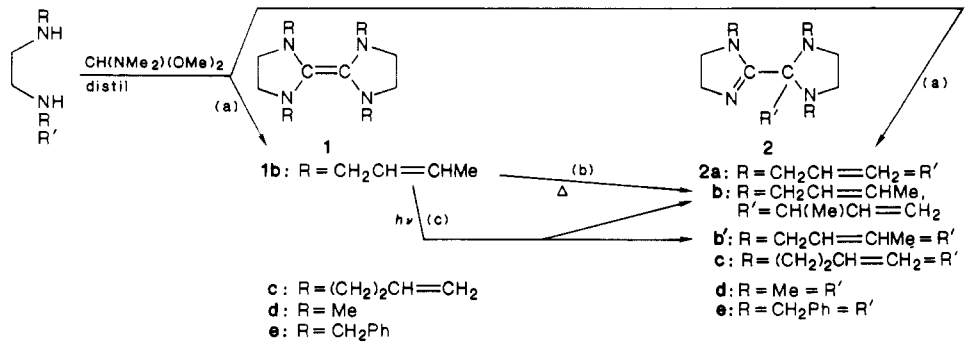
Scheme I[a]



[a] Reagents: (a) $C_6H_{11}Me$, reflux, 3 h, then elimination of MeOH and Me_2NH by distillation; (b) PhMe, reflux, 3 h; (c) irradiation in C_6D_6 at 350 nm, 2.5 h.

for $C_{10}H_{22}Cl_2N_2$: C, 49.8; H, 9.1; N, 11.6. Found: C, 49.6; H, 9.7; N, 11.3. IR (film, cm^{-1}): 3300 (NH), 1640 (C=C). ^1H NMR (360 MHz, $CDCl_3$): δ 1.2 (s, 2 H), 2-2.6 (m, 6 H), 4.8-5 (m, 4 H), 5.4-5.9 (m, 2 H). $^{13}C\{^1H\}$ NMR (90.5 MHz, C_6D_6): δ 48.9 (s, NCH_2CH_2N), 49.3 (s, $NCH_2CH_2CH=CH_2$), 115.2 (s, $CH=CH_2$) 136.7 (s, $NCH_2CH=$).

1,3,1',3'-Tetracrotyl- (1b) and Tetrabut-1'-enylbiimidazolidinylidene (1c). The appropriate diamine (30 mmol) and an excess of *N,N*-dimethylformamide dimethyl acetal (40 mmol) were heated under reflux for ca. 3 h in methylcyclohexane (100 mL). The reaction mixture was then heated to 130 °C under distillation conditions and the produced methanol and dimethylamine were removed by distillation [together with excess of $CH(NMe_2)(OMe)_2$]. The residual oil was dissolved in benzene and filtered through Celite, and the solvent was removed from the filtrate in vacuo affording the appropriate title compound **1b** or **1c** as a very viscous oil. $^{13}C\{^1H\}$ NMR (90.5 MHz, C_6D_6) **1b** 130.3 (*C*H=CHMe), 126.7 (CH=*C*HMe), 125.6 (C_{sp^2}), 53.9 (*C*H_2CH=), 49.1 (NCH_2CH_2N); **1c** 137.3 (*C*H=CH_2), 115.7 (CH=*C*H_2), 49.9 [$(CH_2)_2CH$], 49.5 (NCH_2CH_2N). Their spectra showed them to be reasonably pure compounds.

[1,3]-Sigmatropic Amino-Claisen Rearrangement Product (2a) of 1,3,1',3'-Tetraallylbiimidazolidinylidene (1a). A stirred solution of *N,N*-dimethylformamide dimethyl acetal (4.9 g, 40 mmol) and 1,2-bis(allylamino)ethane (4.37 g, 30 mmol) was heated under reflux for 3 h at 90 °C. The reaction mixture was then heated at 120 °C under distillation conditions and the produced methanol and dimethylamine as well as other volatiles were distilled off. The residue was freed from further volatile materials at 30 °C (10^{-2} Torr) to yield a yellow oil. This was extracted with pentane and the extract was filtered through Celite. After elimination from the filtrate of pentane in vacuo **2a** (2.55 g, 58%) was obtained. Anal. Calcd for $C_{18}H_{28}N_4$: C, 72.2, H, 9.3; N, 18.7. Found: C, 72.2; H, 9.4; N, 18.6. ^1H NMR (360 MHz, C_6D_6): δ 2.5 (m, 2 H), 2.7 (m, 6 H), 3.0 (m, 2 H), 3.2 (m, 2 H), 3.3 (m, 2 H), 3.8 (d, 2 H), 4.8 (m, 8 H), 5.6 (m, 3 H), 5.9 (m, 1 H) (the spectrum was assigned with the aid of computer simulation). $^{13}C\{^1H\}$ NMR (90.5 MHz, C_6D_6): δ 165.7, 81.9, 52.5, 52.4, 52.1, 52.0, 48.9, 39.4 (each signal was assigned by spin-echo experiments, consistent with the proposed structure).

Thermal Isomerization of 1,3,1',3'-Tetracrotylbiimidazolidinylidene (1b). Compound **1b** (0.1 g, 0.28 mmol) was heated under reflux in toluene (10 mL) for ca. 3 h. The mixture was filtered through Celite. Solvent was eliminated from the filtrate in vacuo to afford a residue (0.08 g), comprised mainly of the rearrangement product **2b** with as principal contaminant unreacted **1b**. ^{13}C NMR (90.5 MHz, spin-echo mode, C_6D_6): δ 47.4 (*C*CHMe), 113.7 (CH=CH_2), 144.5 (*C*H=CH_2), 165.4 (*C*=NCH_2).

Photochemical Isomerization of 1,3,1',3'-Tetracrotylbiimidazolidinylidene (1b). Compound **1b** (0.1 g, 0.28 mmol) was dissolved in benzene-d_6 and its ^1H NMR and ^{13}C NMR spectra were recorded. After irradiation at 350 nm for 2.5 h, the ^1H NMR spectrum showed the presence of some rearranged product. The irradiation was continued for a further 2.5 h, when no starting material was detectable. The identity of the rearranged products **2b** and **2b'** was established by $^{13}C\{^1H\}$ NMR (90.5 MHz, spin-echo mode, C_6D_6): δ **2b** 165.4 (*C*=NCH_2), 144.5 (*C*H=CH_2), 113.7 (CH=CH_2), 47.4 (*C*CHMe); **2b'** 52.1 (*N*CHCH=), 38.08 (*CC*H_2CH=), 18.3 (=CH*C*H_3), 17.7 (=CH*C*H_3).

Acknowledgment. We thank Professor J. N. Murrell for helpful discussions, Professor M. Traetteberg for the electron diffraction data on **1d** in Table I,[4] Drs. P. B. Hitchcock and H. A. Jasim for the X-ray data on **2e** in Table I,[5] and Universidad Nacional Autonoma de Mexico for a grant (to J.A.C.).

Registry No. **1b**, 122145-25-9; **1c**, 122145-26-0; **1d**, 1911-01-9; **2a**, 122171-14-6; **2b**, 122171-15-7; **2b'**, 122145-27-1; **2d**, 122145-28-2; $Br(CH_2)_2Br$, 106-93-4; $CH_3CH=CHCH_2NH_2$, 21035-54-1; $CH_2=CH(CH_2)_2NH_2$, 2524-49-4; $CH(NMe_2)(OMe)_2$, 4637-24-5; $CH_3CH=CHCH_2NH(CH_2)_2NHCH_2CH=CHCH_3$, 65838-12-2; $CH_2=CH(CH_2)_2[NH(CH_2)_2]_2CH=CH_2$, 122145-24-8; $CH_2=CHCH_2NH(CH_2)_2NHCH_2CH=CH_2$, 61798-21-8.

Microbial Transformations. 12. Regiospecific and Asymmetric Oxidation of the Remote Double Bond of Geraniol

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In spite of numerous efforts, the stereospecific oxidation of double bonds is still an important challenge to the organic chemist.[1] In the course of our work related to the microbiological oxidation of various substrates,[2] we have been interested in the possibility of regio- and stereospecifically[3] oxidizing the "remote" double bond of phenylcarbamate derivatives of geraniol and nerol **1** and **2**. This choice of substrate was dictated by three considerations. First, we have previously shown that the bio-

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(3) Owing to the confusing use of the term *enantioselective* made in the current literature, which describes as well synthesis starting from optically active precursors, kinetic differentiation between enantiomers, or stereospecific selection of enantiotopic faces of a prochiral substrate, we consider that this type of reaction—i.e., the stereospecific transformation of a prochiral substrate into one single product enantiomer—should be called an *enantiogenic* reaction (since only one *enantio*mer is *gen*erated), rather than an *enantioselective* reaction (since no *selection* between two enantiomers is made on the starting compound).

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hydroxylation of various substrates may be achieved with generally high efficiency and stereoselectivity, provided that they bear amide or urethane groups.[2,4] Therefore, it was of interest to determine whether this type of functionalization would also allow oxidation of double bonds on olefinic alcohols. Second, whereas the Sharpless oxidation of geraniol and nerol allows direct access to the optically active 2,3-epoxide,[5] no way is yet available to achieve the direct regio- and stereoselective oxidation of the C(6) double bond. Finally, the diols or epoxides obtainable from 1 or 2 appear to be very useful "chirons".[6-8] However, in all cases, the chiral building blocks had to be prepared by following multistep procedures. We here describe a one-step synthesis of the very versatile chiral synthons 3 and 4 obtained from geraniol or nerol phenylcarbamates 1 and 2.

Results

When submitted to a 36-h culture of *Aspergillus niger*, geranyl *N*-phenylcarbamate (1) was metabolized to diol 3, which was isolated by direct crystallization from the crude extract (49% yield) (Scheme I). Its structure was unambiguously established by conventional ^{1}H NMR analysis. The enantiomeric excess of this diol was determined by analysis of its (−)-camphanyl derivative,[9] which indicated an ee >95%.[10]

The absolute configuration at C(6) was determined by using a chemical correlation of 1 with the corresponding acetate 5, which has been previously described by Eschenmoser et al.[6b] Thus, diol 3 was transformed into its acetonide 6, which was further saponified to alcohol 7. This was acetylated and hydrolyzed, to yield 5, which showed an optical rotation of $[\alpha]^{20}_D = -25.1°$ (lit. $[\alpha]_D = -25.7°$ [8] and $-25.1°$ [6b]). This result confirms the previously determined enantiomeric excess and allows the assignment of the *S* absolute configuration to the stereogenic[11] carbon atom C(6).

Similarly, acetonide 6 was efficiently oxidized, via a phase-transfer technique,[12] thus leading to the valuable "chiron" 8, previously described by Terashima et al. in its optically pure form.[9]

Since the epoxide is a versatile substrate for further synthesis, we also have transformed diol (*S*)-3 into its corresponding optically active epoxide 9 of *R* configuration. This was achieved by reaction of diol 3 with tosyl chloride in the presence of sodium hydride. The *R* epoxide 9 thus obtained was hydrolyzed in acidic medium to yield the corresponding *R* diol. This was shown, by HPLC analysis of its camphanyl chloride derivative, to have an enantiomeric excess of 95%, and the *R* absolute configuration at C(6). Our results indicate that the epoxidation reaction, as well as the hydrolysis of epoxide 9, occurs in a stereospecific way, thus allowing preparation of both antipodes of diol 3 with high optical purities.

When submitted to the same bioconversion conditions, neryl *N*-phenylcarbamate 2 was analogously transformed into a diol. Its structure was established by standard methods as being 4. No HPLC separation was observed for its (−)-camphanyl derivative. Its optical purity, as well as the absolute configuration at carbon atom C(6), was determined by phase-transfer oxidation of the isopropylidene derivative of 4, which led to 8. It thus appears that 4 is of *S* absolute configuration and that its optical purity is about 90%.

Discussion

Our results emphasize the influence of the alcohol function substitution in geraniol. Indeed, experiments conducted using geraniol and nerol as substrates indicate that no notable bioconversion occurs, a fact that may be due to at least two factors, i.e., the nonlipophilic properties of these alcohols and the surface toxic effects of acyclic monoterpene alcohols.[13] Surprisingly, incubation of the corresponding acetate with the same fungus led to exclusive hydroxylation of the C(8) allylic position.[14] Thus, it is clear that the functionality borne by the hydroxyl group has an important influence on the nature and regiospecificity of the microbiological oxidation. On the other hand, the *E* or *Z* configuration of the C(2) double bond has no influence on the regioselectivity nor on the stereospecificity of this reaction, the *S* enantiomer being obtained almost exclusively by starting from either geraniol or nerol.

It is also noteworthy that, whereas the Sharpless process exclusively achieves oxidation of the 2,3 double bond of geraniol and nerol, this microbial transformation only oxidizes the 5,6 olefinic bond. This observation suggests that the urethane moiety plays an anchoring and orienting role in the enzyme–substrate complex.[15]

As far as the mechanism of the observed oxidation of 1 and 2 is concerned, we have no indication, at the present time, whether the diol is formed directly from the olefin or via discrete epoxide or dioxetane intermediates. However, it is quite surprising that we did not observe any noticeable formation of the epoxide as described, for instance, by Marumo et al.,[16] a fact that seems to favor the hypothesis of a single-step oxidation pathway. In this case, the *cis*-diol isomer should be preferentially formed.[17,18] We are currently studying further this mechanistic aspect.

Conclusion

This study indicates that geraniol 1 or nerol 2 can be transformed, in a single step, into the highly valuable chiral synthons 3 or 4. Because of their different regioselectivity, these bioconversions (which can be conducted on several-gram-scale experiments) represent a very interesting complement to the Sharpless oxidation of geraniol and nerol.

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Work is in progress in our laboratory in order to explore the scope and limitations of this reaction, as well as to gain some more insight into the mechanism involved in these biotransformations.

Experimental Section

General. The strain of *A. niger* used in this work is registered at the "Museum d'Histoire Naturelle" (Paris) under no. LCP 521 (Lab. de Cryptogamic, 12 rue Bullon, 75005 Paris, France). Corn steep liquor (CSL) is from Roquette S.A. Vapor phase chromatography analyses were performed by using a 25-m capillary column (OV 1701). Separation and purification of the products were achieved by flash chromatography (silica gel 60H from Merck and solvent mixtures consisting of hexane and ether in the range of 100% hexane to 100% ether). Melting points are uncorrected. ^{1}H NMR spectra were recorded at 80, 200, or 400 MHz in deuteriochloroform.

Incubation Experiments. The microorganism was maintained on gelose slopes by using the following medium: corn steep liquor (CSL), 20 g/L; glucose, 10 g/L; KH_2PO_4, 10 g/L; K_2HPO_4, 5 g/L; Bacto-Agar (Difco), 20 g/L.

The 2-L fermentor jar was filled with H_2O, 1 L; CSL, 20 g; and glucose, 10 g. It was sterilized in an autoclave for 20 min at 115 °C. After cooling, the pH was adjusted to 4.8 by addition of 1 N NaOH. The medium was aerated by bubbling sterilized air (100 mL/min) through a sterile membrane. The medium was stirred at 700 rpm. Inoculation of the medium was made by adding, under sterile conditions, a small piece of gelose supporting the mycelium and the black spores. After 36-h growth, the substrate (1 g) was added as a solution in ethanol (10 mL). After 48-h incubation, the mycelium was filtered off and the fungal cake was washed with H_2O. The aqueous phase was continuously extracted with CH_2Cl_2, for 24 h. The extract was washed with 1 N NaOH and then with H_2O and dried ($MgSO_4$).

(6*S*,2*E*)-6,7-Dihydroxy-3,7-dimethyl-2-octen-1-yl Phenylcarbamate (3). This product (550 mg, 49%) was isolated from the crude extract by crystallization from benzene: mp 98–99 °C; IR ($CHCl_3$) 3560 (OH), 3420 (NH), 1720 (C=O), 1590, 1510, 1435, 1300 cm^{-1}; $[\alpha]^{20}_D$ −18.46 (*c* 1.93, MeOH); ^{1}H NMR (400 MHz) 1.18 (s, 3 H), 1.23 (s, 3 H), 1.38–1.53 (m, 1 H, C(5)-H), 1.57–1.68 (m, 1 H, C(5)-H), 1.76 (s, 3 H, CH_3 vinylic), 2.08–2.21 (m, 1 H, allylic), 2.28–2.41 (m, 3 H, allylic and hydroxyl), 3.36 (dd, *J* = 8 and 4 Hz, C(6)-H), 4.7 (d, *J* = 7 Hz, 2 H, C(1)-H), 5.48 (t, *J* = 7 Hz, 1 H, C(2)-H), 6.75 (s, 1 H, NH), 7.06 (t, *J* = 7.5 Hz, 1 H, para aromatic), 7.31 (t, *J* = 7.5 Hz, 2 H, meta aromatic), 7.85 (d, *J* = 7.5 Hz, 2 H, ortho aromatic). Anal. Calcd for $C_{17}H_{25}O_4N$ (307): C, 66.45; H, 8.14; N, 4.56. Found: C, 66.16; H, 8.17; N, 4.45.

(6*S*,2*Z*)-6,7-Dihydroxy-3,7-dimethyl-2-octen-1-yl Phenylcarbamate (4). This compound (450 mg, 40%) was isolated similarly from the crude extract: mp 65–67 °C; IR ($CHCl_3$) same spectrum as for **3**; $[\alpha]^{20}_D$ −2.3° (*c* 1.43, MeOH); ^{1}H NMR (200 MHz) 1.13 (s, 3 H), 1.16 (s, 3 H), 1.41 (m, 1 H, C(5)-H), 1.6 (m, 1 H, C(5)-H), 1.74 (s, 3 H, CH_3 vinylic), 2.3 (m, 2 H, allylic), 3.3 (dd, *J* = 8 and 4 Hz, 1 H, C(6)-H), 4.6 (dd, *J* = 12 and 6.5 Hz, 1 H, C(1)-H), 4.7 (dd, *J* = 12 and 6.5 Hz, 1 H, C(1)-H), 5.4 (t, *J* = 6.5 Hz, 1 H, C(2)-H), 7.0 (t, *J* = 7.5 Hz, 1 H, para aromatic), 7.25 (t, *J* = 7.5 Hz, 2 H, meta aromatic), 7.35 (d, *J* = 7.5 Hz, 2 H, ortho aromatic), 7.55 (s, 1 H, NH). Anal. Calcd for $C_{17}H_{25}O_4N$ (307): C, 66.45; H, 8.14; O, 20.85. Found: C, 66.16; H, 8.17; O, 20.09.

(6*S*,2*E*)-6,7-Dihydroxy-6,7-*O*-isopropylidene-3,7-dimethyl-2-octen-1-yl Phenylcarbamate (6). To a suspension of **3** (500 mg) in 5 mL of 2,2-dimethoxypropane was added a catalytic amount of *p*-toluenesulfonic acid. Dissolution occurred readily, and 5 mL of 1 N NaOH was added. The mixture was extracted with ether, and the organic phase was washed with H_2O and dried ($MgSO_4$). Solvent and excess dimethoxypropane were evaporated under vacuum, and the residue was submitted to a flash chromatography. The acetonide **6** (508 mg, 90%) was obtained as a colorless oil: IR (film) 3420 (NH), 1720 (C=O), 1590, 1500, 1430, 1360, 1300 cm^{-1}; ^{1}H NMR (80 MHz) 1.05, 1.2, 1.25 and 1.4 (4 s, 4 × 3 H), 1.7 (s, 3 H, CH_3 vinylic), 3.6 (dd, *J* = 8 and 4 Hz, 1 H, (C5)-H), 4.6 (d, *J* = 7 Hz, 2 H, C(1)-H), 5.4 (t, *J* = 7 Hz, 1 H, C(2)-H), 6.8–7.5 (m, 6 H, aromatic and NH). Anal. Calcd for $C_{20}H_{29}O_4N$ (347): C, 69.16; H, 8.35; N, 4.03. Found: C, 69.13; H, 8.13; N, 4.01.

(6*S*,2*Z*)-6,7-Dihydroxy-6,7-*O*-isopropylidene-3,7-dimethyl-2-octen-1-yl Phenylcarbamate (10). The *Z* isomer of **6** was obtained by the same process: IR (film): same spectrum as for **6**; ^{1}H NMR (80 MHz) 1.1, 1.2, 1.3 and 1.4 (4 s, 4 × 3 H), 1.75 (s, 3 H, CH_3 vinylic) 2.3 (t, *J* = 8 Hz, 2 H allylic), 3.6 (dd, *J* = 8 and 4 Hz, 1 H, C(5)-H), 4.67 (d, *J* = 7 Hz, 2 H, C(1)-H), 5.4 (t, *J* = 7 Hz, 1 H, C(2)-H), 6.8 (s, 1 H, NH), 6.9–7.5 (m, 5 H, aromatic). Anal. Calcd for $C_{20}H_{29}O_4N$ (347): C, 69.16; H, 8.35; N, 4.03. Found: C, 69.16; H, 8.27; N, 3.96.

(6*S*,2*E*)-6,7-Dihydroxy-6,7-*O*-isopropylidene-3,7-dimethyl-2-octen-1-ol (7). A solution of acetonide **6** (350 mg, 1 mmol) in ethanol (10 mL) and 5 N NaOH (2 mL) was heated at reflux overnight. Excess ethanol was removed by distillation, and the aqueous phase was extracted with ether. The organic phase was washed with H_2O and dried (Na_2SO_4). The crude product led, after distillation using Kugelrohr (at 140–150 °C, 0.1 mm), to alcohol **7** as a colorless oil (182 mg, 80%). The purity, determined by vapor-phase chromatography at 140 °C, is not less than 98%. The physical properties of **7** are identical with those described by Meier et al.[5]

(6*S*,2*E*)-6,7-Dihydroxy-3,7-dimethyl-2-octen-1-yl Acetate (5). This acetate is obtained (70% yield) from **7** by acetylation and hydrolysis according to a literature procedure.[9] The product has physical properties similar to those previously described, except $[\alpha]^{20}_D$ −25.1° (*c* 0.71, EtOH) (lit.[6] $[\alpha]^{22}_D$ −25.7° (*c* 0.736, EtOH), $[\alpha]^{20}_D$ −25.1° (*c* 0.832, EtOH)).

(6*S*)-5,6-Dihydroxy-5,6-*O*-isopropylidene-6-methylheptan-2-one (8). To a stirred solution of $KMnO_4$ (480 mg, 3 mmol) and NBu_4Br (20 mg) in water (5 mL) was added a solution of **6** (350 mg, 1 mmol) in 2 mL of benzene. After 15 h at room temperature, 5 mL of a saturated solution of $Na_2S_2O_3$ was added. The precipitate was filtered, and the aqueous phase was extracted with ether. The combined organic layers were washed with H_2O and dried ($MgSO_4$). The solvents were evaporated, and the crude product was distilled by using Kugelrohr (at 120 °C, 0.5 mm) to yield ketone **8** (160 mg, 80%): IR (film) 1705 (C=O) cm^{-1}; ^{1}H NMR (80 MHz) 1.1, 1.25, 1.3, 1.4 (4 s, 4 × 3 H), 1.6 (m, 2 H, C(4)-H), 2.15 (s, 3 H, CH_3C=O), 2.6 (m, 2 H, C(3)), 3.6 (dd, *J* = 8 and 6 Hz, 1 H, C(5)-H); $[\alpha]^{20}_D$ −13.5° (*c* 2, MeOH) (lit.[9] $[\alpha]^{27}_D$ −14.8° (*c* 1.4, MeOH)).

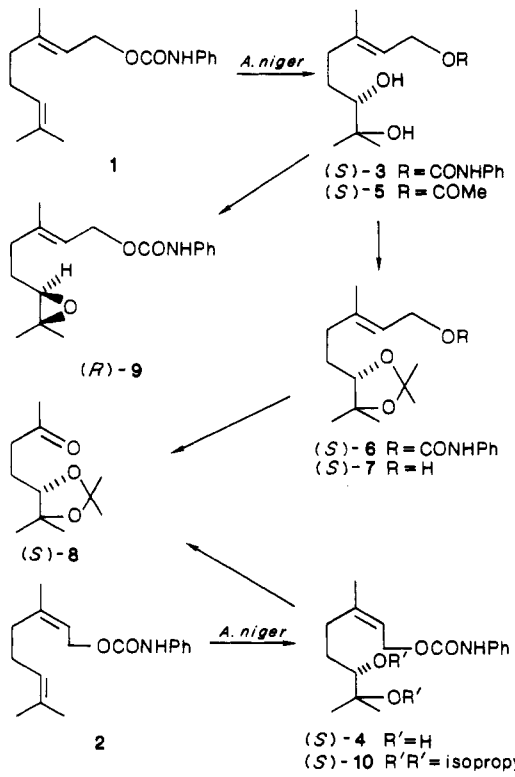
This process, applied to the isopropylidene derivative **10** of the *Z* isomer **4**, also led to ketone **8** with $[\alpha]^{20}_D$ −14.5° (*c* 2.3, MeOH).

Camphanoyl Derivative of (6*S*)-3. To a solution of **3** (100 mg, 0.3 mmol) in 1 mL of anhydrous pyridine was added (1*S*)-(−)-camphanic acid chloride (Fluka) (150 mg, 0.7 mmol). The mixture was stirred for 3 h at room temperature and poured into 10% HCl (10 mL). Extraction with CH_2Cl_2, washing with H_2O, and drying over $MgSO_4$ led to a crude product, which was directly analyzed by HPLC with a 25/0.4 cm column filled with 5-μm silica gel using hexane/ethanol (96/4) as eluent and UV detection at 254 nm. This indicated an enantiomeric excess higher than 95% for **3**. This camphanoyl derivative of **3** can be purified by silica gel chromatography and by recrystallization in CH_2Cl_2/hexane: mp 135–136 °C; $[\alpha]^{20}_D \approx 0°$ (*c* 1.88, MeOH); IR ($CHCl_3$) 3420 (NH), 1780 (C=O, lactone), 1720 (C=O, carbamate), 1590, 1510, 1440 cm^{-1}; ^{1}H NMR (200 MHz) 1.0, 1.1, 1.12, 1.2, 1.23 (5 s, 5 × 3 H), 1.72 (s, 3 H, CH_3 vinylic), 4.67 (d, *J* = 7 Hz, C(1)-H), 4.94 (dd, *J* = 8 and 3 Hz, C(6)-H), 5.38 (t, *J* = 7 Hz, C(2)-H), 6.86 (s, 1 H, NH), 7.08 (t, *J* = 7.5 Hz, 1 H, para aromatic), 7.30 (t, *J* = 7.5 Hz, 2 H, meta aromatic), 7.38 (d, *J* = 7.5, 2 H, ortho aromatic). Anal. Calcd for $C_{27}H_{37}O_7N$ (487): C, 66.53; H, 7.59; N, 2.89. Found: C, 66.12; H, 7.62; N, 2.80.

This purified compound was methanolized back to **3** by treatment with K_2CO_3 (50 mg) in MeOH (1 mL) overnight. Water was added, and the mixture was extracted with CH_2Cl_2. HPLC analysis showed the exclusive formation of **3**. After evaporation of the solvent, the crude product was esterified by (1*S*)-(−)-camphanic acid chloride (the same pot was used) in anhydrous pyridine. The usual workup led to a crude product, submitted to HPLC analysis. The thus-obtained derivative only shows one peak in the conditions previously used.

Racemic (2*E*)-6,7-Dihydroxy-3,7-dimethyl-2-octen-1-yl Phenylcarbamate (3). To a solution of **1** (2.57 g, 10 mmol) in THF (10 mL) was added water to the saturation point. *N*-

Scheme I



Bromosuccinimide (1.8 g) was added in small portions. The reaction was monitored by TLC analysis (silica gel, ether). At the end of the addition, 5 N NaOH (2 mL) and THF were added to keep the homogeneity of the medium. When all the bromohydrin was consumed, 20% H_2SO_4 (3 mL) was carefully added. At the end of the reaction, water was added and the medium was extracted with ether. The organic phase was washed with water and dried ($MgSO_4$). Recrystallization of the crude product from benzene gave the racemic diol **3** (2 g, 65%): mp 77–80 °C. Derivatization of the racemic diol with (1*S*)-(−)-camphanic acid chloride was performed exactly as previously described. The oily diastereoisomeric mixture had $[\alpha]^{20}_D$ −2.3° (*c* 1.7, MeOH).

(6*R*,2*E*)-6,7-Epoxy-3,7-dimethyl-2-octen-1-yl Phenylcarbamate (9). Diol **3** (300 mg, 1 mmol) and *p*-toluenesulfonyl chloride (200 mg, 1.05 mmol) were dissolved in dry benzene (20 mL). NaH (80% in oil, 100 mg, 3.3 mmol) was added in small portions. At the end of the reaction (monitored by TLC), water was carefully added and the organic layer was washed with water, dried ($MgSO_4$), and evaporated. Purification of the crude product by flash chromatography led to the colorless oily epoxide **9** (245 mg, 85%): $[\alpha]^{20}_D$ 0.5° (*c* 1.2, MeOH); IR (film) 3420 (NH), 1720 (C=O), 1590, 1500, 1430, 1360, 1300 cm^{-1}; ^1H NMR (80 MHz) 1.16, 1.18 (2 s, 2 × 3 H), 1.74 (s, 3 H, CH_3 vinylic), 1.5–2.3 (m, 2 H, allylic), 2.5 (t, J = 6 Hz, 1 H, C(6)-H), 4.46 (d, J = 7 Hz, 2 H, C(1)-H), 5.3 (t, J = 7 Hz, 1 H, C(2)-H), 6.8–7.5 (m, 6 H, aromatic and NH).

(6*R*,2*E*)-6,7-Dihydroxy-3,7-dimethyl-2-octen-1-yl Phenylcarbamate. This compound was obtained from **9** (200 mg) according to a literature procedure.[6b] The diol (170 mg, 85% after flash chromatography) had mp 90–91 °C (from benzene) and $[\alpha]^{20}_D$ 25.2° (*c* 0.87, EtOH). Derivatization of this (*R*)-diol with (1*S*)-(−)-camphanic acid chloride was performed as described previously on a 100-mg portion. The oily product has the same IR and ^1H NMR spectra as its diastereoisomer except for $[\alpha]^{20}_D$ −4.7° (*c* 1.2, MeOH). HPLC analysis indicated a 95% enantiomeric excess.

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Synthesis of Monotritiomethyl Iodide from Thioethers. Hydrogenolysis in the Presence of Thioethers

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Monotritiomethyl iodide with high specific activity is a valuable reagent for the incorporation of a tritiated methyl group and has attracted much attention in recent years.[1] The reagent can be used for specific tritium labeling of amines, alcohols, and thiols and for C-methylation of peptidic amino acid residues.[2,3] This reagent was previously prepared from bis(chloromethyl) ether at nearly theoretical specific activity.[4] However, this technique has received limited applications because the precursor is known to be a powerful carcinogen and the resulting tritiated ether is highly volatile (bp −24.8 °C) and difficult to control under the reaction conditions.

We recently reported a new procedure for the synthesis of monotritiomethyl iodide by the preparation of chloromethyl esters, followed by tritiodehalogenation with carrier free tritium gas and subsequent cleavage of the [$^3H_1$]ester by lithium iodide.[5] Due to the time necessary for C–Cl bond hydrogenolysis in these esters (normally 12 h), we observed significant isotopic dilution, and the theoretical specific activity was not attainable. Also, in most cases, only 75–80% of the precursor's specific activity could be preserved in the N-methylated products. To overcome these deficiencies, we have continued our investigations and now report a procedure that effectively proceeds with rapid tritium incorporation and essentially no isotope dilution.

Monotritiomethyl iodide can now be prepared from monotritiomethyl phenyl sulfide (**2**) as the precursor. When chloromethyl phenyl sulfide (**1**) was exposed to deuterium gas in the presence of Pd/C, we observed that hydrogenolysis of the C–Cl bond in this compound occurred within 3 h at room temperature and gave a single product in 95% yield. The product was identified as monodeuteriomethyl phenyl sulfide (GC and deuterium NMR evidence). This result was surprising because sulfides have long been known to poison the catalyst through direct linkage of the hetero atom to the catalyst.[6] Hydrogenolysis of the precursor with carrier-free tritium gas and 10% Pd/C gave the desired product in 95% yield and with a specific activity of 20 Ci/mmol. The reaction was much faster (less than 1 h) with 30% Pd/C as the catalyst (Scheme I). In this case, at 1 atm of carrier-free tritium gas, the rapid uptake of tritium was complete after 1 h and the monotritio thioether was obtained with a specific activity of 28.5 Ci/mmol (theoretical value, 29 Ci/mmol). The ^3H NMR spectrium of this compound showed a singlet

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