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Asymmetric Induction by the Cholestanic Moiety on *Tropos* Species: Synthesis and Stereochemical Characterization of Bile Acid-Based Biphenyl Phosphites

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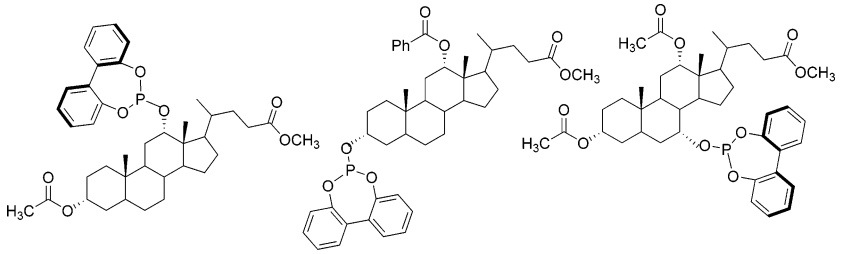

Three different bile acid-derived biphenyl phosphites were synthesized, starting from cholic and deoxycholic acids and biphenol, and their stereochemical features were checked by CD and NMR spectroscopies. On the basis of the spectroscopic results, the capability of the cholestanic system to induce a prevalent sense of twist on the biphenyl moiety of the bile acid-derived phosphites as well as their *tropos* nature was inferred.

Introduction

An elegant approach to asymmetric activation of *tropos* catalysts[1] is the diastereoisomeric control of *tropos* ligands combined with a chiral subunit, which adopts a preferential conformation of a diastereoisomeric complex.[2] According to such a concept, phosphite and phosphoramidite ligands based on a chiral unit and a *tropos* biphenol moiety have been employed in asymmetric hydrogenation[3] and hydroformylation,[4] in the rhodium-catalyzed conjugate addition of phenylboronic acid,[5] and in the copper-catalyzed conjugate addition of dialkylzinc reagents[6] to induce high enantioselectivities. Their success lies in the capability of the configurationally stable unit to induce a prevalent screw sense in the flexible moiety: this guarantees the presence of a largely prevailing diastereoisomer and hence the achievement of high ee's.

Recently, we have demonstrated that good levels of asymmetric induction can be reached in the copper-catalyzed conjugate addition of dialkylzincs to enones using deoxycholic acid-based binaphthyl phosphites.[7] The enantioselectivity of the reaction depended on the absolute configuration of the binaphthyl moiety as well as on its position on the cholestanic backbone, suggesting that the cholestanic structure plays a fundamental role in the asymmetric induction.[7] Prompted by these results, we became interested in investigating the capability of the cholestanic moiety to induce a prevalent screw sense on the *tropos* unit of biphenyl phosphite, to obtain bile acid-based biphenyl phosphites to be used in asymmetric catalysis. Bile

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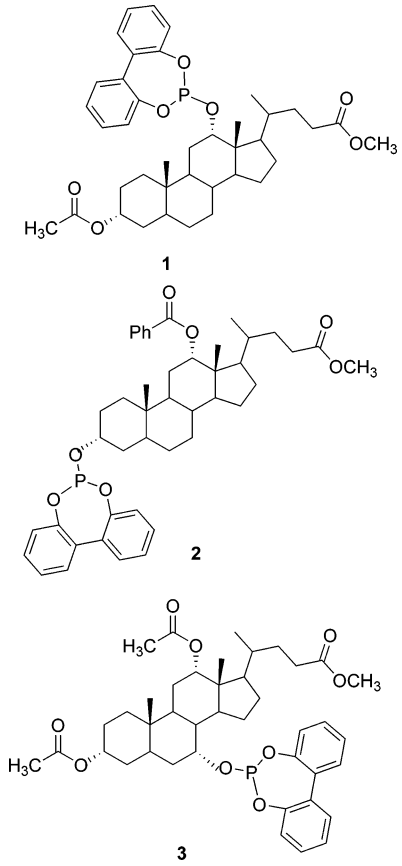

FIGURE 1. Structures of phosphites **1**−**3**.

acids possess two (deoxycholic acid) or three (cholic acid) different hydroxyl substituted positions, at which the biphenyl phosphite moiety can be linked to obtain different phosphites. Because these positions are in stereochemically different environments, the asymmetric induction exerted by the cholestanic moiety upon the *tropos* unit could depend on the position at which this unit is linked as far as both sense of twist of the biphenyl moiety and extent of its prevalence are concerned. Therefore, deoxycholic acid-derived phosphites **1** and **2** and cholic acid-derived phosphite **3** (Figure 1) were synthesized and their stereochemical features were assayed by circular dichroism (CD) and NMR spectroscopies.

Results and Discussion

Synthesis of Phosphites. The synthesis of the deoxycholic acid-derived phosphites **1** and **2**, performed according to the method used for synthesizing the analogous deoxycholic acid-based binaphthyl phosphites,[7] is summarized in Scheme 1.

To obtain **1**, bearing the biphenyl phosphite moiety at the position 12 of the cholestanic skeleton, protection of both carboxylic and 3-OH functions was required. This double protection was realized in one step by reacting deoxycholic acid with methyl acetate in the presence of *p*-toluensulfonic acid and water,[8] obtaining the 3-acethoxymethylcholate in good yield because under these experimental conditions 12-OH did not react. Derivative **1** was obtained in 70% yield after chromatographic purification, by reacting **5** with biphenylchlorophosphite, obtained by standard procedures, in the presence of triethylamine and DMAP.[9] The synthesis of derivative **2** required protection of 12-OH. Because this hydroxyl group is less reactive than 3-OH, its selective protection was not possible. However, selective deprotection of the 3-OH group is obtained easily because of its higher reactivity; therefore, compound **5** was reacted with benzoyl chloride,[10] to obtain **6**, from which the desired derivative **7**, having protected 12-OH and free 3-OH, was obtained after removing the acetyl group under mild acidic conditions that does not hydrolyze the 12-benzoate.

Phosphite **2** was then obtained in 76% yield after chromatographic purification, by reacting **7** with biphenylchlorophosphite in the presence of triethylamine and DMAP.[7]

The synthetic route to the cholic acid-derived phosphite **3** is outlined in Scheme 2. Selective introduction of the biphenyl phosphite moiety at the position 7 of the cholestanic backbone requires protection of both the 3- and 12-OH groups. Because both 12- and 7-OH are axial, their reactivity is very similar, and hence, direct selective protection of 12-OH was not possible. However, selective protection of the 7-hydroxy group can be accomplished by means of its regioselective oxidation with NBS:[11] in fact, it is well-known that the reduction with $NaBH_4$ of the carbonyl function takes place with complete stereoselectivity, the stereogenic center being restored to the same absolute configuration as that in cholic acid.[10] Therefore, **9**, obtained by treating cholic acid with methyl acetate in the presence of *p*-toluenesulfonic acid and water, was reacted with NBS in acetone, giving **10**, which was acetylated at the 12-position by means of acetic anhydride in the presence of triethylamine. The reaction of **11** with $NaBH_4$ in THF−MeOH afforded in quantitative yield the desired cholic acid derivative **12** having protected both 3- and 12-OH. By reacting **12** with biphenylchlorophosphite under the same conditions used for preparing **1** and **2**, phosphite **3** was obtained in 40% yield after chromatographic purification.

Stereochemical Characterization. A. Circular Dichroism Measurements. The circular dichroism (CD) spectroscopy in the UV region represents the most suitable way to determine not only the capability of the cholestanic moiety to induce a prevalent screw sense to the biphenyl unit but also its sense of twist in the phosphites **1**−**3**. In fact, the only absorbing chromophore in the wavelength region between 300 and 230 nm is the substituted biphenyl moiety,[12] and Cotton effects in this region can be present only if this moiety, linked to the bile acid system, is twisted in a prevalent screw sense.[12] In addition, the sign of the Cotton effects will depend only on the sense of twist of the biphenyl unit, given that the same biphenyl phosphite chromophore is present in the three phosphites.

The UV spectrum of **1** (Figure 2) shows two absorption bands, the first one at 280 nm (ϵ 8000) and the second one at 250 nm (ϵ 19000), attributable to the electrically dipole-allowed transitions of the substituted biphenyl moiety.[12] The CD spectrum shows two positive Cotton effects corresponding to the UV absorption bands, at 280 nm ($\Delta\epsilon$ 1) and at 250 nm ($\Delta\epsilon$ 4.3). The presence of these Cotton effects indicates that the electrically dipole-allowed transitions of the biphenyl chromophore are optically active, and hence, the biphenyl group is twisted in a prevalent screw sense. This means that the

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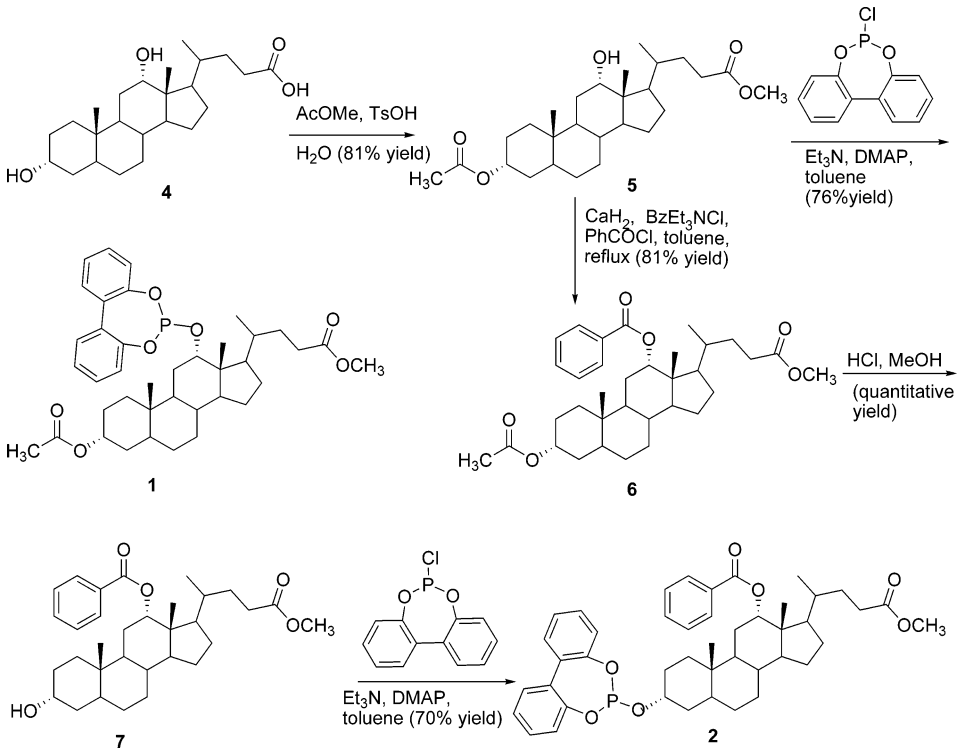
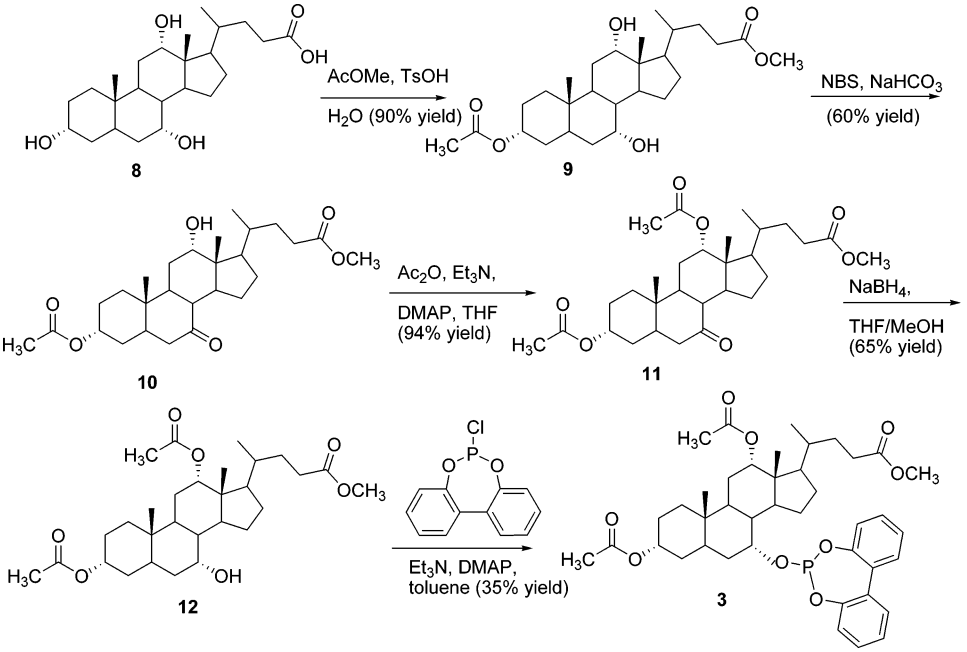
SCHEME 1. Synthesis of Phosphites 1 and 2



SCHEME 2. Synthesis of Phosphite 3



cholestanic system is able to induce a prevalent sense of twist to the biphenyl unit when the biphenyl phosphite moiety is linked at the 12-position of the deoxycholic acid.

The UV spectrum of phosphite **2** (Figure 3) is very similar to the UV spectrum of **1**, as far as number, position, and intensity of the absorption bands are concerned in the 300−240 nm wavelength region; by contrast, the CD spectrum (Figure 3) is very different with respect to the CD spectrum of **1** because it is lacking of any Cotton effect in the wavelength region between 300 and 240 nm. A negative CD band is present at 230 nm ($\Delta\epsilon$ −5), attributable to the transition of the benzoate chromophore,[13] which is optically active because this group is linked to a stereogenic center. The lack of CD bands in the 300−240 nm region means that the transitions of the biphenyl chromophore are not optically active, and hence, the biphenyl moiety of **2** is not twisted in a prevalent screw sense.

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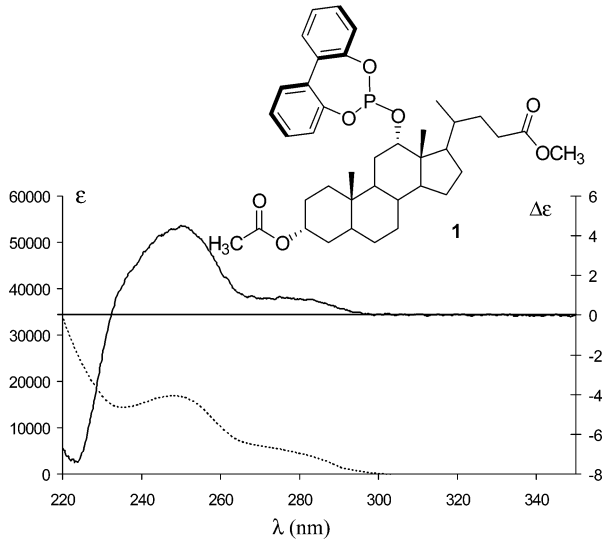

FIGURE 2. Absorption (dotted line) and CD (solid line) spectra of **1**.

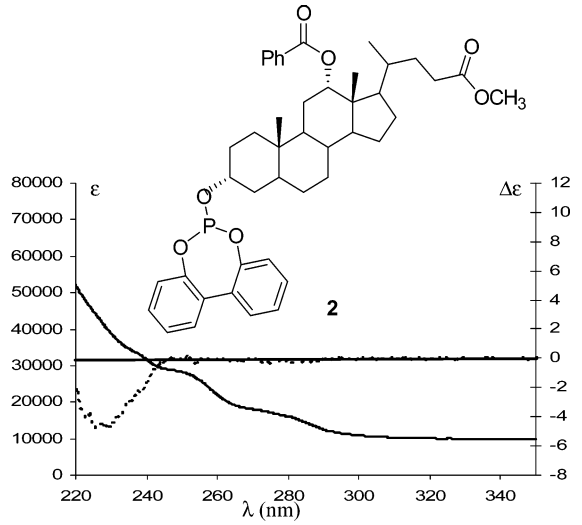

FIGURE 3. Absorption (solid line) and CD (dotted line) spectra of **2**.

The UV spectrum of **3** (Figure 4), as expected, is very similar to the UV spectrum of phosphite **1**, as far as number, position, and intensity of the absorption bands are concerned. The CD spectrum (Figure 4) shows two negative Cotton effects at 280 ($\Delta\epsilon$ −1) and 250 nm ($\Delta\epsilon$ −4.3) and is in an enantiomeric relationship with the CD spectrum of **1**. Therefore, the biphenyl unit of phosphite **3** is twisted in a prevalent screw sense, which is opposite to the sense of twist of the biphenyl moiety of **1**, as the opposite sign of the Cotton effects suggests; furthermore, the extent of the prevalence must be similar to that of phosphite **1**, as indicated by the similar intensity of the CD bands.

This means that the cholestanic moiety is able to induce a prevalent sense of twist to the biphenyl unit also when the biphenyl phosphite system is linked at the 7-position of cholic acid.

The sense of twist of the biphenyl unit of phosphites **1** and **3** was determined by comparison of the experimental CD spectra of **1** and **3** with theoretical CD spectra generated by Gaussian 03[14] for the methylbiphenyl phosphite having P-torsion, assumed as the model compound. The molecular geometry adopted for these calculations was obtained from the geometry optimization

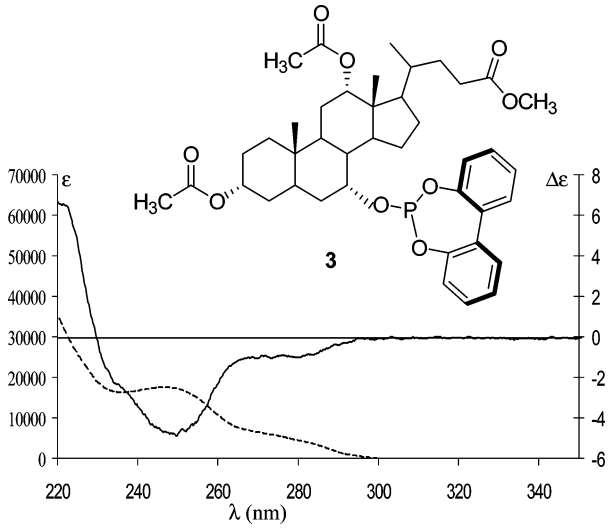

FIGURE 4. Absorption (dotted line) and CD (solid line) spectra of **3**.

using the MMFF94s force field by the Spartan 02 package[15] and was fully optimized at the DFT/B3LYP/631G* level.

The rotatory strengths for the lowest-energy 30 excited states were calculated using the time-dependent density functional theory (TDDFT) with the B3LYP hybrid functional and the 6-31G* basis set. The rotatory strengths were obtained using the dipole-length formalism as well as the dipole-velocity formalism. The calculated CD spectra in de units were obtained using overlapping Gaussian functions.[16]

It is noteworthy that the CD spectra calculated with the two formalisms are almost coincident: this guarantees that the molecular wave functions used are of good quality. The calculated CD spectra show, in the region 300−240 nm wavelength, a large negative band, which is likely originated by the superimposition of two negative CD bands, corresponding to those observed in the experimental spectrum of **3**, which is qualitatively reproduced. By comparing the calculated CD spectra for the methylbiphenyl phosphite having P-torsion (Figure 5) with the experimental CD spectra of phosphites **1** and **3** (Figures 2 and 4), we can infer a prevalent M-torsion for the biphenyl unit of **1** and a prevalent P-torsion for the biphenyl unit of **3**.

B. NMR Measurements. Once we determined the sense of twist of the biphenyl unit of both phosphites **1** and **3**, two questions remained open, one concerning the extent of the prevalence of the screw sense, and the other concerning the

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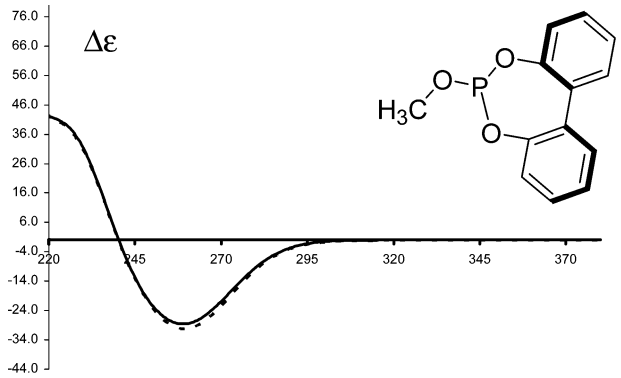

FIGURE 5. Calculated CD spectra from the dipole-length formalism (dotted line) and dipole-velocity formalism (solid line) of methyl-biphenyl phosphite having P torsion.

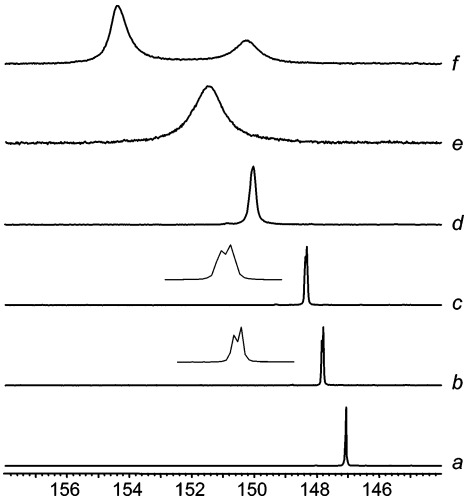

FIGURE 6. ^{31}P NMR (121.4 MHz, CD_2Cl_2) spectra of **2** at: (a) 25 °C, (b) 0 °C, (c) −10 °C, (d) −40 °C, (e) −60 °C, and (f) −80 °C.

tropos nature of phosphites **1**−**3**. In fact, the asymmetric induction of the cholestanic system on the flexible biphenyl unit could result either in the formation of two diastereoisomeric stable species or in the existence of rapidly interconverting M−P diastereoisomers.

Satisfactory answers to these questions came from NMR investigations, involving variable-temperature ^{31}P NMR and NOE measurements. ^{31}P NMR analyses were carried out in CD_2Cl_2 and in DMSO-d_6, allowing us to perform low- and high-temperature measurements, respectively; dipolar interactions were detected by NOE measurements in C_6D_6 as solvent, in which a good spectral resolution was obtained. On the hypothesis that only diastereoisomeric species could be distinguished in the NMR spectra, the three derivatives were expected to produce very simple ^{31}P NMR spectra, containing one to two signals due to the two possible M and P forms.

The presence of two species of **2** was clearly established on the basis of the variable-temperature profile of its ^{31}P NMR spectra (Figure 6). As a matter of fact, already, at 0 °C, two partially superimposed broad resonances were detected at 147.9 and 147.8 ppm, the integrated areas of which were very similar. At −40 °C, the two resonances were completely superimposed, and at −80 ° C, two well-separated signals were detected at 154.4 and 150.3 ppm, the integrated areas of which, respectively, were in the ratio 65:35. The above-described spectral pattern is

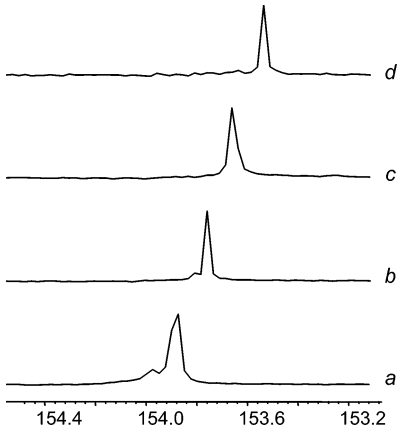

FIGURE 7. ^{31}P NMR (121.4 MHz, DMSO) spectra of **3** at: (a) 25 °C, (b) 40 °C, (c) 60 °C, and (d) 70 °C.

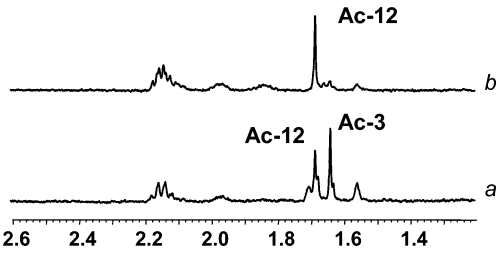

FIGURE 8. 1D NOE spectra (600 MHz, C_6D_6, 25 °C) of **3** corresponding to the selective excitation at: (a) 7.23 ppm and (b) 7.18 ppm.

in keeping with the presence of two interconverting M−P stereoisomers, which are equally populated at room temperature. At −80 °C, the two slowly interconverting species give rise to a 30% prevalence of one on the other.

Derivative **3** showed a completely different spectral pattern of ^{31}P NMR resonances: two well-separated resonances were detected between 25 and −80 °C (Figure S1, Supporting Information). The ratio of their integrated areas was 90:10, which did not undergo any change within the above said temperature range. These two signals were attributed to slowly interconverting M−P diastereomeric species on the basis of the variable-temperature profile within the range 25−70°C. The resonances approach each other on rising of the temperature and coalesce at 70 °C (Figure 7).

Therefore, the presence of a largely prevalent stereoisomeric form of **3** is confirmed, the structure of which was ascertained by 1D NOE measurements in C_6D_6 at room temperature. Very useful in this regard was the comparison between NOE patterns of the two aromatic protons of biphenyl rings, which are adjacent to phosphite oxygens.

The two protons gave well-separated doublets centered at 7.23 ppm (Ha) and 7.18 ppm (Hb). The higher-frequency shifted aromatic proton Ha originated dipolar interactions with both acetyl moieties at 1.68 and 1.64 ppm (Figure 8a), at the C12 and C3 sites, respectively, whereas the aromatic proton centered at 7.18 ppm (Figure 8b) selectively produced NOEs at the frequency of the acetyl methyl at 1.68 ppm, which is directly bound to the C12 carbon atom.

Therefore, the biphenyl plane lies almost perpendicular to the cholestanic skeleton (Figure 9) on the same side of the two acetyl moieties and in a well-defined conformation with respect to them: proton Ha points at the spatial region between the

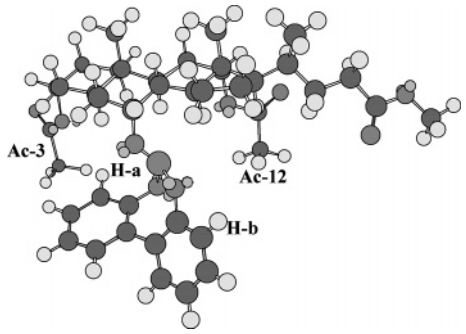

FIGURE 9. Representation of **3** corresponding to NOE data.

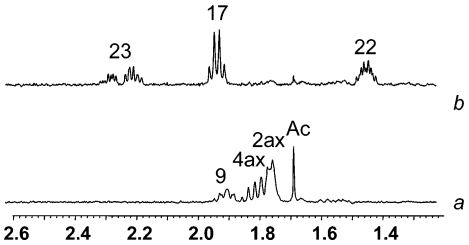

FIGURE 10. 1D NOE spectra (600 MHz, C_6D_6, 25 °C) of **1** corresponding to the excitation at: (a) 7.37 ppm and (b) 7.31 ppm.

two acetyl functions, whereas Hb is directed toward the C12 site and partially directed at the external of the cholestanic plane. Remarkably different NOE dipolar interactions of Ha and Hb are in keeping with a strong degree of conformational preference, as expected on the basis of the presence of a largely prevalent stereoisomeric form.

The ^{31}P NMR spectrum of **1** showed only one resonance between 25 and −80 °C (Figure S2, Supporting Information), the presence of which could be interpreted as being due to a single diastereoisomer or two rapidly interconverting stereoisomeric forms, with a very high prevalence of one of them. Dipolar interaction patterns detected by 1D NOE measurements unequivocally pointed out the presence of a largely prevalent conformation. As a matter of fact, in the ^{1}H NMR spectrum, the two aromatic protons of **1**, adjacent to the phosphite oxygen atoms, showed well-separated doublets centered at 7.31 ppm, named Hb, and at 7.37 ppm, named Ha. The proton at 7.31 ppm produced NOE effects (Figure 10b) only with the side-chain protons H22 and H23, in addition to a relevant effect on H17. A very low dipolar interaction is also detected at the H12 frequency. The other aromatic proton centered at 7.37 ppm (Figure 10a) originated dipolar interactions with completely different cholestanic protons. As a matter of fact, relevant effects were measured at the protons H2 and H4, which are in pseudoaxial position; a dipolar interaction was also detected at the H9 frequency and on the acetyl group. Therefore, a largely prevailing conformation of **1** was detected in solution, in which the biphenyl plane and the cholestanic skeleton are almost perpendicular, as depicted in Figure 11.

These results definitively point out the *tropos* nature[17] of phosphites **2** and **3**. They exist in solution as interconverting M−P diastereoisomeric mixtures, and the interconversion barrier has been evaluated on the basis of the variable-temperature NMR measurements,[18] at about 15 kcal/mol for **2** and 18 kcal/mol for **3**. The equilibrium is strongly shifted toward one diastereoisomer in the case of **3**, whereas a 1:1 ratio of the two forms is found for **2**.

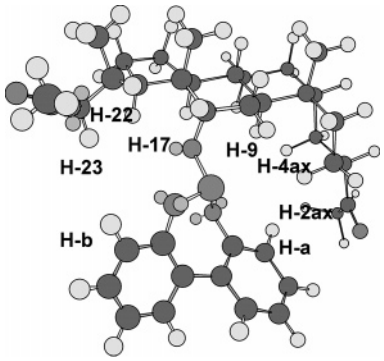

FIGURE 11. Representation of **1** corresponding to NOE data.

Dependence of the Screw Sense on the Solvent. The NMR data did not allow us to gain any insight into the *tropos* nature of **1**, which was ascertained in a different way.

Preliminary results showed that the use of **1** as a chiral ligand in the copper-catalyzed addition of diethylzinc to chalcone gave moderate ee's of the product having an *S* absolute configuration.[19] In an attempt to improve the extent of the asymmetric induction, different reaction conditions were screened. As far as the reaction solvent was concerned, we observed a reverse asymmetric induction in passing from toluene, Et_2O, and CH_2Cl_2 to THF.[19]

This was judged a very unusual result, perhaps due to a change of screw sense of the biphenyl moiety in passing from toluene, acetonitrile (ACN), etc. to THF because the sense of asymmetric induction in the reaction promoted by bile acid-based biaryl phosphite depended on the absolute configuration of the biaryl moiety. To verify this hypothesis, a CD spectrum of **1** in THF solution was measured. This CD spectrum (Figure 12) shows in the wavelength region of the biphenyl absorptions two negative Cotton effects at 280 nm ($\Delta\epsilon$ −0.4) and at 240 nm ($\Delta\epsilon$ −1.5), suggesting a prevalent P-torsion for the biphenyl unit of **1**. The lower intensity of these CD bands with respect to those observed in the spectrum measured on the ACN solution can be attributed both to a lower prevalence of one sense of twist, which should explain the lower ee obtained using THF as reaction solvent,[19] and to a different dihedral angle between the two aromatic rings in passing from ACN to THF solution. Anyway, the dependence of the screw sense of the biphenyl unit of **1** on the solvent points out its *tropos* nature and represents an unusual behavior, found, to the best of our knowledge, only in very few cases[20] and never observed with biphenyl phosphites.[21] In addition, this happens only in the case of phosphite **1**: in fact, the sense of twist of the biphenyl unit

(17) Oki, M.; Yamamoto, G. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 266−270. Oki, M. *Top. Stereochem.* **1983**, *14*, 1−81.

(18) Binsch, G. In *Band-Shape Analysis in Dynamic Nuclear Magnetic Resonance Spectroscopy*; Jackman, L. M., Cotton, F. A., Eds.; Academic Press: New York, 1975; pp 45−81.

(19) The reactions were performed under the following conditions:[7] 1 mol of chalcone, 1.5 mol of $ZnEt_2$, ligand-to-copper ratio of 1.2, $Cu(OTf)_2$ as copper salt (2.5% mol), temperature of −50 °C. Using toluene as solvent, (*S*)-1,3-diphenylpentan-1-one was obtained in 89% yield and 44% ee. Using THF as reaction solvent, (*R*)-1,3-diphenylpentan-1-one was obtained in 55% yield and 35% ee. Work, aimed at optimizing reaction conditions, is in progress. These results together with some others concerning the use of different biphenyl phosphites of bile acids as chiral ligands will be reported in due course.

(20) Eguchi, T.; Kondo, K.; i Kakinuma, K.; Uekusa, H.; Ohashi, Y.; Mizoue, K.; Qiao, Y.-F. *J. Org. Chem.* **1999**, *64*, 5371−5376.

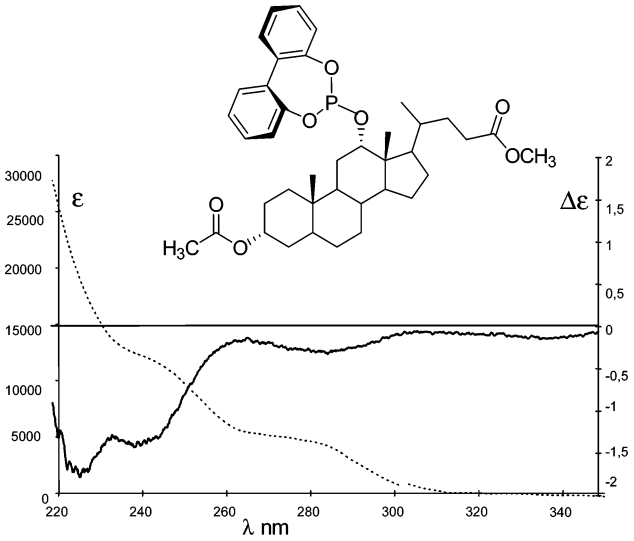

FIGURE 12. Absorption (dotted line) and CD (solid line) spectra of **1** in THF solution.

does not depend on the solvent in the case of phosphite **3**, which shows the same CD spectrum both in ACN and in THF, due to the higher interconversion barrier.

Conclusions

The cholestanic moiety of cholic and deoxycholic acids was capable of inducing a prevalent sense of twist to the biphenyl phosphite moiety linked at the 3, 7, and 12 positions of the steroidal backbone. The asymmetric induction exerted by the bile acid system deeply depends on the position of the appended biphenyl phosphite moiety. As a matter of fact, the CD analysis showed that at room temperature a prevalent sense of twist of the biphenyl unit is present in the case of **1** and **3**, where the biphenyl phosphite appendage is located at the more stereochemically demanding 7 and 12 positions. In addition, the sense of twist is opposite, being M for the biphenyl unit of **1** and P for that of **3**, as assayed by comparison of the experimental CD spectra of **1** and **3** with the calculated CD spectrum for the biphenyl phosphite fragment having P-torsion. By contrast, no prevalence of one screw sense is observed, at room temperature, in the case of phosphite **2**, where the biphenyl phosphite moiety is linked at the position 3 of the cholestanic backbone. The bile acid moiety is capable of exerting asymmetric induction on the sense of twist of the biphenyl unit of the biphenyl phosphite appendage linked at the position 3 at low temperature (−80 °C), affording a prevalence (65:35) of one diastereoisomer on the other. NMR analysis showed a high prevalence (90:10) of the P diastereoisomer in the case of phosphite **3** and a very large prevalence (>99%) of the M diastereoisomer in the case of phosphite **1**. The three bile acid-derived biphenyl phosphites **1**−**3** are all *tropos* species. The *tropos* nature of **2** and **3**, which show an interconversion M−P barrier of 15 and 18 kcal/mol, respectively, was ascertained by variable-temperature NMR measurements. Phosphite **1** showed an unusual dependence of the sense of twist of the biphenyl moiety on the solvent that definitively pointed out its *tropos* nature: the equilibrium M−P is shifted toward the M form in ACN and toward the P form in THF. The achievement of a bile acid-based biphenyl phosphite having opposite screw sense depending on the solvent represents an important result, as far as its use as a chiral ligand in the copper-catalyzed conjugate addition of diethylzinc to enones. In fact, the *tropos* nature of phosphite **1**, joined to a low interconversion M−P barrier of its biphenyl moiety, which determines the dependence of its sense of twist on the solvent, will allow the different enantiomers of the same product to be obtained using the same chiral inducer, simply by changing the reaction solvent.

(21) A dependence of the *tropo*-inversion kinetics on the solvent has been found in the case of the DABN−BIPHEP−Rh complex: Mikami, K.; Kataoka, S.; Yusa, Y.; Aikawa, K. *Org. Lett.* **2004**, *6*, 3699−3701.

Experimental Section

General experimental details can be found in the Supporting Information.

Methyl 3α-Acetyloxy-7-oxo-12α-hydroxy-5*β*-cholan-24-oate, 10. A solution of **6** (5.2 g, 11.2 mmol), NBS (1.25 equiv), and water (70 mL) in acetone (100 mL) was stirred overnight at room temperature. The solvent was evaporated in vacuo, and the product was dissolved in CH_2Cl_2. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent in vacuo followed by purification by flash chromatography (SiO_2, CH_2Cl_2−acetone, 95:5) gave 3.2 g (60% yield) of pure product.

Mp: 166−168°C; $[\alpha]^{26}_D$= +14.0 (c = 1.05, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 0.69 (s, 3H), 0.98 (d, J = 6.0 Hz), 1.18 (S, 3H), 2.04 (s, 3H), 0.8−2.5 (m, 24H), 2.85 (dd, J_1 = 7 Hz, J_2 = 6 Hz, 1H), 3.67 (s, 3H), 4.02 (m, 1H), 4.68 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 13.1, 17.7, 21.5, 23.1, 24.5, 26.2, 27.8, 29.5, 31.1, 31.3, 33.4, 34.0, 34.9, 35.1, 36.2, 41.0, 45.4, 46.0, 46.8, 46.9, 49.7, 51.7, 72.3, 73.1, 170.8, 174.8, 211.3. IR (KBr, cm^{-1}): 3552, 2950, 2871, 2358, 2343, 1738, 1721, 1700, 1436, 1380, 1365, 1260, 1170, 1025. Anal. Calcd for $C_{27}H_{42}O_6$: C, 70.10; H, 9.15; O, 20.75. Found: C, 69.85; H, 9.20.

Methyl 3α,12α-Diacetyloxy-7-oxo-5*β*-cholan-24-oate, 11. A solution of **10** (2.2 g, 4.75 mmol), acetic anhydride (3 equiv), Et_3N (1.5 equiv), and catalytic DMAP in dry THF was stirred at room temperature overnight. The solvent was evaporated in vacuo, and the product was dissolved in CH_2Cl_2. The organic layer was washed with a 10% HCl solution, saturated $NaHCO_3$ solution, and water in that order, then dried over anhydrous Na_2SO_4. Evaporation of the solvent gave **11** as a white solid (2.25 g, 4.46 mmol, 94% yield).

$[\alpha]^{26}_D$ = +33.8 (c = 1.47, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 0.71 (s, 3H), 0.79 (d, J = 5.8 Hz, 3H), 1.15 (s, 3H), 1.96 (s, 3H), 2.19 (s, 3H), 1.0−2.5 (m, 23H), 2.84 (dd, J_1 = 6.6 Hz, J_2 = 6.3 Hz, 1H), 3.64 (s, 3H), 4.65 (m, 1H), 5.08 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 12.7, 17.8, 21.4, 21.5, 22.4, 23.0, 24.3, 26.3, 26.6, 27.7, 31.1, 31.2, 33.4, 33.8, 34.8, 34.9, 37.1, 42.2, 45.2, 45.3, 46.0, 47.0, 49.4, 51.7, 73.0, 74.9, 170.6, 170.7, 174.7, 211.3. IR (KBr, cm^{-1}): 2964.0, 2877.5, 1826.0, 1735.6, 1711.6. Anal. Calcd for $C_{29}H_{44}O_7$: C, 69.02; H, 8.79; O, 22.19. Found: C, 68.92; H, 8.85.

Methyl 3α,12α-Diacetyloxy-7α-hydroxy-5*β*-cholan-24-oate, 12. A solution of **11** (1.89 g, 3.75 mmol), $NaBH_4$ (0.22 g, 5.25 mmol), and dry THF (4 mL) in 20 mL of methanol was stirred at room temperature, and the reaction was followed by TLC. After disappearance of the starting material, the solvent was evaporated in vacuo, and the product was dissolved in CH_2Cl_2. The organic layer was washed with $NaHCO_3$, brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by chromatographic purification (SiO_2, CH_2Cl_2−acetone, 96:4) gave **12** as a white solid (1.24 g, 2.45 mmol, 65% yield).

Mp: 145−146°C. $[\alpha]^{24}_D$ = +71.9 (c = 1.01; CH_2Cl_2). ^{1}H NMR (200 MHz, DCl_3, δ): 0.72 (s, 3H), 0.79 (d, J = 5.8 Hz, 3H), 0.87 (s, 3H), 1.97 (s, 3H), 2.06 (s, 3H), 0.9−2.34 (m, 25H), 3.64 (s, 3H), 3.85 (m, 1H), 4.54 (m, 1H), 5.07 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$, δ): 12.2, 17.4, 21.4, 21.4, 22.5, 22.9, 25.4, 26.7, 27.2, 27.6, 30.7, 30.9, 34.3, 34.5, 34.6, 35.2, 39.2, 41.1, 43.4, 45.0, 47.4, 51.5, 68.0, 74.2, 75.4, 170.5, 170.6, 174.5. IR (KBr, cm^{-1}): 3545.8,

2941.7, 2874.3, 1747.8, 1782.7, 1715.8. Anal. Calcd for $C_{29}H_{46}O_7$: C, 68.74; H, 9.15; O, 22.10. Found: C, 68.85; H, 9.07.

Preparation of the Phosphites: Representative Procedure. A warm solution (60°C) of 2,2′-biphenol (382 mg, 2.05 mmol) in dry toluene (25 mL) was added in 5 min to a cooled solution (−60°C) of PCl_3 (184.5 μL, 2.05 mmol) and Et_3N (587.6 μL, 4.1 mmol), in dry toluene (5 mL). After 2 h of stirring, the reaction mixture was warmed to room temperature and filtered under argon atmosphere. The solution was dropwise added to a solution of DMAP (0.095 g, 0.78 mmol) and Et_3N (1.05 mL, 7.29 mmol) in dry toluene (50 mL) at −60 °C over 2 h. The bile acid derivative (2.05 mmol) was then added, and the mixture was allowed to warm to room temperature and stirred for 20 h. After removing the solvent at reduced pressure, the crude product was purified by column chromatography (SiO_2, CH_2Cl_2−acetone, 96:4), affording the pure phosphite.

Methyl 3α-Acetyloxy-12α-(biphenyl-2,2′-diyl)phosphite-5*β*-cholan-24-oate, 1. 1.1 g (1.66 mmol, 76%).

Mp: 42−43°C. $[\alpha]^{25}_D = +47.22$ ($c = 1.025$, CH_2Cl_2). ^{1}H NMR (200 MHz, benzene-d_6, δ): 0.55 (s, 3H), 0.82 (s, 3H), 1.18 (d, $J =$ 6.1 Hz, 3H), 1.80 (s, 3H), 0.78−2.33 (m, 26H), 3.42 (s, 3H), 4.66 (m, 1H), 4.92 (m, 1H), 7.0−7.5 (m, 8H). ^{13}C NMR (50 MHz, benzene-d_6, δ): 12.4, 17.8, 17.8, 21.0, 23.0, 23.8, 26.2, 26.9, 27.3, 27.8, 28.9, 29.0, 31.2, 31.3, 32.6, 33.6, 34.3, 35.2, 36.0, 36.0, 41.9, 46.6, 46.7, 46.8, 47.8, 51.0, 74.1, 78.5, 78.9, 122.5, 125.2, 125.3, 125.6, 128.3, 129.2, 130.4, 131.9, 133.9, 150.2, 150.3, 150.5, 150.6, 169.6, 173.8. ^{31}P NMR (121 MHz, benzene-d_6, δ): 154.8. IR (KBr, cm^{-1}): 2934.3, 1734.3, 1247.7, 1027.6, 895.5. Anal. Calcd for $C_{40}H_{54}O_7P$: C, 70.88; H, 8.03; O, 16.52; P, 4.57. Found: C, 71.02; H, 8.01; P, 4.55.

Methyl 3α-(Biphenyl-2,2′-diyl)phosphite-12α-benzoyloxy-5*β*-cholan-24-oate, 2. 1.13 g (1.56 mmol, 70%).

Mp: 43−45°C. $[\alpha]^{18}_D = -69.58$ ($c = 1.075$, CH_2Cl_2). ^{1}H NMR (200 MHz, benzene-d_6, δ): 0.65 (s, 3H), 0.74 (s, 3H), 1.05 (d, $J =$ 5.8 Hz, 3H), 0.62−2.12 (m, 26H), 3.36 (s, 3H), 4.21 (m, 1H), 5.59 (m, 1H), 6.97−7.27 (m, 11H), 8.34 (m, 2H). ^{13}C NMR (50 MHz, benzene-d_6, δ): 12.7, 17.7, 22.9, 22.9, 23.7, 26.2, 26.3, 27.0, 27.6, 29.6, 31.0, 33.8, 34.8, 35.1, 35.6, 35.9, 42.0, 45.7, 48.3, 50.5, 50.9, 75.7, 75.8, 76.2, 122.2, 122.3, 125.0, 125.6, 128.3, 128.9, 129.3, 129.6, 130.2, 131.5, 131.6, 131.6, 131.7, 131.8, 133.0, 150.4, 150.5, 150.7, 150.8, 165.8, 173.6. ^{31}P NMR (121 MHz, benzene-d_6, δ): 142.3. IR (KBr, cm^{-1}): 2946, 2866.3, 1738.1, 1712.6, 1601.4, 1583.8, 1567.7, 1498.8, 1476.0, 1499.9, 1435.7, 1370.3, 1328.4, 1272.3, 1248.3, 1186.6, 1112.1, 1010.0, 992.0, 894.7, 764.0, 712.0. Anal. Calcd for $C_{45}H_{56}O_7P$: C, 73.05; H, 7.63; O, 15.14; P, 4.19. Found: C, 73.12; H, 7.61; P, 4.18.

Methyl 3α,12α-Diacetyloxy-7α-(biphenyl-2,2′-diyl)phosphite-5*β*-cholan-24-oate, 3. 0.49 g (0.68 mmol, 35%).

Mp: 65−67°C. $[\alpha]^{25}_D = +35.5$ ($c = 1.09$, CH_2Cl_2). ^{1}H NMR (200 MHz, benzene-d_6, δ): 0.58 (s, 3H), 0.62 (s, 3H), 0.96 (d, $J =$ 5.9 Hz, 3H), 1.78 (s, 3H), 1.83 (s, 3H), 0.54−2.27 (m, 24H), 3.41 (s, 3H), 4.37 (m, 1H), 4.70 (m, 1H), 5.23 (m, 1H), 6.99−7.35 (m, 8H). ^{13}C NMR (50 MHz, benzene-d_6, δ): 12.4, 17.7, 20.7, 21.2, 22.4, 23.2, 23.3, 25.5, 27.1, 27.5, 27.8, 31.1, 31.2, 34.0, 34.5, 34.9, 35.0, 35.4, 37.3, 39.7, 41.2, 43.0, 45.3, 47.7, 50.9, 73.1, 73.5, 74.0, 75.1, 122.5, 122.6, 125.0, 125.2, 126.3, 129.2, 130.2, 131.8, 150.1, 169.5, 169.6, 173.7. ^{31}P NMR (121 MHz, benzene-d_6, δ): 153.8 (major diastereoisomer), 154.7 (minor diastereoisomer). IR (KBr, cm^{-1}): 2945.5, 1733.9, 1498.9, 1475.9, 1436.1, 1377.9, 1249.6, 1097.2, 1024.3, 892.1, 851.5, 770.6, 702.1, 602.2, 518.4. Anal. Calcd for $C_{42}H_{56}O_9P$: C, 68.55; H, 7.67; O, 19.57; P, 4.21. Found: C, 68.42; H, 7.69; P, 4.19.

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Supporting Information Available: General experimental details and ^{31}P NMR spectra of **1** and **3** at variable temperature. This material is available free of charge via the Internet at http://pubs.acs.org.

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