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Radical Mediated Enantioselective Construction of C-1 to C-9 Segment of Rhizoxin

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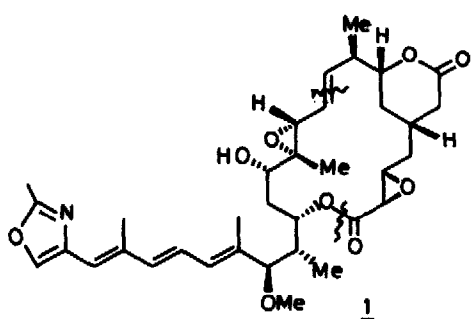
Abstract: A highly enantioselective route has been devised for the synthesis of the 3,5-cis-disubstituted valerolactone moiety (C-1 to C-9 segment) of rhizoxin via intramolecular radical cyclisation of suitably functionalised 6-heptenyl radical.

Rhizoxin (**1**) is a 16-membered antitumor macrolide antibiotic isolated[1] from Rhizopus chinensis Rh-2, the pathogen of the rice seedling blight. It exhibits[2,3] potent antifungal and antimitotic activities and showed similar chemotherapeutic effects to those of vincristine against L1210 and P388 leukemia-bearing mice. Its absolute structure also has been determined by extensive spectroscopic investigations[4]. The structure-activity studies[5] revealed that the uncommon cis-disubstituted 6-membered lactone moiety is important along with the 16-membered lactone conformation. The unique structural and functional features along with its appreciative antitumor activity has prompted us to undertake a total synthesis of **1**. In this direction, herein we describe the first synthetic route for the construction of the rare lactone moiety **2**, constituting C-1 to C-9 carbon framework of rhizoxin (**1**), by a highly regio- and stereoselective intramolecular radical cyclisation approach.



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From the retrosynthetic reasoning of **2** (Scheme 1), it was envisioned that the 3,5-cis-disubstituted valerolactone **2** could be stereoselectively made by a regioselective intramolecular Michael type of cyclisation of a radical generated from ω-alkenyl halide, to α,β -unsaturated ester. Mixed bromoacetal **3**, a prerequisite for radical cyclisation would come from the chiral

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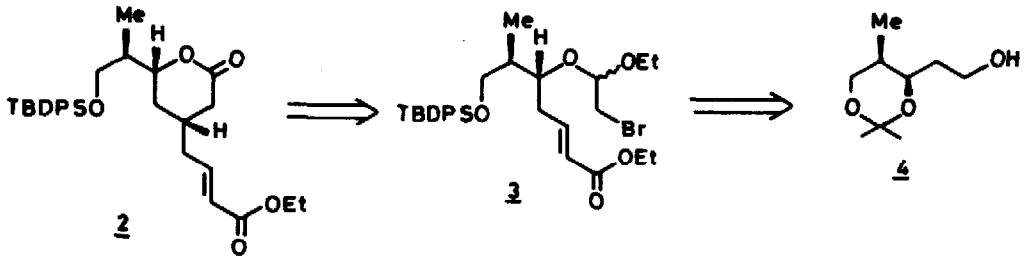
1,3-propane diol **4**, which in turn could be reasoned from the cis-allylic alcohol **9**. Thus the key step in the synthetic strategy for the formation of lactone **2** involves a much less investigated radical cyclisation of a 6-heptenyl radical system[6].

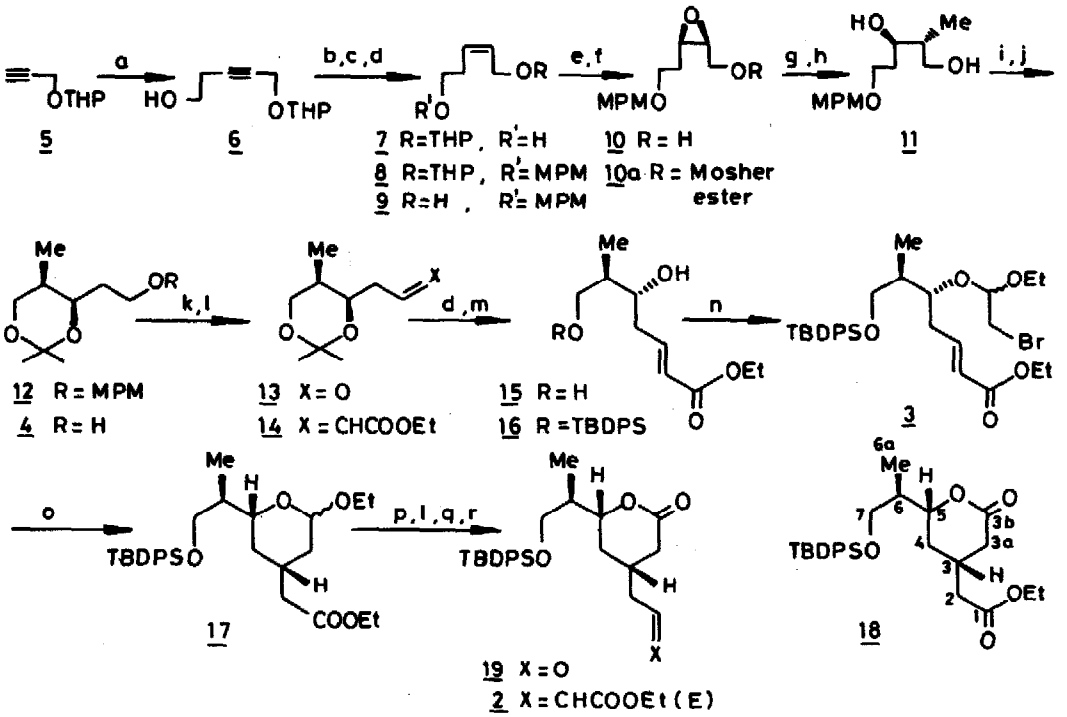
Scheme 1



The chiral 1,3-propane diol **4** was made starting from propargyl alcohol (Scheme 2). Thus, hydroxy alkylation of 3-tetrahydropyranyloxy propyne **5** with ethylene oxide furnished homopropargyl alcohol **6** which on semihydrogenation in the presence of $P(II)Ni/H_2$ afforded the cis-allylic alcohol **7**. Protection of hydroxy functionality in **7** with MPMBr, followed by depyranylation of **8** with HCl gave the alcohol **9**. Sharpless asymmetric epoxidation[7] of **9** with (+)DIPT provided the epoxy alcohol **10**, $[\alpha]_D$ -9.02 (c 2.83, $CHCl_3$), whose optical purity (92% ee) was estimated from ^{19}F NMR (400 MHz) spectrum of the corresponding (S)-α-methoxy-α (trifluoromethyl)phenyl acetate (**10a**). The chiral 1,3-propane diol **11** was obtained in a 2 step sequence from **10**. Regioselective ring opening of epoxide **10** with Me_2CuLi in ether at -78°C furnished a mixture of 1,2 and 1,3-diols, which as such was subjected to $NaIO_4$ cleavage affording the requisite 1,3-diol **11**, $[\alpha]_D$ -7.71 (c 1.4, $CHCl_3$). Diol **11** on acetonation with dimethoxy propane furnished the 1,3-O-isopropylidene derivative **12** $[\alpha]_D$ +18.3° (c 1.15, $CHCl_3$) which on subsequent reaction with DDQ gave the alcohol **4**. Swern oxidation of hydroxy function in **4** followed by Wittig olefination of the resultant **13** with (ethoxymethylene)triphenylphosphorane provided the (E)-α,β-unsaturated ester **14**.[8].

The requisite bromoacetal **3** was then obtained from **14** in a 3 step sequence. Accordingly acid catalysed hydrolysis of **14** and subsequent selective protection of the primary hydroxy group in the resultant diol **15** with TBDPSCl gave **16**. Alkoxy bromination of ethyl vinyl ether with homoallylic alcohol **16** in the presence of NBS[9,10] afforded the mixed bromo acetal **3**. The crucial intramolecular radical[11] ring closure to give the tetrahydropyran ring was performed by refluxing **3** in the presence of a catalytic amount of Bu_3SnCl and $NaCNBH_3$[12] in t-butanol containing catalytic amount of AIBN to provide **17** as a diastereomeric mixture. The cyclisation indeed occurred from the expected 6-exo mode[13,14], as was evident from the ^1H NMR (400 MHz) spectrum of **18**. Hydrolysis of compound **17** with 70% aq. AcOH and subsequent oxidation of the resultant lactol with PDC gave the lactone **18**. From the ^1H NMR spectrum studies of **18**, it was amply evident that H-3 and H-5 are in 1,3-cis diaxial relationship. Thus the high stereoselectivity in the exclusive formation of only one isomer of **18** can be attributed

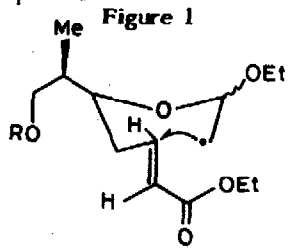
Scheme - 2



a) $LiNH_2$/liq.NH_3, ethylene oxide, 10 h, 65%; b) P(II)Ni, H_2, EtOH, 3 h; c) NaH, MPMBr, THF, 6 h; d) conc. HCl, MeOH, 2 h; e) (+)DIPT, TIP, TBHP, CH_2Cl_2, -20°, 48 h, 76%; f) MTPACl, Et_3N, CH_2Cl_2; g) Me_2CuLi, ether, -78°, 5 h, 71%; h) $NaIO_4$, aq. THF (1:1), 2 h, 1,3-diol (59%); i) Dimethoxypropane, PTSA, 2 h; j) DDQ, CH_2Cl_2-H_2O (19:1), 30 min; k) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78°, 86%; l) $Ph_3P{=}CHCO_2Et$, benzene, 8 h, 73%; m) TBDPSCl, imidazole, DMF, 12 h, 71%; n) NBS, ethylvinylether, CH_2Cl_2, -10° to RT, 5 h, 88%; o) Bu_3SnCl, $NaCNBH_3$, AIBN, t-BuOH, 1 h, 78%; p) DIBAL-H, CH_2Cl_2, -15°, 2 h, q) Aq. AcOH (70%), 60°, 2 h; r) PDC, CH_2Cl_2, 7 h, 78%.

to the cyclisation through the most stable conformation as shown in Fig.1. The most stable conformer for 6-exo ring closure of a heptenyl radical resembles a distorted chair form in which the olefinic double bond exists in a pseudo equatorial position, thereby resulting in the exclusive formation of only one product.

Figure 1



Having confirmed the stereochemistry of the newly formed C-C bond by spectral studies, a further sequence of reactions was carried out on **17** to furnish the target moiety **2**. DIBAL-H reduction of the ester function in **17** and subsequent Wittig reaction on **19** with (ethoxymethylene)triphenylphosphorane furnished **20** as a diastereomeric mixture. Hydrolysis of **20** with aq. AcOH followed by PDC oxidation of the lactol gave the lactone **2**, $[\alpha]_D$ -9.56 (c 0.23, $CHCl_3$), whose structure was unambiguously confirmed from ^1H NMR spectrum.

Thus, in conclusion, the regio- and stereocontrolled radical cyclisation of suitably functionalised 6-heptenyl radical led to the construction of the requisite lactone **2**. This further extension of the 6-heptenyl radical cyclisation may find wide applicability in natural products synthesis.

References and Notes:

1. Iwasaki, S; Kobayashi, H; Furukawa, J; Namikoshi, M; Okuda, S; Sato, Z; Matsuda, I; Noda, T; J. Antibiotics, 1984, **37**, 354-362.
2. Tsuruo, T; Oh-hara, T; Ida, H; Tsukagoshi, S; Sato, Z; Matsuda, I; Iwasaki, S; Shimizu, F; Sasagawa, K; Fukami, M; Fukuda, K; Arakawa, M; Cancer Res, 1986, **46**, 381-385.
3. Ibaragi, T; Ann. Phytopath. Soc. Jpn, 1973, **39**, 141.
4. Iwasaki, S; Namikoshi, M; Kobayashi, H; Furukawa, J; Okuda, S; Itai, A; Kasuya, A; Iitaka, Y; Sato, Z; J. Antibiotics, 1986, **39**, 424-429.
5. Kato, Y; Ogawa, Y; Imada, T; Iwasaki, S; J. Antibiotics, 1991, **44**, 66-75.
6. Ihara, M; Yasui, K; Taniguchi, N; Fukumoto, K; J. Chem. Soc. Perkin Trans-I, 1990, 1469-1476.
7. a)Sharpless, K.B; Katsuki, T; J. Am. Chem. Soc., 1980, **102**, 5974-5976; b) Gao, Y; Hanson, R.M; Klunder, J.M; Ko, S.Y; Masamune, H; Sharpless, K.B.; J. Am. Chem. Soc., 1987, **109**, 5765-5780.
8. All the new compounds gave satisfactory spectral data.
   ^1H NMR data: **18**: (400 MHz, $CDCl_3$, TMS, δ in ppm, J in Hz): 0.9 (d, 3H, $J_{6,6a}$ 5.3, 6a), 1.02 (s, 9H), 1.25 (t, 3H), 1.4 and 1.93 (m, 2H, H-4), 1.95 (m, 1H, H-3), 2.08 (dd, 1H, $J_{3a,3a}$ 17.0, $J_{3a,3}$ 10.4, H-5a), 2.25 (m, 2H, H-2), 2.42 (m, 1H, H-6), 2.79 (dd, 1H, H-5a), 3.6-3.77 (A_2B_2, 2H, H-7), 4.18 (q, 2H, -OC$\underline{H}_2$-), 4.55 (ddd, 1H, $J_{5,4}$ 2.9, 12.0; $J_{5,6}$ 9.1, H-5), 7.4 (m, 6H, ArH), 7.64 (m, 4H, ArH).
9. Stork, G; Mook, Jr, R; Biller, S.A; Rychnovsky, S.D; J. Am. Chem. Soc. 1983, **105**, 3741-3742.
10. a) Ueno, Y; Chino, K; Watanabe, M; Mosiya, O; Okawama, M; J. Am. Chem. Soc. 1982, **104**, 5564-5566; b) Ueno, Y; Chino, K; J. Chem. Soc. Perkin Trans I, 1986, 1351-1356.
11. Giese, B; "Radicals in Organic Synthesis : Formation of Carbon-Carbon bonds" Pergamon Press, Oxford, 1986.
12. Corey, E.J; Suggs, J.W.; J. Org. Chem. 1975, **40**, 2554-2557.
13. a) Hanessian, S; Dhanoa, D.S; Beaulieu, P.L; Can. J. Chem. 1987, **65**, 1859-1866.
14. Beckwith, A.L.J; Schiesser, C.H; Tetrahedron, 1985, **41**, 3925-3941.

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