Central to Axial Transfer of Chirality in Menthone or Camphor-Derived 2,2′-Biphenols

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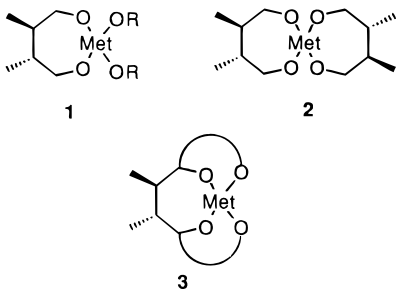
A study aimed at defining a molecular arrangement where a chiral fragment derived from menthone or camphor transfers its central chirality to a 2,2′-biphenol residue, inducing an axial chirality, is reported. The menthol or isoborneol groups are attached at the two benzylic positions at 3,3′ in order to maximize efficiency in practical applications. A reliable and high-yielding procedure for the synthesis of such C_2-symmetric molecules substituted at the 3,3′-positions has been developed. The procedure entails Mannich condensation with paraformaldehyde and morpholine, protection of the hydroxylic functions, chlorination, metalation, and addition to (−)-menthone and (+)-camphor. The use of samarium diiodide is essential in the latter step for optimum selectivity and efficiency. The tetrols exhibit intramolecular hydrogen bonding between phenolic and alcoholic hydroxy functions within each monomeric unity, so that they retain their rotational freedom. NOEDS and COSY experiments show that the tetrols are present in more than one rotamer. The tetrols react with tetrachlorosilane to afford siloxanes as pure diastereoisomers, showing that the metal is able to induce preferential helicity at the biphenyl residue; *i.e.*, the central chirality of menthol or isoborneol auxiliary is totally transfered to the axial chirality of the biphenyl. The configurations could be determined by NOEDS and heterocorrelated HMQC experiments. Remarkably, while the menthol derivative induces total *M* helicity, the camphor induces complementary *P* helicity. These results suggest that these tetrols may be useful as ligands in catalysts for asymmetric synthesis.

In recent years a number of enantiopure catalysts consisting of a metal bonded to four hydroxylic functions has been developed. In most cases they have been obtained by the reaction of one diol molecule with the metal prebonded to two alcoholic functions,[1] as exemplified in **1**, or from two molecules of diols with a suitable metallic precursor,[2] as shown in **2**.



1 **2** **3**

In a few cases, these compounds are stable, crystalline solids and could be isolated, characterized, and even subjected to X-ray diffractometric analysis in order to rationalize enantioselective behavior in the catalytic path. In the present work, we describe a first approach to the development of a C_2-symmetric chiral tetrol of type **3**, in principle able to behave as a single ligand in the same processes where three (as in **1**) or two (as in **2**) molecules of ligand are necessary.[3] The tetrols have been planned with a rational design in order to take advantage of the well-known efficiency of atropoisomer binaphthyl systems in enantioselective processes[4] and, at the same time, to avoid the separation of diastereoisomers. To reach this goal, an initial study on the transfer from

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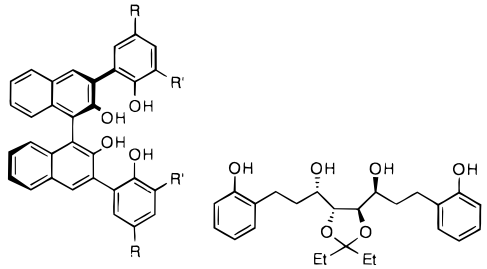
(1) Numerous examples can be found in: Nogradi, M. *Stereoselective Synthesis*; VCH: Weinheim, 1986. Ojima, I. *Catalytic Asymmetric Synthesis*; VCH: New York, 1993. Noyori, R. *Asymmetric Catalyis in Organic Synthesis*; Wiley: New York, 1994. *Advanced Asymmetric Synthesis*; Stephenson, G. R., Ed.; Chapman and Hall: London, 1996.

(2) For example: Seebach, D.; Behrendt, L.; Felix, D. *Angew Chem., Int. Ed. Engl.* **1991**, *30*, 1008. Schmidt, B.; Seebach, D. *Ibid.* **1991**, *30*, 1321. von dem Bussche-Hünnefeld, J. J.; Seebach, D. *Tetrahedron* **1992**, *48*, 5719. Giffels, G.; Dreisbach, C.; Kragl, U.; Weigerding, M.; Waldmann, H.; Wandrey, C. *Ibid.* **1995**, *34*, 2005. Kohra, S.; Hayashida, H.; Tominaga, Y.; Hosomi, A. *Tetrahedron Lett.* **1988**, *29*, 89. Kira, M.; Sato, K.; Sakurai, H. *J. Org. Chem.* **1987**, *52*, 948. Corey, E. J.; Letavic, M. A.; Noe, M. C.; Sarshar, S. *Tetrahedron Lett.* **1994**, *35*, 7553.

(3) To the best of our knowledge, the only examples of molecules of type **3** reported in the literature refer to compound **i**, able of very high performances (yields and ee >99%) in asymmetric Diels−Alder reactions with either boron or titanium as the metal promoters (Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561. Maruoka, K.; Murase, N.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 2938) and to compound **ii** (Corey, E. J.; Cywin, C. L.; Noe, M. C. *Tetrahedron Lett.* **1994**, *35*, 69).



i R = R′ = H or R′ = Me R′ = tri-*o*-tolylsilyl **ii**

(4) Rosini, C.; Franzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503.

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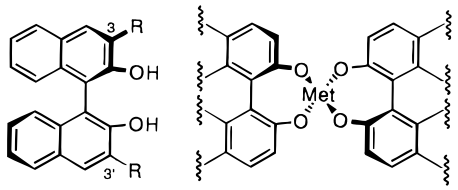
central chirality to axial chirality in two molecules was undertaken and is reported here in detail.

Results and Discussion

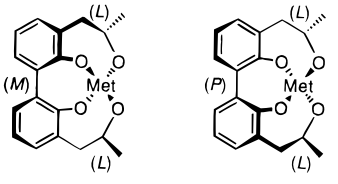
Design of the Tetrol. The starting point in this research is 1,1′-binaphthalene-2,2′-diol (**4**, BINOL), which has become a familiar diol in a number of common transformations[4] because of its availability in enantiomerically pure form,[5] its high efficiency, its simple C_2-geometry and clear rationalization of its reactivity. In a few cases, BINOL has been shown to coordinate around a central metal atom, giving rise to molecules of type **5** which are highly efficient in enantioselective processes.[6]



4 (R = H BINOL) **5**

It is also known that substitution at the 3,3′-positions is beneficial to the efficiency of the catalyst as it increases steric bulk around the metal complex. For example, definite improvement of several enantioselective processes has been obtained with substitution of R in **4** ranging from methyl to triphenylsilyl.[7] Thus, if any substitution is to be introduced in a binaphthyl skeleton, it should ideally occupy the 3,3′-positions.

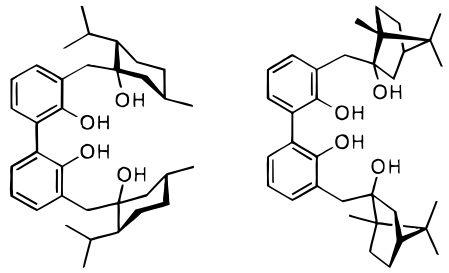
After the substitution pattern was settled, our research plan was to introduce a stereopure chiral fragment at these positions in a biphenyl system. In fact, while with the use of racemic binaphthol two different diastereoisomers were expected (*i.e.*, the stereoisomers composed by the stereopure fragment and BINOL of *M* or *P* configuration), no such an occurrence can be attained in the case of the configurationally labile 2,2′-biphenol. We hoped that the biphenyl residue would have assumed a preferred conformation by virtue of the chiral substituents, thus behaving as a binaphthol but avoiding the separation of stereoisomers and consequent loss of material. The two situations where a chiral stereocenter with central *L* chirality induces a *P* or *M* helicity to the biphenyl system when linked to a metal atom are exemplified in **6** and **6′**.



6 **6′**

A final point in the planning of the molecule is the number of carbons in the side arms at the 3,3′-positions necessary to ensure the efficient binding to the metal. Although this number can vary for different metals and hybridization geometries, we thought that two carbon atoms is the optimal choice for the preferential formation of monomeric species **3** over that of dimeric species **2**. It should also be pointed out that biphenyl systems such as **6** and **6′** may better adapt their geometry to the structural requirements of the metal than similar molecules consisting of binaphthyl systems due to the limitations imposed on the torsional angle in the latter aromatic rings. In other words, the atropoisomeric ligands **6** and **6′** should be able to adopt the dihedral angle that best fits the size and the nature of the metal.

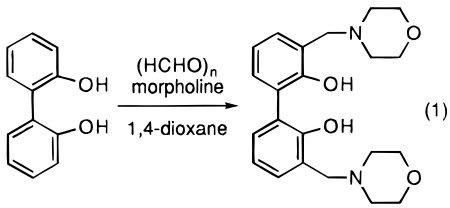
On the basis of these considerations we decided to prepare molecules **7** and **8**, containing chiral residues derived from menthone and camphor.



7 **8**

We hope that this system may enjoy large applicability in forming complexes with different metals and exibit high performance in view of the added chirality derived from the C_2 symmetry,[8] the presence of two centrally chiral fragments, and the induced helicity. These features may contribute synergically to the definition of a highly structured pocket with enhanced chirality capable of high efficiency in asymmetric synthesis.

Synthesis. Most methods available for the functionalization of the 3,3′-positions of BINOL make use of strongly basic conditions and rather expensive reagents[9] or long synthetic procedures.[10] Seeking a simpler and more economic route, we finally applied the Mannich-type reaction of paraformaldehyde and morpholine to 2,2′-biphenol in dioxane,[11] which gives rise to a fair and reproducible 50% yield of the 3,3′-bismorpholinomethyl derivative **9** (eq 1).



(1)

9 (50%)

Protection of the hydroxylic functions was achieved in the most simple and economic way with dichloromethane and sodium hydroxide in dimethyl sulfoxide.[9] The following replacement of morpholine with chlorine occurred

(5) Fabbri, D.; Delogu, G.; De Lucchi, O. *J. Org. Chem.* **1995**, *60*, 6599. De Lucchi, O. *Pure Appl. Chem.* **1996**, *68*, 945.

(6) For example: Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Date, T.; Shibasaki, M. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 104.

(7) Kelly, T. R.; Whiting, A.; Chandrakumar, N. S. *J. Am. Chem. Soc.* **1986**, *108*, 3510. Maruoka, K.; Hoshino, Y.; Shirasaka, T.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 3967. Larsen, D. S.; O'Shea, M.; Brooker, S. *J. Chem. Soc., Chem. Commun.* **1996**, 203.

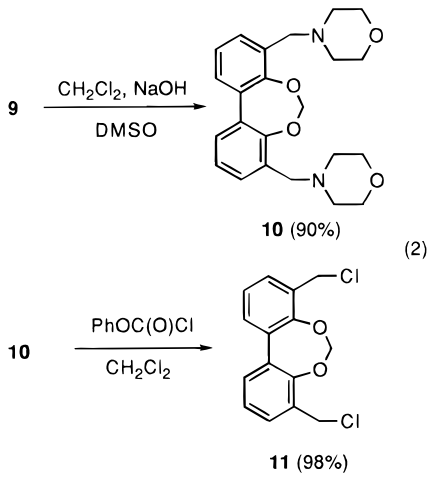
(8) Whitesell, J. K. *Chem Rev.* **1989**, *89*, 1581.

(9) Maruoka, K.; Itoh, T.; Araki, Y.; Shirasaka, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2975. Cox, P. J.; Wang, W.; Snieckus, V. *Tetrahedron Lett.* **1992**, *17*, 2253. Kitajima, H.; Aoki, Y.; Ito, K.; Katsuki, T. *Chem. Lett.* **1995**, 1113. Stock, H. T.; Kellogg, R. M. *J. Org. Chem.* **1996**, *61*, 3093.

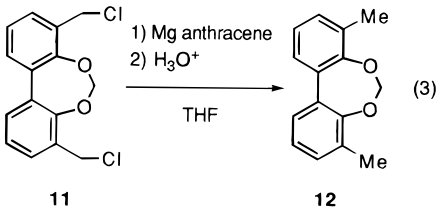
(10) Brunner, H.; Goldbrunner, J. *Chem. Ber.* **1989**, *122*, 2005.

(11) Fukazawa, Y.; Kitayama, H.; Yasuhara, K.; Yoshimura, K.; Usui, S. *J. Org. Chem.* **1995**, *60*, 1696.

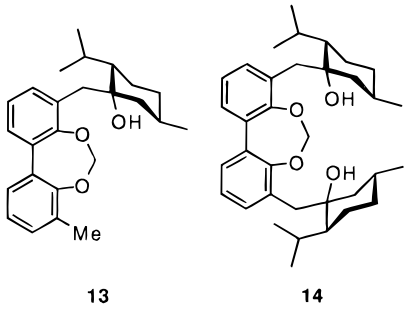
in almost quantitative yield with phenyl chloroformate in dichloromethane (eq 2).[12,13]



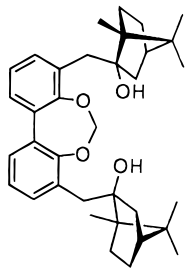
The attachment of the enantiopure ketones (menthone or camphor) to **11** requires its transformation into an organometallic reagent. The use of magnesium, even under special activating techniques as dry stirring,[14] gives rise in most cases to oligomeric material derived from Wurtz-type coupling. The Grignard reagent of **11** was obtained with the use of the complex of magnesium with anthracene, which is known to minimize Wurtz reactivity.[15] However, the Grignard compound formed by this route did not react with menthone and gave high yields of the dimethyl derivative **12** (eq 3) after acidic workup. This route to **12** might be considered as alternative to other methods to obtain 3,3′-dimethyl derivatives of biphenols and might also be applicable to the binaphthyl series.



Better results were obtained when the Grignard reagent of **11** was treated with cerium trichloride[16] before the addition of menthone. In this case the mono- and disubstituted products **13** and **14** were obtained in 36% and 48% yield, respectively.

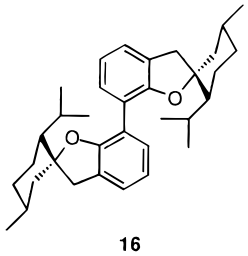


However, the same reaction applied to camphor did not lead to the expected addition product **15**, even after prolonged time or more drastic reaction conditions. The only product isolated from this reaction was the 1,3-dioxepine **12**, derived from hydrolysis of the organometallic intermediate.



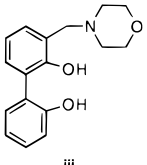
A definite improvement was achieved with the use of freshly prepared samarium diiodide.[17,18] With this reagent the isobornyl-disubstituted product **15** was obtained in almost quantitative yield. These reaction conditions also led to nearly quantitative yield of the menthyl-disubstituted product **14**.

Deprotection of the 1,3-dioxepine **14** with boron trifluoride etherate in ethanethiol[19] affords **7** in 65% yield and the ether **16** in 20% yield. The formation of this product is rationalized as a dehydration of **7** catalyzed by the Lewis acid, and was the sole product if the reaction was carried out for a longer time.



The stereochemistry of product **16** can be predicted on the assumption that the intramolecular attack of phenolic oxygen to the carbocation generated by dehydration of the menthol hydroxy moiety occurs on the face which is not hindered by the isopropyl group. This stereochemical assignment is supported by NOE experiments, which are in good agreement with the distances obtained in the structure **16** minimized at PM3 level.[20] Figure 1 and

(12) Hobson, J. D.; McCluskey, J. D. *J. Chem. Soc. (C)* **1967**, 2015.
(13) It should be noticed that if the reaction is run with 1 equiv of Mannich base, the monoadduct **iii** is obtained in 72% yield.



(14) Baker, K. V.; Brown, J. M.; Hughes, N.; Skarnulis, A. J.; Sexton, A. *J. Org. Chem.* **1991**, *56*, 698.
(15) Raston, C. L.; Salem, G. *J. Chem. Soc. Chem. Commun.* **1984**, 1702. Oppolzer, W.; Schneider, P. *Tetrahedron Lett.* **1984**, *25*, 3305.
(16) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392. Dimitrov, V.; Bratovanov, S.; Simova, S.; Kostova, K. *Tetrahedron Lett.* **1994**, *35*, 6713.
(17) Kagan, H. B.; Namy, J. L.; Girard, P. *Tetrahedron* (*Suppl. 1*) **1981**, *37*, 175.
(18) Namy, J. L.; Girard, P.; Kagan, H. B.; Caro, P. E. *Nouv. J. Chim.* **1981**, *5*, 479.
(19) Node, M.; Hori, H.; Fujita, E. *J. Chem. Soc., Perkin I* **1976**, 2237.
(20) Spartan Version 4.0, Wavefunction Inc., 18401 Karman Ave., #370, Irvine, CA 92715.

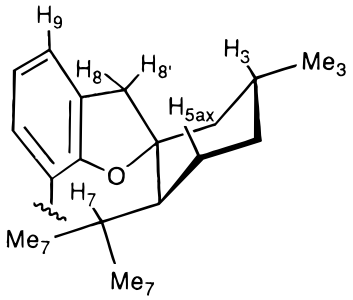


Figure 1. Structure of compound **16**, as determined by PM3 computations.

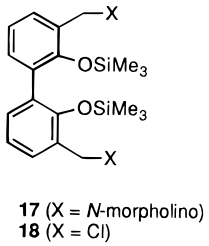
Table 1. Distances between Atoms Giving NOE for Compound 16 As Optimized at the PM3 Computational Level

selected atoms	distances, Å
H9−H8	3.04
H9−H8′	3.03
H8−H5ax	2.38
H8′−H3	2.27
H8−H7	2.94
H8−Me7	1.70[a]

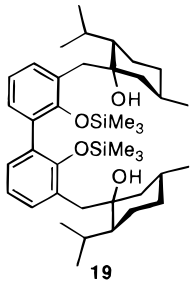
[a] Distance from the nearest proton of Me7.

Table 1 report the structure of compound **16** as minimized at the PM3 level, the calculated distances, and the observed NOEs.

In view of the difficulties in the preparation of reasonable quantities of **7** and **8** via this route and the necessity of avoiding the utilization of the irritating ethanethiol, an alternative procedure was sought. It was reasoned that silyl ethers would be compatible with samarium diiodide and would be easily cleaved under mild acidic conditions. In the first trials, the phenolic functions in **9** were protected as trimethylsilyl ethers, producing **17** in almost quantitative yield. The dimorpholino derivative was transformed into the dichloride **18** as previously described for the dioxepine **11**.[21]

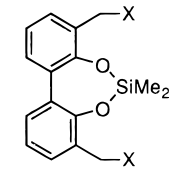


17 (X = *N*-morpholino)
18 (X = Cl)



19

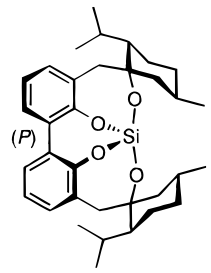
It was noticed that the steric hindrance of the bulky trimethylsilyl groups in **17** and **18** induces atropoisomerism to the biphenyl system, to such an extent that the two benzylic protons are observed as diastereotopic at room temperature in the ^{1}H-NMR spectrum. No such behavior was observed for the related molecules **9**, **10**, and **11**, suggesting that the dioxepine skeleton is not sufficient to freeze the conformation of the biphenyl residue. The dichloride **18** was reacted with samarium diiodide and menthone, obtaining the menthyl derivative **19** in very high yield. The tetrol **7** can be obtained from **19** quantitatively under mild acidic conditions. From a practical viewpoint, it is not necessary to isolate the silyl ether **19**, as tetrol **7** can be obtained directly from the dichloride **18** under acidic workup.



20 (X = *N*-morpholino)
21 (X = Cl)

In contrast, the reaction with camphor did not lead to tetrol **8**, suggesting an unfavorable steric interaction of the trimethylsilyl groups. Therefore, the less hindered silyl ethers **20** and **21** were prepared. The dimethyl silyl ether **21** was obtained from **9** in a one pot reaction, as the intermediate **20** was too unstable to be isolated. The dichloride **21** reacted with camphor in the presence of samarium diiodide producing the tetrol **8** in 85% yield. The same reaction sequence gave the menthyl derivative **7** with high efficiency.

The tetrols **7** and **8** react with tetrachlorosilane and triethylamine in chloroform at reflux to produce siloxanes **22** and **23** in high yield.



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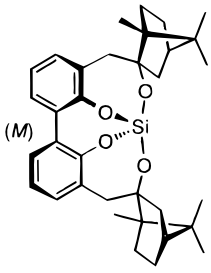

23

Structural Analysis. The configurations of siloxanes **22** and **23** and clear information about the conformational preferences of tetrols **7** and **8** and of ether **16** were established by a careful NMR study, and notably by analysis of the dipolar interactions between relevant protons, accomplished through NOE differential spectroscopy (NOEDS).[22,23] The full assignment of the ^{1}H resonances was accomplished by the combined utilization of COSY spectroscopy and of heterocorrelated reverse detection HMQC spectroscopy.[24−26] This latter technique allowed the unambigous assignment of ^{1}H methylenic and methynic multiplets of the menthol and isoborneol moieties. In some instances, the multiple-bond HMBC spectroscopy was utilized.[25,27] The HMQC and HMBC spectroscopies made also possible the assignment of ^{13}C resonances.

The observed dipolar interactions have been checked on the structures obtained from geometrical optimization at the semiempirical PM3 level. For a meaningful comparison, we assumed that dipolar interactions were

(21) Sunggak, K.; Heung, C. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3669. Sweeley, C. C.; Bentley, R.; Makita, M.; Wells, W. W. *J. Am. Chem. Soc.* **1963**, *85*, 2497.

(22) Neuhaus, D.; Williamson, M. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH Publishers: New York, 1984.

(23) Kinns, M.; Sanders, J. K. M. *J. Magn. Reson.* **1984**, *56*, 518.

(24) Bax, A.; Griggey, R. H.; Hawkins, B. L. *J. Magn. Reson.* **1983**, *55*, 301.

(25) Summers, M. F.; Marzilli, L. G.; Bax, A. *J. Am. Chem. Soc.* **1986**, *108*, 4285.

(26) Bax, A.; Subramanian, S. *J. Magn. Reson.* **1986**, *67*, 565.

(27) Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093.

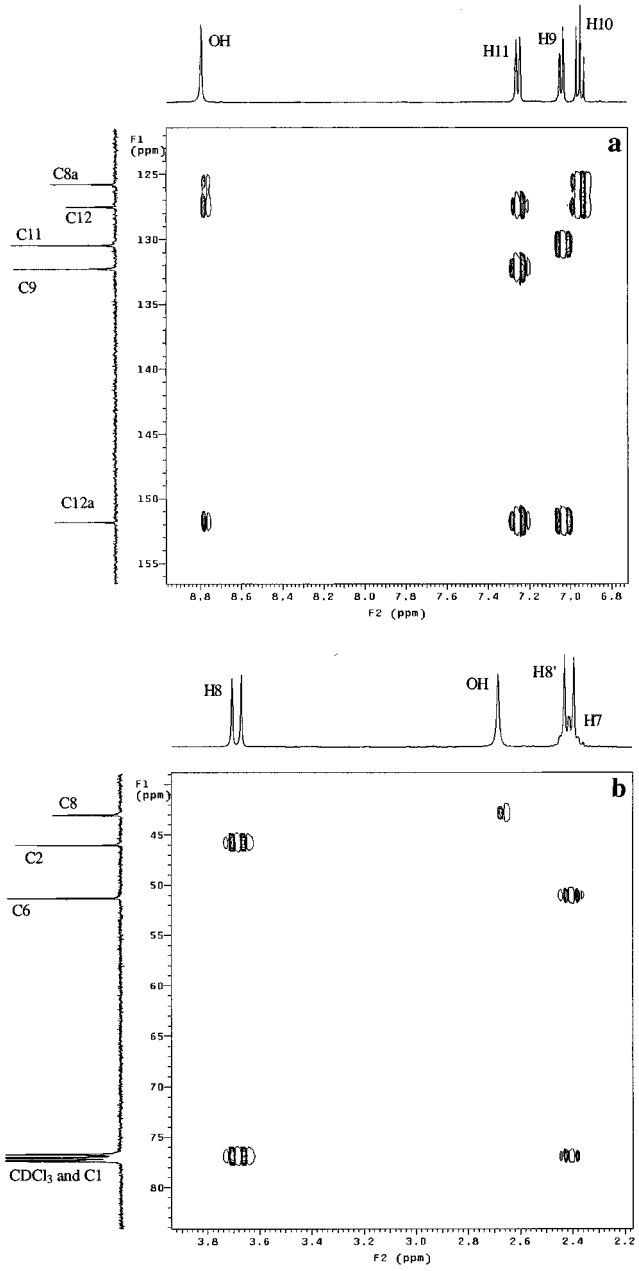

Figure 2. Long-range interactions between low-field hydroxy protons and aryl carbons in HMBC spectrum of **7**. (b) Long-range interactions between high-field hydroxy protons and alkyl carbons in HMBC spectrum of **7**.

observed for interproton through-space distances shorter than the threshold of 3.3 Å.

Tetrols 7 and 8. The inspection of the ^{1}H-NMR spectra and the results of NOEDS experiments reveals two important features.

(*i*) When the compounds are examined in carefully dried $CDCl_3$, the hydroxy protons give rise to two distinct resonances, at about 8.8 and 2.7 ppm. The frequency of the low-field resonance suggests that this hydroxy proton is involved in a good degree of H bonding. On the basis of the acidity scale of phenols and aliphatic alcohols, it may be assumed that the low-field signal at 8.8 ppm is associated with the phenolic proton. This assumption was confirmed by the HMBC analyses of **7** (Figure 2) and **8**.

The HMBC spectrum of **7** shown in Figure 2a displays clear multiple-bond scalar correlations of the hydroxy proton at 8.8 ppm with the *ipso* and *ortho* aromatic carbons C8a, C9, and C12a (Figure 2a and 3), while the correlation of the hydroxy proton at 2.7 ppm is with the methylenic carbon C8 (Figure 2b and 3).

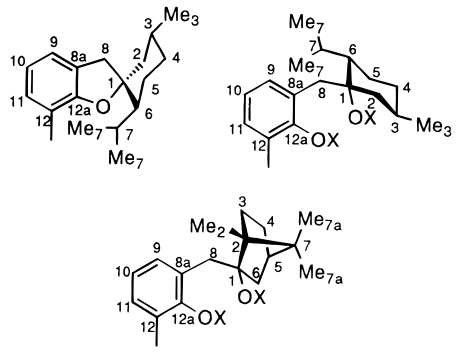

Figure 3. Notations employed in the descriptions ^{1}H- and ^{13}C-NMR spectra of compounds **7**, **8**, **16**, **22**, and **23**.

Thus, most H bonding is between the menthol or isoborneol moiety and the adjacent phenol, so that the rotation around the biphenyl bond is not affected.

(*ii*) Similarly to ether **16**, but at variance with siloxanes **22** and **23** (*vide infra*), the irradiation of the *ortho* aromatic ^{1}H resonance H9 brings about a NOE enhancement of both resonances of methylenic protons H8 and H8′. This fact may be attributed either to the preferred presence of that conformation where the aromatic ring bisects the angle H8−C8−H8′ or, more probably, to the presence of fast interconverting conformers. The presence of H bonding may in principle reduce the number of conformations to one. The optimization of the geometry of tetrols **7** and **8** with the semiempirical PM3 model is of no avail, as H bonding is not adequately described at this computational level. As a matter of fact, the geometrical optimization of **7** and **8** in the absence of constraints generates structures with the phenol hydroxy proton pointing away from the aliphatic hydroxy oxygen.

Also, the optimization of the geometry of tetrols **7** and **8** does not give any hint about their conformational preference around the biphenyl atropoisomeric bond. The observation of only one set of signals in the ^{1}H and ^{13}C spectra of the tetrols can be accounted for by the existence of only one rotamer, but also by the presence of more fast interconverting rotamers. Some calculated rotamers of tetrols **7** and **8** suggested the possibility of NOE dipolar interactions of some aliphatic protons with the aromatic proton H11 of the other non-directly-bonded phenyl. Unfortunatly, no such interactions could be detected even at low temperature, and thus, no information about the conformational preference of tetrols **7** and **8** could be gained.

Siloxane 22. The bonding of silicon with the four oxygen atoms "freezes" the conformational freedom of tetrol **7** around the phenyl−CH_2, CH_2−menthol, and biphenyl bonds. As we observed only one set of ^{1}H and ^{13}C signals, only one diastereoisomer is obtained, while the "freezing" can in principle lead to both diastereoisomers (*P* and *M*). The geometry of both diastereoisomers has been computationally optimized at the semiempirical PM3 level (see Figure 4). The interproton distances relevant for the comparison with the NOE results are reported in Table 2. Distances less than the threshold of 3.3 Å are highlighted by boldface digits.

The results of the NOEDS experiment are reported in Table 2. The discussion of these results requires the

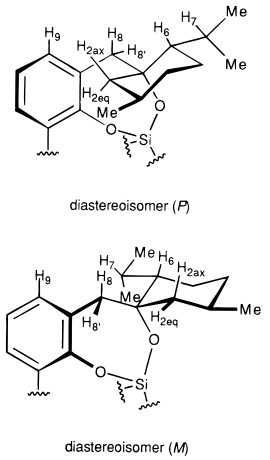

Figure 4. Configurations and conformational preferences of diastereoisomer *P* and *M* of compound **22**, as determined by PM3 computations.

Table 2. Observed NOEs and Interproton Distances for the Two Conformers of Compound 22 As Optimized at the PM3 Computational Level

		distances,[a] Å	
selected protons	observed NOE	*P*	*M*
H9−H8	√	**2.37**	**2.38**
H9−H8′		3.56	3.45
H9−H2ax	√	**3.10**	5.23
H9−H7		4.97	2.57
H8−H2ax	√	**2.54**	**2.91**
H8′−H2ax		3.72	**2.33**
H8′−H2eq		3.81	**2.41**
H8−H6	√	**2.21**	**2.24**
H8−H7	√[b]	**2.63**	**2.30**
H8′−H7	√	**1.85**	3.65

[a] Distances shorter than 3.3 Å are in boldface. [b] Negative enhancements due to the quasi−linear rearrangement of H8−H8′−H7 in *P*.

correct assignment of the H8 and H8′ doublets. Upon saturation of the aromatic H9 resonance only one doublet is enhanced, suggesting that one methylenic proton (marked H8) eclipses the aromatic ring, while the other (H8′) points away. This feature is correctly predicted by the semiempirical PM3 analysis. The other ^{1}H resonances have been assigned by the COSY and HMQC spectroscopies.

It should be noted that the observed NOE enhancements correspond to interproton distances shorter than the threshold in the case of diastereoisomer *P*. In the case of diastereoisomer *M* some observed enhancements correspond to distances longer than the threshold, while some shorter distances are not matched. The interaction between H8 and H7, which leads to negative enhancements, deserves further comment. The negative enhancement suggests the interposition between H8 and H7 of a third proton (H8′) in a quasi-linear H8−H8′−H7 arrangement. This arrangement is found in diastereoisomer *P*, while the isomer *M* has the H8′−H8−H7 arrangement.

The PM3 computed energies of diastereoisomers *P* (−297.04 kcal/mol) and *M* (−273.46 kcal/mol) indicate that the observed diastereoisomer (*P*) is also energetically favored.

Siloxane 23. Also in this case only one diastereoisomer is observed, while the computed geometry optimizations have been performed for both diastereoisomers (Figure 5). The relevant computed interproton distances

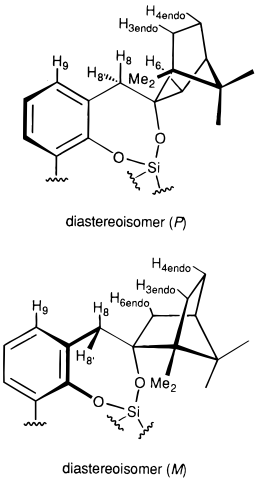

Figure 5. Configurations and conformational preferences of diastereoisomers *P* and *M* of compound **23**, as determined by PM3 computations.

Table 3. Observed NOEs and Interproton Distances for the Two Conformers of Compound 23 As Optimized at the PM3 Computational Level

		distances,[a] Å	
selected protons	observed NOE	*P*	*M*
H9−H8	√	**2.40**	**2.38**
H9−H8′		3.58	3.58
H9−H3endo		**2.23**	3.60
H9−H6endo	√	4.75	**2.85**
H8−H3endo	√	**1.79**	**1.71**
H8−H4endo	√	**2.73**	**2.76**
H8−H6endo	√	**2.39**	**2.87**
H8′−H6endo		**2.48**	3.71
H8−Me2[b]	√[c]	3.54	**3.16**
H8′−Me2[b]	√	4.14	**2.62**

[a] Distances shorter than 3.3 Å are in boldface. [b] Distance from nearest proton of Me2. [c] Negative enhancements due to the quasi−linear arrangement of Me2−H8′−H8 in *M*.

are reported in Table 3. The distance of a given proton from methyl is that from the nearest methyl proton (the one most contributing to or most affected by NOE).

As in the previous case, both NOE analysis and computational results point to methylenic H8 eclipsing the phenyl ring, while geminal H8′ is oriented away. The observed NOE enhancements are exactly matched by distances shorter than the threshold in diastereoisomer *M*, while the match is much poorer in diastereoisomer *P*. Also, the negative enhancements from the interactions between Me2 and H8 reflects the quasi-linear arrangement of Me2−H8′−H8 in *M*, while in *P* the arrangement is Me2−H8−H8′.

Again, the lowest computed energy is that of the diastereoisomer *M*, which is actually observed: *M*, −233.19 kcal/mol; *P*, −229.23 kcal/mol.

The specific formation of different atropoisomers, *P* in **22** and *M* in **23**, makes the two tetrols **7** and **8** potentially complementary in future practical applications, where they are planned to be used as ligands in catalysts for asymmetric synthesis.

Experimental Section

All reactions were performed under nitrogen and carried out with standard techniques. Manipulations of moisture sensitive substances were carried out in a glovebox. All glassware was flame-dried before use. THF was dried over potassium/benzophenone. Reactions were monitored by TLC or ^{1}H NMR. Flash chromatography was performed with 230−

400 mesh silica gel Merck 60. Melting points were determined with a Büchi MP 535 and were uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AC200 using TMS as internal standard. The NOE spectra have been obtained in the differential mode (NOEDS)[23] on a Varian Unity 400 spectrometer. The lines of the selected multiplet were 0.05 s cyclically saturated for a total time of 10 s with the proper attenuation of the decoupling power.[23] The heterocorrelated reverse-mode HMQC[25−27] and HMBC[26,28] (multiple bond HMQC) spectra have been acquired on the same spectrometer. In a typical experiment, a total of 256 t_1 measurements were made in the phase sensitive acquisition mode, with 16 (HMQC) or 32 (HMBC) scans for t_1 value. The delay of the BIRD filter is matched to the average $^1J_{CH} = 140$ Hz. The fixed delay for the detection of multiple-bond correlations is tuned to $^nJ_{CH} = 5$ Hz. IR spectra were collected on a BIO-RAD FTS-40. Optical rotations were observed on a Perkin-Elmer 638 polarimeter.

2-(2-Hydroxy-3-(morpholinomethyl)phenyl)-6-(morpholinomethyl)phenol (9). Paraformaldehyde (9.9 g, 297.7 mmol) was dissolved in morpholine (30 mL, 344.1 mmol) in a round-bottomed flask equipped with a reflux condenser (CAUTION! strongly exothermic reaction). The resulting syrup was diluted with dioxane (10 mL), added dropwise to a solution of 2-(2-hydroxyphenyl)phenol (20.0 g, 107.4 mmol) in dioxane (20 mL), and stirred 2 h at room temperature (rt) and 4 h at reflux. The solvent was removed and the residue was dissolved in CH_2Cl_2 (600 mL), washed with 1 M HCl (3 × 50 mL) and water (3 × 50 mL), dried over Na_2SO_4, and rotoevaporated. The crude material was recrystallized from EtOH to obtain 20.6 g (50% yield) of colorless needles: mp 146−148 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.27 (2 H, dd, J = 7.5 and 1.8 Hz), 7.02 (2 H, dd, J = 7.5 and 1.8 Hz), 6.88 (2 H, t, J = 7.5 Hz), 3.78 (4 H, s), 3.71 (8 H, t, J = 5.8 Hz), 2.59 (8 H, t, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 154.8, 131.0, 128.3, 125.9, 120.8, 118.9, 66.6, 62.0, 52.8. IR (KBr, cm^{-1}) 3443, 2853, 1431, 1118.

4-((8-(Morpholinomethyl)dibenzo[*d*,*f*][1,3]dioxepin-4-yl)methyl)morpholine (10). A slurry of **9** (17.0 g, 44.2 mmol), NaOH (4.0 g, 100.0 mmol), CH_2Cl_2 (50 mL), and DMSO (250 mL) was refluxed at 100 °C for 45 min. The resulting solution was poured into water (2 L), extracted with CH_2Cl_2 (3 × 150 mL), washed with water (4 × 100 mL), dried (Na_2SO_4), and rotoevaporated. The resulting oily residue was recrystallized from EtOH to afford yellow needles: 16.8 g (96% yield); mp 124−126 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.44 (2 H, dd, J = 7.5 and 1.8 Hz), 7.38 (2 H, dd, J = 7.5 and 1.8 Hz), 7.24 (2 H, t, J = 7.5 Hz), 5.85 (2 H, s), 3.73 (8 H, t, J = 4.5 Hz), 3.60 (4 H, s), 2.52 (8 H, t, J = 4.5 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 151.8, 133.1, 130.4, 130.3, 127.6, 124.6, 103.0, 67.2, 57.8, 53.7. IR (KBr, cm^{-1}) 2799, 1113, 1017, 778.

4,8-Bis(chloromethyl)dibenzo[*d*,*f*][1,3]dioxepine (11). A solution of phenylchloroformate (10.0 mL, 79.7 mmol) in dry CH_2Cl_2 (35 mL) was added dropwise under nitrogen to a solution of **10** (14.0 g, 35.3 mmol) in dry CH_2Cl_2 (35 mL) at 0 °C. After stirring 2 h at rt, the resulting solution was diluted in CH_2Cl_2 (400 mL), washed with 10% Na_2CO_3 (4 × 100 mL), dried (Na_2SO_4), and rotoevaporated. The crude residue was recrystallized from EtOH to obtain 6.0 g of colorless plates: mp 104−106 °C. The mother liquor was concentrated and purified by flash chromatography (eluant hexanes/CH_2Cl_2 9:1) to obtain 4.13 g of a pure colorless material for a combined total yield of 98%. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.53 (2 H, d, J = 7.6 Hz), 7.43 (2 H, d, J = 7.6 Hz), 7.27 (2 H, t, J = 7.6 Hz), 5.90 (2 H, s), 4.73 (4 H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 152.0, 131.7, 130.2, 129.5, 125.0 (two coincident signals), 101.8, 41.3. IR (KBr, cm^{-1}) 2976, 1431, 1009, 686.

Samarium Diiodide (0.1 M Solution in THF). A solution of 1,2-diiodoethane (2.82 g, 10 mmol) in dry THF (100 mL) was slowly added to samarium powder (40 mesh) (2.26 g, 15 mmol), with vigorous magnetical stirring, under nitrogen. The deep blue solution was stirred an additional hour and was stored under nitrogen.[18]

(1*R*,2*S*,5*R*)-1-((8-(((1*R*,2*S*,5*R*)-1-Hydroxy-2-isopropyl-5-methylcyclohexyl)methyl)dibenzo[*d*,*f*][1,3]dioxepin-4-yl)methyl)-2-isopropyl-5-methylcyclohexan-1-ol (14). Reaction of 11 with Mg·anthracene·3THF, $CeCl_3$, and menthone. To a dispersion of Mg·anthracene·3THF (1.7 g, 2.55 mmol) in anhydrous THF (5 mL) was added dropwise a solution of **11** (325 mg, 1.1 mmol) in anhydrous THF (6 mL). The resulting solution was added to a previously prepared slurry of (−)-menthone (0.4 mL, 2.3 mmol), and anhydrous $CeCl_3$ (490 mg, 2.0 mmol) in dry THF (2 mL) stirred under nitrogen 1 h at rt. After 12 h, the reaction mixture was filtered through a glass-wool plug, poured into saturated NH_4Cl (100 mL), extracted with Et_2O (5 × 50 mL), and dried over Na_2SO_4. The combined organic layers were concentrated to *ca.* 10 mL. The colorless crystals formed (anthracene) were discarded and the filtrate was concentrated and purified by flash chromatography (eluant CH_2Cl_2/hexane 1:1) eluting in the order monoadduct **13** and bisadduct **14**. **13**: pale yellow oil, 150 mg (36% yield), $[\alpha]_D^{25}$ −18.1 (*c* 2.4, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.50−7.46 (2 H, m), 7.30−7.11 (4 H, m), 5.72 (1 H, 1/2 AB, J = 3.9 Hz), 5.67 (1 H, 1/2 AB, J = 3.9 Hz), 3.93 (2 H, 1/2 AB, J = 13.4 Hz), 2.61 (2 H, 1/2 AB, J = 13.4 Hz), 2.49−2.28 (1 H, m), 2.36 (3 H, s), 1.84−0.70 (8 H, serie di m), 1.01 (3 H, d, J = 6.9 Hz), 1.00 (3 H, d, J = 6.9 Hz), 0.77 (3 H, d, J = 6.5 Hz), (1 H alcohol not observed); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 152.3, 151.5, 132.3, 132.0, 131.9, 130.4, 130.2, 130.0, 127.2, 126.6, 124.6, 124.4, 100.3, 75.0, 50.6, 46.9, 40.4, 35.2, 27.8, 26.1, 23.8, 22.4, 21.0, 18.1, 15.9. IR (film, cm^{-1}) 3567, 2954, 1015, 771. **14**: 280 mg (48% yield), mp 186−187 °C (from pentane), $[\alpha]_D^{22}$ −66.8 (*c* 2.8, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.50−7.40 (2 H, m), 7.30−7.27 (4 H, m), 5.72 (2 H, s), 3.42 (2 H, 1/2 AB, J = 13.5 Hz), 2.59 (2 H, 1/2 AB, J = 13.5 Hz), 2.51−2.28 (2 H, m), 1.86−0.65 (16 H, serie di m), 1.00 (6 H, d, J = 6.9 Hz), 0.78 (3 H, d, J = 6.4 Hz) (2 H alcohol not observed); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 151.9, 132.4, 132.2, 130.1, 127.4, 124.5, 100.6, 75.0, 50.6, 46.8, 40.4, 35.2, 27.8, 26.1, 23.8, 22.4, 21.0, 18.1. IR (KBr, cm^{-1}) 3566, 2956, 1384, 1009, 774.

Reaction of 11 and Menthone with SmI_2. A solution of samarium diiodide 0.1 M in THF (9.0 mL, 0.9 mmol) was introduced via syringe to a solution of **11** (60 mg, 0.2 mmol) and (−)-menthone (100 μL, 0.6 mmol) in dry THF (1.0 mL) at rt under nitrogen. After 30 min the deep blue solution turned yellow. Aqueous hydrochloric acid (0.1 M, 10 mL) was added, and the resulting mixture was stirred 15 min at rt. The acidic solution was extracted with Et_2O (3 × 5 mL), washed with $Na_2S_2O_5$ (5 mL of a 10% solution) and brine (5 mL), dried (Na_2SO_4), and concentrated under vacuum. The crude was purified by flash chromatography (eluant CH_2Cl_2/hexanes 1:1) and recrystallized from CH_2Cl_2/*n*-hexane to obtain 95 mg (90% yield) of colorless crystals, mp 186−187 °C, identical to the sample obtained as above.

(2*S*)-2-((8-((2*S*)-2-Hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)methyl)dibenzo[*d*,*f*][1,3]dioxepin-4-yl)methyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (15). A solution of samarium diiodide 0.1 M in THF (9.0 mL, 0.9 mmol) was introduced via syringe to a solution of **11** (60 mg, 0.2 mmol) and (+)-camphor (90 mg, 0.6 mmol) in dry THF (1.0 mL), at rt under nitrogen. The deep blue solution turned yellow after 1 h. Aqueous hydrochloric acid (0.1 M, 10 mL) was added and the resulting mixture stirred 15 min at rt. The solution was extracted with Et_2O (4 × 5 mL), washed with a 10% solution of $Na_2S_2O_5$ (5 mL) and brine (5 mL), dried over Na_2SO_4, and rotoevaporated. The crude material was purified by flash chromatography (eluant CH_2Cl_2/hexanes 1:1) and recrystallized from CH_2Cl_2/*n*-hexane to obtain 85 mg (80% yield) of colorless crystals: mp 149−51 °C; $[\alpha]_D^{22}$ +105.3 (*c* 0.7, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.40 (2 H, dd, J = 7.5 and 2.0 Hz), 7.34 (2 H, dd, J = 7.5 and 2.0 Hz), 7.24 (2 H, t, J = 7.5 Hz), 5.73 (2 H, s), 3.15 (2 H, 1/2 AB, J = 13.2 Hz), 2.74 (2 H, 1/2 AB, J = 13.2 Hz), 2.19 (2 H, s), 1.94−1.37 (12 H, m), 1.32−1.10 (2 H, m), 1.06 (6 H, s), 0.90 (6 H, s), 0.88 (6 H, s); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 186.2, 151.4, 132.3, 131.0, 130.4, 127.2, 124.7, 100.2, 80.9, 52.7, 48.8, 44.9, 41.3, 38.0, 30.1, 29.4, 26.8, 21.1, 20.8, 10.0. IR (KBr, cm^{-1}) 3579, 2959, 1207, 1019.

4-(2-((Trimethylsilyl)oxy)-3-(2-((trimethylsilyl)oxy)-3-(morpholinomethyl)phenyl)benzyl)morpholine (17). A solution of trimethylchlorosilane (0.4 mL, 3.04 mmol) in dry Et_2O was added to a solution of **9** (570 mg, 1.48 mmol),

triethylamine (0.72 mL, 4.56 mmol), and DBU (2 drops) in dry Et_2O (5 mL) under nitrogen. The resulting slurry was vigorously stirred 6 h, poured into water (20 mL), and extracted with Et_2O (3 × 10 mL). Combined organic layers were dried over Na_2SO_4 and rotoevaporated. The residue was recrystallized from *n*-pentane to obtain 690 mg (93% yield) of colorless needles: mp 150−2 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.35 (2 H, dd, J = 7.4 and 2.1 Hz), 7.09 (2 H, dd, J = 7.4 and 2.1 Hz), 6.99 (2 H, t, J = 7.4 Hz), 3.74 (8 H, t, J = 4.6 Hz), 3.56 (2 H, 1/2 AB, J = 13.0 Hz), 3.40 (2 H, 1/2 AB, J = 13.0 Hz), 2.51 (8 H, t, J = 4.6 Hz), −0.20 (18 H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 152.9, 132.3, 130.6, 129.9, 128.9, 120.9, 67.0, 58.2, 53.9, 0.3. IR (KBr, cm^{-1}) 2809, 1112, 917, 842, 766.

2-((Trimethylsilyl)oxy)-1-(2-((trimethylsilyl)oxy)-3-(chloromethyl)phenyl)-3-(chloromethyl)benzene (18). A solution of phenylchloroformate (0.2 mL, 1.7 mmol) in dry CH_2Cl_2 (1 mL) was added at 0 °C to a solution of **17** (400 mg, 0.76 mmol) in dry CH_2Cl_2 (1 mL) under nitrogen. The mixture was stirred at the same temperature 3 h, diluted with CH_2Cl_2 (50 mL), washed with water (3 × 10 mL), dried over Na_2SO_4, and rotoevaporated. The residue was purified by rapid filtration through a short silica-gel pad (eluant CH_2Cl_2/hexanes 1:1) to obtain 300 mg (92% yield) of colorless needles: mp 85−6 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.41 (2 H, dd, J = 7.4 and 1.8 Hz), 7.18 (2 H, dd, J = 7.4 and 1.8 Hz), 7.05 (2 H, t, J = 7.4 Hz), 4.70 (2 H, 1/2 AB, J = 11.1 Hz), 4.57 (2 H, 1/2 AB, J = 11.1 Hz), −0.14 (18 H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 142.5, 132.3, 131.9, 130.5, 129.2, 121.7, 41.9, 0.1. IR (KBr, cm^{-1}) 2955, 1266, 927, 843, 766.

(1*R*,2*S*,5*R*)-1-(2-((Trimethylsilyl)oxy)-3-((2-((trimethylsilyl)oxy)-3-((1*R*,2*S*,5*R*)-1-hydroxy-2-isopropyl-5-methylcyclohexyl)methyl)phenyl)benzyl)-2-isopropyl-5-methylcyclohexan-1-ol (19). A 0.1 M solution of samarium diiodide in THF (36 mL, 3.6 mmol) was introduced via syringe through a septum to a solution of **18** (310 mg, 0.72 mmol) and (-)-menthone (370 μL, 2.18 mmol) in dry THF (1.0 mL) at rt under nitrogen. The deep blue solution turned yellow after 3 h. Aqueous hydrochloric acid (0.1 M, 36 mL) was added, and the resulting mixture was rapidly extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with a 10% solution of $Na_2S_2O_5$ (10 mL) and brine (10 mL), dried over Na_2SO_4, and rotoevaporated. The crude reaction mixture was purified by flash chromatography (eluant CH_2Cl_2/hexanes 6:4) and recrystallized from CH_2Cl_2/*n*-hexane to obtain 170 mg (42% yield) of colorless crystals: mp 195−198 °C; $[\alpha]_D^{24}$ −50.2 (*c* 2.5, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.13−6.94 (6 H, series of m), 3.61 (2 H, 1/2 AB, J = 13.6 Hz), 2.96 (2 H, s), 2.34 (2 H, heptet, J = 6.8 Hz), 2.54 (2 H, 1/2 AB, J = 13.6 Hz), 1.85−1.35 (10 H, series of m), 1.16−0.64 (6 H, series of m), 1.02 (6 H, d, J = 6.8 Hz), 0.98 (6 H, d, J = 6.8 Hz), 0.74 (6 H, d, J = 6.4 Hz), −0.14 (18 H, s); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 152.3, 133.3, 132.5, 131.1, 130.0, 121.7, 75.7, 51.6, 46.8, 42.6, 35.4, 27.6, 25.8, 24.0, 22.4, 21.4, 18.6, 0.1. IR (KBr, cm^{-1}) 3513, 2953, 1256, 845.

4,8-Bis(chloromethyl)-6,6-dimethyldibenzo[*d*,*f*][1,3,2]dioxasilepine (21). A solution of dimethyldichlorosilane (0.36 mL, 3.0 mmol) in dry CH_2Cl_2 (10 mL) was added at 0 °C to a solution of **9** (1.00 g, 2.8 mmol), triethylamine (0.13 mL, 9.0 mmol), and DBU (3 drops) in dry CH_2Cl_2 (10 mL) under nitrogen. The reaction mixture was stirred 1 h at 0 °C. A small sample (*ca.* 0.5 mL) of the reaction mixture was rotoevaporated and submitted to ^{1}H NMR, showing quantitative conversion into **20**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.42 (2 H, dd, J = 7.4 and 1.8 Hz), 7.29 (2 H, dd, J = 7.4 and 1.8 Hz), 7.11 (2 H, t, J = 7.4 Hz), 3.72 (4 H, t, J = 4.1 Hz), 3.56 (4 H, s), 2.51 (4 H, t, J = 4.1 Hz), 0.39 (6 H, s). A solution of phenyl chloroformate (0.9 mL, 7.2 mmol) in dry CH_2Cl_2 (5 mL) was added at 0 °C and the resulting mixture was stirred at the same temperature for 3 h, diluted with CH_2Cl_2 (150 mL), washed with water (3 × 10 mL), dried over Na_2SO_4, and rotoevaporated. The crude reaction mixture was recrystallized from *n*-pentane to obtain 120 mg of colorless needles: mp 108−10 °C. The mother liquors were concentrated and purified by rapid filtration through a short silica-gel column (eluant CH_2Cl_2/hexanes 1:1) to obtain further 490 mg of pure material (64% overall yield). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.47 (2 H, dd, J = 7.6 and 1.8 Hz), 7.36 (2 H, dd, J = 7.6 and 1.8 Hz), 7.16 (2 H, t, J = 7.6 Hz), 4.70 (4 H, s), 0.48 (6 H, s); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 149.7, 132.2, 130.5, 129.6, 126.3, 123.3, 41.2, −2.1. IR (KBr, cm^{-1}) 3059, 1437, 1260, 931.

(1*R*,2*S*,5*R*)-1-(2-hydroxy-3-((2-hydroxy-3-((1*R*,2*S*,5*R*)-1-hydroxy-2-isopropyl-5-methylcyclohexyl)methyl)phenyl)benzyl)-2-isopropyl-5-methylcyclohexan-1-ol (7). Via Deacetalization of 14. One drop of BF_3·OEt_2 was added to a solution of **14** (130 mg, 0.25 mmol) in EtSH. After stirring 20 min at rt, the solution was poured into saturated $NaHCO_3$ (5 mL) and saturated brine (15 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The organic extracts were dried over Na_2SO_4 and rotoevaporated. The residue was purified by flash chromatography (CH_2Cl_2/hexanes 7:3) to obtain two main fractions. First fraction: **16**, colorless oil, 25 mg (20% yield); $[\alpha]_D^{25}$ −48.4 (*c* 2.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50 (d, H11, $J_{10,11}$ = 7.6 Hz), 7.04 (d, H9, $J_{9,10}$ = 7.3 Hz), 6.82 (t, H10), 3.26 (d, H8, $J_{8,8'}$ = 15.8 Hz), 2.88 (d, H8′), 1.89 (d, H2eq, $J_{2eq,2ax}$ = 12.6 Hz), 1.87 (m, H7), 1.80 (dm, H5eq, $J_{5eq,5ax}$ = 13.3 Hz), 1.73 (dm, H4eq, $J_{4eq,4ax}$ = 12.8 Hz), 1.58 (m, H6), 1.54 (m, H3), 1.35 (t, H2ax, $J_{2ax,3}$ = 12.4 Hz), 1.12 (qd, H5ax, $J_{4ax,5ax}$ = $J_{5ax,6}$ = 13.1 Hz, $J_{4eq,5ax}$ = 3.4 Hz), 0.96 (m, H4ax), 0.92 (d, Me7, $J_{7,Me7}$ = 6.7 Hz), 0.91 (d, Me3, $J_{3,Me3}$ = 6.5 Hz), 0.83 (d, Me7′, $J_{7,Me7'}$ = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.4, 129.2 (C11), 127.5, 123.6 (C9), 119.4, 119.20 (C10), 92.0, 50.7 (C3), 48.5 (C2), 35.0 (C8), 34.8 (C4), 30.2 (C6), 26.9 (C7), 25.5 (C5), 24.4 (Me7), 22.1 (Me3), 19.8 (Me7′). IR (KBr, cm^{-1}) 2953, 1455, 1421, 760. Second fraction: **7**, 85 mg (65% yield), colorless crystals from CH_2Cl_2/*n*-hexane, mp 191−193 °C; $[\alpha]_D^{20}$ −229.4 (*c* 1.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.80 (s, OH12a), 7.25 (dd, H11, $J_{10,11}$ = 7.7 Hz, $J_{9,11}$ = 1.8 Hz), 7.04 (dd, H9, $J_{9,10}$ = 7.4 Hz), 6.95 (t, H10), 3.69 (d, H8, $J_{8,8'}$ = 14.1 Hz), 2.68 (s, OH1), 2.41 (m, H7), 2.41 (d, H8′), 1.76 (dm, H4eq, $J_{4ax,4eq}$ = 12.8 Hz), 1.61 (dm, H5eq, $J_{5ax,5eq}$ = 13.5 Hz), 1.47 (m, H2eq and H3), 1.38 (qd, H5ax, $J_{4ax,5ax}$ = $J_{5ax,6}$ = 12.9 Hz, $J_{4eq,5ax}$ = 3.3 Hz), 1.23 (dm, H6), 0.98 and 0.98 (d, Me7 and Me7′, $J_{Me7,7}$ = $J_{Me7,7'}$ = 6.9 Hz), 0.91 (t, H2ax, $J_{2ax,2eq}$ = $J_{2ax,3}$ = 13.8 Hz), 0.89 (m, H4ax), 0.80 (d, Me3, $J_{3,Me3}$ = 6.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.8 (C12a), 132.2 (C9), 130.4 (C11), 127.5 (C12), 125.8 (C8a), 120.6 (C10), 77.1 (C1), 51.3 (C6), 45.9 (C2), 43.0 (C8), 34.9 (C4), 28.1 (C3), 25.8 (C7), 23.7 (Me7), 22.3 (Me3), 20.9 (C5), 18.1 (Me7′). IR (KBr, cm^{-1}) 3489, 2952, 1446, 1387.

Via Reaction of 18 with SmI_2. A 0.1 M solution of samarium diiodide in THF (36 mL, 3.6 mmol) was introduced via syringe through a septum to a solution of **18** (310 mg, 0.72 mmol) and (−)-menthone (370 μL, 2.2 mmol) in dry THF (1.0 mL) at rt under nitrogen. The deep blue solution turned yellow after 2 h. Aqueous hydrochloric acid (0.1 M, 40 mL) was added, and the resulting mixture was stirred 15 min. The solution was extracted with Et_2O (3 × 10 mL), and the organic layers were combined and washed with a 10% solution of $Na_2S_2O_5$ (10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash chromatography (eluant CH_2Cl_2/hexanes 6:4) and recrystallized from CH_2Cl_2/*n*-hexane to obtain 340 mg (90% yield) of colorless crystals, mp 191−193 °C, identical to the sample obtained as above.

Via Reaction of 21 with SmI_2. A 0.1 M solution of samarium diiodide in THF (9.0 mL, 0.9 mmol) was introduced via syringe through a septum to a solution of **21** (67 mg, 0.2 mmol) and (−)-menthone (100 μL, 0.6 mmol) in dry THF (1.0 mL) at rt under nitrogen. The deep blue solution turned yellow after 2 h. Aqueous hydrochloric acid (0.1 M, 10 mL) was added and the resulting mixture was stirred 15 min. The solution was extracted with Et_2O (3 × 5 mL), and the combined organic layers were washed with a 10% solution of $Na_2S_2O_5$ (5 mL) and brine (5 mL), dried over Na_2SO_4, and rotoevaporated. The crude reaction mixture was purified by flash chromatography (eluant CH_2Cl_2/hexanes 6:4) and recrystallized from CH_2Cl_2/*n*-hexane to obtain 95 mg (90% yield) of colorless crystals, mp 191−193 °C, identical to the sample obtained as above.

(1*R*,2*S*,4*R*)-2-(2-hydroxy-3-((2-hydroxy-3-((1*R*,2*S*,4*R*)-2-hydroxy-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl)methyl)-phenyl)benzyl)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-ol (8). A 0.1 M solution of samarium diiodide in THF (50 mL,

5.0 mmol) was introduced via syringe through a septum to a solution of **21** (340 mg, 1.0 mmol) and (+)-camphor (455 mg, 3.0 mmol) in dry THF (1.0 mL) at rt under nitrogen. The deep blue solution turned yellow after 3 h. Aqueous hydrochloric acid (0.1 M, 15 mL) was added. The resulting mixture was stirred 15 min, extracted with Et_2O (3 × 10 mL), washed with a 10% solution of $Na_2S_2O_5$ (5 mL) and brine (5 mL), dried over Na_2SO_4, and rotoevaporated. The crude reaction mixture was purified by flash chromatography (eluant CH_2Cl_2/hexanes 6:4) and recrystallized from CH_2Cl_2/*n*-hexane to obtain 520 mg (85% yield) of colorless crystals: mp 166−8 °C; $[\alpha]_D^{22}$ +41.9 (*c* 0.6, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.78 (s, OH12a), 7.21 (dd, H11, $J_{10,11}$ = 7.7 Hz, $J_{9,11}$ = 1.7 Hz), 7.17 (dd, H9, $J_{9,10}$ = 7.5), 6.96 (t, H10), 3.14 (d, H8, $J_{8,8'}$ = 13.9 Hz), 2.93 (s, OH1), 2.83 (d, H8′), 1.88 (dm, H6exo, $J_{6endo,6exo}$ = 13.7 Hz), 1.74 (m, H3, H4 and H6endo), 1.52 (m, H4′), 1.19 (m, H3′), 1.06 (s, Me7s), 0.88 (s, Me7a), 0.87 (s, Me2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.0 (C12a), 132.1 (C9), 130.5 (C11), 127.3 (C12), 126.6 (C8a), 120.9 (C10), 84.1 (C1), 52.9 (C2), 49.4 (C7), 45.8 (C6), 44.9 (C5), 40.6 (C8), 30.6 (C4), 26.9 (C3), 21.4 (Me7s), 21.1 (Me7a), 10.5 (Me2). IR (KBr, cm^{-1}) 3478, 2955, 1431, 1384.

(1′*R*,2*S*,2″*S*,3′*R*,5*R*,5″*R*)-2,2″-Diisopropyl-5,5″-dimethyldispiro[cyclohexane-1,16′-2′,17′,18′,21′-tetraoxa-1′-silapentacyclo[8.7.2.2^{1,9}.0^{5,20}.0^{14,19}]henicosa-5′,7′,9′-(20′),10′,12′,14′(19′)-hexaene-3′,1″-cyclohexane] (22). Freshly distilled tetrachlorosilane (25 μL, 0.22 mmol) was added to a solution of **7** (100 mg, 0.20 mmol), triethylamine (140 μL, 1.0 mmol) and DBU (2 μL) in dry $CHCl_3$ (4 mL) under nitrogen. The solution was refluxed 3 h, poured into water (5 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The organic layer was dried over Na_2SO_4 and rotoevaporated. The residue was purified by flash chromatography (eluant CH_2Cl_2/hexanes 1:3) to obtain 90 mg (85% yield) of a colorless oil: $[\alpha]_D^{23}$ −27.0 (*c* 1.9, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (d, H11, $J_{10,11}$ = 7.6 Hz), 7.11 (t, H10, $J_{9,10}$ = 7.5 Hz), 7.03 (d, H9), 4.22 (d, H8, $J_{8,8'}$ = 13.9 Hz), 2.44 (m, H7), 2.15 (d, H8′), 1.70 (dm, H4eq, $J_{4eq,4ax}$ = 12.6 Hz), 1.58 (m, H3), 1.47 (m, H5ax and H5eq), 1.13 (dm, H6, $J_{5ax,6}$ = 11.8 Hz), 1.03 (m, H2eq), 1.00 (d, Me7, $J_{7,Me7}$ = 10.0 Hz), 0.98 (d, Me7′, $J_{7,Me7'}$ = 10.0 Hz), 0.79 (qd, H4ax, $J_{3ax,4ax}$ = $J_{4ax,5ax}$ = 12.2 Hz, $J_{4ax,5eq}$ = 4.0 Hz), 0.70 (d, Me3, $J_{3,Me3}$ = 6.6 Hz), 0.59 (dd, H2ax, $J_{2ax,2eq}$ = 13.8 Hz, $J_{2ax,3}$ = 12.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.5 (C12a), 131.2 (C12), 130.8 (C8a), 130.1 (C9), 126.0 (C11), 123.6 (C10), 85.0 (C1), 52.3 (C6), 46.2 (C2), 41.3 (C8), 35.2 (C4), 27.6 (C3), 26.4 (C7), 24.0 (Me7′), 22.3 (Me3), 20.8 (C5), 17.7 (Me7). IR (film, cm^{-1}) 2953, 2927, 1444, 1071.

(1*R*,1″*R*,2′*S*,3′*S*,4*S*,4″*S*)-1,1″,7,7,7″,7″-Hexamethyldispiro[bicyclo[2.2.1]heptane-2,16′-2′,17′,18′,21′-tetraoxa-1′-silapentacyclo[8.7.2.2^{1,9}.0^{5,20}.0^{14,19}]henicosa-5′,7′,9′-(20′),10′,12′,14′(19′)-hexaene-3′,2″-bicyclo[2.2.1]heptane] (23). Freshly distilled tetrachlorosilane (25 μL, 0.22 mmol) was added to a solution of **8** (100 mg, 0.20 mmol), triethylamine (140 μL, 1.0 mmol), and DBU (2 μL) in dry $CHCl_3$ (4 mL) under nitrogen. The solution was refluxed 3 h, poured into water (5 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were dried over Na_2SO_4 and rotoevaporated. The residue was purified by flash chromatography (eluant CH_2Cl_2/hexanes 1:3) to obtain 80 mg (75% yield) of colorless oil: $[\alpha]_D^{23}$ −23.7 (*c* 1.4, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (dd, H11, $J_{10,11}$ = 7.6 Hz, $J_{9,10}$ = 2.5 Hz), 7.14 (dd, H10, $J_{10,9}$ = $J_{10,11}$ = 7.6 Hz), 7.12 (dd, H9, $J_{9,10}$ = 7.6 Hz, $J_{9,11}$ = 2.5 Hz), 3.66 (d, H8, $J_{8,8'}$ = 13.3 Hz), 2.46 (d, H8′), 1.73 (m, H4exo, H5 and H6exo), 1.56 (m, H3endo and H3exo), 1.44 (d, H6endo, $J_{6endo,6exo}$ = 13.1 Hz), 1.09 (s, Me7s), 1.08 (m, H4endo), 1.02 (s, Me2), 0.19 (s, Me7a); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.4, 131.7, 130.8, 130.2, 126.2 (C11), 123.8, 92.3, 54.4, 49.5, 45.0 (C5), 44.8 (C6), 38.5 (C8), 30.7 (C3), 26.8 (C4), 21.9 (Me7a), 21.4 (Me7s), 10.8 (Me2). IR (film, cm^{-1}) 2949, 2925, 1080.

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Supporting Information Available: ^{1}H- and ^{13}C-NMR spectra of compounds **7**−**11**, **13**−**19**, **21**−**23** and HMQC, HMBC, NOEDS, and NOESY of compounds **7**, **8**, **16**, **22**, and **23** (55 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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