the same quantities of reagents and solvent. To the yellow-orange ylide C3 at room temperature was added 0.34 mL (2.6 mmol) of 2-phenylpropanal. After 84 h, workup and chromatography (5% ether–hexanes) afforded 185 mg (21%) of ester C4 as a clear oil: ^{1}H NMR ($CDCl_3$) δ 1.29 (e, CH_2s), 1.39 (d, J = 6 Hz, CH_3), 1.86–2.48 (m, allylic CH_2), 3.72 (s, CO_2Me), 3.55–3.83 (m, allylic CH), 4.82–5.13 (m, terminal vinyl CH_2), 5.56–6.04 (m, terminal vinyl H), 6.85 (d, J = 9 Hz, H-3), 7.28 (s, aryl H). Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.01. Found: C, 80.75; H, 10.04.

Equilibration of Conjugated Esters. A. Methyl (*E*)-2-(10-Undecenyl)-2-undecenoate (B8). A solution of 172 mg (0.49 mmol) of an 87:13 mixture of *Z* and *E* esters B11 and B8 and 1 mL (0.5 mmol) of 0.5 M sodium isopropylthiolate in 1 mL of DMF was heated at 130 °C for 3 h.[7b] The reaction mixture was cooled, diluted with water, and extracted with ether. These extracts were essentially devoid of material related to esters B8 or B11, a consequence of ester cleavage by the thiolate. The aqueous layer was acidified with 10% aqueous HCl and extracted with ether. The ether extracts were dried over $MgSO_4$ and concentrated under reduced pressure to an oil. The oil was dissolved in 3 mL of ether and treated with a ca. 3-fold excess of ethereal diazomethane at 0 °C for 30 min. The solvent was removed and the oil was purified by silica gel chromatography (3% ether–hexanes) to afford 164 mg (95%) of material consisting of 56% B8, 24% B11, and 20% of an impurity (possibly the β,γ-unsaturated isomer) according to glass capillary GC.

B. Methyl (*E*)-2-Methyl-2-undecenoate (8). A solution of 119 mg (0.56 mmol) of a 96:4 mixture of *Z* and *E* esters **9** and **8** and 140 μL (0.056 mmol) of 0.4 M sodium isopropylthiolate in DMF in 1 mL of DMF was heated at 90 °C for 30 min. Analysis of the reaction solution by capillary GC showed a 90:10 mixture of *E* and *Z* isomers.

Acknowledgment. Support from the National Institute of General Medical Sciences through Research Grant 2 RO1-GM 29475 is gratefully acknowledged. A generous gift of geraniol was kindly provided by Dr. Alan Hochstetler, Givaudan Corporation, Clifton, NJ. We thank the South Carolina Regional NMR Center for cooperation in securing high field NMR spectra.

Registry No. **2**, 101419-98-1; **3**, 101419-99-2; **4** (R^2 = Et), 101420-04-6; **5** (R^2 = Et), 101420-05-7; **6**, 99699-33-9; **7**, 99699-34-0; **8**, 101420-17-1; **9**, 101420-16-0; **A1**, 90460-86-9; **A2**, 101419-88-9; **A3**, 101419-89-0; **A4**, 101419-90-3; **A5**, 101419-91-4; **A6**, 101419-92-5; **A7**, 101419-93-6; **A8**, 101419-94-7; **a9**, 101419-95-8; **A10**, 101419-96-9; **A11**, 101419-97-0; **B2**, 7766-49-6; **B3**, 101420-00-2; **B4**, 101420-01-3; **b5**, 101420-02-4; **b6**, 101420-08-0; **B7**, 101420-10-4; **B8**, 101420-11-5; **B9**, 101420-09-1; **B10**, 101470-97-7; **B11**, 101420-12-6; **C3**, 101420-14-8; **C4**, 101420-15-9; KHMDS, 40949-94-8; $(i\text{-PrO})_2POCH_2CO_2Et$, 24074-26-8; $(MeO)_2POCH_2CO_2Me$, 5927-18-4; EtCHO, 123-38-6; $OHCCH_2CH_2CH{=}C(CH_3)CH_2CH_2CH{=}CHCH_2OTBS$, 101420-03-5; $n\text{-}C_8H_{17}CHO$, 124-19-6; *trans*-$THPOCH_2CH{=}C(CH_3)CH_2CH_2CH{=}C(CO_2Me)CH_2CH_2CH{=}C(CH_3)CH_2CH_2CH{=}CHCH_2OTBS$, 101420-06-8; *cis*-$THPOCH_2CH{=}C(CH_3)CH_2CH_2CH{=}C(CO_2Me)CH_2CH_2CH{=}C(CH_3)CH_2CH_2CH{=}CHCH_2OTBS$, 101420-07-9; $(CF_3CH_2O)_2POCH_2CO_2Me$, 88738-78-7; $CH_2{=}CH(CH_2)_8CH_2PPh_3{}^+Cl^-$, 101420-13-7; $CH_3CH(Ph)CHO$, 93-53-8; $OHCCH(OBn)CH(CH_2SO_2Ph)C(CH_3){=}CH_2$, 101420-18-2; *trans*-$H_2C{=}C(CH_3)CH(CH_2SO_2Ph)CH(OBn)CH{=}C(CO_2CH_3)CH_2CH_2CH{=}C(CH_3)CH_2CH_2CH{=}C(CH_3)CH_2OTBS$, 101540-29-8; $Ph_3P{=}C(CO_2CH_3)CH_2CH_2CH{=}C(CH_3)CH_2CH_2CH{=}eC(CH_3)CH_2OTBS$, 100572-54-1; *trans*-$CH_2{=}CH(CH_2)_8C(CO_2CH_3){=}CHCH(OBn)CH(CH_2SO_2Ph)C(CH_3){=}CH_2$, 101420-19-3; *trans*-$CH_2{=}CH(CH_2)_8C(CO_2CH_3){=}CHCH_2CH_3$, 101420-20-6; *trans*-$n\text{-}C_8H_{17}CH{=}C(CO_2CH_3)(CH_2)_8CH{=}CH_2$, 101420-21-7; $MePPh_3{}^+Br^-$, 1779-49-3.

Microbial Transformations in Organic Synthesis. 4. Stereoselective Fungal Metabolism of 7-Methylglaucine

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The time courses for the fungal metabolism of racemic *cis*- and *trans*-7-methylglaucine (**4**/**5**, **6**/**7**, respectively) by *Fusarium solani* (ATCC 12823) and *Aspergillus flavipes* (ATCC 1030) are described. Only *cis*-7-methylglaucine (**4**/**5**) was biotransformed to 7-methyldehydroglaucine (**8**) with either culture, indicating that the reaction involves an overall cis elimination of hydrogen. The destructive resolution of **4**/**5** by the fungi was undertaken, and the enantiomeric purities and absolute configurations of residual substrates from microbiological incubations were determined by ^{1}H NMR by using the chiral shift reagent Eu(tfc)$_3$, by optical rotation (OR), and by optical rotary dispersion (ORD). A 10% enantiomeric excess of (6a*R*,7*R*)-7-methylglaucine (**5**) was isolated from *F. solani* incubations, indicative of a stereoselective oxidation of the 6a*S*,7*S* stereoisomer, while the residual substrate from *A. flavipes* was shown to be the enantiomerically pure (6a*S*,7*S*)-7-methylglaucine (**4**), indicative of a stereoselective oxidation of the 6a*R*,7*R* stereoisomer.

A potentially useful application of microorganisms in organic synthesis is the oxidation of the aporphine alkaloid (*S*)-(+)-glaucine (**1**) and the unnatural enantiomer (*R*)-(−)-glaucine (**2**) to dehydroglaucine **3** by the fungi *Fusarium solani* (ATCC 12823) and *Aspergillus flavipes* (ATCC 1030), respectively (Figure 1). The stereospecific and quantitative nature of these reactions, which allows for the destructive resolution of a racemic mixture of **1**/**2**, has been fully described.[1,2] In order to extend this reaction to the resolution of other aporphines and related alkaloids, a study was initiated to determine the mechanism of the microbial oxidation, i.e., whether an overall a cis or trans elimination of hydrogen is operative. The first approach was to study the metabolism of "methyl-blocked" analogues of glaucine, a strategy successfully employed in the steroid field to show that microbial 1,2-dehydrogenation follows a trans-1,2-diaxial course.[3,4] A previous report described the synthesis and characterization of *cis*- and

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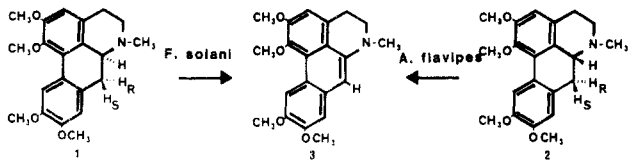

Figure 1. Stereospecific and quantitative metabolism of glaucine (1 and 2) to dehydroglaucine (3) by the fungi *Fusarium solani* and *Aspergillus flavipes*.

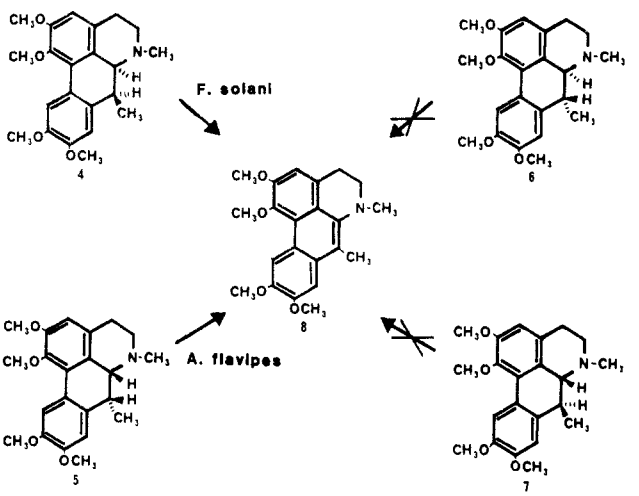

Figure 2. Stereoselective metabolism of 7-methylglaucine 4–7 to 7-methyldehydroglaucine (8) by the fungi *Fusarium solani* and *Aspergillus flavipes*.

trans-7-methylglaucine 4–7 as microbial substrates,[5] and this report concerns the results of the microbial metabolism of stereoisomeric 7-methylglaucines 4–7. Initially, analytical-scale experiments were conducted to examine the metabolism of **4/5** and **6/7** in growing cells of the fungi *A. flavipes* and *F. solani*.[5] In these metabolism studies, only *cis*-7-methylglaucine (**4/5**) was diastereoselectively metabolized by both fungi to 7-methyldehydroglaucine (**8**) and to a level of approximately 50% residual substrate, suggesting an enantioselective reaction similar to that observed for glaucine **1/2** (Figures 1 and 2). Further microbiological incubations on a semipreparative scale allowed for the destructive resolution of **4/5** by both fungi and a full description of the stereochemical course. This is the subject of this report. An elucidation of the stereochemical course of these reactions is important in deciphering the mechanism(s) of catalysis by these cultures and in extending these synthetically useful biotransformations to other compounds of interest in organic and natural products chemistry.

Experimental Section

Reagents, Chemicals, and Substrates. All solvents were analytical grade or better in quality. Solvents for high-performance liquid chromatography (HPLC) were of HPLC grade (Omnisolv, MCB Manufacturing Chemists, Cincinatti, OH). (*S*)-(+)-Glaucine (**1**) and (*R*)-(−)-glaucine (**2**) as well as *cis*- and *trans*-7-methylglaucine **4–7** were prepared as described previously.[5] Papaverine (HPLC internal standard) and boldine (for ORD studies) were obtained from Sigma Chemical Co., St. Louis, MO. Apomorphine for ORD studies was purchased from McFarland Smith Ltd., Edinburg, Scotland. The chiral shift reagent tris-[3-((trifluoromethyl)hydroxymethylene)-*d*-camphorato]europium (III) or Eu(tfc)$_3$ was purchased from Aldrich Chemical Co., Milwaukee, WI.

Analytical Procedures. All NMR Spectra were obtained in $CDCl_3$ with tetramethylsilane as the internal standard, and were generated on a Nicolet Model 200 (200 MHz) instrument. ^1H NMR studies with chiral shift reagents followed the procedure of Shaath and Soine.[6] Mass spectra were obtained from a Du Pont Model 21491 spectrometer by direct probe insertion. Point-determined ORD curves were generated on a Perkin-Elmer 241 MC polarimeter for boldine, (*S*)-(+)-glaucine, (*R*)-(−)-glaucine, apomorphine, and residual *cis*-7-methylglaucine from the *A. flavipes* fungal incubation. The ORD cell temperature was maintained with a water jacket (27–29 °C), and in all cases the aporphines (c = 1.0) were dissolved in MeOH. Measurements were taken in 5-nm increments from 290–380 nm, allowing for the observation of the Cotton effect in this region.[7] Optical rotations were measured at the Na D line with the same instrument.

Thin-layer chromatography (TLC) was conducted on plastic-backed 0.25-mm silica gel GF-254 plates (Polygram, Brinkman, Houston, TX) eluted with ethyl acetate–methanol–diethylamine (90:10:1) (R_f **4/5** = 0.38; R_f **6/7** = 0.50; R_f **8** = 0.83). Developed plates were visualized under UV light (254 and 280 nm) and by spraying with ceric ammonium sulfate (1% in 50% phosphoric acid) (**4/5** and **6/7** blue and **8** brown-yellow).

HPLC analysis of time course of metabolism studies was conducted as described previously.[5,8] Low-pressure liquid chromatography (LPLC) of microbiological extracts from destructive resolution experiments was performed with an FMI Model RP-SY low-pressure pump (Fluid Metering Inc., Oyster Bay, NY) and a 2.5 × 25 cm column (Rainin Instruments, Woburn, MA) packed with 66 g of Merck Kieselgel 60, 0.040–0.063 mm (230–400 mesh ASTM) from MCB Manufacturing Chemists, Cincinnati, OH. The mobile phase ethyl acetate–methanol–ammonium hydroxide (100:5:1) was eluted at a flow rate of 0.5 mL/min. Fractions of 10 mL were collected by using an LKB Model 2070 Ultrarac fraction collector (LKB Instruments, Gaithersburg, MD).

Analytical-Scale Microbial Transformation Studies. *F. solani* (ATCC 12823) and *A. flavipes* (ATCC 1030) were grown according to a two-stage fermentation procedure as published previously.[1,2] Time course studies of the racemic *cis*- and racemic *trans*-7-methylglaucine (**4/5, 6/7**) metabolism were conducted on an analytical scale in both growing cells and cell suspension. For the examination of metabolism in growing cells, 15 125-mL stage-2 flasks of *F. solani* and 9 125-mL stage-2 flasks of *A. flavipes* were prepared. All incubations were prepared in triplicate. (*S*)-(+)-Glaucine (**1**) was added as a control for *F. solani*, and (*R*)-(−)-glaucine (**2**) for *A. flavipes* to assure metabolic competency. Additional controls of racemic *cis*- and *trans*-7-methylglaucine (**4/5, 6/7**) in autoclaved (i.e., inactivated) *F. solani* cultures were also examined. The substrates **1**, **2**, **4/5**, and **6/7** were added to incubations of the fungi at levels of 3.5 mg/culture in 25 μL of dimethylformamide per flask. The cultures were incubated at 27 °C and 250 rpm in a G-25 R environmental shaker (New Brunswick Scientific Co., Edison, NJ), and samples of 1 mL were removed at 1, 24, 48, 72, 96, 120, and 168 h after substrate addition.

The examination of 7-methylglaucine (**4/5, 6/7**) metabolism in cell suspension (nongrowing cells in buffer) required the preparation of eight 24-h stage-2 1-L flasks of *F. solani*. (*S*)-(+)-Glaucine (40 mg in 200 μL of DMF) was added as an inducer to four of the *F. solani* stage-2 flasks, and after 72 h, a total of 800 mL of induced and 800 mL of naive (noninduced) cells were centrifuged at 27 °C and 1650*g* (IEC Centra 7R Centrifuge) for 12 min to remove the supernatant. The cells were then resuspended in buffer (pH 8, 0.05 M phosphate buffer) and centrifuged, and the process repeated three separate times. The resultant cell pellets were resuspended in 300 mL of buffer to form a 2.7-fold cell concentrate. Portions of 24 mL were placed in 18 125-mL Bellco-DeLong flasks (nine induced and nine naive cell incubations) and equilibrated for 1 h under the standard incubation conditions. The substrates **1**, **4/5**, and **6/7** were added to triplicate flasks at levels of 3.5 mg/culture in 25 μL of DMF. Samples of 1 mL were removed at 1, 24, 48, 72, 96, and 120 h after substrate addition. Samples from both growing cells and cell suspension were extracted and analyzed by HPLC as described previously.

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Preparative-Scale Microbial Transformation Studies. In the destructive resolution of **4/5**, three stage-2 flasks (1 L) were generated for both *F. solani* and *A. flavipes*. The substrate **4/5** was added to each flask (100 mg in 200 μL of DMF per flask) at 24 h. Incubations were monitered by HPLC and the reaction was stopped (8 days) when only 50% of the substrate remained. After homogenization (Polytron, Brinkman Instruments, Westbury, NY), cultures were made basic with KOH and exhaustively extracted with EtOAc. The organic layers were combined and concentrated in vacuo to yield 1.16 g of syrup from *A. flavipes* and 0.82 g of syrup from *F. solani*. Both extracts were purified by LPLC as described above to obtain residual *cis*-7-methylglaucine from *A. flavipes* (4.17 mg) and *F. solani* (22.23 mg) cultures. The residual substrates were analyzed by TLC, MS, ^{1}H NMR[5] and ^{1}H NMR using the chiral shift reagent Eu(tfc)$_3$,[6] OR, and ORD. Briefly, for NMR studies, spectra for samples (5 mg) of racemic *cis*- and *trans*-7-methylglaucine (**4/5, 6/7**) and the residual *cis*-7-methylglaucine substrate from *A. flavipes* and from *F. solani* (5 mg) were first obtained in $CDCl_3$. The chiral shift reagent (Eu(tfc)$_3$, 0.8 mg) was then added in 25 μL of $CDCl_3$ for shift studies. The chemical shifts and integrals for the H-11 proton was measured as an indication of enantiomeric composition.

Results and Discussion

The utility of microbial systems and purified enzymes in organic synthesis is well documented.[9-15] Often, microbiological techniques are preferred to chemical methods in organic synthesis due to milder reaction conditions and the high degree of stereoselectivity that is often observed. For example, *F. solani* has been shown to stereospecifically and quantitatively convert (*S*)-(+)-glaucine (**1**) to dehydroglaucine (**3**),[1] while the fungus *A. flavipes* stereospecifically and quantitatively oxidizes (*R*)-(−)-glaucine (**2**) to **3**.[2] In obtaining the unnatural *R* enantiomer of glaucine, the microbial reaction with *F. solani* is more facile than fractional crystallization[1,2] and has proven useful in the destructive resolution of racemic mixtures of glaucine (**1/2**).[2]

In order to extend this reaction to other aporphines and related alkaloids, a study was begun to determine the mechanism of oxidation. The stereochemistry of oxidation at position 6a was known; however, the stereochemistry at the prochiral (diastereotopic) C-7 position was not. Following an approach previously taken in the examination of the mechanism of steroid dehydrogenation,[3,4] the methyl-blocked analogues of glaucine, racemic *cis*- and *trans*-7-methylglaucine (**4/5, 6/7**), were synthesized.[5] Metabolic studies then permitted the determination of the overall stereochemistry of glaucine metabolism by *F. solani* and *A. flavipes*. For example, in the case of *F. solani*, a cis elimination of hydrogen would allow only for the metabolism of (6a*S*,7*S*)-7-methylglaucine (**4**) to **8**, whereas a trans elimination mechanism would involve only the metabolism of (6a*S*,7*R*)-7-methylglaucine (**6**) (see Figure 2).

The metabolism time courses with racemic *cis*-7-methylglaucine (**4/5**) and *trans*-7-methylglaucine (**6/7**)

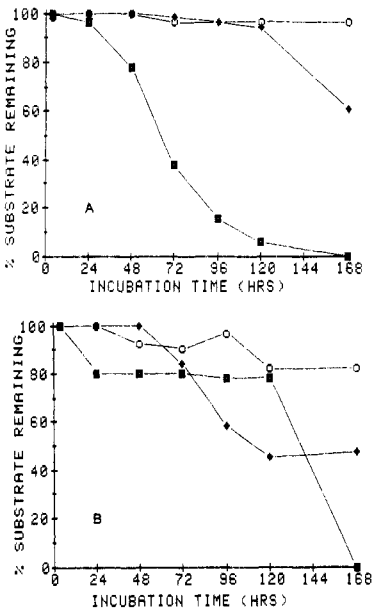

Figure 3. Time course for the metabolism of *cis*- and *trans*-7-methylglaucine **4–7** in growing cells of *Fusarium solani* (A) and *Aspergillus flavipes* (B). A: (■) (*S*)-(+)-glaucine; (♦) *cis*-7-methylglaucine; (○) *trans*-7-methylglaucine. B: (■) (*R*)-(−)-glaucine; (♦) *cis*-7-methylglaucine; (○) *trans*-7-methylglaucine.

were determined in growing cells of *F. solani* and *A. flavipes* (Figure 3A,B, respectively). Metabolism of (*S*)-(+)-glaucine (**1**) by *F. solani* and (*R*)-(−)-glaucine (**2**) by *A. flavipes* were included as controls to assure the metabolic capabilities of the fungi in the formation of **3**. In addition, the formation of metabolite **8** was not observed in autoclaved controls. The absence of metabolism of racemic *trans*-7-methylglaucine (**6/7**) by both fungi is evident, based on remaining substrate and a lack of formation of the dehydro product **8**. Only the cis pair of enantiomers **4/5** was metabolized by these fungi to dehydro-7-methylglaucine (**8**) and to a level of approximately 50% residual substrate, suggesting stereoselective metabolism. Since aporphine metabolism has been shown to be inducible by (*S*)-(+)-glaucine in cell suspensions of *F. solani* (unpublished results), it was thought possible that both *cis*- and *trans*-7-methylglaucine could serve as substrates but differ in that *trans*-7-methylglaucine (**6/7**) may not induce the enzyme(s) responsible for metabolism. Thus, the time course studies of 7-methylglaucine metabolism were extended to cell suspensions of this organism to determine if prior induction with glaucine would allow for the metabolism of *trans*-7-methylglaucine (**6/7**). Essentially the same metabolic profiles were observed for cell suspensions as in growing cells; i.e., only the *cis*-7-methylglaucine diastereomeric set of enantiomers **4/5** was metabolized in both induced and noninduced cell suspensions of *F. solani* and again to approximately the 50% level. *trans*-7-Methylglaucine (**6/7**) was not biotransformed. In both growing cells and cell suspension, the complete absence of metabolism of the *trans*-7-methylglaucine diastereomeric pair of enantiomers (**6/7**) and the metabolism of the cis pair of enantiomers **4/5** to a level of 50% residual substrate by both fungi suggests stereoselective metabolism and an overall cis elimination of hydrogens.

With the objective of confirming stereoselectivity in the metabolism of *cis*-7-methylglaucine (**4/5**), a semipreparative destructive resolution of the racemate by both fungi was initiated. The structures of residual substrates obtained from microbiological incubations were confirmed by cochromatography, MS, and ^{1}H NMR,[5] and enantiom-

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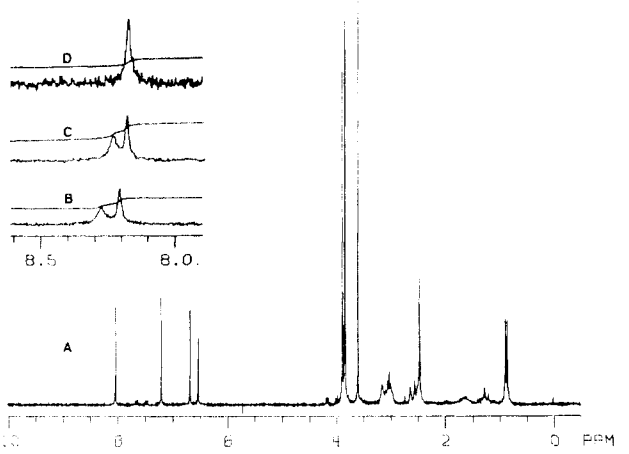

Figure 4. ^{1}H NMR spectrum (200 MHz) for *cis*-7-methylglaucine (**4**/**5**) (A), Eu(tfc)$_3$-induced shifts for the H-11 protons of racemic **4**/**5** (B), and residual substrate from *Fusarium solani* (C) and *Aspergillus flavipes* (D).

eric composition was assessed by the use of the ^{1}H NMR chiral shift reagent Eu(tfc)$_3$.[6] Figure 4 illustrates the normal spectrum (Figure 4A) and the Eu(tfc)$_3$-induced shifts of the pseudodiastereotropic H-11 protons in racemic *cis*-7-methylglaucine (Figure 4B). The proton of the *S* enantiomer is assigned to the farthest downfield signal as previously reported with racemic glaucine (**1**/**2**),[6] and integration for H-11 signals determined actual enantiomeric ratios. Subsequent analyses of residual *cis*-7-methylglaucine (**4**/**5**) substrates from *F. solani* and *A. flavipes* incubations (Figure 4C,D, respectively) indicate a modest enantiomeric excess of the *R* enantiomer from *F. solani* (Figure 4C; see below) and complete resolution to yield a single enantiomer with *A. flavipes* (Figure 4D). Since the chemical shifts of the pseudodiastereotopic H-11 protons are markedly dependent on the ratio of shift reagent to aporphine (see, for example, Figure 4B,C), and since only one singlet was evident in Figure 4D, it was difficult at this point to assign the absolute configuration of the residual substrate in the case of *A. flavipes*. However, these experiments suggest that metabolism is enantioselective with both fungi, in that *F. solani* metabolizes principally the (6a*S*,7*S*)-7-methylglaucine enantiomer (**4**) and *A. flavipes* metabolizes a single enantiomer (**5**; see below) to dehydro-7-methylglaucine (**8**).

Confirmation of the absolute stereochemistry of residual substrates was obtained from OR and ORD data. The point-determined ORD curves for a number of aporphines of the *R* configuration ((*R*)-(−)-apomorphine and (*R*)-(−)-glaucine) and of the *S* configuration ((*S*)-(+)-glaucine and (*S*)-(+)-boldine) were examined from 290–380 nm and compared with those obtained for residual substrates. As expected, the *S* aporphines display a negative Cotton effect in this region, whereas the *R* aporphines display a positive Cotton curve as reported by Djerassi et al.[7] In addition, (*S*)-aporphines exhibit a positive optical rotation at the Na D line.[16] The negative Cotton effect ($[M]^{27}_{315}$ −150,000 (*c* 0.1, methanol)) and positive OR ($[\alpha]^{27}_{D}$ +200° (*c* 0.1, methanol)) exhibited by the residual substrate from *A. flavipes*, along with the ^{1}H NMR data, establish that this is the (6a*S*,7*S*)-methylglaucine enantiomer **4**. Although the residual substrate obtained from *F. solani* cultures was not totally resolved, the OR ($[M]^{29}_{315}$ +221 (*c* 0.1, methanol)) and the ^{1}H NMR chiral shift reagent data confirm that it is enriched in (6a*R*,7*R*)-methylglaucine (**5**; in an enantiomeric excess of 10%).

These results establish that the microbial transformations of 7-methylglaucine are diastereoselective for *cis*-7-methylglaucine. Although the transformation of *cis*-7-methylglaucine **4**/**5** by the fungus *A. flavipes* was completely enantioselective, some degree of enantioselectivity was lost in the metabolism of **4**/**5** by *F. solani*, since residue **5** was found in only 10% enantiomeric excess. Regardless, both biotransformations proceeded with an overall cis elimination of hydrogen (Figure 2). Parallels can thus be drawn to the oxidation of glaucine by these fungi. Consequently, the biooxidation of (*S*)-(+)-glaucine (**1**) by *F. solani* presumably involves the 6a*S* and 7 *pro-R* hydrogens, while *A. flavipes* eliminates the 6a*R* and 7 *pro-S* hydrogens of (*R*)-(−)-glaucine (**2**) (see Figure 1). It should be recognized that structural modification of glaucine by the addition of a C-7 methyl group could influence the stereochemical recognition of the substrate by the enzyme(s) involved or the stereochemical course of the reaction. Studies involving isotopic labeling should confirm the results obtained with 7-methyl blocked analogues as demonstrated previously with steroidal substrates.[3,4] However, the stereochemical course described herein contributes to an understanding of the substrate structural requirements and tolerances in these biotransformations. This should also allow for the extension of these synthetically useful reactions to the resolution of other substituted aporphines and related compounds of interest in organic and natural products chemistry.

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