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Synthesis of a C1–C9 fragment of rhizoxin

Richard J. Davenport and Andrew C. Regan*

Department of Chemistry, The University of Manchester, Oxford Road, Manchester M13 9PL, UK

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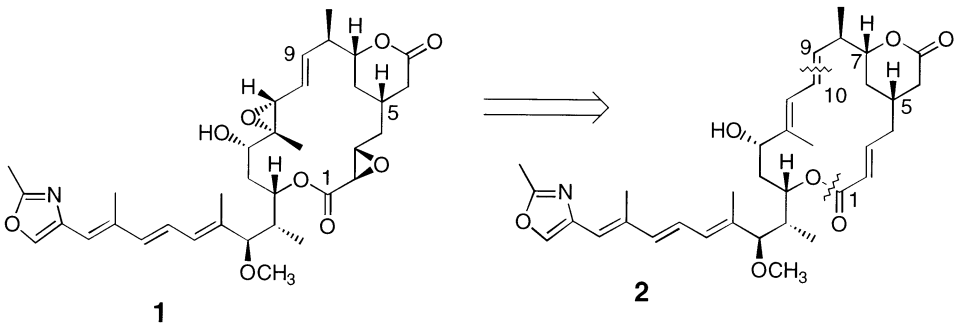
Abstract

A C1–C9 fragment of the antitumour macrolide rhizoxin has been synthesised. An Evans' asymmetric aldol reaction was used to set up the first two chiral centres, and an α,β-unsaturated δ-lactone was then formed on the acyclic system by an intramolecular Wadsworth–Emmons reaction. Stereoselective hydrogenation was used to set up the *cis* relative stereochemistry in the saturated δ-lactone ring. © 2000 Published by Elsevier Science Ltd.

Rhizoxin **1**, a macrolide isolated from *Rhizopus chinensis* in 1984,[1] has a 16-membered macrocyclic ring structure, which also unusually bears two epoxides, and a δ-lactone at C5–C7. Rhizoxin has antitumour activity, and acts as an antimitotic agent by binding to tubulin.[2] It has recently undergone clinical trials for a variety of cancers.[3] The didesepoxy macrolide rhizoxin D **2** is a putative biosynthetic precursor of rhizoxin.[4] Not surprisingly, in view of its biological activity and structural complexity, rhizoxin has attracted considerable synthetic interest,[5] and both rhizoxin[6] and rhizoxin D[7] have recently been synthesised.



Scheme 1.

* Corresponding author. Fax: +44 161 275 4617; e-mail: andrew.regan@man.ac.uk

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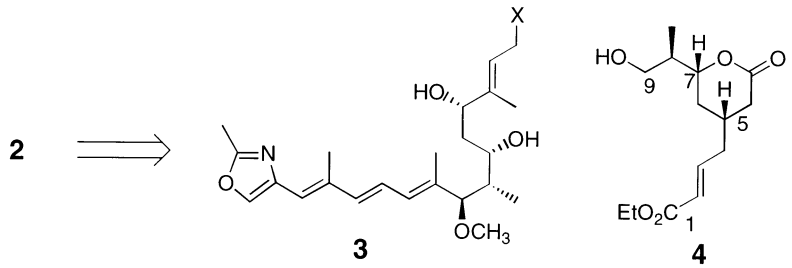
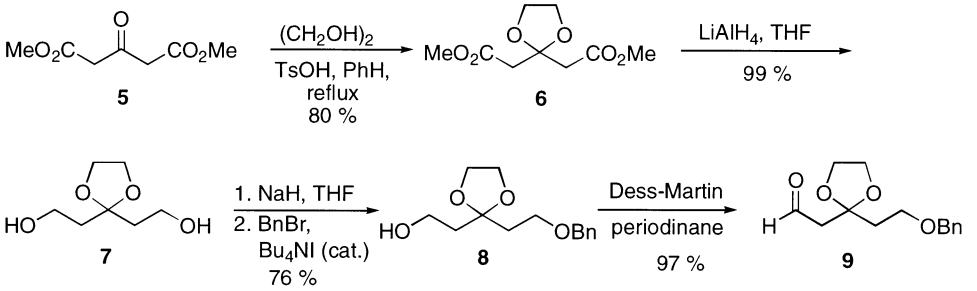
The retrosynthetic analysis for our planned synthesis of rhizoxin is shown in Schemes 1 and 2. Disconnection of the macrolide ring in **2** at the C–O bond of the lactone and at the C9–C10 alkene gives the two fragments **3** and **4**. A similar disconnection strategy has also been used by other groups.[5b,d,h,6,7c] Our approach to the C1–C9 fragment **4** is based upon formation of the 5,7-*cis* stereochemistry about the δ-lactone by stereoselective hydrogenation of a suitable α,β-unsaturated lactone, which in turn will be created by an intramolecular Wadsworth–Emmons ring closure. The two stereogenic centres in the acyclic precursor will be formed using an Evans' asymmetric aldol reaction on the protected aldehyde **9** (Scheme 3).



Scheme 2.

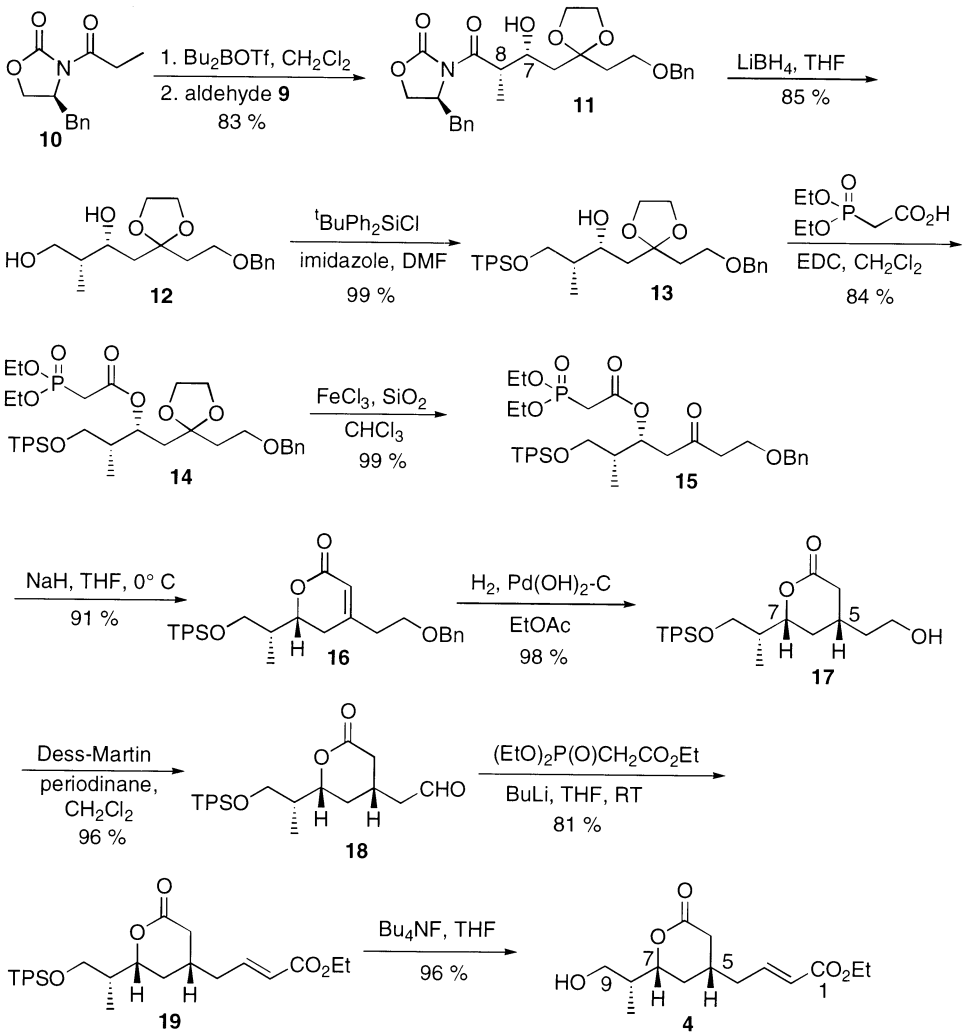


Scheme 3.

Dimethyl acetonedicarboxylate **5** was chosen as the starting material for the preparation of aldehyde **9**, since it already contains a five-carbon chain with the required 1,3,5-oxygenation pattern. The ethylene ketal **6** was prepared in conventional manner (Scheme 3), and the two ester groups were then reduced to primary alcohols using lithium aluminium hydride. Monoprotection of the resulting diol **7** afforded the monobenzyl ether **8** in a greater than statistically expected yield of 76%. Finally the remaining hydroxyl group was oxidised using the Dess–Martin periodinane[8] to give the aldehyde **9**.

An Evans' asymmetric aldol reaction[9] between the *N*-propionyloxazolidinone **10** and aldehyde **9** was then used to set up the first two chiral centres at C7 and C8 in **11** (Scheme 4). The aldol product **11** was formed as a single diastereoisomer, as judged by 500 MHz ^{1}H NMR spectroscopy, and the 7,8-*syn* relationship was confirmed by the small vicinal coupling constant of 5 Hz. The chiral auxiliary was removed by reduction with $LiBH_4$ to give the diol **12**, which was then selectively protected on the primary alcohol group as the *tert*-butyldiphenylsilyl ether. The remaining secondary alcohol group in **13** was then converted into the diethyl phosphonoacetate ester **14** using a carbodiimide coupling, and the ethylene ketal protecting group was selectively removed with $FeCl_3$ on silica gel,[10] to give the ketone **15**. Intramolecular Wadsworth–Emmons reaction[11] of **15** using sodium hydride as the base then gave the unsaturated lactone **16**

in 67% yield (91% based on unrecovered starting material), whereas the combination of lithium halide salts and amine bases resulted in substantial amounts of β-elimination.



Scheme 4.

Stereoselective hydrogenation of the unsaturated lactone **16** gave exclusively the *cis*-disubstituted lactone **17**, and the stereochemistry was confirmed by observation of the expected large *trans*-diaxial coupling constants.[12] The benzyl protecting group on the side chain had been chosen from the outset in order that it would also be removed during this hydrogenation step. The primary alcohol group thus revealed in **17** was oxidised to the aldehyde **18** using the Dess–Martin periodinane, and the side chain was then extended in a Wadsworth–Emmons reaction, to give the *E*-α,β-unsaturated ester **19**. Finally, deprotection of the silyl group afforded the target C1–C9 fragment **4** of rhizoxin.

In summary an efficient route to a C1–C9 fragment of rhizoxin has been developed (13 steps, 24% overall yield to the protected fragment **19**), which compares well with other approaches to related C1–C9 intermediates.

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12. ^{1}H NMR coupling constants: O=C·CH$_{ax}$–CH$_{ax}$ $J=10.5$ Hz, and O–CH$_{ax}$–CH$_{ax}$ $J=13.0$ Hz.