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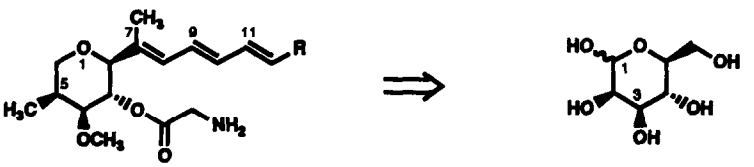
Total Synthesis of Restricticin

Stefan Jendrzejewski* and Peter Ermann

Bristol-Myers Squibb Pharmaceutical Research Institute,
Regensburg, Germany

Abstract: The novel antifungal antibiotic restricticin was synthesized from L-mannose

Restricticin **1**, isolated by Merck [1] and Roche [2] from fungi of the genus *Penicillium* represents a novel type of polyene antibiotics. Independently, **1** (scopularin) and its relative lanomycin (**2**) were discovered by Bristol-Myers Squibb [3,4] in fermentations of *Scopulariopsis sp.* and *Pycnidiophora sp.*, respectively. Structures closely related to **1** and **2** with different substituents at the glycyl nitrogen and the tetrahydropyran ring have also been isolated from the above sources.[1-4] Restricticin and lanomycin possess potent antifungal activity due to their action as P_{450} lanosterol C-14 demethylase inhibitors.[4,5] The biosynthetic origins have been shown for **2** to be a polyketide precursor, methionine and glycine.[6]



1 R = n-C_3H_7 **Restricticin (Scopularin)**
2 R = CH_3 **Lanomycin**

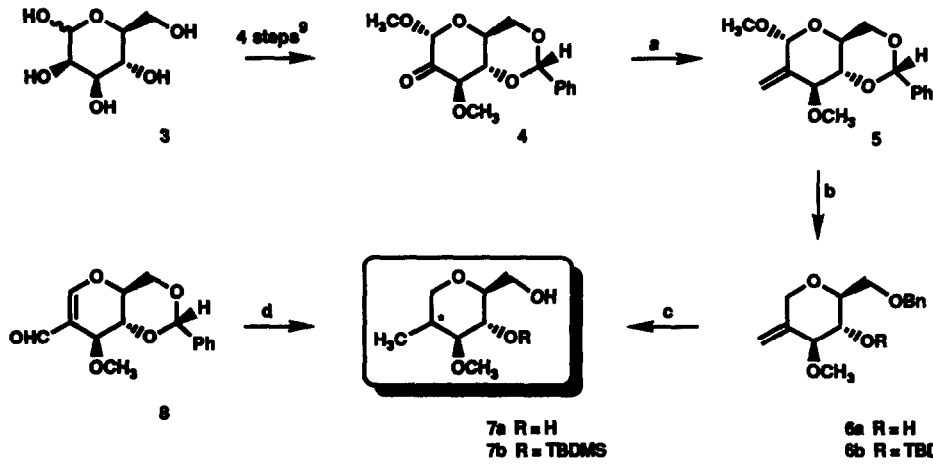
3 **L-Mannose**

Scheme 1.

Herein we report the first total synthesis [7] of restricticin (scopularin) which confirms the structure and in addition is flexible enough to allow access independent of fermentative procedures to some of the other members of this antibiotic family. Retrosynthetic analysis suggested L-mannose (**3**) as a starting material [8] which provides the absolute configuration of the chiral centres at C-2, C-3 and C-4 of restricticin (scopularin). Deoxygenation of L-mannose at C-1 and the transformation of the 2-OH to a methyl group should set up the complete substitution pattern of the restricticine (scopularin) tetrahydropyran ring with (*S*)-configuration at C-5.

As a suitable precursor for key intermediate **7b** (Scheme 2) we chose ketone **4**, readily available [9] from L -mannose in analogy to the synthesis of its enantiomer. Wittig reaction [10] of **4** (Ph_3PCH_3Cl, n-BuLi, -20°C, 75%) gave the methylene derivative **5** which was reduced ($NaCNBH_3$,[11] THF, ether-HCl_{gas}, 60-70%) in a one-pot reaction under carefully controlled conditions [12] to **6a**. Catalytic hydrogenation of **6a** (Pd/C, MeOH, 80 %) or its TBDMS ether **6b** (Pd/C, EtOAc, 90-100 %) yields a mixture of epimers **7a** and **7b** [13], respectively.

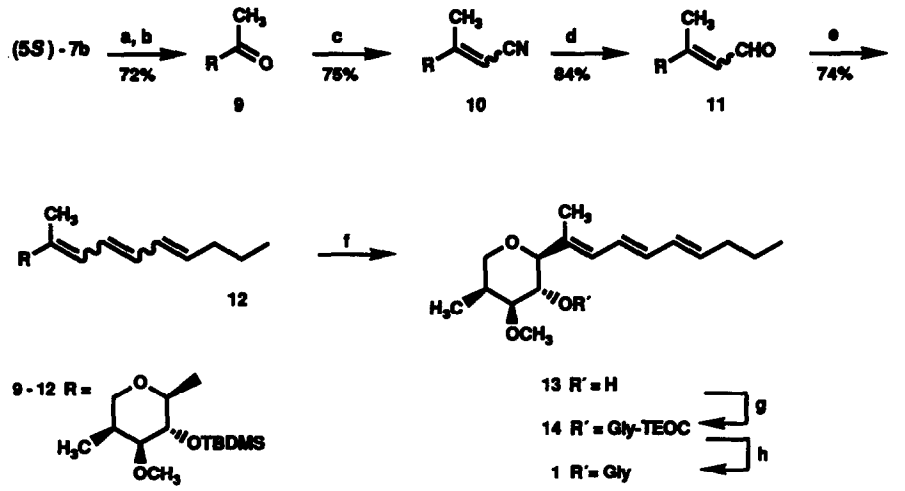
The desired (5*S*)-isomer predominantly present in these mixtures [14] could in the case of **7b** be separated on a preparative scale. The proton at C-5 of the compounds **7** exhibits in the ^{1}H-NMR spectrum ($CDCl_3$) a characteristic multiplet with a shift around δ= 2.1 for the (5*S*)- and δ=1.8 for the (5*R*)-configuration. Another access to **7a** was found in the smooth hydrogenation (Pd/C, MeOH, 93%) of formylglycal **8** [15]. The dialcohols **7a** can be converted by persilylation (TBDMS-Cl, imidazole, DMF, 75 %) and subsequent selective silyl ether cleavage (THF/TFA 2:1, 25 eq. H_2O, -15°C, 91%) to **7b** which is suitably protected for the steps to follow.



hydrogenation of	product	*ratio 5*R* : 5*S*
6a	7a	2.4 : 7.6
6b	7b	1.6 : 8.4
8	7a	1.4 : 8.6

Scheme 2. (a) Ph_3PCH_3Cl, n-BuLi, THF, -20°C → r.t. (b) $NaCNBH_3$, THF, slow addn. of ether/HCl_{gas} (c) H_2, Pd/C, EtOAc or THF, separation of isomers **7b** by MPLC on silica with pentane/EtOAc (d) H_2, Pd/C, MeOH.

The construction of the triene side chain in a Wittig-approach (Scheme 3) requires the methylketone **9** which is obtained from (5*S*)-**7b** in a three step transformation (72% overall). Compound **9** [16] does not undergo olefin formation with Wittig reagents (triphenylalkylidenephosphoranes) but suffers elimination to the 2,3-unsaturated ketone instead. The application of the Horner-Emmons variant with the weakly basic cyanomethylene reagent overcame this problem and gave the nitriles **10** (*E* : *Z* = 8.3 : 1.7) which as a mixture were converted to the corresponding aldehydes **11**. Wittig reaction of this material (2-(*E*)-hexenyltriphenylphosphonium bromide, n-BuLi, toluene, 5°C, 74%) furnished a mixture of three of the four possible isomers **12**. After the removal of the TBDMS-protecting group (MeOH, 1% HCl_{gas}, 75%) the corresponding alcohols could be separated by chromatography and the last compound eluted (32%) was identified as the (*E*,*E*,*E*)-alcohol restrictinol (**13**).[17] Finally, the attachment of the glycyl residue was performed with TEOC-glycine (WSC, DMAP, CH_2Cl_2, 85%) which allows a mild removal of the protecting group (1.6 eq. TBAF, THF, 40°C, 3 hrs, 61 %) to give **1** identical with the natural product.



Scheme 3. (a) DMSO, $C_2O_2Cl_2$, -60°C, 5 eq. Et_3N, aq. workup then 3 eq. CH_3MgBr, ether (b) 5 eq. pyridinium chlorochromate, CH_2Cl_2 (c) $(EtO)_2POCH_2CN$, n-BuLi (d) DIBAH, toluene then H_2O, pH = 2-3 (e) (*E*)-$BrPh_3PCH_2CH$=CH-n-C_3H_7, n-BuLi (f) MeOH, HCl_{gas} (1%) r.t., separation of the (*E,E,E*)-isomer by CC on silica with hexane/EtOAc 9:1 (g) ethyl-3-(3-dimethylamino)-propyl-carbodiimide hydrochloride (WSC), HO-Gly-TEOC CH_2Cl_2 (h) TBAF, THF, 40°C, CC on silica with EtOAc / isopropanol 4:1.

In summary, a practical total synthesis was accomplished which not only makes available substantial amounts of restricticin (scopularin) but also includes synthetic intermediates of interest for the structural modification of this novel antifungal agent.

References and Notes

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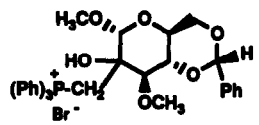
6. Remsburg, B.; Philipson, D. W; O'Sullivan, J., *J. Antibiot.* **1992**, *45*, 655-658.
7. All new compounds gave satisfactory elemental analyses and spectral data. ^{1}H-NMR spectra were recorded at 200 MHz.

8. L-mannose was prepared according to Sowden, J. C. in: Whistler, R. L.; Wolfrom, M. L., Eds., Methods in Carbohydrate Chemistry Vol.I, Academic Press: New York, London, 1962; pp, 132-135 method b.

9. Swern oxidation (DMSO, $C_2O_2Cl_2$, Et_3N, -60°C, 88%) of methyl-4,6-O-benzylidene-3-O-methyl-α-L-mannopyranoside prepared analogous to the protocol for the corresponding D-compound by Nashed, M. A., *Carbohydr. Res.* **1978**, *60*, 200-205.

10. The primary adduct of methyltriphenylphosphorane to ketone **4** converts slowly to **5**. The intermediate could be trapped as the chloroform-soluble phosphonium bromide **16** by adding methanol to the reaction mixture. The phosphorous resonance is observed at 22 ppm ($CHCl_3$, internal standard phosphoric acid). **16** decomposes in solution at r.t. with a half-life of 4 hrs to **5** and triphenylphosphine oxide.

^{1}H-NMR ($CDCl_3$) of **5**: δ=3.37 (s, 3H, 3-OCH_3),.3.54 (t, 1H, J=9.4, 4-H); 3.60 (s, 3H, 1-OCH_3), 3.73 (t, 1H, J=10.0, CH_2), 3.99 (dt, 1H, J=4.7, 9.6, 5-H), 4.19 (dt, 1H, J=9.6, 2.2, 3-H), 4.27 (dd, 1H, J=10.0, 4.7, CH_2), 5.00 (s, 1H, 1-H), 5.18 (m, 1H, =CH_2), 5.35 (m, 1H, =CH2), 5.53 (s, 1H, acetal-H), 7.25-7.55 (m, 5H, -Ph), ring numbering as in **3**.



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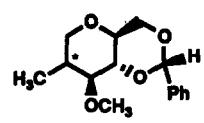

17

11. Chapleur, Y.; Boquel, P.; Chretien, F., *J. Chem. Soc. Perkin Trans. I* **1989**, 703-705.

12. 2 l of a 0.5 M solution of HCl_{gas} in ether are added dropwise over 1.5 hrs to 0.04 mol of **5** and 0.4 mol of $NaCNBH_3$ in 300 ml THF at 0°. After the evaporation of the solvents the crude product is dissolved in 200 ml methanol, neutralized with 2 N NaOH and stirred overnight. The methanol is evaporated and the obtained residue is worked up with ethyl acetate/water. Chromatography on silica with ethyl acetate/pentane (1:2) yields **6a**, ^{1}H-NMR (DMSO-d_6, TFA-d) δ=3.09 (t, 1H, J=9.1, 3-H), 3.37, (ddd, 1H, J=, 9.2, 6.0, 1.6, 2-H), 3.44 (s, 3H, OCH_3), 3.48 (dd, 1H, J=10.5, 6.0, CH_2OBn), 3.58 (dt, 1H, J=8.8, 2.0, 4-H), 3.68 (dd, 1H, J=10.3, 1.4, CH_2OBn), 3.81 (d, 1H, J=12.0, 6-CH_2), 4.10 (d, 1H, J=12.0, 6-CH_2), 4.46 (s, 2H, CH_2Ph), 4.93 (s br, 1H, =CH_2), 4.95 (t, 1H, J=2.0, =CH_2), 7.20-7.40 (m, 5H, -Ph).

13. **(5*R*)-7b**: ^{1}H-NMR ($CDCl_3$) δ=0.05 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.85 (s, 9H, t.-Bu), 0.93 (d, 3H, J=7.5, 5-CH_3), 1.77 (m, 1H, 5-H), 2.73 (dd, 1H, J=10.3, 8.5, 4-H), 3.09 (t, J=11.4, 6-CH_2), 3.17 (m, 1H, 2-H), 3.34 (dd, 1H, J=9.2, 8.4, 3-H), 3.47 (s, 3H, OCH_3), 3.57 (dd, 1H, J=11.4, 6.0, CH_2OH), 3.78 (dd, 1H, J=11.4, 7.3, CH_2OH), 3.79 (d, J=11.4, 6-CH_2);

(5*S*)-7b: ^{1}H-NMR ($CDCl_3$) δ=0.01 and 0.03 (2xs, 6H, $Si(CH_3)_2$), 0.77 (s, 9H, t.-Bu), 0.92 (d, 3H, J=7.3, 5-CH_3), 2.15 (m, 1H, 5-H), 3.10 (dd, 1H, J=8.7, 5.3, 4-H), 3.13 (m, 1H, 2-H), 3.26 (s, 3H, OCH_3), 3.53 (t, 1H, J=9.0, 3H), 3.55 (dd, 1H, J=11.5, 2.3, 6-CH_2), 3.62 (dd, 1H, J=11.3, 5.7, CH_2OH), 3.74 (t, 1H, J=11.2, CH_2OH), 3.80 (t, 1H, J=11.4, 6-CH_2).

14. For an exact analysis of the epimeric ratios, the crude hydrogenation products of **6a**, **6b** and **8** were transformed to the corresponding acetals **17** which were separated by chromatography on silica with hexane/EtOAc 12:1.

15. Prepared from **4** as described for the enantiomer by Burnouf, C.; Lopez, J. C.; de los A. Laborde, M.; Olesker, A.; Lukacs, G., *Tetrahedron. Lett.* **1988**, *29*, 5533-5534.

16. ^{1}H-NMR ($CDCl_3$) δ=0.04 (s, 3H, $SiCH_3$), 0.07 (s, 3H, $SiCH_3$), 0.85 (s, 9H, t.-Bu), 0.91 (d, 3H, J=7.1, 5-CH_3), 2.22 (s, 3H, $COCH_3$), 2.30 (m, 1H, 5-H), 3.07 (dd, 1H, J=6.4, 3.8, 4-H), 3.25 (s, 3H, OCH_3), 3.53 (dd, 1H, J=11.3, 5.6, 6-H_a), 3.69 (d, 1H, J=5.6, 2-H), 3.72 (dd, 1H, J=11.4, 6.5, 6-H_e), 4.09 (t, 1H, J=6.0, 3-H).

17. A minor product (7%), assigned the (*Z,Z,E*)-configuration and the (*E,Z,E*)-isomer (36%) were eluted first. The trienes were always handled with added stabilizer 2,6-di *tert.*-butyl-4-methylphenol. For the spectroscopic data of **13** see lit. 1b and 2.

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