triacetates (51 mg, 0.14 mmol) in dry benzene (1.4 mL) contained in a 10-mL round-bottomed flask equipped with a condenser.[87] The mixture was lowered into a bath preheated at 65 °C and stirring was continued for 8 h. The mixture was cooled and evaporated (oil pump vacuum) to give the crude bromides **19a**, which were used without purification for the next step. The bromides are rather unstable, and, therefore, were kept under argon and protected from moisture.

4,6-Di-*O*-acetyl-1,5-anhydro-2,3-dideoxy-3-(2-ethoxy-2-oxoethyl)-D-*arabino*-hex-1-enitol (19b). The general procedure for thermal radical ring-opening was followed, using the crude bromides **19a** (about 0.143 mmol) in dry benzene (1.4 mL), Bu_3SnH (94 μL, 0.35 mmol), and AIBN (2 mg, 0.012 mmol). Refluxing was continued for 2 h, and the mixture was cooled and evaporated. Flash chromatography (twice) of the residue over silica gel (1 × 15 cm) using 25% EtOAc–hexane afforded **19b** [34.0 mg, 79% based on the anomeric acetates (see part c above)]: FT-IR ($CHCl_3$ cast) 2980, 1744, 1651, 1374, 1237, 1062, 1039 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.26 (t, J = 7.2 Hz, 3 H), 2.09 (s, 6 H), 2.21 (dd, J = 16.0, 9.5 Hz, 1 H), 2.49 (dd, J = 16.0, 5.0 Hz, 1 H), 2.88 (m, 1 H), 3.99 (ddd, J = 10.0, 5.0, 2.4 Hz, 1 H), 4.14 (q, J = 7.2 Hz) and 4.17 (d, J = 12.3 Hz) [both signals together correspond to 3 H], 4.36 (dd, J = 12.3, 5.0 Hz, 1 H), 4.68 (dd, J = 6.0, 2.0 Hz, 1 H), 4.97 (t, J = 9.4 Hz, 1 H), 6.38 (dd, J = 6.0, 2.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 14.21, 20.76, 20.85, 35.32, 37.29, 60.63, 62.12, 68.83, 74.86, 102.14, 143.06, 170.09, 170.76, 171.68; exact mass, m/z calcd for $C_{12}H_{17}O_5$ [$(M - C_2H_3O_2)^+$] 255.0869, found 255.0865; mass (chemical ionization, NH_3) 318 [$(M + 18)^+$]. Anal. Calcd for $C_{14}H_{20}O_7$: C, 55.99; H, 6.71. Found: C, 55.78; H, 6.86.

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Supplementary Material Available: Appropriate spectroscopic and analytical data for **7b**, **7e**, **8b**, **8c**, **9f**, **11b**, **11c**, **13b**, **13c**, **14d**, (17α)-3-methoxyestra-1,3,5(10),15-tetraen-17-yl benzoate, a mixture of **15d** and **14e**, **18a**, methyl (*R*)-4,6-di-*O*-acetyl-2,3-dideoxy-2,3-[(ethoxycarbonyl)methylene]-α-D-mannopyranoside, methyl (*R*)-1,4,6-tri-*O*-acetyl-2,3-dideoxy-2,3-[(ethoxycarbonyl)-methylene]-α-D-mannopyranose, and methyl (*R*)-1,4,6-tri-*O*-acetyl-2,3-dideoxy-2,3-[(ethoxycarbonyl)methylene]-β-D-mannopyranose (6 pages). Ordering information is given on any current masthead page.

Microbiological Transformations. 19. Asymmetric Dihydroxylation of the Remote Double Bond of Geraniol: A Unique Stereochemical Control Allowing Easy Access to Both Enantiomers of Geraniol-6,7-diol

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The microbiological oxygenation of the geraniol *N*-phenylcarbamate **1** by *Aspergillus niger* is described, which leads regiospecifically to a formal dihydroxylation of its C(6)=C(7) double bond. By use of different pH values of the incubation medium, it is possible to modulate the stereochemical outcome of this reaction. Thus, 6*S* diol **3** (ee > 95%) is obtained at pH 2, whereas 6*R* diol **3** (ee > 95%) is formed at pH 6–7. The mechanism of this reaction has been studied by $^{18}O_2$ labeling. It is shown that, in a first step, the 6*S* epoxide **2** is almost exclusively formed. The second step involves hydrolysis of this key intermediate via a spontaneous acid-catalyzed hydrolysis at pH 2 or an enzymatic hydrolysis at pH 6–7.

Asymmetric dihydroxylation reactions of simple olefins are, at the present time, a widely used approach to prepare chiral building blocks.[1] Although these methods lead in some cases to diols showing ee values as high as 95%, the reactions seem to be limited to monoolefins of quite simple structure. We have recently[2] described an asymmetric biooxidation of the remote double bond of geraniol *N*-phenylcarbamate (**1**) by the fungus *Aspergillus niger*, which led to diol (6*S*)-**3** (49% yield, ee 95%) (Figure 1). Since this diol is a valuable chiral synthon,[3] it would be of great synthetic interest to obtain its 6*R* enantiomer stereospecifically. Whereas the challenge of obtaining a specific enantiomer of product can often be accomplished by asymmetric chemical reactions by using the appropriate enantiomer of catalyst, achieving such selectivity is less predictable in the case of bioconversions, although various options exist, i.e., by chemically modifying the substrate[4] or searching for other microorganisms (or enzymes) of opposite stereoselectivity.[5] We report here a more direct approach in which the stereochemical outcome is controlled simply by modifying the bioconversion conditions.

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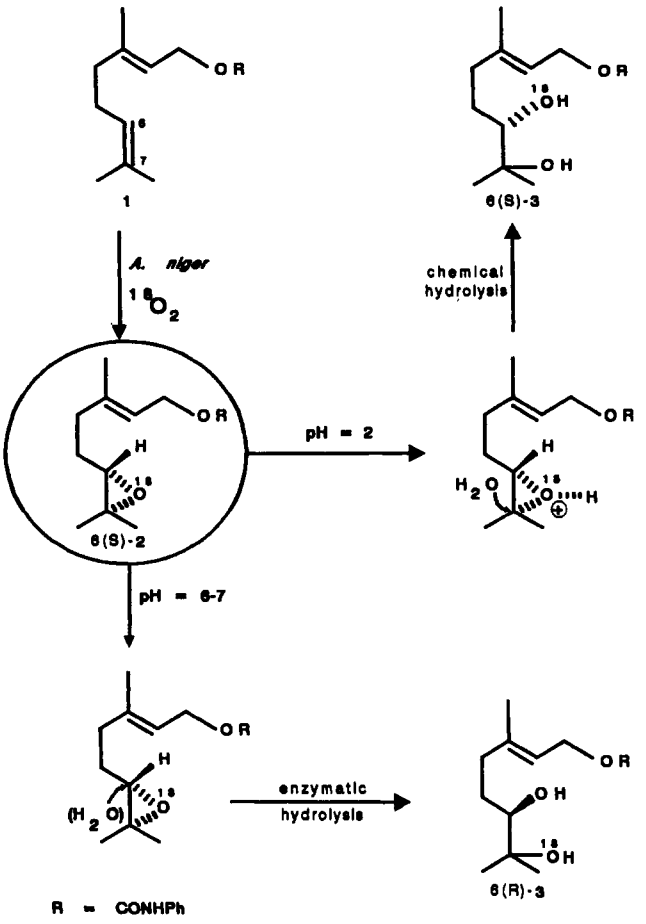


Figure 1.

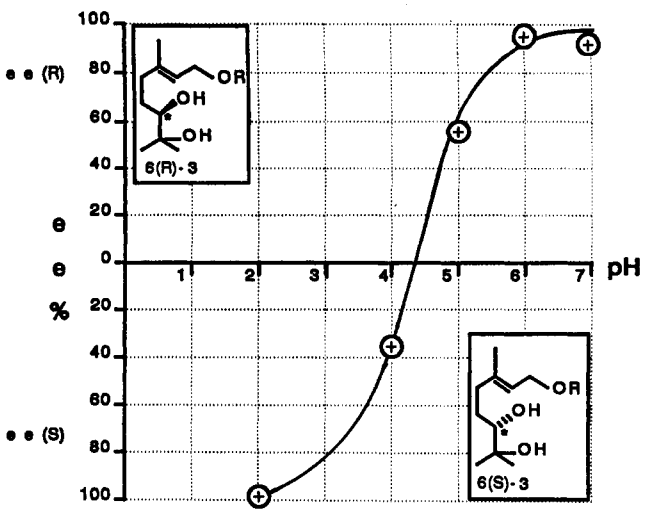


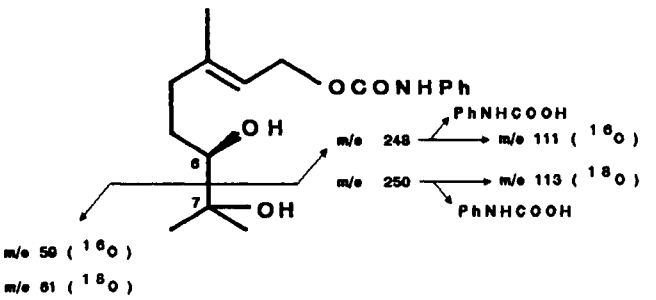
Figure 2. Determination of enantiomeric excess of diols through conversion into the diastereoisomeric esters with (−)-camphanic chloride followed by HPLC analysis.[2]

Results and Discussion

As we previously described,[2] it is possible to prepare the 6*R* diol 3 starting from the corresponding 6*S* diol via a two-step chemical procedure. As this requires further steps, we decided to explore another more direct way to the 6*R* enantiomer. In particular, if a stereospecific epoxidation occurred during this biooxidation, we thought it might be possible to control the hydrolysis of this epoxide intermediate by changing the pH of the medium. To investigate this possibility, we studied the influence of the medium pH on the enantiomeric excess of the diol formed by fungal oxidation of 1. The results obtained show that *A. niger* is able to convert 1 to 3 across the pH 2–7 range but that a dramatic shift of the absolute configuration of the diol formed occurs as the pH value increased from ~2 to 6–7 (Figure 2). Indeed, the absolute configuration at carbon atom C(6) changed from 6*S* to 6*R*. Thus, this very simple modification of the bioconversion conditions makes it possible to prepare each enantiomer of diol 3 in ~50% yield, both of them showing ee of about 95%. This is conveniently achieved on a several-gram scale, i.e., 4 g of 1 lead to ~2 g of either enantiomer of 3 (using a 7-L fermentor jar containing 4 L of culture medium). In spite of the fact that we observe a total conversion of the starting material, no other products were detectable that could account for the 50% loss in the mass balance. This is probably consumed via another metabolic process, since no other products could be extracted from the mycelium itself.

It was of interest to determine whether the diol was formed directly from the olefin or via discrete epoxide or dioxetane intermediates. The most obvious explanation for our results is to consider the (almost) exclusive stereoselective formation of the 6*S* epoxide 2, although it is not possible to rule out, a priori, formation of the 6*R* epoxide at nearly neutral pH. These epoxides could then be hydrolyzed by an epoxide hydrolase leading to either the 6*S* or the 6*R* diol, depending upon the epoxide configuration and/or on the hydrolytic reaction mechanism.[6] Control experiments showed that, in the absence of fungus, epoxide 2 is hydrolyzed very quickly in KCl–HCl (pH 2) buffer, whereas its rate of hydrolysis is very slow at pH 7. The same experiments, conducted in the presence of the fungus, lead to rapid hydrolysis even at pH 7.

Table I



pH	total ^{18}O incorp in diol 3[a] (%)	^{18}O content at C(6) (% of total)	^{18}O content at C(7) (% of total)	ee (%)	*R*/*S*
2	84[b]	95	5	95	*S*
7	92	5	95	90	*R*

[a] Based on an ^{18}O content of 98.2% in the $^{18}O_2$ used. [b] Only 84% of the product was labeled because a slight leakage occured during the bioconversion.

In order to answer this point definitively, experiments were carried out with use of $^{18}O_2$ at pH 2 or 7. The localization of the oxygen isotope incorporated into the diols was determined by mass spectrometry. The ^{18}O distribution between C(6) and C(7) hydroxyl groups was obtained from the peak intensities of the isotopic ions arising from fission of the C(6)–C(7) bond (Table I). When the incubation was carried out at pH 2, the distribution of ^{18}O label was 95% on C(6) and 5% on C(7). This ratio was inverted at pH 7, leading to 95% ^{18}O on C(7) and 5% on C(6).[7] These results show clearly that, whatever

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the pH, molecular oxygen was involved in these biooxidations but that only one labeled oxygen atom was incorporated into the diols. This is consistent with a two-step mechanism in which the first step would be formation of an *epoxide* by action of a monooxygenase. Furthermore, the distribution of the ^{18}O label observed in the product diols reflects a high degree of regiospecificity in the hydration of the intermediate epoxide. Indeed at pH 2 the main part of the nucleophilic attack occurred at C(7) while at pH 7 the site of epoxide cleavage was at the C(6) carbon atom. These results are clearly consistent with two competiting mechanisms. At pH 2, a simple acid-catalyzed epoxide opening occurs (borderline S_N2),[8] logically involving nucleophilic attack of water at the most hindered C(7) carbon atom of the *protonated oxirane*. At pH 7, an epoxide hydrolase achieves specific activation of water and facilitates nucleophilic attack at the less substituted oxirane carbon atom C(6).

It was also important to determine whether epoxide formation was stereoselective and which enantiomer was preferentially formed. To clarify this point, the hydrolysis of the *R* and *S* epoxides (each of ee = 95%) was studied at pH 2 and 7. The 6*S* epoxide yielded only 6*S* diol at pH 2 but afforded 6*R* diol at pH 7, while these results were reversed for the same reactions starting from 6*R* epoxide. Thus, the enzymatic hydration of both epoxide enantiomers always occurred via a *trans opening process*, in contrast with the results described previously by Marumo et al. in the case of 10,11-epoxyfarnesol using the fungus *Helminthosporium sativum* where trans and cis hydration occurred concurrently.[6] On the basis of these results, we propose the stepwise mechanism detailed in Figure 1, in which the 6*S* enantiomer of epoxide **2** is formed in a first step by stereospecific oxygenation of the *si* enantiotopic face of the C(6)=C(7) double bond of **1**.

By use of this reaction, it is thus possible to prepare (with high ee) both enantiomers of various derivatives showing biological activities, e.g., Bower's compounds of general structure **2**, where R is replaced by various types of groups. These compounds have been described in a large number of patents since they show important insect juvenile hormone activities.[9] Other natural products such as linalool oxide (a constituent of *Geranium bourbon* essential oil[10] or of papaya fruit pulp[11]) or marmin (a natural constituent of *Aster praealtus*[12]) are directly accessible in their optically active forms starting from (6*S*)- or (6*R*)-**3**.[3c,13]

Conclusion

The salient result of this study is the unique ability to prepare either enantiomer of diol **3** at will, simply by changing the pH of the medium. Our results strongly suggest a mechanism that involves stereoselective formation of (6*S*)-**2** in the first step. If this reaction is carried out in acidic medium (pH 2), this intermediate epoxide can be diverted efficiently from enzymatic hydration to chemical hydrolysis, whereas at pH 6–7 enzymatic hydration predominates. Thus, this leads to (6*S*)-**3** (which implies retention of configuration at C(6)) at pH 2 or to (6*R*)-**3** (inversion at C(6)) at nearly neutral pH). Similar microbiological approaches are in progress in our laboratory in order to synthesize new enantiomerically pure synthons or natural products.

Experimental Part

Influence of the Medium pH. The small-scale biotransformations were carried out as described[2] previously except that the pH of the culture medium was adjusted just before substrate addition (1 g/L) and regulated to the pH value studied using automatic addition of hydrochloric acid (10%) or NaOH (10%). After 48 h of incubation, the diol was extracted from the medium culture by the usual procedure[2] but the purification of the crude extract was achieved by flash chromatography (without crystallization) (silica gel 60 H from Merck and solvent mixtures consisting of hexane and ether in the range of 100% hexane to 100% ether). The purified diols were submitted to HPLC analysis as their (*S*)-(−)-camphanate esters.[2]

The large-scale bioconversions were carried out in a 7-L fermentor (SETRIC) jar containing 4 L of culture medium. Before sterilization (30 min at 115 °C), 40 mL of liquid paraffin and 0.2 mL of antifoam silicone 426 R (PROLABO) were added to prevent overflowing during the growth. The medium was stirred at 500 rpm and aerated with sterilized air (48 L/h)

Inoculation of the medium was made by adding a piece of gelose supporting the mycelium and the black spores aged of 3 days. After 36 h of growth at 29 °C, the substrate (4 g) was added as a solution in ethanol (40 mL). The workup was carried out as described previously.

Incorporation of $^{18}O_2$. After 36 h of growth in the fermentor jar under $^{16}O_2$,[2] the mycelium was filtered off and the fungal cake was washed with water. Potassium phosphate buffer (50 mL, 0.05 M, pH 7) or HCl–KCl buffer (50 mL, 0.05 M, pH 2) and 5% by weight of the fungal cake were added to a 250-mL Erlenmeyer flask. The flask was flushed with N_2, evacuated by use of a water suction pump, and placed under an atmosphere of pure $^{18}O_2$ by connection through a flexible tubing to a bottle containing a supply of $^{18}O_2$ (ISOTEC, Inc., 98.2 atom % $^{18}O_2$). Substrate **1** (50 mg in 0.5 mL ethanol) was added via a syringe. The flask was then placed on a reciprocal shaker (100 cpm) at 29 °C. After 48 h of incubation, the mycelium was filtered and the aqueous phase was extracted three times with 30-mL portions of Et_2O. The combined organic phases were dried ($MgSO_4$), and purification of diol **3** was achieved by flash chromatography; 19 mg (34%) of diol **3** was isolated at pH 2 and 11 mg (20%) at pH 7. In order to verify that pure $^{18}O_2$ did not alter the stereochemical course of the reaction, a control experiment was also carried out with an open flask. Similar yields and mass balance were obtained for these experiments.

Mass Spectral Analysis for $^{18}O_2$. Mass spectra were obtained by direct probe and electron impact by use of a VG 70-70E instrument. The ^{18}O content of a fragmentation was calculated as the ratio of peak intensities (m + 2)/(m + (m + 2)) and was corrected by substracting the corresponding value observed for unlabeled material. At least three scans of the peak doublets of interest were averaged for each sample.

Epoxide Hydrolysis. Hydrolysis of (6*S*)- or (6*R*)-**2** epoxides (prepared respectively from (6*R*)-**3** or (6*S*)-**3** as previously described[2]) were carried out in Erlenmeyer flasks (0.5 L) containing phosphate buffer (0.1 L, 0.05 M, pH 7) or KCl–HCl buffer (0.1 L, 0.05 M, pH 2) and 10% by weight of a fungal cake obtained from a 36-h growth fermentor. After substrate addition (30 mg) as a solution in ethanol (0.5 mL), the flasks were stirred during 20 h at 29 °C. The culture medium was extracted, without filtration of the mycelium, with three 50-mL portions of ether, and the organic phase was dried ($MgSO_4$) before purification of diol **3** by flash chromatography. Diols **3** were submitted to HPLC analysis after derivatization with (−)-camphanic acid chloride. The hydrolysis of (6*S*)-**2** epoxide (ee = 95%) yielded 26 mg (81%) of 6*S* diol **3** (ee = 88%) at pH 2 and 24 mg (75%) of 6*R* diol **3** (ee = 92% at pH 7. The hydrolysis of (6*R*)-**2** epoxide (ee = 95%) yielded 25 mg (78%) of 6*R* diol **3** (ee = 88%) at pH 2 but 23 mg

(7) The experiments were carried out under a pure oxygen atmosphere. Several runs under pure oxygen or air atmosphere showed no difference in the course of the biooxidation (same yields and same enantiomeric excesses).

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(73%) of 6S diol 3 (ee = 87%) at pH 7. The same experiments were carried out without fungus at pH 2 and pH 7. At pH 7, (6S)-2 and (6R)-2 epoxides were not hydrolyzed after 20 h of stirring. At pH 2, the hydrolysis of (6S)-2 epoxide yielded 26 mg (81%) of (6S)-3 diol (ee = 92%) and (6R)-2 epoxide yielded 25 mg (78%) of (6R)-3 diol (ee = 93%). It should be noted that the epoxides 2 were completely hydrolyzed after only a few minutes of stirring.

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Registry No. 1, 57706-89-5; 2, 132541-28-7; 3 (6R), 122313-83-1; 3 (6S), 122313-77-3; geraniol, 106-24-1; geraniol-6(S),7-diol, 63955-78-2; geraniol-6(R),7-diol, 63955-79-3.

Stereoselective Synthesis of Seven-Membered Carbocycles by a Tandem Cyclopropanation/Cope Rearrangement between Rhodium(II)-Stabilized Vinylcarbenoids and Dienes

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Rhodium(II)-catalyzed decomposition of vinyldiazomethanes in the presence of dienes generated 1,4-cycloheptadienes by a tandem cyclopropanation/Cope rearrangement. Excellent stereocontrol of up to three stereogenic centers in the cycloheptadienes was achieved. The stereoselectivity of the initial cyclopropanation ranged from 4:1 to >20:1, favoring *cis*-divinylcyclopropanes, and good regiocontrol was observed in the cyclopropanation of unsymmetrical dienes. Unless sterically encumbered, the *cis*-divinylcyclopropanes rearranged cleanly to cycloheptadienes under the reaction conditions. The *trans*-divinylcyclopropanes, when formed, were sufficiently stable to be observed in the crude reaction mixtures, but most were prone to facile 1,5-homodienyl rearrangements.

General synthetic processes to seven-membered carbocycles are very valuable because these rings are present in several important classes of natural products.[1] In recent years several useful annulation protocols to this ring size have been developed. The 3 + 4 cycloaddition between dienes and allyl or iron oxyallyl cations has been widely used,[2,3] while related approaches have been reported by Trost[4] and Molander.[5] The recently discovered concerted $4\pi + 2\pi$ cycloaddition between a nucleophilic vinylcarbene and electron-deficient cyclic dienes is another intriguing approach.[6] Other methods based on 5 + 2 annulations have also been described.[7]

Table I. Synthesis and Rhodium(II) Acetate Catalyzed Decomposition of 2 in the Presence of Cyclopentadiene as Outlined in Eq 2

substrate	R^1	R^2	R^3	2 (% yield)	product (% yield)
1a	COOEt	COOEt	H	**2a** (87)	**3a** (98)
1b	COOEt	CH=CHPh	H	**2b** (56)	**3b** (72)
1c	COOEt	SO_2Ph	H	**2c** (24)	**3c** (80)
1d	COOMe	Ph	H	**2d** (89)	**3d** (73)
1e	COMe	Ph	H	**2e** (66)	**3e** (66)
1f	COOEt	COOEt	OEt	**2f** (86)	**4** (77)

We have been engaged in a program to develop an alternative strategy for the synthesis of seven-membered rings through a tandem cyclopropanation/Cope rearrangement sequence between rhodium(II)-stabilized vinylcarbenoids[8,9] and dienes as illustrated in eq 1.[10,11] The Cope rearrangement of divinylcyclopropanes has been extensively used for the synthesis of seven-membered

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