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The First Total Synthesis of the Antitumor Macrolide Rhizoxin: Synthesis of the Key Building Blocks

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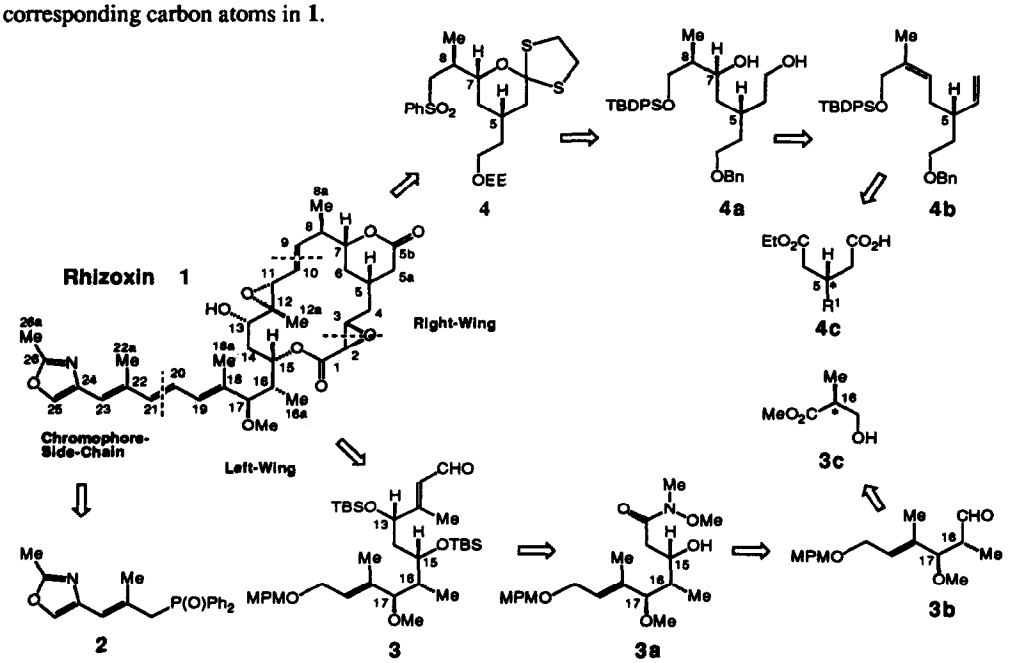
Summary: The construction in optically pure form of the key building blocks, arising from our retrosynthetic analysis of the antitumor macrolide rhizoxin is described.

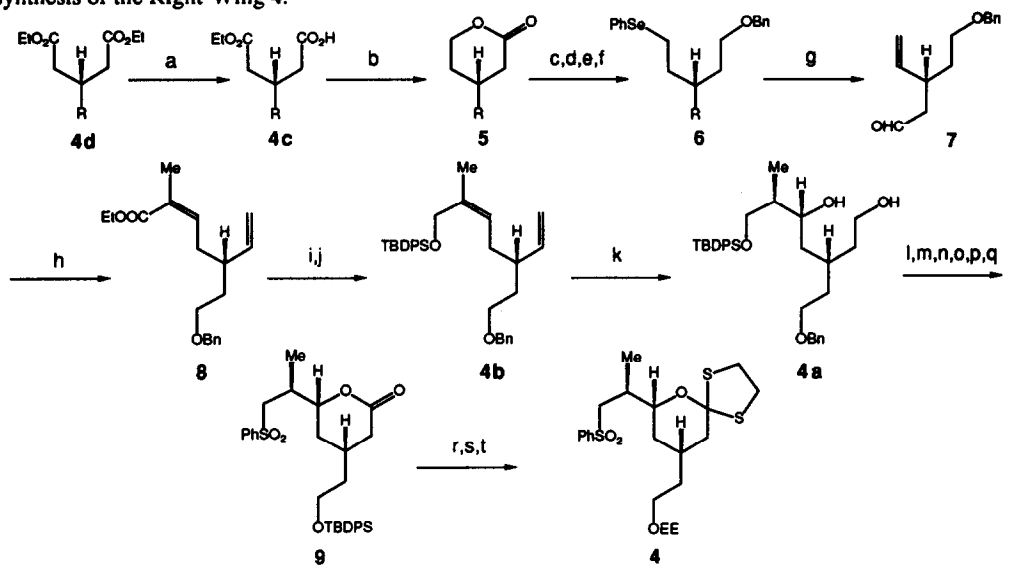
Rhizoxin, isolated in 1984 from *Rhizopus chinensis* Rh-2 as the pathogen of rice seedling blight[1], binds to β-tubulin at the same site as maytansine[1d,2] causing either inhibition of polymerization or depolymerizaton of tubulin. In addition to antifungal activity[3], it exhibits remarkable antitumor activity. Rhizoxin is a novel type of 16-membered ring macrolide differing from others previously known in its biological activities[2,3], biosynthesis[1e], and unprecedented structure[1], which contains two epoxides, a δ-lactone in the macrocyclic ring, and a chromophore terminating in an oxazole. These facts led us to undertake a synthetic study of rhizoxin and homologues. We now wish to report the construction of the key fragments required for the first total synthesis of the antitumor macrolide rhizoxin.

Scheme I shows our retrosynthetic analysis of rhizoxin **1** and bond disconnections to the Right-Wing **4**, Left-Wing **3**, and Chromophore-side-chain **2**. The Right- and Left-Wings are ultimately derived from readily available chiral starting materials. The numbering used in **Scheme I** represents the position of the corresponding carbon atoms in **1**.



Scheme I Structure and Retrosynthetic Analysis of Rhizoxin

As shown in **Scheme II**, synthesis of the Right-Wing started from the chiral half ester **4c** (>91%*ee*) generated by asymmetric hydrolysis of the corresponding *meso*-diester **4d** using pig liver esterase[4]. We planned to construct the remaining chiral centers of fragment **4**, C7, C8, by 1,3- and 1,4-asymmetric induction using cyclic hydroboration[5] of the diene **4b**. To synthesize **4b**, **4c** was transformed as follows. Selective reduction of the ester **4c** with $LiBH_4$, followed by dehydration (Ac_2O, py) gave the crystalline δ-lactone **5** (mp.89°C, AcOEt-Hexane; $[\alpha]_D$+26.0°(C=2.40, $CHCl_3$)). The recrystallized optically pure δ-lactone **5** was converted to selenide **6**, which was then treated with O_3 (-78°C), Me_2S (-78°C to r.t.), and TEA (CH_2Cl_2, reflux) to afford aldehyde **7**. The aldehyde **7** was reacted with the Z-selective phosphonate[6] under the conditions shown in **Scheme II** to afford **8** (Z : E = >20:1). The ester **8** was reduced to the alcohol with DIBAL-H, and converted to its silyl ether **4b**. Cyclic hydroboration of **4b** was initially carried out with B_2H_6 in THF, but the selectivity was low (2:1). However, it could be raised, as shown, to a reasonable level for synthetic purposes (7:1)[7]. Diol **4a** was then converted to the Right-Wing **4** via δ-lactone **9**. For the coupling of the fragments and subsequent transformations, the δ-lactone of **9** was protected as its 1,3-dithiolane[8] and the primary hydroxyl group was protected as its 1-ethoxyethyl ether to complete the synthesis of the Right-Wing **4**.

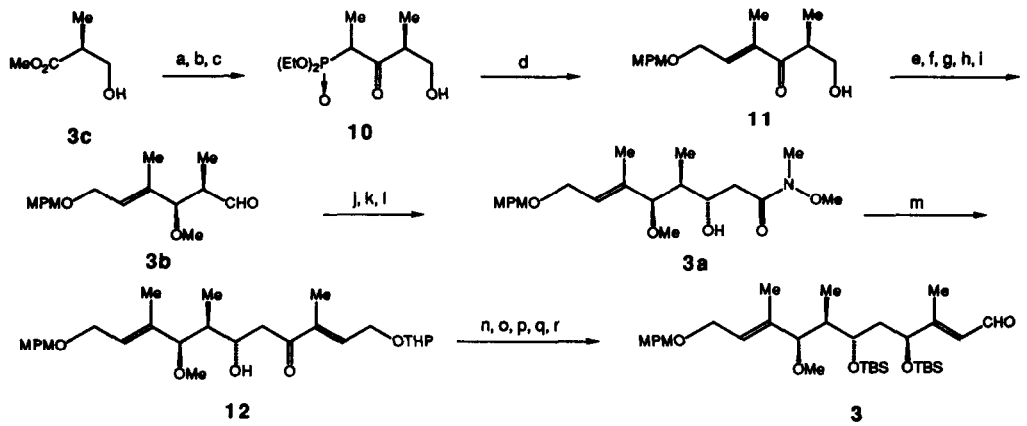


R = PhCHCHCH$_2$, Bn = PhCH$_2$-, TBDPS = *t*-BuPh$_2$Si-, EE = 1-ethoxyethyl. Conditions:(a)Pig Liver Esterase, 0.1M KPB(pH8.0), 10% Acetone, r.t., quant. (>91%ee); (b)$LiBH_4$, MeOH, DME, reflux, 1h; Ac_2O, py, CH_2Cl_2, 12h, 81% from **4c** ; (c)KOH, MeOH, 0°C, 1h; CH_2N_2; MsCl, TEA, 0°C, 30min, 88% from **5** ; (d) (PhSe-)$_2$, $NaBH_4$, EtOH,0°C → reflux, 1h, 85%; (e)$LiAlH_4$, Et_2O, 0°C, 30min, 95%; (f)BnBr, NaH, THF, DMF, r.t., 12h, 91%; (g)O_3, CH_2Cl_2, -78°C, 45min; Me_2S; TEA, CH_2Cl_2, reflux, 1h, 50% from **6**; (h)$(CF_3CH_2O)_2P(O)CH(CH_3)CHCO_2Et$, $KNTMS_2$, 18-crown-6, THF, -78°C, 30min, 95%; (i)DIBAL-H, CH_2Cl_2, -78°C, 20min, 98%; (j)TBDPSCl, imidazole, 0°C → r.t., 2h, 98%; (k)thexylborane,THF,-78 → 0°C 12h; NaOH, H_2O_2, 0°C, 30min, 70% (7 : 1); (l) Ag_2CO_3/Celite,C_6H_6,reflux,12h,88%; (m)n-Bu_4NF, AcOH, r.t, 12h, 96%; (n)MsCl, TEA, CH_2Cl_2, 0°C → r.t., 1h, 98%; (o)$PhSO_2Na$, DMF, 100°C, 12h, 86%; (p)H_2 Pd(OH)$_2$, AcOEt, r.t., 12h, 100%; (q)TBDPSCl, imidazole, 0°C → r.t., 6h, 99%; (r)Me_3Al, $(CH_2SH)_2$, r.t., 12h; ppTs, CH_2Cl_2, r.t., 3h, 98%(2steps); (s)n-Bu_4NF, THF, r.t., 3h, 98%; (t)$C_2H_5OCHCH_2$, ppTs, CH_2Cl_2, r.t., 12h, 100%

Scheme II Synthesis of the Right-Wing

Scheme III shows the synthesis of the Left-Wing **3** starting from readily available **3c**, (S)-methyl 3-hydroxy-2-methylpropionate. The problem here was control of the three chiral centers, C13, C15, and C18. We confirmed that all of them could be constructed by stereoselective reductions. To build the C18-C19 trisubstituted olefin by the Horner-Emmons reaction, **3c** was converted to the phosphonate **10**, and this was then treated with $MPMOCH_2CHO$ under the conditions[9] shown in **Scheme III** to afford selectively the E-α,β-unsaturated ketone (72%). Selective reduction with $Zn(BH_4)_2$[10] afforded the diol (>20:1)[11], which was tritylated, methylated, detritylated[12], then converted to the key intermediate **3b** by Swern oxidation[13]. Expecting that addition to **3b** would occur stereoselectively in a chelation controlled manner[14], a variety of non-chiral enolates were reacted with **3b**. Unfortunately, selectivity was not achieved in any of these cases, and the diastereomeric mixtures[14] formed were difficult to separate by silica gel chromatography. Therefore, the product mixture was at once oxidized[15] to the ketone and this was reduced under non-chelation controlled conditions with L-Selectride®[16] to afford **3a** stereoselectively (>20:1). The amide **3a** was reacted with the appropriate vinyllithium[17] to afford **12**. Selective reduction of **12** with $Me_4NBH(OAc)_3$[19] and subsequent transformation to **3** were accomplished as shown in **Scheme III**.

Now, the stage is set for the convergent and first total synthesis of rhizoxin, and in the following paper we describe the coupling of the fragments, and the subsequent transformations leading to rhizoxin[20,21], including the stereoselective epoxidations of the macrocycle suggested by the proposed biosynthetic pathway[22].



MPM = *p*-$MeOPhCH_2$-, THP = tetrahydropyranyl-, TBS = *t*-$BuMe_2Si$-.Conditions:(a)$PhCH_2OCH_2Cl$, DIPEA, 0°C → r.t., 12h, 100%; (b)$(EtO)_2P(O)CH_2CH_3$, n-butyllithium, THF, -78°C, 10min, 86%; (c)H_2, Pd, EtOH r.t., 12h, 100%; (d)$MPMOCH_2CHO$, LiCl, DIPEA, CH_3CN, r.t., 24h, 72%; (e)$Zn(BH_4)_2$, Et_2O, 0°C, 30min, 94%; (f)TrBr, py, CH_2Cl_2, r.t., 12h, 97%; (g)MeI, NaH, THF, r.t., 12h, 100%; (h)CSA, MeOH, CH_2Cl_2, r.t., 12h, 97%; (i)$(COCl)_2$, DMSO, DIPEA, CH_2Cl_2, -60°C, 98%; (j) $CH_3CONMe(OMe)$, LDA, THF, -78°C, 20min, 92%; (k) $(COCl)_2$, DMSO, DIPEA, CH_2Cl_2, -60°C, 88%; (l)L-Selectride, THF, -78°C, 30min, 91%; (m) *E*-$CH_3CHBrCHCH_2OTHP$, *t*-butyllithium, pentane, Et_2O, THF, -100°C → -78°C, 20min, 75%; (n) $Me_4NBH(OAc)_3$, CH_3CN, AcOH, -20°C, 24h; ppTs, MeOH, r.t., 12h, 78%(>15:1); (o)Me_3CCOCl, py, CH_2Cl_2, r.t., 12h, 90%; (p)TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C, 15min, 81%; (q)$LiAlH_4$, Et_2O, 0°C, 30min, 99%; (r)MnO_2, CH_2Cl_2, r.t., 30min, 97%

Scheme III Synthesis of the Left-Wing

References

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1.a) Iwasaki, S.; Kobayashi, H.; Furukawa, J.; Namikoshi, M.; Okuda, S.; Sato, Z.; Matsuda,I; Oda, T. *J. Antibiot.* **1984**, *37*, 354. b) Iwasaki, S.; Namikoshi, M.; Kobayashi, H.; Furukawa, J.; Okuda, S.;Itai, A.; Kasuya, A.; Iitaka, Y.; Sato, Z. *J. Antibiot.* **1986**, *39*, 424. c) Iwasaki, S.; Namikoshi, M.; Kobayashi, H.; Furukawa, J.; Okuda, S. *Chem. Pharm. Bull.* **1986**, *34*, 1384. d) Takahashi, M.; Iwasaki, S.; Kobayashi, H.; Okuda, S.; Murai, T.; Sato, Y.; Haraguchi-Hiraoka, T.; Nagano, H. *J. Antibiot.* **1987**, *40*, 66. e) Kobayashi, H.; Iwasaki, S.; Yamada, E.; Okuda, S. *J. Chem. Soc., Chem.Commun.* **1986**, 1702.

2.a) Takahashi, M.; Iwasaki, S.; Kobayashi, H.; Okuda, S.; Murai, T.; Sato, Y. *Biochem. Biophys. Acta* **1987**, *926*, 215. b) Sullivan, A. S.; Plasad, V.; Roach, M. C.; Takahashi, M.; Iwasaki, S.; Luduena, R. F. *Cancer Res.* **1990**, *50*, 4277. c) Kato, Y.; Ogawa, Y.; Imada, T.; Iwasaki, S.; Shimazaki, N.; Kobayashi, T.; Komai, T. *J. Antibiot.* **1991**, *44*, 66.

3.Tsuruo, T.; Oh-hara, T.; Iida, H.; Tsukagoshi, S.; Sato, Z.; Matsuda, S.; Iwasaki, S.; Okuda, S.; Shimizu, F.; Sasagawa, K.; Fukami, M.; Fukuda, K.; Arakawa, M. *Cancer Res.* **1986**, *46*, 381.

4.Nakada, M.; Kobayashi, S.; Ohno, M.; Iwasaki, S.; Okuda, S. *Tetrahedron Lett.* **1988**, 3951.

5.a) Brown, H. C.; Negishi, E.; *Tetrahedron* **1977**, *33*, 2331. b) Chan, K. -K.; Saucy, G. *J. Org. Chem.* **1977**, *42*, 3828. c) Still, W. C.; Darst, K. P. *J. Am. Chem. Soc.* **1977**, *42*, 3828. d) Still, W. C.; Shaw, K. R. *Tetrahedron Lett.* **1981**, 3725.

6.Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, 4405.

7.The major diastereomer was confirmed to be **4a** by 400MHz ^{1}H NMR after conversion to **9**.

8.a) Corey, E. J.; Beams, D. J. *J. Am. Chem. Soc.* **1973**, *95*, 582. b) Corey, E. J.; Kozikowski, A. P. *Tetrahedron Lett.* **1975**, 925.

9.a) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, 2183.

10.Nakata, T.; Oishi, T. *Tetrahedron Lett.***1980**, 1641.

11.The stereochemistry of the diol was confirmed as *syn* by 400 MHz ^{1}H-NMR after conversion to the acetonide ($J_{C16\text{-}17}$ = 11.8 Hz).

12.The optical purity was confirmed as >98%*ee* by 400 MHz ^{1}H-NMR using Eu(hfc)$_3$.

13.Mancuso, A. J.; Huang, S, -L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

14.Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526.

15.Parikh, J. R.; von E. Doering, W. *J. Am. Chem. Soc.* **1967**, *89*, 5505.

16.For mechanistic considerations, it was speculated that the reduction would lead to **3a**, and this result is also well explained by the Felkin-Anh model. see; Cherest, M.; Felkin, H.; Prudent, N. *Tatrahedron Lett.* **1968**, 2199.; Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61.; see also; Midland, M. M.; Kwon, Y. C. *J. Am. Chem. Soc.* **1983**, *105*, 3725.

17.Prepared from the corresponding bromide[18] with *t*-butyllithium (2eq.) in pentane-Et_2O-THF(3:4:6) at -100°C.

18.Corey, E. J.; Bock, M. G.; Kozikowski, A. P.; Rama Rao, A. V. *Tetrahedron lett.* **1978**, 1051.

19.Evans, D. A.; Chapman, K. T.; Carreira, E, M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

20.Nakada, M.; Kobayashi, S.; Shibasaki, M.; Iwasaki, S.; Ohno, M. following paper in this issue.

21.All new compounds exhibited satisfactory analytical data. Yields refer to spectroscopically and chromatographically homogenous materials.

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