SYNTHESIS OF RESTRICTINOL AND 9,10,11,12-TETRAHYDRO-7-DESMETHYLRESTRICTICIN

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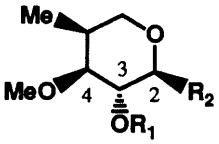
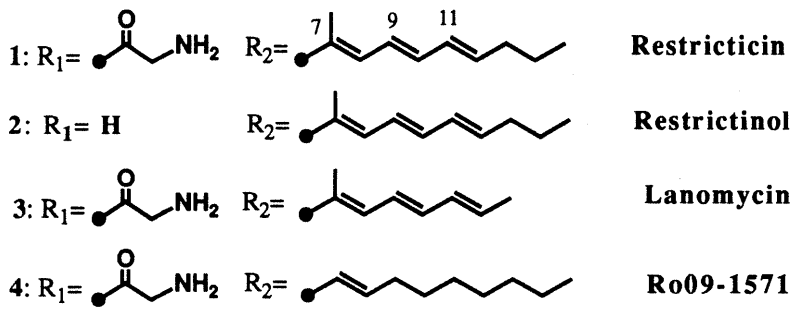
Restrictinol **2** and 9,10,11,12-tetrahydro-7-desmethylrestricticin (Ro 09-1571) have been synthesized from L-glucose. Ro 09-1571 showed improved *in vitro* antifungal activity and chemical stability as compared with Restricticin **1**.

KEYWORDS Restrictinol; Restricticin; 9,10,11,12-tetrahydro-7-desmethylrestricticin; antifungal agent; synthesis

Restricticin **1**, Restrictinol **2**, and Lanomycin **3** groups were isolated from cultured broth of *Penicillium* sp. and *Pycnidiophara* sp. by Merck,[1] Bristol-Myers Squibb,[2] and Roche [3] as novel types of antifungal substances. The mode of action of Restricticin **1** and Lanomycin **3** was found to be the inhibition of P_{450} lanosterol C_{-14} demethylase.[2,4]





Because Restricticin **1** showed rather weak antifungal activity against *Cryptococcus neoformans*, and its triene moiety was highly susceptible to air oxidation, chemical modification of the natural product was needed to develop a clinically useful antifungal agent. After extensive chemical modification, we found that 9,10,11,12-tetrahydro-7-desmethylrestricticin (Ro 09-1571) showed more potent antifungal activity and better chemical stability to air oxidation than Restricticin **1**. Detailed structure-activity relationships of the Ro 09-1571 analogs will be reported elsewhere. In this communication, we wish to report the synthesis of Restrictinol **2**[5] and Ro 09-1571 .

We chose L-glucose as a starting material which has a tetrahydropyrane ring with absolute configurations corresponding to those at C-2, C-3, and C-4 of Restrictinol **2**. Alcohol **5** was readily available from L-glucose in a manner analogous to the synthesis of its enantiomer in 8 steps.[6] The attempt to invert the α–hydroxyl group of **5** under the Mitsunobu condition[7] resulted in the β–elimination of the hydroxyl group. This problem was overcome by oxidation of alcohol **5** followed by reduction of the resulting ketone **6** with $LiAlH_4$ to give equatorial alcohol **7**(**5**:**7**=1:16). Methylation of alcohol **7** followed by catalytic hydrogenation gave diol **8** . Diol **8** was converted to a suitably protected key intermediate **9** in 3 steps, as shown in Chart 1. Treatment of aldehyde **9** with methyllithium followed by oxidation of the resulting secondary alcohol gave methyl ketone **10**. Horner-Emmons olefination of ketone **10** with diethyl cyanophosphonate gave nitrile **11** as an inseparable mixture (E:Z=25:1). Reduction of nitrile **11** with DIBAL gave a separable mixture of α, β-unsaturated aldehyde **12** (E:Z=5:1). After separation of the isomers, Wittig reaction of E aldehyde **12** with 2-(E)-hexenyltriphenylphosphonium bromide provided triene **13**. Removal of the TBS protecting group with n-Bu_4NF gave Restrictinol **2**, which was identical to the natural product.[8]

Using key intermediate **9**, we also synthesized Ro 09-1571. Wittig olefination of aldehyde **9** furnished the cis olefin **14**. Isomerization of cis olefin **14** to the trans olefin **15** was accomplished by the photochemical method.[9] After removal of the TBS protecting group, esterification of the corresponding alcohol with Boc-glycine followed by removal of the Boc group with trifluoroacetic acid gave Ro 09-1571 as a TFA salt.

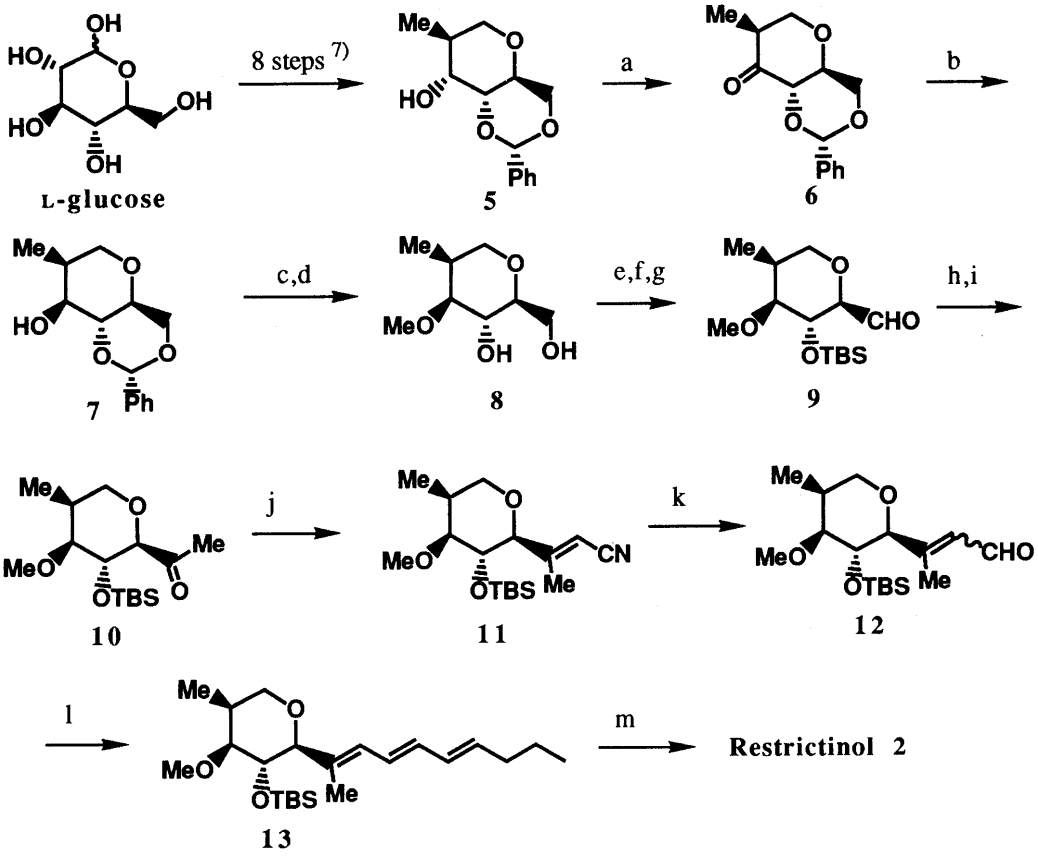


Chart 1. (a) $(COCl)_2$, DMSO then Et_3N (98%) (b) $LiAlH_4$, Et_2O, -60°C(79%) (c) MeI, NaH, DMF(98%) (d) H_2, Pd -black, methanol(97%) (e) TBSCl, imidazole, DMF(82%) (f) TFA, THF, H_2O(1:2:2)(92%) (g) PCC, 4AMS,CH_2Cl_2(81%) (h) MeLi, Et_2O(83%) (i)PCC, 4AMS,CH_2Cl_2(84%) (j) diethyl cyanomethylphosphonate, NaH, DMF(80%) (k) DIBAL, hexane(68%) (l) (E)-$BrPh_3PCH_2CH$=CH-n-C_3H_7,n-BuLi, THF(25%, **12** was recovered in 26%) (m) n-Bu_4NF, THF(57%)

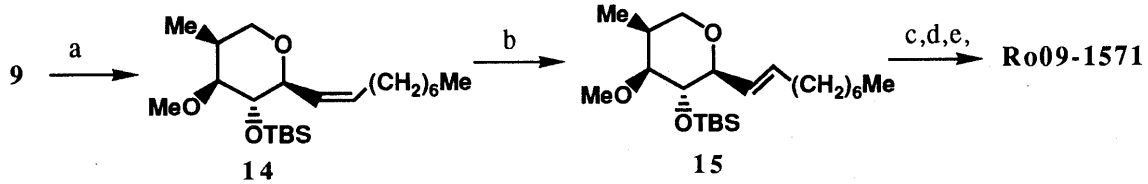


Chart 2. (a) $BrPh_3P(CH_2)_7Me$, n-BuLi, THF, HMPA(81%) (b) hυ, PhSSPh, hexane(85%) (c) nBu_4NF, THF(92%) (d) HO-Gly-Boc, DCC, DMAP(87%) (e) TFA, CH_2Cl_2(98%)

Table 1. *In vitro* Antifungal Activity of Ro 09-1571

	MIC: μg/ml			
Strains	Ketoconazole	Fluconazole	Ro 09-1571	Restricticin
C.albicans CY1005	>200	>200	50	>200
C.albicans CY3003	25	>200	25	200
C.albicans CY1002	>200	>200	25	>200
C.neoformans CY1057	0.025	12.5	3.13	1.56
C.neoformans CY1061	0.05	50	12.5	3.13
C.neoformans CY1059	0.1	25	6.25	3.13
A.fumigatus CF1003	3.13	>200	3.13	100
A.fumigatus CF1023	3.13	>200	3.13	100
A.fumigatus CF1004	3.13	>200	3.13	100

Agar dilution method, medium: YNB+K_2HPO_4+LMPA (pH7.0), inoculum size: $1x10^5$cfu/ml, incubation : 3 days at 27°C.

The *in vitro* antifungal activity of Ro 09-1571 is summarized in Table 1 in comparison with those of Restricticin **1**, Fluconazol, and Ketoconazole. Ro 09-1571 showed much more potent *in vitro* antifungal activity against *Candida albicans* and *Aspergillus fumigatus* , and nearly comparable activity against *Cryptococcus neoformans* when compared with natural product Restricticin **1**. The antifungal activities of Ro 09-1571 against *Candida* and *Aspergillus* sp. are comparable with those of Ketoconazole. Moreover, it is noteworthy that the trans-1-nonenyl chain of Ro 09-1571 is no longer air-sensitive.

In summary, we have accomplished the synthesis of Restrictinol **2** and its analog, Ro 09-1571, with potent antifungal activity.

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Spectral data

7 ^{1}H-NMR($CDCl_3$) δ: 1.18(d, J=7.3Hz, 3H), 2.20(m, 1H), 3.33(dt, J=4.4, 9.5Hz, 1H), 3.6-3.8(m, 4H), 3.95 (dd, J=5.8, 9.5Hz, 1H), 4.28(dd, J=4.4, 10.2Hz, 1H), 5.57(s, 1H), 7.37(m, 3H), 7.91(m, 2H); MS(EI) m/z:250(M^+).

11 (E-isomer) ^{1}H-NMR(C_6D_6) δ: 0.00(s, 3H), 0.10(s, 3H), 0.81(d, J=7.3Hz, 1H), 0.93(s, 3H), 1.50(m, 1H), 1.89(d, J=1.0 Hz, 3H), 2.67(dd, J=9.0, 4.9Hz, 1H), 2.89(s, 3H), 2.97(dd, J=11.0, 2.0Hz, 1H), 3.10(d, J=9.0Hz, 1H), 3.36(dd, J=2.1, 11.0Hz, 1H), 3.38(t, J=9.0Hz, 1H), 5.00(s, 1H); MS(EI) m/z:268(M^+-tBu).

12 (E-isomer)^{1}H-NMR(C_6D_6) δ: 0.00(s, 3H), 0.41(s, 3H), 0.89(d, J=6.9Hz, 3H), 0.94(s, 9H), 1.60(m, 1H), 1.88(d, J=1.3 Hz, 3H), 2.75(dd, J=8.6, 5.3Hz, 1H), 2.93(s, 3H), 3.05(dd, J=11.6, 2.0Hz, 1H), 3.30(d, J=8.6Hz, 1H), 3.43(dd, J=11.6, 1.5Hz, 1H), 3.54(t, J=8.6Hz, 1H), 6.13(d, J=7.6Hz, 1H), 9.95(d, J=7.6Hz, 1H); MS(EI) m/z:328(M^+).

13 ^{1}H-NMR(C_6D_6) δ: 0.16(s, 3H), 0.27(s, 3H), 0.89(t, J=7.4Hz, 3H), 1.06(s, 9H), 1.07(d, J=6.3Hz, 3H), 1.37(sext, J=6.7 Hz, 2H), 1.95(s, 3H), 2.00(q, J=7Hz, 2H), 2.1-2.3(m, 1H), 2.97(dd, J=8.9, 4.8Hz, 1H), 3.06(s, 3H), 3.29(dd, J=11.6, 2. 0Hz, 1H), 3.59(d, J=8.9Hz, 1H), 3.61(dd, J=11.6, 1.7Hz, 1H), 3.77(t, J=8.9Hz, 1H), 5.63(dt, J=14.9, 7.1Hz, 1H), 6.17 (dd, J=14.9, 10.4Hz, 1H), 6.30(dd, J=14.6, 10.4Hz, 1H), 6.33(dd, J=11.2, 1.1Hz, 1H), 6.49(dd, J=14.6, 11.2Hz, 1H); MS(EI) m/z:394(M^+).

14 ^{1}H-NMR($CDCl_3$) δ: 0.02(s, 3H), 0.06(s, 3H), 0.84(s, 9H), 0.88(t, J=6.6Hz, 1H), 0.99(d, J=7.1Hz, 3H), 1.2-1.4(m, 11H), 2.0-2.3(m, 2H), 3.13(dd, J=5.8, 8.8Hz, 1H), 3.28(s, 3H), 3.43(t, J=8.8Hz, 1H), 3.56(dd, J=2.2, 11.8Hz, 1H), 3.75(dd, J=2.2, 11.8Hz, 1H), 3.80(t, J=8.8Hz, 1H), 5.35(t, J=9.0Hz, 1H), 5.64(dt, J=9.0, 11.5Hz, 1H); MS(EI) m/z 327(M^+-tBu).

Ro 09-1571

^{1}H-NMR($CDCl_3$) δ: 0.86(t, J=6.3Hz, 3H), 1.04(d, J=7.4Hz, 3H), 1.24(m, 10H), 2.0(m, 2H), 2.2(m, 1H), 3.28(3H, s), 3.35(dd, J=5.2, 9.4Hz, 1H), 3.56(br.d, J=11.2Hz, 1H), 3.62(br.t, J=9.4Hz, 1H), 3.7-3.9(m, 3H), 4.90(t, J=9.4Hz,1H), 5.38(1H, dd, J=15.3, 8.2Hz, 1H), 5.76(dt, J=15.3, 6.0Hz, 1H); MS(EI) m/z:327(M^+-TFA).

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