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# ENANTIOSELECTIVE SYNTHESIS OF THE OPTICAL ISOMERS OF BROAD-SPECTRUM ORALLY ACTIVE ANTIFUNGAL AZOLES, SCH 42538 AND SCH 45012

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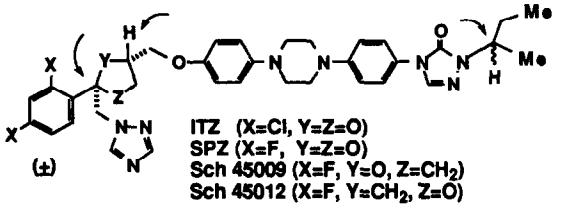
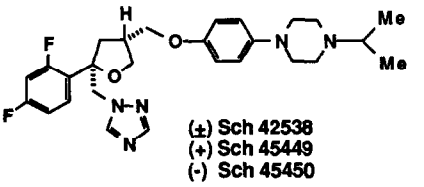
**Abstract:** Sharpless-Katsuki asymmetric epoxidation of 1 provided the *(R)*-(+)- and *(S)*-(-) epoxy alcohols **2R** and **2S** as key intermediates towards all six stereoisomers of the title compounds. Sch 50001 and Sch 50002 (the "eutomers" of Sch 45012) are novel antifungals which display greatly improved oral activity over itraconazole and saperconazole.

In marked contrast to antibacterials, the pace of discovery of newer antifungals for systemic infections has been rather slow. The widespread incidence of life threatening *Candidiasis, Cryptococcosis* and *Aspergillosis* in immunocompromised patients has underscored the need for safer and efficacious antifungal agents.[1] The azole class of antifungals have potential for a broad antimycotic spectrum, which includes almost all forms of human mycoses. They primarily inhibit cytochrome P-450 dependent oxidative 14α-demethylation of lanosterol, causing blockade of ergosterol biosynthesis within the fungal cell. Itraconazole (ITZ), a relatively selective inhibitor of fungal cytochrome P-450, now also in clinical use, offers certain advantages over other agents (e.g., fluconazole and ketoconazole) in terms of spectrum, oral efficacy, and side effects.[1b] Saperconazole (SPZ) is an investigational azole reported to have better activity than ITZ against a wide range of *Aspergillus* strains *in vitro* and *in vivo*.[2]




**ITZ (X=Cl, Y=Z=O)**
**SPZ (X=F, Y=Z=O)**
**Sch 45009 (X=F, Y=O, Z=$CH_2$)**
**Sch 45012 (X=F, Y=$CH_2$, Z=O)**

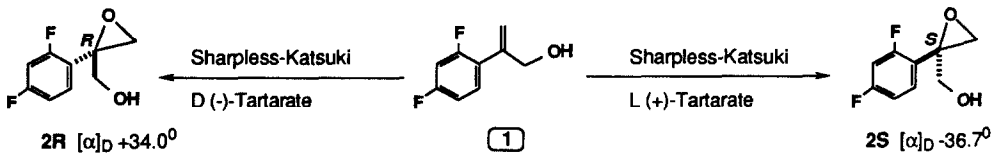


**(±) Sch 42538**
**(+) Sch 45449**
**(-) Sch 45450**

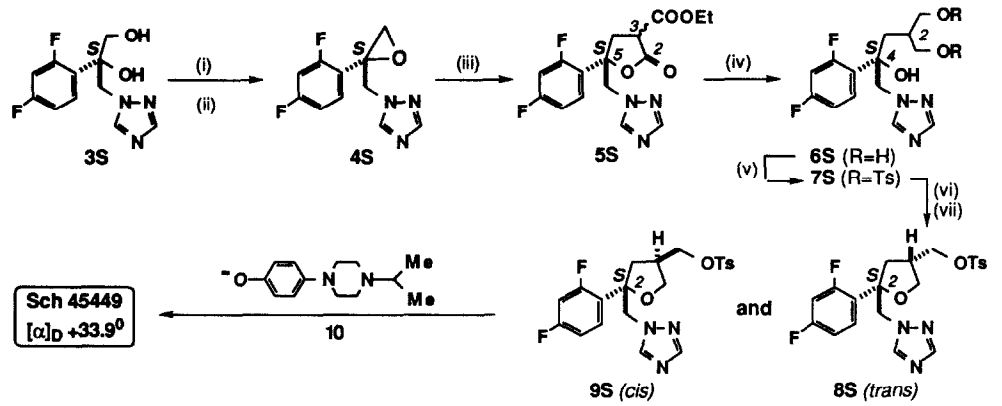
Recently we reported on the synthesis of Sch 45009 and Sch 45012 and compared their activities with ITZ and SPZ in systemic *Candida* and pulmonary *Aspergillus* infection models.[3a,b] While all four compounds had comparable broad-spectrum activity *in vitro*, Sch 45012 was shown to be clearly more active than Sch 45009, ITZ and SPZ in the above infection models. We had also accomplished direct optical resolution of (±)Sch 42538 by chiral HPLC providing each enantiomer in high purity (>95% ee). At this stage we were unable to assign absolute configuration to these enantiomers, but (-) Sch 45450, the "eutomer" was more active orally than (±)Sch 42538 with (+)Sch 45449 being the inactive "dystomer".[4a,b]

In view of the above results, we were interested in enantioselective routes to Sch 45012 and Sch 42538 optical isomers (and their analogs) for a detailed biological evaluation. With its three chiral centers (arrows), two in a defined *cis*-stereochemical relationship, Sch 45012 is a mixture of four stereoisomers.[5]

It appeared that the Sharpless-Katsuki asymmetric epoxidation[6a] of the readily available allyl alcohol 1,[6b] may provide convenient access to the above optical isomers through common chiral intermediates. Indeed 1 could be converted to both epoxy alcohols **2R** and **2S** in over 95% yields with reasonable enantioselectivity (88-92% ee).[7]




The remaining steps leading up to the key **9S** and **9R** tosylates are herein described, using the epoxy alcohol **2R** as an example. Treatment of **2R** with sodium triazole (1.1 equiv.) and triazole (~ 2 equiv.) in anhydrous DMF provided the diol **3S**, m.p. 99-100°C, $[\alpha]_D^{25}$ + 70.5°.[8] The optical purity of **3S** improved to >98% ee after one crystallization, was quite adequate to proceed. Mesylation of the diol **3S** proceeded cleanly at the primary hydroxyl group. The monomesylate so obtained was cyclized in the presence of sodium hydride to the chiral epoxide **4S**.[9]




**Reagents:** (i) MsCl, $Et_3N$, $CH_2Cl_2$, 0-5°C; (ii) NaH,DMF; (iii) Na-diethylmalonate, DMSO, 50-55°C; (iv) $NaBH_4$, LiCl, EtOH; (v) TsCl, $Et_3N$, DMAP, $CH_2Cl_2$-THF (1:1, v/v); (vi) NaH, toluene, 100°C; (vii) Chromatography

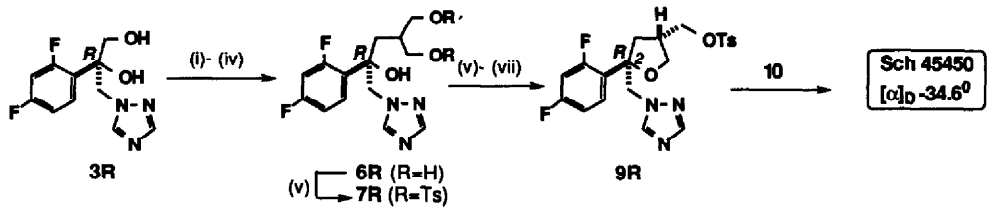
**SCHEME I**

Reaction of the epoxide **4S** with the malonate anion was best carried out under anhydrous conditions in DMSO to provide the 2-oxo-3-furane carboxylate **5S** as an equilibrated mixture of *[(5S)-cis]-* and *[(5S)-trans]-* isomers.[10] Our initial attempts to reduce **5S** with $LiBH_4$ or $LiAlH_4$ in THF led to intractable metal complexes of **6S**. However, reduction of **5S** with $LiBH_4$ generated *in-situ* in ethanol cleanly provided the *(+)-(4S)*-triol **6S**.

Since cationic cyclization of optically pure diol **6S** would no doubt lead to racemization, a base catalyzed cyclization of preferably the asymmetrized **6S** was sought. All steps from **2R** to the **6S** were carried out in 70-90% yields. However, the only concession we made for expediency at this juncture, was to postpone investigating the 2,4-stereoinduction possibilities. Thus, the ditosylate **7S**[11] available from **6S**, upon treatment with sodium hydride in toluene or cyclohexane gave a mixture of *(2S-trans)-* and *(2S-cis)-* isomers **8S** and **9S** in a 6:4 ratio.[12] Chromatography then afforded the desired *cis*-tosylate **9S**, m.p. 96-98°C, $[\alpha]_D^{25}$ + 39.7° (c = 1, $CHCl_3$) in 35% yield. (Scheme I)

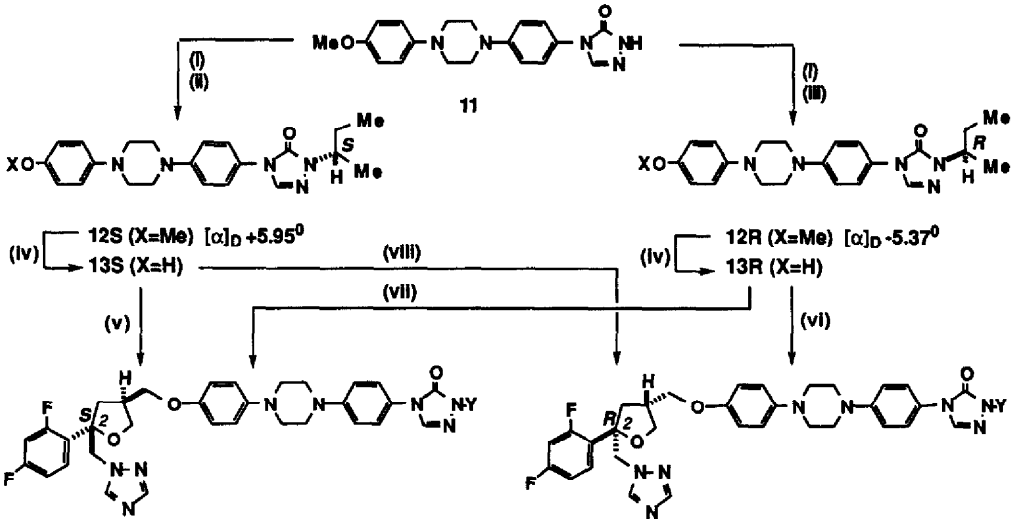
Using the corresponding **3R** diol, $[\alpha]_D^{25}$ - 71.5° (c = 1.0, MeOH), prepared from the epoxy alcohol **2S**, the same set of reactions as above produced the *(-)-(2R)-cis*-tosylate, m.p. 96-97°C, $[\alpha]_D^{25}$ - 39.6°. (Scheme II)

Treatment of the *cis*-tosylates **9S** and **9R** separately with the phenoxide **10** under standard conditions,[13a] gave *(+)-(2S)* Sch 45449 and *(-)-(2R)* Sch 45450; assigning their absolute configurations for the first time. Both compounds were optically pure (>98% e.e.) by Chiralcel® chromatography, confirming the chiral integrity of the key intermediates including the **9S** and **9R** *cis*-tosylates.[14]




**SCHEME II**

Now turning back to the Sch 45012 optical isomers, alkylation of the known triazolone **11**[13b] with (-)-*(R)*-2-butanol tosylate, $[\alpha]_D^{25}$ -11.9° (c = 1, MeOH) and (+)-*(S)*-2- butanol tosylate, $[\alpha]_D^{25}$ +10.53° derived from *(R)*- and *(S)*-2-butanols, followed by O-demethylation provided the requisite side chains **13S** and **13R** respectively. Alkylation of sodium or potassium salts of these side chains with the *cis*-tosylates **9S** and **9R** provided the four diastereomers of Sch 45012 in the following manner (80-90% yields): Reaction of **9S** with **13S** and **13R** gave (+)-Sch 49999 and (+) Sch 50000 respectively; the remaining two isomers, (-)-Sch 50001 and (-)-Sch 50002 were obtained from the reaction of **9R** with **13R** and **13S** under the same conditions. (Scheme III)




**Reagents**: (i) NaH, DMSO; (ii) *(R)*-[TsOCH(Me)Et], 65°; (iii) *(S)*-[TsOCH(Me)Et], 65°; (iv) Aq. 48% HBr; (v)**13S** Na-Salt, DMSO, **9S**, 60°; (vi) **13R** Na-Salt, DMSO, **9R**, 60°; (vii) **13R** Na-Salt, DMSO, **9S**, 60°; (viii) **13S** Na-Salt, DMSO, **9S**, 60°.

**SCHEME III**

Based on the predictable course of Sharpless-Katsuki asymmetric epoxidation[6] and the origin of the chiral side chains from the known *(R)* and *(S)*-2-butanols, the above diastereomers were assigned relative[7] and absolute stereochemistry. Recently, the structure of Sch 50002 was also confirmed by a single crystal X-ray crystallography.[17]

We have described here enantioselective routes to the broad-spectrum, orally active, antifungal azoles Sch 45450, Sch 50001 and Sch 50002. The weakest step in the above sequence was the poor stereoselectivity in the cyclization of **6R** to the *cis*-tosylate **9R**. In essence we were unable to take advantage of the chirality established at the -

**TABLE 1.** Oral Activity (and MICs) of Sch 45012 Isomers in CF-1 Mice infected with *C. Albicans* [a] (5 Million CFU).

| Compound | Vehicle | Dose (mpk)[b] | % Survival[c] | CFU (GM)[d] | MICs[e] |
|---|---|---|---|---|---|
| 49999 | PEG-200 | 50 | 20 | 7.84 | 0.0625 |
| | | 25 | 0 | 9.00 | |
| 50000 | PEG-200 | 50 | 0 | 9.00 | 0.0313 |
| | | 25 | 0 | 9.00 | |
| **50001** | PEG-200 | 50 | **90** | 5.62 | 0.0039 |
| | | 25 | **80** | 5.90 | |
| | | 10 | 50 | 6.78 | |
| **50002** | PEG-200 | 50 | **100** | 4.99 | 0.0039 |
| | | 25 | **100** | 5.14 | |
| | | 10 | 40 | 7.42 | |
| | HPβCD[f] | 10 | **90** | 5.92 | |
| ITZ | PEG-200 | 50 | 60 | 6.68 | 0.0078 |
| | | 25 | 0 | 9.00 | |
| | HPβCD[g] | 10 | 10 | 8.87 | |
| SPZ | PEG-200 | 50 | 20 | 8.20 | 0.0039 |
| - | PEG-200 | - | 0 | 9.00 | |

[a]Strain C-43. Treatment: Once a day x 4 days; [b]mg/Kg
[c]4 days post infection. [d]colony forming units, kidneys (geometric mean; log 10; limit of detection: 2.00).
Vehicles: PEG-200 - polyethylene glycol 200. HPβCD - hydroxypropyl-β-cyclodextrin.
[e]Eagles essential medium, pH 7.0, 48 h.
[f]Solubility: 5.5 mg/ml.
[g]Solubility: 0.4 mg/ml.

**TABLE 2.** Oral Activity and (MICs) of Sch 45012 Isomers in compromised CF-1 Mice infected by inhalation with *Aspergillus flavus* .[a]

| Compound | Dose (mpk)[b] | % Survival[c] | CFU (GM)[d] of Survivors[e] | MICs[f] |
|---|---|---|---|---|
| 49999 | 100 | 20 | ND[g] | >8.0000 |
| | 66 | 0 | ND | |
| 50000 | 100 | 10 | ND | >8.0000 |
| | 66 | 0 | ND | |
| **50001** | 100 | **70** | 1.85 | 0.0625 |
| | 66 | 10 | ND | |
| **50002** | 100 | **100** | 1.95 | 0.0625 |
| | 66 | 50 | 2.25 | |
| ITZ | 100 | 20 | ND | 0.1250 |
| | 66 | 0 | ND | |
| SPZ | 100 | 0 | ND | 0.0313 |

[a]Strain ND 134; infected via inhalation chamber with prior and post-infection treatment with 100 mpk cortisone acetate subcutaneous.
[b]Once a day for 4 days; treatment commenced 24 hours after infection.
[c]18 Days post-infection.
[d]Colony forming units, lungs (geometric mean; log 10; limit of detection: 1.00).
[e]Lung tissue cultured for *Aspergillus flavus*.
Vehicle: PEG-200.
[f]Sabouraud dextrose broth, pH 5.7, 72 h.
[g]Not determined.

benzylic carbon via the Sharpless-Katsuki asymmetric epoxidation, an excellent step by itself. One solution to this problem, and an alternative synthesis of **3R** diol, using an enzymatic approach, is described in a separate communication.[15]

Biological results indicated that the two (+)-*(2S)*-isomers, Sch 49999 and Sch 50000 were virtually inactive "dystomers" and the two (-)-*(2R)*-isomers, Sch 50001 and Sch 50002, identified as the two "eutomers" of Sch 45012. In terms of *in vitro* activity both Sch 50001 and Sch 50002 were equiactive; *in vivo* however, both isomers (as summarized below) displayed greatly improved activity over itraconazole (ITZ) and saperconazole (SPZ), **Sch 50002** being the most active in *Candida* as well as *Aspergillus* infection models. *The importance of absolute stereochemistry in the tetrahydrofuran ring is highlighted by the fact that the only isomers of Sch 42538 and Sch 45012 having antifungal activity have 2R absolute configuration at the benzylic carbon.*

In a systemic *Candida albicans* infection in CF-1 mice, Sch 45012 stereoisomers were administered orally and their efficacy was compared with ITZ and SPZ. The results are shown in Table 1. Both Sch 50001 and Sch 50002 were clearly more active than ITZ and SPZ the latter compounds providing no protection at 25 mpk dose. The oral bioavailibility of ITZ and SPZ (in mice) was improved by complexation with hydroxypropyl-β-cyclodextrin (HPβCD).[16] We noted a marked improvement in oral efficacy of **Sch 50002** at 10 mpk when complexed with HPβCD. In contrast ITZ provided virtually no protection in this vehicle at the same dose.

The *in vivo* activity of the above compounds against *Aspergillus* was determined in a pulmonary infection model in mice; the infection was induced via an inhalation route.[3b] Mice were compromised with cortisone acetate (100 mpk subcutaneously) once daily for three days. On the second day of this treatment mice were exposed to *Aspergillus flavus* spores. Once a day treatment (10, 66, 100 mpk) began 24 hours post infection and continued for 4 days. Survival was followed for 18 days. As shown in Table 2, **Sch 50002** was clearly the most efficacious compound in this severe infection model.

Alternative routes towards the key *cis*-tosylate **9R** are under active investigation and will be discussed elsewhere. We shall report on our further studies in this series in future communications.[17]

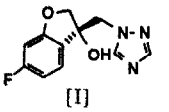
**Acknowledgements:** We would like to cordially thank Professor Ronald Breslow and Dr. Frank Bennett for stimulating discussions. We would also like to thank Drs. Birendra Pramanik and Mohinder S. Puar for high resolution mass spectral and nmr data.

**References and Notes:**

1. Reviews: (a) Hay, R. J. "Recent Advances in Chemistry of Antiinfective Agents", *Royal Society of Chemistry, Special Publication No. 119,* **1993,** p. 163; (b) Como, J. A.; Dismukes, W. E. *The New England Journal of Medicine,* **1994,** 330, p. 263.
2. Van Cutsem, J.; Van Gerven, F. and Janssen, P. A. J. *Drugs of The Future,* **1989,** 14, 1167.
3. (a) Saksena, A. K.; Girijavallabhan, V. M.; Rane, D. R.; Pike, R. E.; Desai, J. A.; Cooper, A. B.; Jao, E.; Ganguly, A. K.; Loebenberg, D.; Hare, R. S. and Parmegiani, R. *9th International Symposium on Future Trends in Chemotherapy, Geneva, Switzerland,* 26-28, March **1990,** Abstract No. 128; (b) For a detailed description of these infection models, see: Loebenberg, D.; Cacciapuoti, A..; Parmagiani, R.; Moss, E. L.; Menzel, F.; Antonacci, B.; Norris, C.; Tomaine, T. Y.; Hare, R. S. and Miller, G. H. *Antimicrobial Agents and Chemotherapy,* **1992,** 36, 498.
4. (a) Sch 45450 is a water soluble (as HCl salt) antifungal having excellent activity in *Candida* infection models comparable to fluconazole, a clinically useful antifungal[1b]; (b) The terms "eutomer" and "dystomer" were coined

by Prof. E.J. Ariens (University of Nijmegen, The Netherlands), to denote the more active and the "other" enantiomer respectively. See: *Chem. and Eng. News,* Sept. 27, **1993**, p. 40.

5. By the same analogy ITZ and SPZ (and Sch 45009) also exist as mixtures of four diastereomers. To the best of our knowledge no reports exist on synthesis and/or biological activity of these isomers.
6. (a) Katsuki, T. and Sharpless, K. B. *J. Am. Chem. Soc.,* **1980**, 102, 5974; Review: Pfenninger, A. *Synthesis,* **1986**, 89; (b) The allyl alcohol **1** was prepared from commercially available 2-chloro-2',4'-difluoroacetophenone (Aldrich Chemical Co.) as follows: (i) Reaction with NaOAc in DMF ($20^0$C) and (ii) Wittig reaction of the resulting phenacyl acetate followed by hydrolysis (aq. KOH). For a more practical synthesis of **1** and an alternative synthesis of **3R** using Sharpless ADH reaction see: Blundell, P.; Ganguly, A. K. and Girijavallabhan, V. M. *Synlett,* **1994**, No. 4, 263.
7. All new compounds were characterized by $^1$H, $^{13}$C, NMR and high resolution mass spectra. When necessary 1D NOE and 2D NOESY NMR spectra were obtained to confirm relative stereochemistry. Elemental analyses were obtained for crystalline compounds only. Yields refer to isolated products and have not been optimized. Selected spectral data is given here.
8. Free 1,2,4-triazole was used here as a proton source. Use of Na-triazole alone led to a major byproduct [I] resulting from intramolecular oxyanion displacement of the ortho-fluoro substituent.
   **3S** and **3R**: $^1$H NMR [DMSO] δ 8.25 (s, 1H), 7.66 (s, 1H), 7.33 (m, 1H), 7.09 (r, 1H), 6.90 (t, 1H), 5.72 (s, 1H), 5.05 (t, 1H), 4.53 (s, 2H), 3.61 (m, 2H).



[I]

9. **4S** and **4R**: $^1$H NMR [$CDCl_3$] δ 7.97 (s, 1H), 7.77 (s, 1H), 7.07 (m, 1H), 6.73 (m, 2H), 4.73 (d, 1H), 4.41 (d, 1H), 2.84 (d, 1), 2.78 (d, 1H).
10. **5S** and **5R**: $^1$H NMR [$CDCl_3$] δ 8.08 (s, 2H), 7.91 (s, 1H), 7.71 (s, 1H), 7.42 (m, 1H), 7.13 (m, 1H), 7.85 (m, 2H), 4.60 (m, 4H), 4.10 (m, 4H), 3.49 (t, 1H), 3.14 (t, 1H, 3.89 (m, 4H), 1.18 (m, 6H.
11. **7S** and **7R**: $^1$H NMR [$CDCl_3$] δ 7.95 (s, 1H), 7.67 (m, 5H), 7.30 (m, 6H), 6.70 (t, 2H), 4.74 (d, 1H), 4.53 (d, 1H), 4.13 (m, 1H), 3.97 (m, 1H), 3.8 (m, 2H), 2.43 (s, 6H), 1.95 (m, 2H), 1.77 (m, 1H).
12. Use of polar solvents (THF, dioxane, DMF etc.) encouraged formation of the undesired *trans* isomers even more so.[17]
    **8S** and **8R**: $^1$H NMR [$CDCl_3$].δ 8.05 (s, 1H), 7.85 (s, 1H), 7.63 (m. 2H), 7.25 (m, 3H), 6.85 (m, 2H), 4.37 (AB q, 2H), 3.96 (m, 1H), 3.72 (m, 2H), 3.53 (m, 1H), 2.62 (m, 1H), 2.45 (s, 3H), 2.14 (m, 1H), 1.87 (m, 1H).
    **9S** and **9R**: $^1$H NMR [$CDCl_3$] δ 8.09 (s, 1H), 7.88 (m, 3H), 7.31 (m, 3H), 6.81 (m, 2H), 4.52 (AB q, 2H), 3.99 (m, 1H), 3.85 (m, 1H), 3.70 (m, 1H), 3.59 (m, 1H), 2.49 (m, 2H), 2.47 (s, 3H), 1.90 (m, 1H).
13. (a) Heeres, J. ; Hendrickx, R. and Van Cutsem, J. *J. Med. Chem.,* **1983**, 26, 611; (b) Heeres, J.; Backx, L. J. J.; Van Cutsem, J. *ibid.*, **1984**, 27, 894.
14. Chiralcel® OD Analytical Columns (Chiral Technologies Inc.) were used to determine optical purity of a number of final compounds. Where this technique did not apply due to lack of baseline resolution, e.e.s were determined by NMR of Mosher esters (e.g., compounds **2S**, **2R**).
15. Lovey, R. G.; Saksena, A. K.; Girijavallabhan, V. M. *Tetrahedron Lett.* **1994**, accepted for publication.
16. Hostetler, J. S.; Hanson, L. H.and Stevens, D. A. *Antimicrobial Agents and Chemotherapy,* **1992**, 36, 477.
17. Full details of this work (chemistry and biology) including X-ray crystallography of Sch 50002 by Professor Andrew T. McPhail, (Duke University) will be published elsewhere.

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