Chiral Recognition of Diastereomeric Esters and Acetals by EPR and NMR Investigations

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The reaction of the racemic phenols **I** and **II** with chiral auxiliaries like the acid chloride **III** and particularly the lactols **IV** and **V** (Noe's reagent) leads to diastereomeric esters and acetals, respectively. The products may be synthesized either in the EPR sample tube or under preparative conditions with subsequent separation of the diastereomers by chromatographic methods. Oxidation of the phenols with lead dioxide in inert solvents provides the corresponding phenoxyls, which are investigated by EPR and ENDOR spectroscopy. The most striking features of these spectra are the differences in the β-proton coupling constants of up to several Gauss, indicating a significant alteration of the hyperconjugation angle. These results are interpreted in terms of the population of specific conformations favored by stereoelectronic and steric interactions, which are confirmed by careful investigations of the shielding and deshielding effects in the ^{1}H-NMR spectra of the corresponding phenols.

The unequivocal detection of enantiomeric compounds and the determination of their relative concentrations are gaining increasing importance. Hitherto, chiroptic methods and, with use of chiral auxiliaries, NMR spectroscopy as well as chromatographic methods have been employed. The auxiliaries together with the enantiomers form diastereomeric compounds or at least adducts which may be distinguished due to their different chemical and physical properties.

Thus, diastereomeric radicals may exhibit different EPR and ENDOR parameters as first shown by Fessenden in his investigation of the oxidation of ascorbic and isoascorbic acid in aqueous solution[1]. In pyridine, using organothallium counter ions, Dao-Ba[2] has reported similar differences in the coupling constants for both diastereomers and, furthermore, different g values. Diastereomeric phenoxyls[3,4] and nitroxides[5–7] are described in the literature.

The application of EPR and ENDOR spectroscopy to the detection and quantitative determination of enantiomers was investigated for the first time in 1986[8]. For this reason, the racemic phenols **I** and **II** (see Scheme 1) have been prepared. These compounds bear in the *p* position a chiral carbon atom carrying an alkyl group, a hydroxy group, and a hydrogen atom. A substitution pattern of this type is very common in numerous natural products. Oxidation of the phenols **I** and **II** leads to the corresponding phenoxyl radicals and, in the presence of chiral amines, to their diastereomeric complexes which have been detected by ENDOR spectroscopy.

The investigation of these diastereomeric associates is complicated due to an equilibrium between the phenoxyl, the chiral auxiliary, and the solvent[9]. In order to avoid these disadvantages and, probably, to enhance the differences in the appropriate coupling constants of the diastereomers, we have synthesized compounds in which the auxiliary is covalently bound to the enantiomeric radical investigated. The great advantage of such molecules is that the information desired may be directly obtained by EPR spectroscopy. The time-consuming ENDOR measurements are avoidable and, therefore, quantitative information can be obtained which is not available from a double-resonance experiment. Furthermore, systematic investigations concerning the mechanism responsible for observed different splitting constants can be carried out.

As the preparation of the diastereomeric compounds is expected to be very simple, the complete reaction can be performed in the EPR tube immediately prior to measurement. The number of bonds between the asymmetric carbon atoms of the phenols and those of the auxiliary should be adjustable to allow the study of steric interactions. Furthermore, the reaction has to proceed with retention of configuration if data on the enantiomeric composition of the starting material are to be obtained.

Synthesis of Diastereomers

The requirements discussed are fulfilled by the following reactions of **I** and **II**.

(1) Straightforward esterification with (±)-2-phenylbutyryl chloride (**III**) followed by subsequent oxidation in the EPR tube.

(2) Acetalization with the enantiomers of *endo*- and *exo*-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-ol (*endo*/*exo*-MBF-OH) (+)-**IV**-OH and (−)-**V**-OH. This reaction can be performed both on a preparative and analytical scale.

Furthermore, the acetal **7**, obtained by reaction of **I** with dihydropyran (DHP, **VI**), was investigated. However, this compound cannot be used for chiral recognition, because

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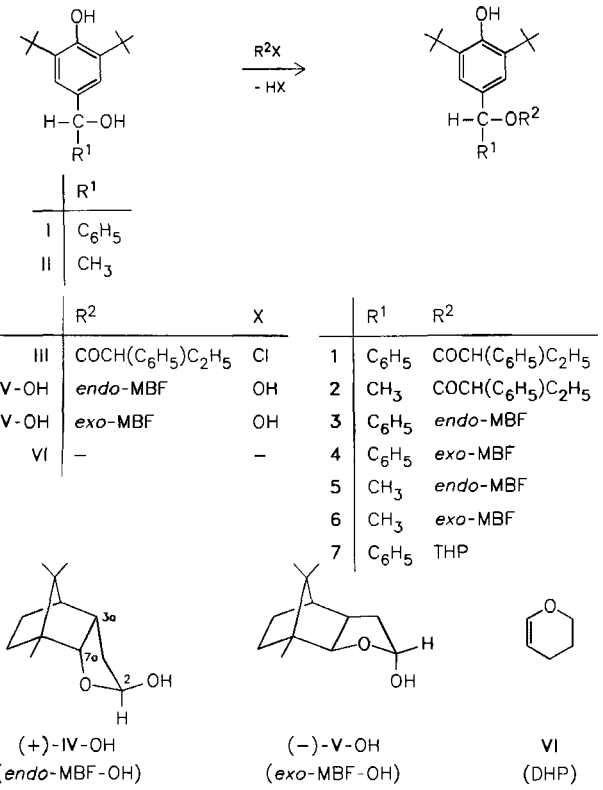
Scheme 1



	R^1
I	C_6H_5
II	CH_3

	R^2	X
III	$COCH(C_6H_5)C_2H_5$	Cl
IV-OH	*endo*-MBF	OH
V-OH	*exo*-MBF	OH
VI	–	–

	R^1	R^2
1	C_6H_5	$COCH(C_6H_5)C_2H_5$
2	CH_3	$COCH(C_6H_5)C_2H_5$
3	C_6H_5	*endo*-MBF
4	C_6H_5	*exo*-MBF
5	CH_3	*endo*-MBF
6	CH_3	*exo*-MBF
7	C_6H_5	THP

(+)-IV-OH (*endo*-MBF-OH) (−)-V-OH (*exo*-MBF-OH) VI (DHP)

the chiral center of the 6-membered ring is formed during the reaction.

The protecting groups **IV** and **V** introduced by Noe[10,11], however, avoid this disadvantage due to the anomeric effect[13] which favors acetalization at C-2 in the pseudo-axial α or *exo* position, whereas the corresponding β or *endo* isomers are only formed in low yield. Thus the requirement of the retention of the configuration of the auxiliary is fulfilled.

The two diastereomers obtained by the reaction of the racemic phenol with the chiral auxiliaries are distinguished as follows: The isomer with the smaller EPR H_β-coupling constant is arbitrarily denoted by ′and the other diastereomer by ″.

EPR and ENDOR Results

Oxidation of the diastereomeric phenols **1**−**7** with lead dioxide yields the corresponding phenoxyls **1**′−**7**′. They are considerably more stable than the radicals derived from the starting phenols **I** and **II**. They have half-life periods of the order of several hours and may be conveniently determined by EPR and ENDOR spectroscopy. The derivatives of phenol **I** generally showed a hyperfine structure (HFS); due to the equivalent protons in *m* position of the phenoxyl ring and the β proton attached to the chiral carbon atom. Consequently, a doublet of triplets is observed (Figure 2). The EPR spectra of the radicals derived from phenol **II** show in addition to these couplings a quartet splitting which is assigned to the methyl substituent of the side chain. Due to the increasing number of interacting nuclei, the HFS is somewhat more complicated (Figure 3).

A diastereomeric couple shows only significant differences of the β-proton splittings, whereas the other coupling constants and the *g* factors are comparable. Typical values are 1.8 G for the *m* protons, and 0.7 G assigned to the methyl group in derivatives of **II**. The linewidth is determined by the unresolved HFS of the *tert*-butyl protons and amounts to 0.45 G.

Table 1. Starting materials, synthesized diastereomeric pairs, and β-proton coupling constants at room temperatur

Starting materials	Diastereomeric pairs	Solvent	Coupling constant $a(H_\beta)$ [G]
I + III	**1′′/1‴**	CCl_4	7.4/ 8.6
II + III	**2′′/2‴**	*n*-hexane	6.2/ 6.4[a]
I + IV-OH	**α-3′′/α-3‴**	CCl_4	6.3/ 9.8
I + IV-OH	**β-3′′/β-3‴**	*n*-hexane	5.6/11.2
I + V-OH	**α-4′′/α-4‴**	CCl_4	6.4/ 9.7
II + IV-OH	**α-5′′/α-5‴**	*n*-hexane	5.4/ 5.9[a]
II + V-OH	**α-6′′/α-6‴**	*n*-hexane	5.6/ 6.0[a]
I + VI	**7′′/7‴**	toluene	6.5/10.3

[a] Diastereomers separated by HPLC.

The coupling of the proton bound to the chiral carbon atom is interpreted in terms of a hyperconjugation mechanism[14] and can be quantitatively described by the well-known equation (1).

$$a(H_\beta) = B \cdot \langle \cos^2\Theta \rangle \cdot \varrho(C_\alpha) \qquad (1)$$

The *m*-coupling constants of the diastereomeric couples are identical – as mentioned before – and exhibit the same values as the phenoxyl radicals **I**′ or **II**′, respectively. From this we conclude that the spin density distribution is not affected by the formation of the diastereomers. If an independent hyperconjugation parameter *B* is assumed, then the different β-coupling constants observed for the corresponding diastereomers (Table 1) are due to a variation of the hyperconjugation angle Θ. Presuming a rigid model and using $B \cdot \varrho(C_\alpha) = 22.2$ G[15], we can calculate the torsion angles Θ by means of eq. (1). Consequently, the values of the diastereomeric couple **α-3**′, 6.3 and 9.8 G, result in the angles of 58 and 48 degrees, respectively.

The radicals **1**′, **3**′, **4**′, and **7**′ derived from phenoxyl **I**′, generally show large differences in the *p*-proton coupling constants; thus, a distinction of the diastereomers can be made by simple EPR spectroscopy.

Figure 1 shows the EPR spectrum directly obtained from the reaction mixture consisting of **I** and (+)-**IV-OH** in carbon tetrachloride.The HFS is similar to a doublet of quadruplets and results from a superposition of the spectra of two species with the accidental ratio $\Delta a(H_\beta) \approx 2\, a(H_m)$. The diastereomers present in the reaction mixture may be separated by column chromatography prior to oxidation to the corresponding radicals. The *exo* anomer **α-3**′ isolated in this way shows, after oxidation with lead dioxide, the expected doublet-of-triplets HFS (Figure 2a).

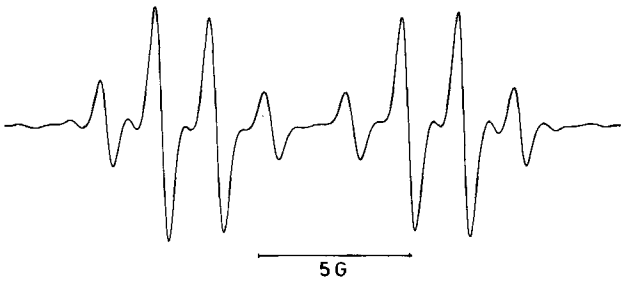


Figure 1. EPR spectrum of a diastereomeric mixture of **3'** in carbon tetrachloride at room temperatur

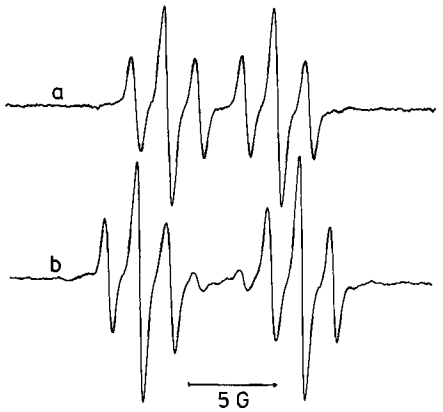


Figure 2. EPR spectra of **α-3''** (a) and **α-3'''** (b) in toluene at room temperature

Another sample of this chromatographic fraction has been treated with an excess of (−)-IV-OH; the subsequent reaction with **α-3'** yields the other enantiomer **α-3''**. Oxidation of the latter affords a product the EPR spectrum of which is shown in Figure 2b. It exhibits a significantly larger doublet splitting. The lines with small intensity near the center are assigned to the starting isomer **α-3''**. Despite the excess of the other enantiomer of **IV**-OH in the mixture, low concentrations of **α-3''** are expected, because the acetalization is an equilibrium reaction.

A remarkable larger difference of the β splittings is observed for the *endo* anomers **β-3''** and **β-3'''** (Table 1). These by-products are only formed in small amounts, and their HFS components are detectable in Figure 1, predominantly at the wings of the spectrum. The concentration of their diamagnetic precursors can be enhanced by column chromatography and then characterized by NMR spectroscopy.

The reaction of (−)-V-OH with the phenol **I** generally yields comparable results (compare **3** with **4**, Table 1), but no *endo* anomers can be detected. The diastereomeric products **7''** and **7'''** show β-proton coupling constants of 6.5 and 10.3 G, respectively.

The radicals **2'**, **5'**, and **6'** derived from the phenoxyl **II'** exhibit a more complicated HFS (Figure 3) but the important β-proton splitting can be easily derived from the EPR spectra. However, due to the small difference of the splitting constants of a diastereomeric couple, the values are similar to the linewidth, and only averages are available. However, after HPLC separation of the diamagnetic precursors, the individual coupling constants can be obtained by EPR investigation of the radicals. For example, the isomers **α-5** are isolated in this way. Their EPR spectra obtained directly by measurement of the eluate of the analytical HPLC after oxidation with lead dioxide are shown in Figure 3. A spectroscopic resolution of such a typical mixture can be performed alternatively by ENDOR spectroscopy. These double-resonance spectra are completely resolved, and the coupling constants desired can easily be determined.

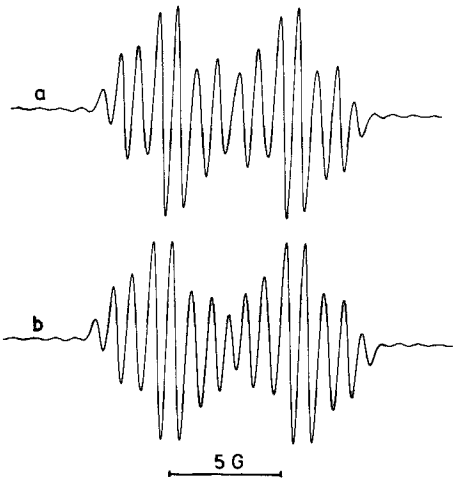


Figure 3. EPR spectra of **α-5''** (a) and **α-5'''** (b) in *n*-hexane at room temperature

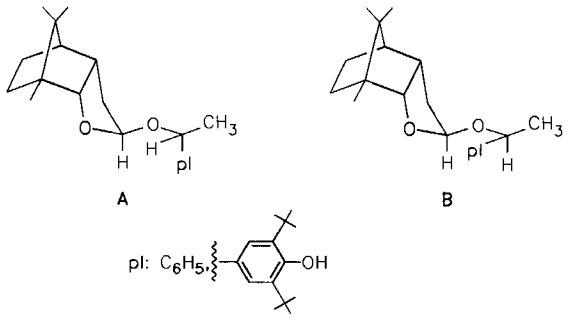
Discussion of the Configuration and Conformation

The conformations of the compounds **1**, **2**, and **7** have not yet been studied. For the acetals **3**−**6**, however, a correlation with the results obtained for analogous compounds by Noe et al.[11,12,16,17] can be established. According to these investigations, the phenol **II** consists of an asymmetric carbon atom bearing a hydroxy group, a hydrogen atom, a bulky methyl group, and the planar phenol substituent. If the steric properties of the compounds **5** and **6** are comparable with those of Noe's alcohols, then their favorable conformations can be concluded.

In this connection it must be emphasized that, for simplification, only rigid molecules are considered, but in reality rotatory and vibratory motions also occur at room temperature. For this reason, the structures discussed should be considered as conformations representing energy minima. At temperatures near room temperature surely higher terms are also populated which are responsible for the remarkable temperature dependence of the EPR spectra.

Keeping this in mind, the alkoxy group occupies a position in which one of the non-bonding electron pairs of the oxygen atom is antiperiplanar to the cyclic C−O bond. This conformation leads to a stabilization by the *exo*-anomeric effect. With respect to the C-2−O bond, for steric reasons, this conformation is favored which minimizes the interaction between the alkoxy group and the tetrahydrofuran ring. The substituents of the exocyclic oxygen atom and the adjacent chiral carbon atom are staggered. The bulky methyl group occupies a position which minimizes non-bonding interac-

tions with the MBF moiety. Now, depending on the configuration of the alcohol investigated, the planar phenyl group (pl) is located either in front of the acetal hydrogen atom (formula **A**) or in front of the ring oxygen atom (formula **B**).



The proximity of the phenyl group to the furan oxygen (formula **B**) leads – due to non-bonding interactions – to a clockwise torsion leaving the energetically favored position. In formula **A**, however, an additional stabilization is expected, attributed to a bonding interaction of the other lone pair at the oxygen atom with the σ* orbital of the $C_{sp^3}-C_{sp^2}$ bond, known as the generalized anomeric effect[13]. For these reasons an enantioselectivity in favor of the conformer **A** was observed by Noe[11,12]. According to these preferred conformations a deshielding effect of the phenyl substituent on the acetal hydrogen atom in **A** and on the hydrogen atom attached to C-7a in **B** is expected. Actually, the diastereomers can be distinguished by the NMR signals of these protons. Consequently, compounds **5** and **6** can be assigned by a comparison of the intensities of the ^{1}H-NMR spectra with those of the HPL chromatograms as follows: **α-5′** and **α-6′** have structure **B**, whereas **α-5″** and **α-6″** are assigned to **A**.

The enantioselectivity of the acetalization reaction can be confirmed qualitatively in the case of **5** and **6**. A quantitative determination of the diastereomer ratio has not been undertaken.

Table 2. ^{1}H-NMR shifts of protons 2-H and 7a-H of the compounds **α-5** and **α-6** (values in parentheses of diastereomers from **IV**-OH or **V**-OH, respectively, and 1-phenylethanol[11,12])

Diastereomer	2-H	7a-H
α-5′ (B)	5.49 (5.49)	4.06 (3.95)
α-5″ (A)	5.17 (5.12)	4.33 (4.32)
α-6′ (B)	5.34 (5.33)	3.74 (3.65)
α-6″ (A)	5.01 (4.94)	3.99 (3.97)

The good agreement between the chemical shifts of the protons 2-H in form **B**, and 7a-H in the form **A** observed for **5** and **6** confirms Noe's interpretation. The small differences in the shifts of the other protons may be interpreted in terms of the influence of the other phenyl substituents.

The reaction products **3** and **4** derived from the phenol **I** are significantly different from the compounds mentioned before. These phenols are bearing two different planar substituents at the chiral carbon atom. The preparative-scale reaction of **I** with (+)-**IV**-OH yields basically four diastereomeric acetals **3**. The mixture contains about 95% of **α-3**. The by-product **β-3** could be enriched by column chromatography and was characterized by ^{13}C-NMR spectroscopy. The assignment was mainly made with the help of the shift differences of C-7a and C-3a. The *exo* anomers show a shift to higher field due to the γ effect[18].

Table 3. ^{13}C-NMR shifts of atoms C-7a and C-3a of the compounds **α-3′/α-3″** and **β-3′/β-3″** (values in parentheses of the anomers from **IV**-OH and diphenylmethanol[10])

Diastereomeric couple	C-7a	C-3a
α-3′/α-3″ (*exo* anomer)	89.6 (89.6)	40.3 (40.2)
β-3′/β-3″ (*endo* anomer)	92.1/91.8 (92.2)	41.3 (41.2)

The reaction of **I** with (–)-**V**-OH does not lead to *endo* anomers in detectable amounts. The ratio of the diastereomeric *exo* anomers is in both cases 1:1 according to the ^{1}H-NMR spectra.

The basic conformations of the acetals **α-3** and **α-4** are governed by the same rules outlined above for **α-5** and **α-6**. The acetalization of alcohols bearing two planar substituents is described in the literature[17]. In these examples one is a phenyl group whereas the other substituent is a nitrile, alkinyl, or aldehyde function. The favored conformation of these molecules has the phenyl group in the bulky position as indicated by the methyl group in the formulae **A** and **B**. This conformation leads according to Noe[17] to remarkable differences of the chemical shifts for the protons 2-H and 7a-H. In contrast to these results, the diastereomers synthesized by us exhibit only minor differences of the appropriate shifts. The corresponding values observed are $\Delta\delta = 0.05$ and $\Delta\delta = 0.12$ as shown in Figure 4.

Table 4. ^{1}H-NMR shifts of protons 2-H and 7a-H of the compounds **α-3** and **α-4**

Diastereomer	2-H	7a-H
α-3′	5.37	4.26
α-3″	5.32	4.38
α-4′	5.19	3.93
α-4″	5.15	4.03

For this reason, a major contribution of conformations similar to **A** and **B** is very unlikely. Moreover, it is insignificant which phenyl group is in the bulky position. Surely, a staggered geometry minimizes the steric interactions and particularly a conformation with the smallest substituent adjacent to cyclic oxygen atom will be favored. Furthermore, an arrangement of this type will be additionally stabilized by the generalized anomeric effect. These proposed structures are represented by the formulae **C** and **D**.

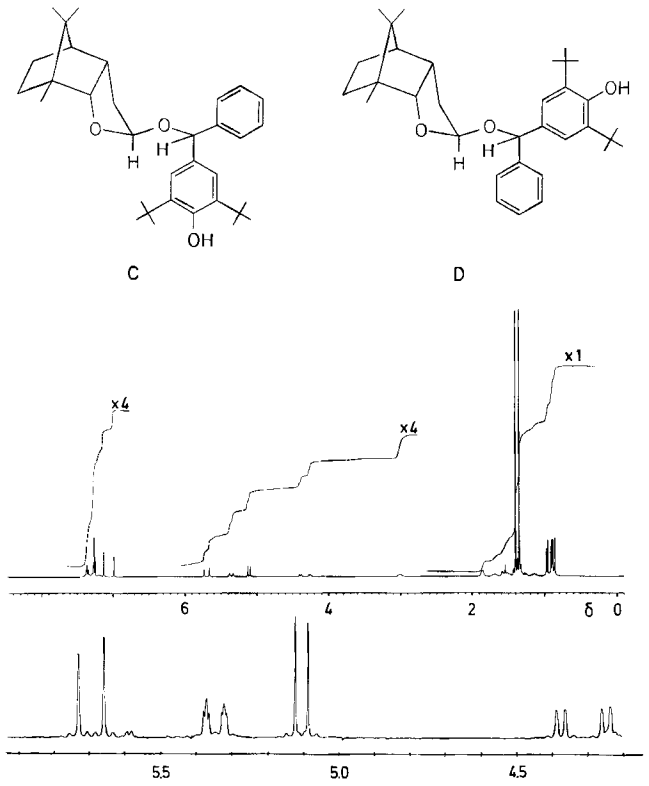
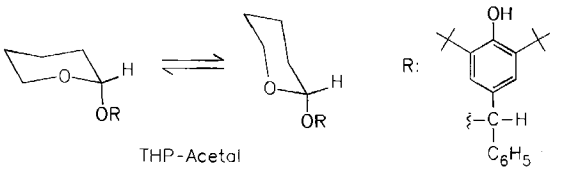


Figure 4. ^{1}H-NMR spectrum of a diastereomeric mixture of **α-3'** and **α-3''** (400 MHz, $CDCl_3$, room temperature): total spectrum (top); section of δ = 4.2–5.9 (below)

The small chemical shift differences observed for 2-H and 7a-H and the lack of selectivity of the acetalization are in good agreement with these structures. The *endo* anomers may have analogous conformations which are likewise stabilized by *exo*-anomeric and generalized anomeric effects.

The radicals investigated are obtained by oxidation of the corresponding precursors at the phenolic hydroxy group. This function is far away from the chiral carbon atom in *p*-position and, therefore, we can assume that the phenols and the corresponding phenoxyl radicals have very similar conformations. Thus, the different coupling constants of a diastereomeric couple observed in the EPR and ENDOR spectra can be interpreted. Obviously, the hyperconjugation angle is very sensitive to the steric environment and can be used to make a distinction between the structures **A** and **B** or **C** and **D**, respectively. The acetals **α-5'** and **α-6'** exhibit a difference of the torsion angles of 1.5°, provided the existence of a rigid molecule. This small value is due to the fact that in **A** as well as in **B** the phenoxyl ring is in proximity to the MBF group. In **A** there is a steric interaction with the hydrogen at C-2, whereas in **B** the interaction takes place with the cyclic oxygen; this results in both cases in hyperconjugation angles of approximately 60°.

Very similar is the situation for structure **C** assigned to the radicals **α-3'** and **α-4'**, because the phenoxyl group has a position close to the MBF moiety. However, in structure **D** the phenol ring does not suffer from steric interactions, and, therefore, rotates freely around the $C_{sp^2}-C_{sp^3}$ bond. The experimentally determined β-splitting constants are in good agreement with this concept. Consequently, the diastereomers **α-3''** and **α-4''** with a torsion angle of about 58° must be assigned to formula **C**, whereas the isomers **α-3'''** and **α-4'''** are represented by structure **D**. Likewise, the β couplings of the *endo* anomers **β-3''** and **β-3'''** with their calculated angles of 60° and 45°, respectively, are in very good agreement with this interpretation. These results may be used for the determination of the absolute configuration which will be discussed elsewhere.



THP is commonly used as a protecting group for alcohols. The formation of diastereomers in the course of this reaction is generally unimportant. The EPR spectra of **7'** show two β couplings assigned to these isomers. The difference in these couplings can be interpreted by a comparison with those of the radicals **3'** and **4'** in terms of a rapid interconversion of the THP ring. These processes, if they occur rapidly compared to the EPR time scale, will average the splitting constants assigned to species with axially or equatorially bound 6-membered ring in consideration of their populations.

According to the anomeric effect, the configuration with the exocyclic oxygen atom in the axial position is favored. This confirms our interpretation that the differences found in the NMR and EPR spectra are due to the stereoelectronic effect in general and not to the specific character of a particular protecting group.

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Experimental

Melting points were determined with a Büchi apparatus (Dr. Tottoli). – Elemental analyses: Microanalytical Laboratory, Chemisches Institut der Universität Tübingen, *W. Bock*. – 90-MHz ^{1}H NMR: Bruker WH 90; 250-MHz ^{1}H, 62.9-MHz ^{13}C NMR: Bruker AC 250; 400-MHz ^{1}H, 100.6-MHz ^{13}C NMR: Bruker WM 400. – IR (KBr): Perkin-Elmer IR 281 B. – MS (70 eV): Varian MAT-711 A. – EPR: Varian E 12, Bruker ESP 300. – ENDOR: Varian E-Line-Century EPR spectrometer equipped with a Bruker ENDOR ER 810 unit and a Bruker ER 140 data system. – HPLC: Waters 501 HPLC pump; Grom HPLC column Nucleosil Si 100, 5 μm, 250 × 4.6 mm; Biotronic UV detector BT 3030; Shimadzu C-R5A-Chromatopac data system. – Column chromatography (CC) on Merck silica gel (particle size 0.063–0.2 mm), deactivated with triethylamin according to ref.[11]. – *endo*-MBF: [3a*S*-(2α,3aα,4α,7α,7aα)]-2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl; *exo*-MBF: [3a*R*-(2α,3aα,4β,7β,7aα)]-2,3,3a,4,5,6,7,7a-octahydro-7,8,8-trimethyl-4,7-methanobenzofuran-2-yl.

The racemates of the phenols (3,5-di-*tert*-butyl-4-hydroxyphenyl)phenylmethanol (**I**) and 1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-ethanol (**II**) were synthesized according to well-known methods[19]

from 2,6-di-*tert*-butylphenol by Friedel-Crafts-acylation with benzoyl chloride or acetyl chloride and subsequent reduction in methanol with magnesium or sodium borohydride, respectively.

The MBF protecting groups **IV** and **V** were used as pure enantiomers of the dimers (MBF-OH dimer, Noe's reagent).

EPR Measurements: The acetals **3**–**7** were prepared directly in the EPR tube by mixing some crystals of the racemic alcohol with an excess of the chiral auxiliary (MBF-OH dimer or dihydropyran, respectively). Then, a catalytic amount of toluenesulfonic acid was added. The mixture was dissolved in an inert solvent like toluene or carbon tetrachloride. The oxygen was removed by bubbling with nitrogen for half an hour. Then, the mixture consisting of the diastereomers was oxidized by the addition of lead dioxide and bubbling for a minute.

The diastereomers of **2**, **5**, and **6** are synthesized on a semipreparative scale and subsequently separated by HPLC. A mixture of *n*-hexane/diethyl ether (98:2) was used as the mobile phase. Directly after leaving the UV detector, the samples were colleted in EPR tubes and bubbled with nitrogen to remove oxygen and ether. Then, they were oxidized as described above.

(3,5-Di-tert-butyl-4-hydroxyphenyl)phenylmethyl 2-Phenylbutyrate (Diastereomeric Mixture **1′/1″**): 1.1 g (6 mmol) of (±)-2-phenylbutyryl chloride was dissolved in 5 ml of pyridine and mixed with 50 mg (0.41 mmol) of 4-dimethylaminopyridine. A solution of 1 g (3.2 mmol) of **I** in 5 ml of pyridine was added dropwise, and the mixture was stirred for 8 h. After pouring the mixture on ice, the pH value was adjusted to 5.5 by the addition of hydrochloric acid. The aqueous layer was extracted with ether four times. The organic layer was treated carefully with a sodium carbonate solution and then washed with water. After desiccation with magnesium sulfate, the solvent was removed. The remaining yellow oil crystallized after several days and was recrystallized twice from *n*-hexane to yield 0.53 g (36%) of colorless crystals. During purification, the diastereomer **1′** was enriched to a large extent. – Melting range 100–102°C. – IR: $\tilde{\nu}$ = 3620 cm^{-1} (OH), 3070/3030 (aromat. CH), 2960/2910/2880 (aliphat. CH), 1730 (C=O). – MS: *m/z* (%) = 458 (23) [M^+], 295 (91), 294 (71), 279 (69), 251 (46), 237 (76), 164 (34), 119 (48), 91 (100). – ^{1}H NMR ($CDCl_3$), characteristic shifts: diastereomer **1′**; alcohol moiety: δ = 7.06 [s, 2H, aromat. H (HOPh)], 6.77 (s, 1H, HCO), 5.20 (s, 1H, OH), 1.37 (s, 18H, C_4H_9); acid moiety: δ = 3.57 (t, *J* = 7.7 Hz, 1H, HCC=O), 2.23–2.05 and 1.91–1.74 (2 m, 2H, CH_2), 0.87 (t, *J* = 7.4 Hz, 3H, CH_3); diastereomer **1″**; alcohol moiety: δ = 6.94 [s, 2H, aromat. H (HOPh)], 6.78 (s, 1H, HCO), 5.14 (s, 1H, OH), 1.31 (s, 18H, C_4H_9); acid moiety: δ = 3.56 (t, *J* = 7.7 Hz, 1H, HCC=O), 2.22–2.04 and 1.90–1.72 (2 m, 2H, CH_2), 0.86 (t, *J* = 7.4 Hz, 3H, CH_3). – EPR (CCl_4): diastereomer **1′**•: *g* = 2.0046, *a*(H_β) = 7.4 G; diastereomer **1″**•: *g* = 2.0046, *a*(H_β) = 8.6 G. – ENDOR (CCl_4, 253 K): diastereomer **1′**•: *a* = 7.18 G (H_β), 1.83 (*m*-H), 0.08 (C_4H_9); diastereomer **1″**•: *a* = 8.74 G (H_β), 1.82 (*m*-H), 0.08 (C_4H_9).

$C_{31}H_{38}O_3$ (458.6) Calcd. C 81.18 H 8.35
Found C 81.42 H 8.41

1-(3,5-Di-tert-butyl-4-hydroxyphenyl)ethyl 2-Phenylbutyrate (Diastereomeric Mixture **2′/2″**): 2.3 g (12.6 mmol) of (±)-2-phenylbutyryl chloride was dissolved in 5 ml of pyridine and mixed with 60 mg (0.49 mmol) of 4-dimethylaminopyridine. A solution of 0.75 g (3 mmol) **II** in 5 ml of pyridine was added dropwise, and the mixture was stirred for 18 h. After pouring the mixture on ice, it was acidified with concentrated hydrochloric acid to afford the pyridine hydrochloride and extracted four times with ether. The organic layer was separated and washed neutral with water. After desiccation with magnesium sulfate, the solvent was removed. The residue was purified by filtration [silica gel; petroleum ether/ether (20:1)]. After removal of the solvent, the oil obtained crystallized after several days and was recrystallized from *n*-hexane to yield 0.83 g (70%) of colorless crystals. During purification the diastereomer **2′** was enriched. – Melting range 90–98°C. – IR: $\tilde{\nu}$ = 3590 cm^{-1} (OH), 3070/3030 (aromat. CH), 2970/2880 (aliphat. CH), 1710 (C=O). – MS: *m/z* (%) = 396 (9) [M^+], 233 (100), 217 (85), 175 (37), 119 (37), 91 (89), 57 (43), 41 (30). – ^{1}H NMR ($CDCl_3$): diastereomer **2′**; alcohol moiety: δ = 7.11 (s, 2H, aromat. H), 5.83 (q, *J* = 6.5 Hz, 1H, HCO), 5.20 (s, 1H, OH), 1.42 (s, 18H, C_4H_9), 1.41 (d, *J* = 6.5 Hz, 3H, $OCCH_3$); acid moiety: δ = 7.32–7.20 (m, 5H, aromat. H), 3.47 (t, *J* = 7.7 Hz, 1H, HCC=O), 2.19–2.01 and 1.87–1.70 (2 m, 2H, CH_2), 0.86 (t, *J* = 7.5 Hz, 3H, CH_3); diastereomer **2″**; alcohol moiety: δ = 6.99 (s, 2H, aromat. H), 5.83 (q, *J* = 6.5 Hz, 1H, HCO), 5.14 (s, 1H, OH), 1.50 (d, *J* = 6.5 Hz, 3H, $OCCH_3$), 1.36 (s, 18H, C_4H_9); acid moiety: δ = 7.32–7.20 (m, 5H, aromat. H), 3.47 (t, *J* = 7.7 Hz, 1H, HCC=O), 2.20–2.03 and 1.87–1.70 (2 m, 2H, CH_2), 0.89 (t, *J* = 7.4 Hz, 3H, CH_3). – EPR (*n*-hexane): diastereomer **2′**•: *g* = 2.0046, *a*(H_β) = 6.2 G; diastereomer **2″**•: *g* = 2.0046, *a*(H_β) = 6.4 G. – ENDOR (*n*-hexane, 233 K): diastereomer **2′**•: *a* = 5.90 G (H_β), 1.83 (*m*-H), 0.69 (CH_3), 0.08 (C_4H_9); diastereomer **2″**•: *a* = 6.23 G (H_β), 1.82 (*m*-H), 0.66 (CH_3), 0.09 (C_4H_9).

$C_{26}H_{36}O_3$ (396.6) Calcd. C 78.75 H 9.15
Found C 78.67 H 9.44

The acetals **3**–**6** were synthesized on a preparative scale according to the general instructions in ref.[11]. In addition to the desired products and starting materials, the reaction mixtures consisted of variable amounts of quinone methides and their consecutive products.

The diastereomers of **3** and **4** were enriched by column chromatography. Compound **α-3′** was obtained in diastereomeric pure form by repeated CC. In the course of this separation, a fraction could be collected containing the *endo* anomers **β-3′** and **β-3″**.

The acetals **5** and **6** were separated from the remaining alcohol by filtration (silica gel, deactivated with triethylamin).

Purification of the acetals by recrystallization could not be achieved due to their unfavorable crystallization properties and insufficient stability in solution. NMR data of the acetals **3**–**6** were obtained from mixtures of these diastereomers with different fractions.

Acetal **3** (Diastereomeric Mixture **α-3′/α-3″/β-3′/β-3″**): ^{1}H NMR ($CDCl_3$), characteristic shifts: diastereomer **α-3′**; alcohol moiety: δ = 7.12 [s, 2H, aromat. H (HOPh)], 5.66 (s, 1H, HCO), 5.12 (s, 1H, OH), 1.40 (s, 18H, C_4H_9); lactol moiety: δ = 5.37 (t, *J* = 3 Hz, 1H, 2-H), 4.26 (d, *J* = 9.5 Hz, 1H, 7a-H), 0.95 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 0.85 (s, 3H, CH_3); diastereomer **α-3″**; alcohol moiety: δ = 6.98 [s, 2H, aromat. H (HOPh)], 5.72 (s, 1H, HCO), 5.09 (s, 1H, OH), 1.34 (s, 18H, C_4H_9); lactol moiety: δ = 5.32 (t, *J* = 3 Hz, 1H, 2-H), 4.38 (d, *J* = 9.5 Hz, 1H, 7a-H), 0.97 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.88 (s, 3H, CH_3); diastereomers **β-3′** and **β-3″** (assignment to the individual *endo* anomers could not be achieved); alcohol moiety: δ = 7.13/7.08 [s, 2H, aromat. H (HOPh)], 5.79/5.71 (s, 1H, HCO), 5.11/5.08 (s, 1H, OH), 1.39/1.34 (s, 18H, C_4H_9); lactol moiety: δ = 5.34–5.28 (m, 1H, 2-H), 4.23/4.21 (d, *J* = 9 Hz, 1H, 7a-H). – ^{13}C NMR ($CDCl_3$, noise decoupled):diastereomers **α-3′** and **α-3″** (assignment to the individual *exo* anomers could not be achieved); alcohol moiety: δ = 153.0/152.9 [C-4 (HOPh)], 143.7/141.4 [C-1 (Ph)], 135.6/135.2 [C-3, -5 (HOPh)], 133.4/132.0 [C-1 (HOPh)], 128.2–124.4 (aromat. CH), 79.1/78.6 (CO), 34.4/34.3 [$C(CH_3)_3$], 30.4/30.2 [$C(CH_3)_3$]; lactol moiety: δ = 106.3 (C-2), 89.6 (C-7a), 52.7/52.6 (C-7), 48.6 (C-8), 47.5/47.4 (C-4), 40.3 (C-3a), 32.5/

32.4 (C-3), 26.5 (C-6), 21.0 and 20.6 (C-5 and 8-CH_3), 18.8/18.7 (8-CH_3), 14.8 (7-CH_3); diastereomers **β-3′** and **β-3″** (assignment to the individual *endo* anomers could not be achieved); alcohol moiety: δ = 153.2 [C-4 (HOPh)], 141.8 [C-1 (Ph)], 135.3/135.1 [C-3, -5 (HOPh)], 133.3/132.5 [C-1 (HOPh)], 128.2–124.2 (aromat. CH), 80.7/80.5 (CO), 34.4 [*C*(CH_3)$_3$], 30.3/30.2 [C(*C*H_3)$_3$]; lactol moiety: δ = 106.9 (C-2), 92.1/91.8 (C-7a), 52.5 (C-7), 49.3 (C-8), 48.3/48.2 (C-4), 41.3 (C-3a), 33.0/32.9 (C-3), 27.5/27.3 (C-6), 20.9 and 20.8 (C-5 and 8-CH_3), 18.8/18.7 (8-CH_3), 15.0 (7-CH_3). – EPR: diastereomeric mixture **α-3′•/α-3″•** (CCl_4): g = 2.0046, a(H_β) = 6.3/9.8 G; diastereomeric mixture **β-3′•/β-3″•** (*n*-hexane): g = 2.0046, a(H_β) = 5.6/11.2 G. – ENDOR: diastereomeric mixture **α-3′•/α-3″•** (CCl_4, 253 K): a = 6.02/9.95 G (H_β), 1.77 (*m*-H), 0.08 (C_4H_9); diastereomeric mixture **β-3′•/β-3″•** (toluene, 213 K): a = 4.45/12.83 G (H_β), 1.72 (*m*-H), 0.08 (C_4H_9).

Acetal **4** (Diastereomeric Mixture **α-4′/α-4″**): ^{1}H NMR ($CDCl_3$), characteristic shifts: diastereomer **α-4′**; alcohol moiety: δ = 7.13 [s, 2H, aromat. H (HOPh)], 5.66 (s, 1H, HCO), 5.13 (s, 1H, OH), 1.41 (s, 18H, C_4H_9); lactol moiety: δ = 5.19 (d, J = 4.9 Hz, 1H, 2-H), 3.93 (d, J = 7.5 Hz, 1H, 7a-H), 0.98 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 0.79 (s, 3H, CH_3); diastereomer **α-4″**: alcohol moiety: δ = 7.01 [s, 2H, aromat. H (HOPh)], 5.73 (s, 1H, HCO), 5.10 (s, 1H, OH), 1.37 (s, 18H, C_4H_9); lactol moiety: δ = 5.15 (d, J = 5.0 Hz, 1H, 2-H), 4.03 (d, J = 7.5 Hz, 1H, 7a-H), 1.00 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 0.79 (s, 3H, CH_3). – ^{13}C NMR ($CDCl_3$, noise-decoupled): diastereomer **α-4′**; alcohol moiety: δ = 153.2 [C-4 (HOPh)], 143.7 [C-1 (Ph)], 135.5 [C-3, -5 (HOPh)], 131.9 [C-1 (HOPh)], 128.2–124.6 (aromat. CH), 78.6 (CO), 34.3 [*C*(CH_3)$_3$], 30.4 [C(*C*H_3)$_3$]; lactol moiety: δ = 102.7 (C-2), 91.3 (C-7a), 48.5 (C-4), 47.6 (C-7), 47.0 (C-8), 46.1 (C-3a), 38.6 (C-3), 32.5 (C-6), 28.9 (C-5), 22.9 (CH_3), 20.6 (CH_3), 11.7 (CH_3); diastereomer **α-4″**; alcohol moiety: δ = 152.9 [C-4 (HOPh)], 141.4 [C-1 (Ph)], 135.2 [C-3, -5 (HOPh)], 133.4 [C-1 (HOPh)], 128.0–124.4 (aromat. CH), 78.3 (CO), 34.3 [*C*(CH_3)$_3$], 30.2 [C(*C*H_3)$_3$]; lactol moiety: δ = 102.7 (C-2), 91.3 (C-7a), 48.4 (C-4), 47.6 (C-7), 47.0 (C-8), 46.1 (C-3a), 38.5 (C-3), 32.7 (C-6), 29.0 (C-5), 22.9 (CH_3), 20.5 (CH_3), 11.7 (CH_3). – EPR: diastereomeric mixture **α-4′•/α-4″•** (CCl_4): g = 2.0046, a(H_β) = 6.4/9.7 G. – ENDOR (CCl_4, 253 K): diastereomeric mixture **α-4′•/α-4″•**: a = 6.36/9.76 G (H_β), 1.77 (*m*-H), 0.08 (C_4H_9).

Acetal **5** (Diastereomeric Mixture **α-5′/α-5″**): ^{1}H NMR ($CDCl_3$), characteristic shifts: diastereomer **α-5′**; alcohol moiety: δ = 7.13 (s, 2H, aromat. H), 5.08 (s, 1H, OH), 4.67 (q, J = 6.5 Hz, 1H, HCO), 1.41 (s, 18H, C_4H_9); lactol moiety: δ = 5.49 (d, J = 4.6 Hz, 1H, 2-H), 4.06 (dd, J = 9.4/1.5 Hz, 1H, 7a-H); diastereomer **α-5″**; alcohol moiety: δ = 7.08 (s, 2H, aromat. H), 5.11 (s, 1H, OH), 4.70 (q, J = 6.5 Hz, 1H, HCO), 1.41 (s, 18H, C_4H_9); lactol moiety: δ = 5.17 (dd, J = 5.2/2.4 Hz, 1H, 2-H), 4.33 (dd, J = 9.4/1.5 Hz, 1H, 7a-H). – EPR (*n*-hexane): diastereomer **α-5′•**: g = 2.0046, a(H_β) = 5.4 G; diastereomer **α-5″•**: g = 2.0046, a(H_β) = 5.9 G. – ENDOR (CCl_4, 253 K): diastereomeric mixture **α-5′•/α-5″•**: a = 5.01/5.63 G (H_β), 1.73 (*m*-H), 0.81 (CH_3), 0.08 (C_4H_9).

Acetal **6** (Diastereomeric Mixture **α-6′/α-6″**): ^{1}H NMR ($CDCl_3$), characteristic shifts: diastereomer **α-6′**; alcohol moiety: δ = 7.16 (s, 2H, aromat. H), 5.11 (s, 1H, OH), 4.69 (q, J = 6.5 Hz, 1H, HCO), 1.44 (s, 18H, C_4H_9); lactol moiety: δ = 5.34 (d, J = 4.2 Hz, 1H, 2-H), 3.74 (d, J = 7.6 Hz, 1H, 7a-H); diastereomer **α-6″**; alcohol moiety: δ = 7.09 (s, 2H, aromat. H), 5.12 (s, 1H, OH), 4.70 (q, J = 6.5 Hz, 1H, HCO), 1.43 (s, 18H, C_4H_9); lactol moiety: δ = 5.01 (d, J = 4.8 Hz, 1H, 2-H), 3.99 (d, J = 7.6 Hz, 1H, 7a-H). – EPR (*n*-hexane): diastereomer **α-6′•**: g = 2.0046, a(H_β) = 5.6 G; diastereomer **α-6″•**: g = 2.0046, a(H_β) = 6.0 G. – ENDOR (toluene, 253 K): diastereomeric mixture **α-6′•/α-6″•**: a = 6.01/6.28 G (H_β), 1.73 (*m*-H), 0.80 (CH_3), 0.07 (C_4H_9).

(3,5-Di-tert-butyl-4-hydroxyphenyl)phenylmethanol 2-Tetrahydropyranyl Acetal (Diastereomeric Mixture **7′•/7″•**, in situ, EPR tube): EPR (toluene): g = 2.0045, a(H_β) = 6.5/10.3 G. – ENDOR: (toluene, 253 K): a = 6.13/10.74 G (H_β), 1.76 (*m*-H), 0.08 (C_4H_9).

CAS Registry Numbers

(±)-**1′**: 126504-48-1 / (±)-**1′•**: 126504-52-7 / (±)-**1″**: 126504-49-2 / (±)-**1″•**: 126504-53-8 / (±)-**2′**: 126504-50-5 / (±)-**2′•**: 126504-54-9 / (±)-**2″**: 126504-51-6 / (±)-**2″•**: 126504-55-0 / **α-3′**: 126504-56-1 / **β-3′**: 126638-19-5 / **α-3′•**: 126504-59-4 / **β-3′•**: 126638-24-2 / **α-3″**: 126638-18-4 / **β-3″**: 126640-48-0 / **α-3″•**: 126638-23-1 / **β-3″•**: 126638-25-3 / **α-4′**: 126640-49-1 / **α-4′•**: 126638-26-4 / **α-4″**: 126638-20-8 / **α-4″•**: 126638-27-5 / **α-5′**: 126504-57-2 / **α-5′•**: 126504-60-7 / **α-5″**: 126638-21-9 / **α-5″•**: 126638-28-6 / **α-6′**: 126638-22-0 / **α-6′•**: 126638-29-7 / **α-6″**: 126504-58-3 / **α-6″•**: 126638-30-0 / (±)-**7′•**: 126504-61-8 / (±)-**7″•**: 126504-62-9 / (±)-**I**: 126504-47-0 / (±7-**II**: 104438-67-7 / (±)-**III**: 51260-63-0 / (*S*)-(+)-**IV**: 81925-09-9 / (*R*)-(−)-**V**: 108031-76-1 / **VI**: 110-87-2

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