DIBALH (2 equiv, −78 °C) to afford an equilibrating mixture of lactols **10**.[10] Upon silylation (TBS-Cl, DMF, imidazole) a *single* silyl ether **11** (71% from **9**) was produced, which then underwent Wittig chain extension to afford the desired intermediate **12**.

The second approach, expected to be more amenable to large-scale preparations, began with an Evans[11] aldol condensation of (*S*)-4-(phenylmethyl)-2-oxazolidinone with aldehyde **13**,[12] which afforded the desired aldol product as a single diastereomer; reductive removal of the Evans auxiliary gave the key diol **14** in 72% overall yield. After selective protection of the primary hydroxyl in **14**,[13] oxidative cleavage of the terminal vinyl units afforded (NMR analysis) the same equilibrating mixture of lactols as obtained *via* the former route; silylation as before then yielded **11**.



χ_N = (S)-4-(phenylmethyl)-2-oxazolidinone

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Supplementary Material Available: Complete experimental details and spectral and characterization data for all new compounds (32 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(10) These are easily distinguished by NMR spectroscopy.

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(12) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1726.

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(14) For other recent synthetic studies on rhizoxin, see: (a) Rama Rao, A. V.; Sharma, G. V. M.; Bhanu, M. N. *Tetrahedron Lett.* **1992**, *27*, 3907. (b) Boger, D. L.; Curran, T. T. *J. Org. Chem.* **1992**, *57*, 2235. (c) Rama Rao, A. V.; Bhanu, M. N.; Sharma, G. V. M. *Tetrahedron Lett.* **1993**, *34*, 707.