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Studies Directed Towards the Total Synthesis of Rhizoxin[1] : Stereoselective Synthesis of C-12 to C-18 Segment

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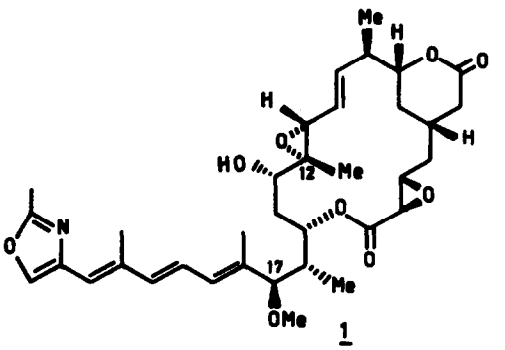
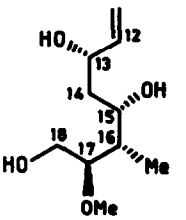
Keywords: Butanolide chiral template; Chiral carbinol; Intramolecular radical cyclisation; Vinyl Grignard reaction.

Abstract: Chiral carbinol **5**, made by a titanocene mediated ring opening of epoxy alcohol **11**, was converted via an intramolecular radical cyclisation into a 'butanolide template' which was then transformed to the C-12 to C-18 segment **2** of rhizoxin (**1**).

Rhizoxin (**1**), a 16-membered antinumor macrolide antibiotic is produced by Rhizopus chinensis[2]. It has shown[3] potent antifungal, antimicrobial, cytotoxic and antitumor activities and therapeutic effects similar to those of Vincristine against L1210 and P388 leukemia-bearing mice. Extensive spectroscopic studies in conjuction with a single crystal X-ray analysis[2a,4] revealed **1** to be a 16-membered lactone ring embodied with 11 stereocentres. The potential usefulness of **1**, with its unique structural features has prompted our investigation of the total synthesis of **1**, which had earlier resulted in the synthesis of the C-1 to C-9 segment[1]. In continuation of our efforts towards the total synthesis of **1**, we report herein the first approach for the synthesis of the C-12 to C-18 segment **2** of rhizoxin (**1**).



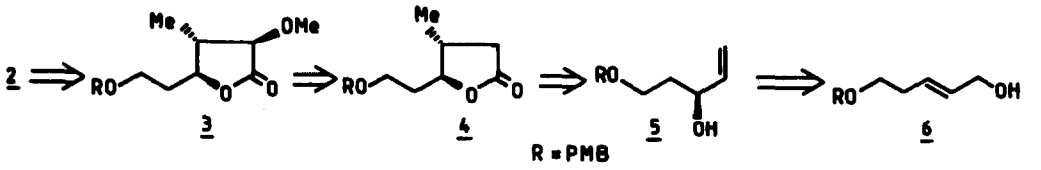
1



2

Our strategy for the synthesis of **2** was based on the retrosynthetic analysis shown in scheme 1. **2** could be envisioned from the furanone **3** - containing three contiguous stereocentres - which in turn would result from the 'butanolide chiral template' **4**. Lactone **4** could be made via an intramolecular radical cyclisation of carbinol **5**, which is obtained by a titanocene mediated regioselective ring opening of epoxy alcohol generated from allylic alcohol **6**.

Scheme 1



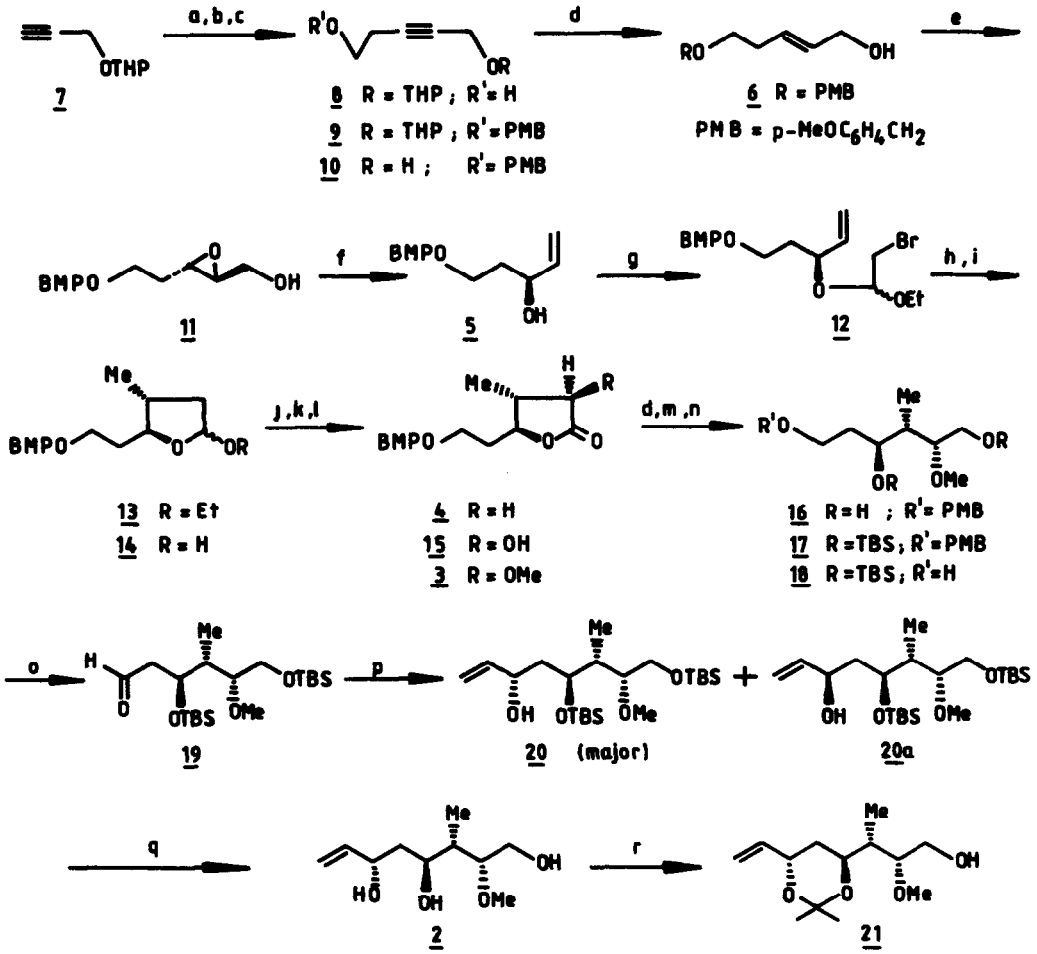
The first phase of the synthesis of **2** was aimed at the construction of carbinol **5**, whose lone stereocentre is correlated to the C-15 of rhizoxin (**1**), starting from commercially available propargyl alcohol (Scheme 2). Accordingly, 3-tetrahydropyranyloxy propyne (**7**) on hydroxy alkylation (ethylene oxide, $LiNH_2$/liq. NH_3) and subsequent protection of the hydroxy function in **8** (PMBBr, NaH, THF)[5] afforded **9** (87%). Acid (aq. HCl, THF)-catalysed depyranylation of **9** followed by reduction of **10** (LAH, THF) gave the allyl alcohol **5** (88%). Alcohol **5** under standard Sharpless asymmetric epoxidation[6] conditions using (+)-DIPT (TBHP, Ti^{i}P, DCM, 2 h) furnished the epoxy alcohol **11** with high optical purity (95%, ee), $[\alpha]_D$ -32.1° (c 1.7, $CHCl_3$). The regioselective ring opening of **11** with titanocene[7] in presence of zinc in the form of $ZnCl_2$ in THF at room temperature proceeded smoothly and provided the chiral carbinol **5** in 62% yield, $[\alpha]_D$ +8.5° (c 2.0, $CHCl_3$).

At this stage, the stereospecific introduction of the methyl group (C-16 of **1**) was attempted using a very well documented[8] intramolecular radical cyclisation of a 5-hexenyl radical through the corresponding mixed bromo acetal. Accordingly, carbinol **5** was subjected to a reaction with ethyl vinyl ether in presence of NBS[9,10] to afford the mixed bromoacetal **12** (75%), the prerequisite for radical cyclisation reaction. The crucial intramolecular radical cyclisation of **12** was effected (n-Bu_3SnCl, $NaCNBH_3$[11], AIBN) in t-butanol at reflux in a regio- and stereoselective fashion by a 5-exo mode to provide the furan **13** (72%). Thus the absolute stereogenecity at C-methyl in **13** was effectively controlled by the hydroxy stereocentre of carbinol **5** during the radical cyclisation[12] of 5-hexenyl radical. Acid hydrolysis (aq. HCl) of **13** and subsequent oxidation of the resultant lactol **14** with PDC in DCM afforded the furanone **4** in 72% yield, $[\alpha]_D$ -58.9° (c 1.1, $CHCl_3$).

The butanolide chiral template **4** thus generated was efficiently utilised for the stereoselective incorporation of the hydroxy functionality (C-17 of **1**). When **4** was subjected to MoOPH oxidation[13] under standard reaction conditions [LiN($SiMe_3$)$_2$, MoOPH, THF], the hydroxylation directed by the methyl substituent took place from the β-face thereby providing 3-β-hydroxy-4-α-methyl-2-furanone (**15**) (68%), which on direct subjection to methylation (wet Ag_2O, MeI) afforded **3**, $[\alpha]_D$ -22.1° (c 0.34, $CHCl_3$). Thus, the stereocenter introduced in **5** by Sharpless asymmetric epoxidation has been translated by the sequential introduction of methyl and hydroxy functions on the fully functionalised lactone **3**, the C-2, C-3 and C-4 of which correspond to the C-17, C-16 and C-15 of **1** respectively.

Having made the lactone **3** with three sequential stereocentres (correlated to C-15 to C-17 of **1**), our efforts were then directed toward the introduction of hydroxy group of **2** (correlated to C-13 of **1**). Accordingly, lactone **3** was subjected to LAH reduction to afford diol **16**, which on silylation (TBSCl, imidazole, DMF) gave the disilylate **17**. Deprotection of

Scheme - 2



a) $LiNH_2$/liq. NH_3, ethylene oxide; b) NaH, PMBBr, THF; c) aq. HCl, THF; d) LAH, THF; e) DIPT, TIP, TBHP, CH_2Cl_2; f) titanocene, Zn, $ZnCl_2$, THF; g) NBS, ethyl vinyl ether, CH_2Cl_2; h) Bu_3SnCl, $NaCNBH_3$, AIBN, t-BuOH; i) aq. HCl; j) PDC, CH_2Cl_2; k) $LiN(SiMe_3)_2$, MoOPH, THF; l) wet Ag_2O, MeI, CH_2Cl_2; m) TBDMSCl, imidazole, DMF; n) DDQ, CH_2Cl_2-H_2O (19:1); o) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2; p) Vinyl magnesium bromide, THF; q) Bu_4NF, THF; r) dimethoxypropane, PTSA.

PMB ether in **17** (DDQ[5], aq. DCM, 1:19) gave **18** which on Swern oxidation furnished the aldehyde **19**. Addition of vinyl Grignard to **19** in THF proceeded with a modest level of selectivity to provide the required trans-1,3-diol **2** (82%) in 2.5:1 as a readily separable mixture of stereoisomers (**20**,**20a**; silica gel-Acme, 60-120 mesh, hexane-ethyl acetate; 9:1). Finally the stereochemistry of the newly created center in **20** was confirmed from the NMR anlysis[14] of the corresponding acetonide **21** prepared in two steps from **20**: a) desilylation of **20** (n-Bu_4NF,

THF) and b) acetonation of resultant **2** (dimethoxy propane, PTSA).

Thus, in conclusion **2** has been made in its absolute stereochemical confirmation from the carbinol **5**, the stereochemistry of which has been very well exploited in the generation of two more contiguous stereocentres by a radical cyclisation reaction and MoOPH oxidation. Having made the right half[1] and the left half **2** with well differentiated ends, further work in the direction of total synthesis of **1** is in progress.

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