Pergamon

Tetrahedron Letters, Vol. 36, No. 34, pp. 6033-6036, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01194-3

RHIZOXIN SYNTHETIC STUDIES. 2. SYNTHESIS OF THE LEFT HAND [C(10) TO C(19)] AND POLYENE FRAGMENTS

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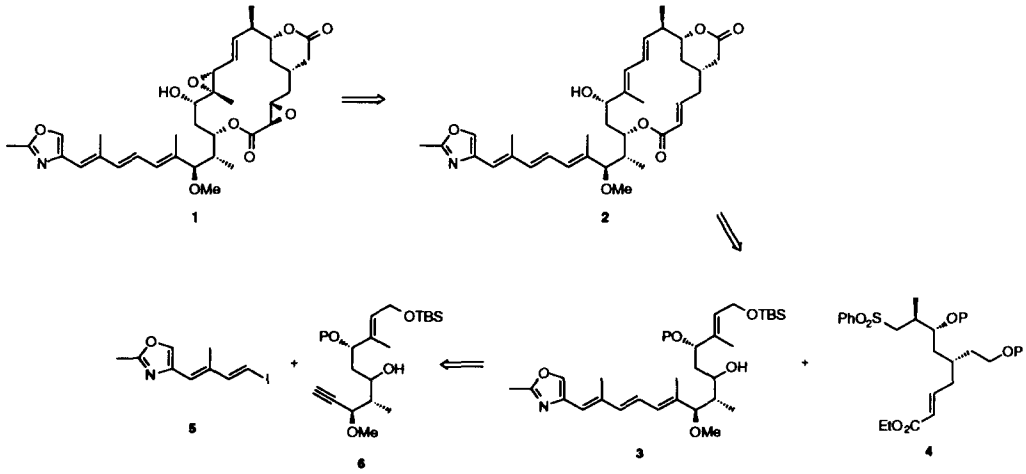
Abstract: The syntheses of the central core and the polyene fragments of the antitumor macrolide rhizoxin have been achieved in an efficient manner. The core has been prepared in enantiopure form via an asymmetric allylation/aldol protocol. The selective oxidation of dienes was studied and realized in fair yield to generate the requisite aldol precursor. The oxazole polyene fragment was generated in six steps from serine.

We have recently embarked on an endeavor aimed at the enantioselective total synthesis of rhizoxin (**1**, Scheme I).[1] This 16-membered macrolide exhibits profound antimitotic activity, and is currently under phase II clinical trials as a potential anticancer treatment.[2] Rhizoxin contains a number of intriguing structural features, including a polyene oxazole moiety and a pair of epoxides on the macrocycle.[3] We wish to report here our synthetic efforts toward the generation of the central C(10) - C(19) fragment as well as the C(20) to C(26a) olefinic oxazole portion.

We will prepare rhizoxin from the related natural product WF-1360C (**2**).[4] Disconnection about the olefinic linkage and the macrolide leads to the initial targets **3** and **4**. The natural stereochemistry of rhizoxin

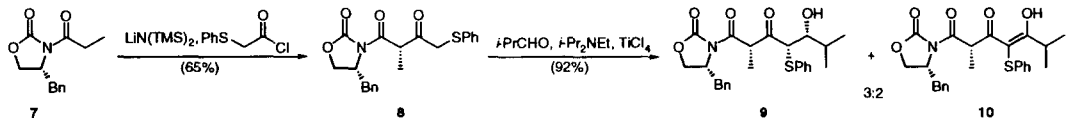
Scheme I



is such that an aldol with the *anti*-stereochemical outcome would need to be employed if standard macrolactonization methods were to be employed.[5] We have undertaken an effort to realize an effective method for the generation of *anti*-aldol products.[6] However, Mitsunobu macrolactonizations have been proven effective without adding any additional synthetic manipulations.[7] Therefore, we approached **3** and **6** as synthetic targets that would allow considerable flexibility in their preparation via either a *syn* or *anti* aldol addition. Advanced target **3** will be prepared via a Negishi carbometallation coupling of **5** and **6**,[8] which will allow for the preparation of the trisubstituted olefin without concern over potential stereochemical outcome. We will detail here the syntheses of these two fragments of rhizoxin.

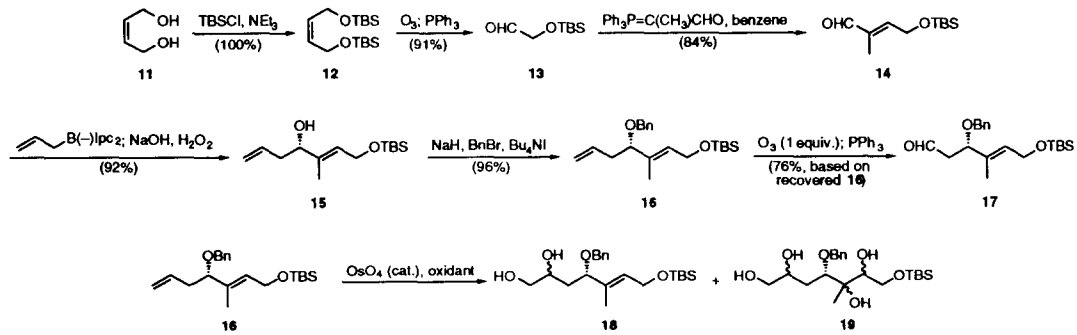
One of our original attractions to this project was the ability to address methods for the synthesis of *anti*-aldol adducts. We had originally intended to expand upon the β-ketoimide methodology developed by Evans.[9] Specifically, we sought to use a thioether substituted ketoimide that could be reductively removed at a later stage in the synthesis. Directed reduction of the ketone or intramolecular Tishchenko reaction would effect the overall *anti*-aldol addition.[10] In reality, however, the aldol addition gave a mixture of two products (Scheme II).[11] The main byproduct was in fact oxidized adduct **10**. While we have not abandoned our efforts to derive *anti*-aldol connections, we turned our attention in this case to the more easily accessible *syn*-adduct.

Scheme II



Following bis-silylation of *cis*-2-buten-1,4-diol, ozonolysis gave the requisite aldehyde **13** (Scheme III). Wittig olefination with 2-(triphenylphosphoranylidene)propionaldehyde gave **14** as a single isomer, and asymmetric allylation in the manner of Brown afforded allylic alcohol **15** in good yield and high enantiomeric purity (88% ee).[12] The allylic alcohol thus formed was protected as a benzylic ether (**16**). Selective ozonolysis of **16** was accomplished to generate the desired aldehyde, which we were able to use in our subsequent synthetic endeavor. However, we were also interested in the possibility of an alternative selective oxidation of the terminal olefin. We were unsure of the viability of performing this in a selective fashion, since Sharpless had previously reported on the selective kinetic dihydroxylation of trisubstituted olefins in the

Scheme III

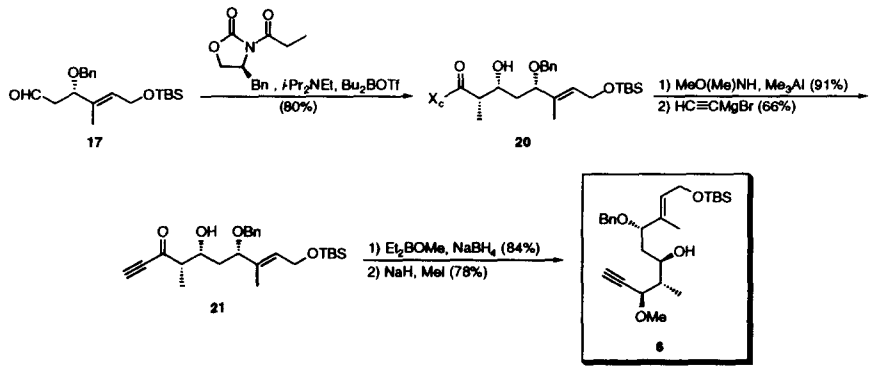


stoichiometric oxidant	yield	ratio (18/19)
$K_3Fe(CN)_6$	65%	2:1
N-Methylmorpholine *N*-oxide	73%	5:1

presence of other olefins (including primary olefins).[13] However, the presence of allylic oxidation appears to retard this selectivity.[14] Given that our substrate possesses two allylic ethers, we rationalized that we might be able to control this oxidation. Toward this end, osmylation with potassium ferrocyanide as the stoichiometric oxidant led to a 2:1 mixture of products, where the major isomer was oxidized exclusively at the terminal olefinic position. Optimization of this reaction with NMO as the oxidant led to an improved yield and ratio, but unfortunately was still not synthetically useful. It is noteworthy, however, that under no circumstances did we observe exclusive oxidation of the more substituted olefin. Work is underway in our group to optimize conditions for the selective oxidation of functionalized polyenes.

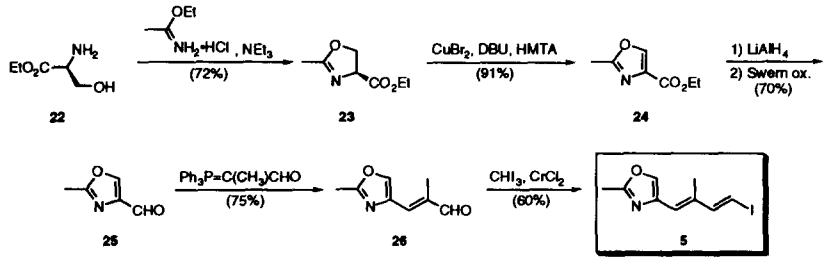
The aldehyde obtained above was subjected to boron aldol conditions to yield **20** as a single product (Scheme IV). Following conversion of the auxiliary to the Weinreb amide,[15] ethynylmagnesium bromide was added to give the corresponding acetylenic ketone (**21**). Chelation controlled reduction installed the final stereocenter with complete selectivity,[16] and selective methylation of the propargylic alcohol provided the first of our two targets.

Scheme IV



The point of departure for the preparation of the polyene fragment was L-serine ethyl ester (**22**, Scheme V). Treatment with ethyl acetimidate generated the oxazoline, and oxidation in the manner of Myers provided the requisite oxazole (**24**).[17] The ester was transformed into the corresponding aldehyde via a two-step protocol, and Wittig olefination gave the desired aldehyde **26** as a single isomer. Takai reaction then gave the anticipated *E*-vinyl iodide **5** as the second target.[18]

Scheme V



In conclusion, we have realized efficient syntheses of the C(10) - C(19) and C(20) - C(26a) portions of the antitumor macrolide rhizoxin. Compound **6** was prepared in enantiopure form with the unnatural

stereochemistry at C(15) in anticipation of performing a Mitsunobu macrolactonization. The use of **5** and **6** toward the total synthesis of rhizoxin is currently being pursued in our laboratories.

Acknowledgments. We gratefully acknowledge the National Science Foundation (NSF CHE-9502507) and the University of California Cancer Research Coordinating Committee for their financial support. We also thank the NSF and Eastman Kodak for predoctoral fellowships to JAL and DPP, and the College of Chemistry for providing start-up funds that were used in this endeavor. The technical assistance of Mr. David Zillman in the preparation of large quantities of **26** was greatly appreciated.

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(*Received in USA* 19 *May* 1995; *revised* 21 *June* 1995; *accepted* 22 *June* 1995)