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SYNTHESIS OF THE ANTIFUNGAL AGENT SCH 42427[1](SM 9164)

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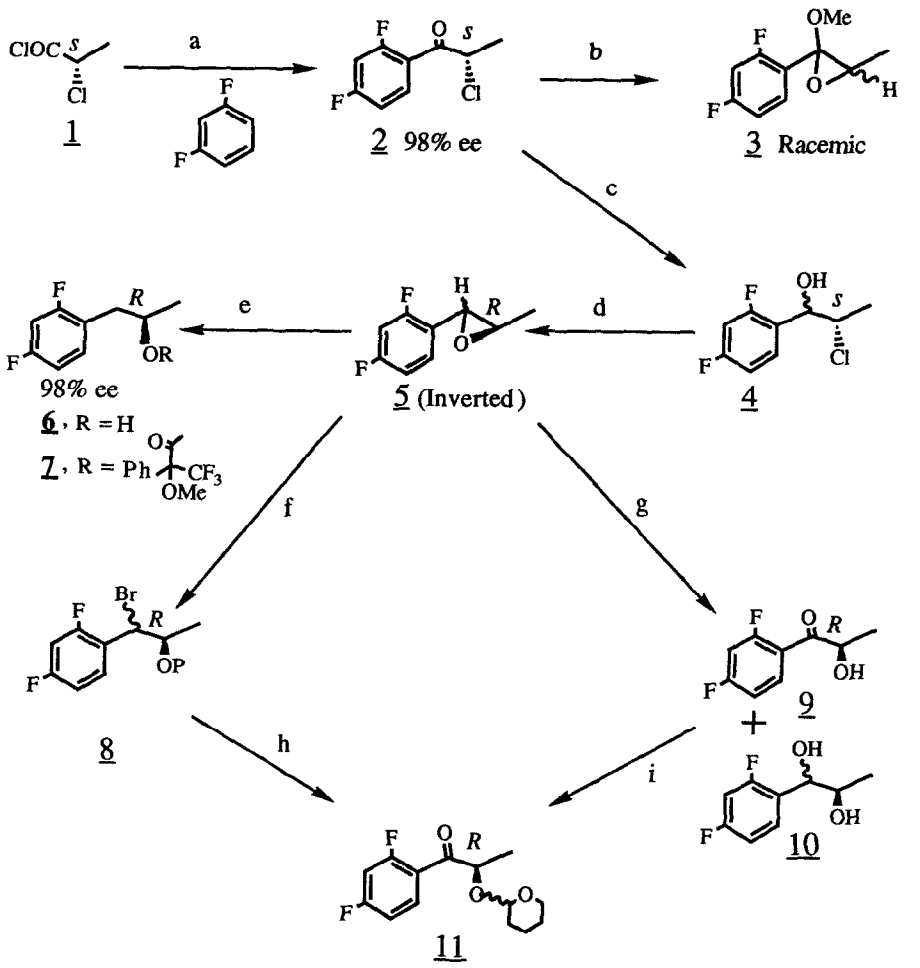
Abstract: A chiral synthesis of the antifungal agent Sch 42427 starting from S-chloropropionic acid is described.

(±)-Sch 39304 (SM 8668),[2, 3] a racemate of *RR* and *SS*-enantiomers, is a highly active broad-spectrum oral antifungal agent,[4, 5, 6] which has shown superior efficacy to existing drugs in a recent clinical study. It is particularly effective against Aspergillosis in immune compromised animal models,[7] an indication of its potential usefulness in AIDS and cancer patients who are more susceptible to *Aspergillus* infections. Sch 42427 (SM 9164), the *RR* enantiomer, is the biologically active constituent of (±)Sch 39304.[3,8]

A practical asymmetric synthesis of Sch 42427 is described here starting from the readily available and inexpensive *(S)*-chloropropionic acid (*SCHEME 1)* . The acid chloride **1** (98% ee) under Friedel-Crafts conditions reacted with m-difluorobenzene affording the chloroketone **2** (>98% yield) without any loss of chiral integrity as determined by NMR shift reagent experiments.[9] The α-chloroketone **2**, not surprisingly, racemizes extremely rapidly even under mild basic conditions: K_2CO_3/MeOH gave the racemic epoxy methyl ether **3**, an intermediate in the (±) SM 8668 synthesis.[3] Reduction of **2** with sodium cyanoborohydride cleanly generated the diastereomeric alcohols **4**, which were then converted to the epoxide **5**, effecting a 100% inversion to *R*-configuration at the chloride carbon atom. Reduction of the epoxide **5** to the alcohol **6**, followed by preparation of its Mosher's ester **7** confirmed the preservation of the enantiomeric purity in the above transformations. Regioselective opening of the epoxide **5** at the benzylic position by nucleophiles proved to be a problem. However, the oxirane could be opened very efficiently to the desired bromohydrin **8** (P = H; >85% yield) using trimethylsilyl bromide. BF_3 catalyzed oxidative opening[10] of epoxide **5** in dry DMSO gave a mixture of ketol **9** and the diol **10**[11] (2:3 ratio). Displacement of the bromine atom in **8** (P = pyranyl ether) by an oxygen nucleophile was not very successful. However, silver assisted oxidation of **8** (P = pyranyl ether) by DMSO at the benzylic carbon afforded the protected ketone **11** as a diastereomeric mixture at the pyranyl ether[12] anomeric center in 55-60% yield.

SCHEME 1

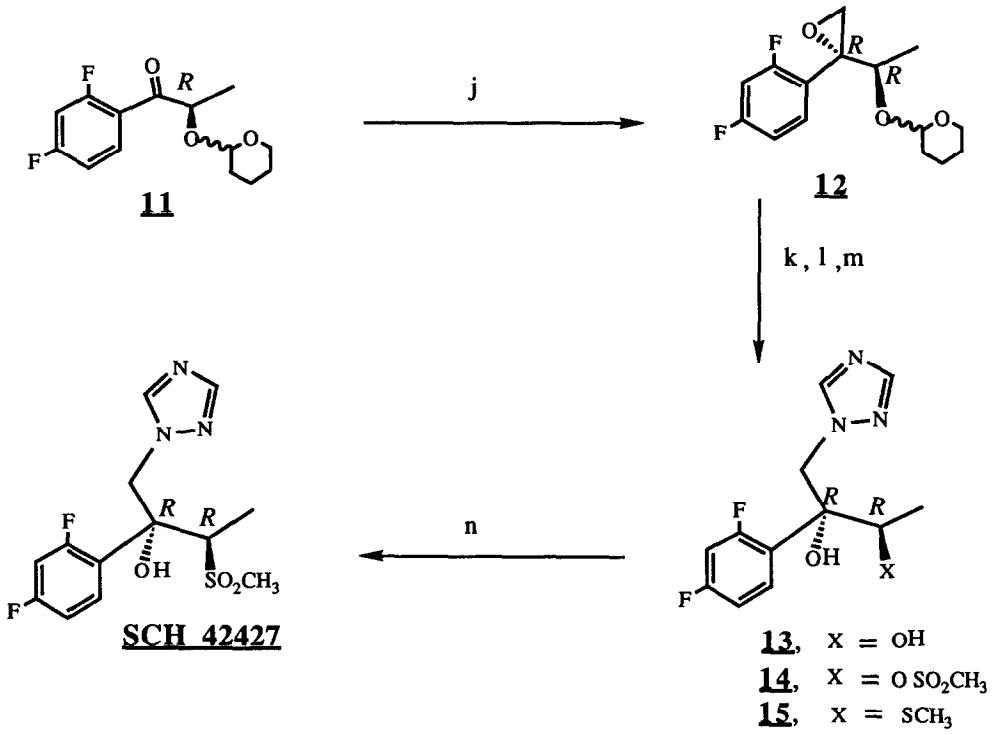


a) $AlCl_3$, 0-5°C, 16 hrs; b) K_2CO_3, MeOH, R.T.; c) THF, AcOH, $NaCNBH_3$; d) K_2CO_3, MeOH, R.T.
e) 10% Pd/C, H_2 40 psi; f) Et_3SiBr, CH_2Cl_2, -10°C, 1 hr; g) Dry DMSO, BF_3, 10°C, 72 hrs..
h) Dry DMSO, Silver benzoate, 60°C, 2 hrs; i) DHP, TsOH, CH_2Cl_2.

Another crucial step in the synthesis involved conversion of ketone **11** to the epoxide **12** under basic conditions, maintaining the *R*-configuration α to the ketone *(SCHEME 2)*. This was achieved by reacting the ketone **11** with dimethylsulfoxonium methylide, which yielded predominantly the desired *RR*- isomer *(RR* {threo}: *SR* {erythro} = 85:15). Opening the epoxide **12** with triazole anion

followed by hydrolysis of the pyranyl ether afforded the crystalline diol **13**. The optical purity of **13** was further confirmed by comparing it with an authentic sample obtained through a resolution process.[3,13] Mesylation of the secondary alcohol group in **13**, displacement of the mesylate group in **14** with sodium methanethiolate to **15** (retention of configuration via epoxide) and finally oxidation to the sulfone as described for (±)-SM 8668 afforded Sch 42427 in an overall 26% yield starting from *(S)*-chloropropionic acid.

SCHEME 2



j) Sodium dimethylsulfoxonium methylide, THF, R.T., 2 hrs.
k) 1) Sodium triazole, 2) H^+/H_2O, l) MsCl/TEA, CH_2Cl_2, m) $NaSCH_3$, EtOH.
n) Peracetic acid, CH_2Cl_2.

References and Notes:

1. Girijavallabhan, V. M; Ganguly, A. K.; Sarre, O. Z.; Pinto, P. A.; Versace, R. W. ISACS Symposium, Oiso, Japan, Sept. 2-7, **1990**, Abstract No. G-50.

2. Okuda, T.; Tanio, T.; Ichise, K.; Nakajima, T. 28th ICAAC Conference, Los Angeles, U.S.A., Oct. 23-26, **1988**, Abstract No. 174.

3. Saji, T.; Ohashi, N.; Tamoto, K.; Tanio, T.; Okuda, T.; Atsumi, T. ibid, Abstract No. 173.

4. Fromtling, R. A.; "Drugs of the Future," Vol. 14, No. 12, **1989**, 1165.

5. Saksena, A. K.; Girijavallabhan, V. M.; Cooper, A. B.; Loebenberg, D. *Ann. Report Med. Chem.*, Vol. 24, **1989**, 111.

6. Proceedings of the 28th ICAAC Conference, Los Angeles, U.S.A., Oct. 23-26, **1988**, Abstracts 161-174.

7. Loebenberg, D.; Parmegiani, R.; Moss, Jr., E. L.; Frank, D.; McHugh, M.; Yarosh-Tomaine, T.; Antonacci, B.; Menzel, Jr., F.; Hare, R. S.; Miller, G. H.. 29th ICAAC Conference, Houston, U.S.A., Sept. 17-20, **1989**, Abstract No. 821.

8. SM 9164 (Sumitomo Pharmaceuticals), ICAFC Symposium **1990**, Oiso, Japan.

9. We thank Dr. M. S. Puar for this experiment.

10. Cohen, T.; Tsuji, T. J. Org. Chem., 26, **1961**, 1681.

11. The sulfoxonium intermediate appears to be sufficiently stable and resilient to losing dimethyl sulfide, leading to formation of the diol during work-up.

12. Even though the pyranyl ether generates a diastereomeric mixture, this protecting group renders a high degree of 'threo selectivity' in the formation of **12**.

13. We thank Sumitomo Pharmaceutical Co. for authentic samples.