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Steric vs Hydrogen-Bonding Control of Atropisomerization: Preparation of Either Diastereomer of Configurationally Stable Allocolchicinoids

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Steric vs hydrogen-bonding atropisomerization control of configurationally stable analogues of the biaryl natural product allocolchicine is described. Intramolecular hydrogen bonding between the C8 hydroxy group and the C7 oxygen functionality in (a*R**,7*R**)-diastereomer **II** of **2** and **4** leads to its thermodynamic stabilization relative to the opposite diastereomer (a*R**,7*S**)-**I**, which is manifested by the strong preference toward **II** under thermal equilibration conditions (>94% de). Protection of C8-OH removes the H-bonding and results in repulsive interaction between C7 and C8 functionalities, which destabilizes **II**. Steric tuning of the C8 protecting group in **7**−**12** allows for almost complete inversion of the axial configuration in **2** under thermal equilibration conditions (>96% de toward **I**). Previously unavailable phenolic allocolchicinoids (a*R**,7*S**)-**2**,**I** are subsequently released by deprotection.

Introduction

During the past decade the field of asymmetric catalysis has experienced explosive growth,[1] thus fueling the development of novel ligands with great structural diversity. The success of ligands possessing a chiral biaryl backbone,[2] the discovery of numerous biologically active natural products[3] with axially chiral structural motifs, and advances in helical polymers[4] have inspired the development of effective methods for the generation and control of axial chirality.[5] Aside from the conventional resolution of racemic mixtures,[6] numerous atropisomer-selective approaches have been recently reported.[7,8] These can be formally divided into two groups on the basis of the intermolecular or intramolecular nature of the asymmetric induction. The first group[7] relies upon the participation of a chiral nonracemic additive: kinetic[7a] and dynamic kinetic[7b,c] resolution of racemic substrates, desymmetrization of prochiral biaryls,[7d,e] and asymmetric coupling.[7e−k] Among these, catalytic asymmetric processes[7e−i] are the most convenient, but their efficiency and stereochemical outcome are mitigated by the great extent of their substrate dependence. All chirality-transfer methods belong to the second group.[8] Here, axial chirality is induced from the existing central,[8a−f] axial,[8g] or planar[8h−j] asymmetry present in the substrate, which either is available from the pool of chiral compounds or can be efficiently installed by known methods. This approach is especially valuable when such directing

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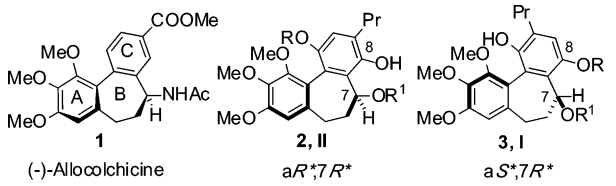


FIGURE 1. (−)-Allocolchicine and its configurationally stable analogues.

functionality is part of the target molecule,[8a] since installation and subsequent removal of the chiral auxiliary[8b,c] are disadvantageous. Stereoselective intramolecular group migration[8a] and coupling reactions of planar chiral arene chromium tricarbonyl complexes[8i] can serve as examples of nearly complete atropselectivity.

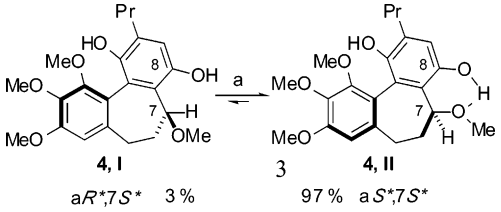
We have recently reported[9] a unique central-to-axial chirality transfer at the time of arene ring formation in the benzannulation reaction of α,β-unsaturated chromium carbene complexes[10] that results in a highly stereoselective preparation of biaryl phenols of type (a*R**,7*R**)-**2**,**II**, which are configurationally stable ring C functionalized analogues[11] of the antimitotic natural product[12] (−)-allocolchicine (**1**) (Figure 1). Similar reaction of regioisomeric carbene complexes with the same alkyne led to phenols (a*R**,7*S**)-**3,I**, albeit with low-to-moderate atropselectivity. Gratifyingly, we have found that this stereoselection can be taken to high levels under thermal equilibration conditions, giving **3,I** with 88−94% de.

Thus, allocolchicinoids of types **2**,**II** and **3**,**I** can be selectively prepared as described above. However, with the goal to prepare and test both diastereomers of configurationally stable allocolchicinoids, it would be highly desirable to develop a method for the selective access to **2**,**I** and **3**,**II**, the diastereomers of **2**,**II** and **3**,**I**.

Results and Discussion

We have subsequently prepared (a*R**,7*S**)-hydroquinone **4**,**I** (>96% de) from **3a** (**I** or **II**) (R, R^1 = Me) by ceric ammonium nitrate (CAN) oxidation followed by low-temperature $LiAlH_4$ reduction. To our surprise, almost complete inversion of the axial configuration in **4**,**I** was observed under the thermal equilibration conditions, showing greater thermodynamic stability of atropisomer **4**,**II**, contrary to our expectations based on the results with **3**[9] (Scheme 1). In an attempt to explain this phenomenon, we have examined the computer-generated models of diastereomers **I** and **II** of **4**, which revealed the

SCHEME 1. Thermal Equilibrium between Atropisomers I and II of Hydroquinone 4[a]



[a] Reagents and conditions: (a) toluene, 135 °C, 24 h, 92% recovery.

possible formation of a six-membered intramolecular hydrogen-bonding cycle involving phenolic C8-OH and pseudoequatorial C7-OMe groups in **II**, but not in **I**, where the corresponding C7-OMe functionality is pseudoaxial. Further support for this explanation was provided by the ^{1}H NMR spectrum with the observation of a significant ($\Delta\delta$ = 3.7 ppm) hydrogen-bonding-induced shift[13] for C8-OH in **4,II** relative to **4,I**.

To the best of our knowledge, atropisomerization of configurationally stable biaryls controlled by intramolecular H-bonding has not been reported so far, despite the known involvement of this factor in the induction of axial asymmetry in the solid state.[14] It has been proposed[15] that hydrogen bonding between an amine and an amide group influences the relative stereochemistry in atropisomeric amides. Intramolecular hydrogen bonding also has a pronounced effect on the reactivity of atropisomers **I** and **II** of **4**. For example, under the standard acetylation conditions **4,I** quickly and selectively reacted at the least hindered C8-OH, giving the corresponding monoacetate **5,I** in excellent yield (Scheme 2). However, under the same conditions **4,II** reacted only slowly, selectively at the most hindered C11-OH, thus preserving intramolecular hydrogen bonding in the resulting acetate **6,II**.

We have subsequently concluded that our previous failure to access (a*R**,7*S**)-atropisomer **2a,I** (R, R^1 = Me) by thermal epimerization of **2a**,**II** was also attributed to the same kind of intramolecular hydrogen-bonding stabilization. The selective preparation of **2**,**I** was envisioned using a protection−inversion−deprotection routine: protection of the C8 hydroxyl in **2**,**II** would remove the favorable H-bonding interaction and bring about the steric repulsion between C7 and C8 functionalities, which could be relieved by inversion of the axial configuration under thermal equilibration conditions. Subsequent deprotection would release phenols **2**,**I**.

Differently protected substrates **7a,II**−**12a**,**II** have been prepared from phenol **2a**,**II** (Scheme 3) and subjected to thermal equilibration conditions (Table 1). As was the case with **4**,**II**, acetylation of C8-OH in **2a**,**II** under the standard conditions met with no success. Instead, the corresponding acetate **7**,**II** was prepared by the reaction with Ac_2O catalyzed by $FeCl_3$.[16] Quite disappointingly, epimerization of **7,II** gave almost a 1:1 mixture of diastereomers (entry 1). Switching to the

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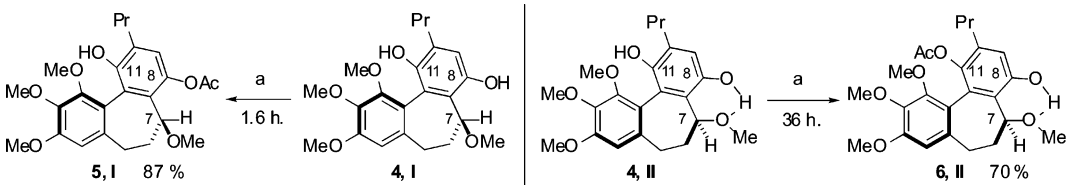
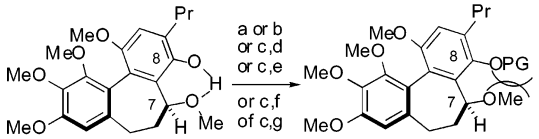
SCHEME 2. Effect of Intramolecular H-Bonding on the Reactivity of Atropisomers I and II of Hydroquinone 4 toward Acetylation[a]



[a] Reagents and conditions: (a) Ac_2O, Py, CH_2Cl_2, rt.

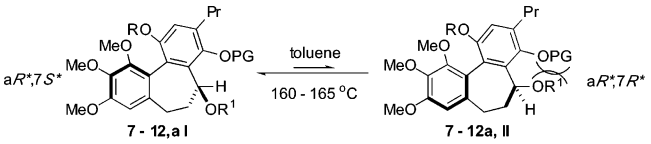
SCHEME 3. Protection of the Hydroxy Group in 2a,II[a]



(a): **7**; (b): **8**; (c,d): **9**; (c,e): **10**; (c,f): **11**; (c,g): **12a**

[a] Reagents and conditions: (a) Ac_2O, catalytic $FeCl_3$, ether, rt; (b) $(t\text{-BuCO})_2O$, catalytic $FeCl_3$, ether, rt; (c) NaH, THF, Δ; (d) MeI, THF, 65 °C; (e) (TMS)Cl, THF, rt; (f) (TBDMS)Cl, THF, rt; (g) (TIPS)Cl, THF, Δ. TMS = trimethylsilyl, TBDMS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

TABLE 1. Thermal Equilibrium between Atropisomers I and II of Protected Phenols 7−12

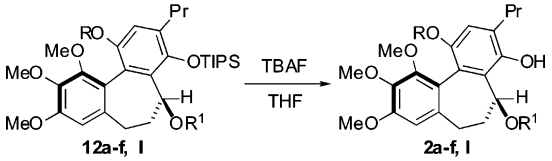


entry	7−12	PG	R	R^1	yield[a] of 7−12, %	T, °C	t, h	dr[b](Δ) of I to II	recovery[c] of I + II, %
1	**7**	MeCO	Me	Me	99	165	30	50:50	96
2	**8**	*t*-BuCO	Me	Me	99	165	30	58:42	92
3	**9**	Me	Me	Me	87	160	20	86:14	97
4	**10**	TMS	Me	Me	90	160	20	91:9	94
5	**11**	TBDMS	Me	Me	92	160	20	95:5	99
6	**12a**	TIPS	Me	Me	97	160	20	98:2	98
7	**12b**	TIPS	Me	Et	95	160	20	>98:2	97
8	**12c**	TIPS	Me	*i*-Pr	93	160	20	>98:2	96
9	**12d**	TIPS	Me	*t*-Bu	85	160	20	>98:2	99
10	**12e**	TIPS	Et	Me	86	160	20	98:2	97
11	**12f**	TIPS	*i*-Pr	Me	91	160	20	98:2	98

[a] Isolated yield from Scheme 3. [b] Determined by ^1H NMR integration. [c] Recovery after column chromatography.

larger pivalyl protecting goup in the analogously prepared **8,II** did not greatly improve the selectivity (entry 2), which has prompted us to explore other protection options. Methyl- and trialkylsilyl-protected substrates **9a,II**−**12a,II** have been effectively obtained by the reaction of electrophiles with the anion of **2,II**. We were glad to discover that the equilibrium mixture strongly favored atropisomer **I of 9a**−**12a** (entries 3−6), the diastereoselectivity increasing with an increase in the steric size of the protecting group, reaching almost complete stereoselection for **12a** (PG = TIPS) (entry 6). Having established the optimal protecting group, we next performed epimerization (160 °C, 20 h) of the series of differently substituted TIPS-protected substrates **12b**−**f,II** (entries 7−11), which were prepared from phenols **2b**−**f,II** as indicated in Scheme 2. An increase in the steric size of the C7 functionality (OR^1) led to further improvement in the selectivity (entries 7−9). Thus, even for **12b** (R^1 = Et) the minor atropisomer **II** could not be detected (entry 7). An increase in the size of the R group had no effect on the equilibrium position. The relative stereochemistry of **2** and **4**−**12** was assigned by comparison of their ^1H NMR spectra with those of the known allocolchicinoids, whose structure had been previously secured by our group[9] and others[12b] using X-ray crystallographic analysis.

SCHEME 4. Preparation of Atropisomer I of Phenols 2 by Deprotection



2a. 93 %; **2b**. 91 %; **2c**. 92 %; **2d**. 96 %; **2e**. 92 %; **2f**. 91 %

Treatment of **12**,**I** with TBAF provided the previously unavailable atropisomer **I** of phenols **2** (Scheme 4). With both diastereomers in hand, thermal epimerization (150 °C) was investigated (Table 2).

As expected, we have observed almost complete preference toward the H-bonding-stabilized isomer **II** in every case. Variations in the size of the R^1 group (entries 1−5) and changing the solvent from toluene to the more polar isobutyl methyl ketone (entry 2 vs entry 1) did not alter the diastereoselectivity. An increase in the size of the R group slightly slowed the attainment of equilibrium. Slow thermal degradation of the material was responsible for lower recovery values.

Intramolecular hydrogen bonding in **2**,**II** induces a downfield shift of the C8-OH signal in the ^1H NMR spectrum and a decrease in the O−H stretching frequency in the IR spectrum. The corresponding values $\Delta\delta(CDCl_3) = \delta(\mathbf{II}) - \delta(\mathbf{I})$ of 4.44−5.26 ppm and $\Delta\nu = \nu(\mathbf{II}) - \nu(\mathbf{I})$ of −92 to −299 cm^{-1} have been determined for these phenols.

Conclusions

We have demonstrated atropisomerization of configurationally stable biaryls controlled by steric vs hydrogen-bonding factors, an example of highly effective central-

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TABLE 2. Thermal Equilibrium between Atropisomers I and II of Phenols 2

entry	**2**	R	R^1	*t*, h	dr[a](Δ) of **I** to **II**	yield of **I** + **II**,[b] %	Δδ,[c] ppm	Δν,[d] cm^{-1}
1	**2a**	Me	Me	24	<2:98	68	4.44	−92
2[e]	**2a**	Me	Me	28	<2:98	70	4.44	−92
3	**2b**	Me	Et	24	<2:98	67	4.80	−156
4	**2c**	Me	*i*-Pr	24	<2:98	68	4.96	−236
5	**2d**	Me	*t*-Bu	24	<2:98	65	5.26	−299
6	**2e**	Et	Me	28	<2:98	64	4.48	−123
7	**2f**	*i*-Pr	Me	30	<2:98	63	4.45	−113

[a] Determined by ^{1}H NMR integration. [b] Recovery after column chromatography. [c] In $CDCl_3$, for the OH absorption: $\Delta\delta = \delta(\mathbf{II}) - \delta(\mathbf{I})$. [d] KBr, pill, for the OH stretch: $\Delta\nu = \nu(\mathbf{II}) - \nu(\mathbf{I})$. [e] In *i*-BuCOMe.

to-axial chirality transfer under thermodynamic conditions. In combination with the benzannulation reaction, it is now possible to selectively prepare either atropisomer of the regioisomeric allocolchicinoids **2** and **3**.

Experimental Section

8,11-Dihydroxy-1,2,3,7-tetramethoxy-10-propyl-5,6-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptenes (4). To a solution of phenol **3** (R, R^1 = Me)[9] (0.53 g, 1.31 mmol) and a 3:1 mixture of (a*R**,7*S**)-**I** and (a*S**,7*S**)-**II** diastereomers in 5 mL of ether was added an aqueous solution of CAN (1.436 g, 2.62 mmol) in 2.7 mL of water with stirring. The mixture turned red almost instantly. After 5 min it was diluted with water, the organic layer was separated, and the aqueous layer was extracted once with ether. The ethereal layers were united and dried over $MgSO_4$. The solvent was removed in vacuo, and the red residue was thoroughly dried under high vacuum and then dissolved in 25 mL of absolute ether. The solution was cooled to −78 °C under Ar, and a 1 M solution of $LiAlH_4$ (2.12 mL, 2.12 mmol) in THF was added to it dropwise. The mixture was stirred at −78 °C for 1 h, then the cooling bath was removed, and the mixture was allowed to reach room temperature. The mixture was carefully quenched under Ar by the dropwise addition of 0.5 mL of water followed by 4 mL of a 10% HCl solution. The organic layer was separated, and the aqueous layer was extracted twice with ether. The organic layers were united and dried over $MgSO_4$. The residue obtained after the solvent removal was checked by ^{1}H NMR and found to contain (a*R*,7*S*;a*S*,7*R*)-diastereomer **I** of the target hydroquinone **4** along with oligomeric products and trace amounts of the intermediate quinone. The signals of the opposite (a*S**,7*S**)-diastereomer **II** were not observed. The crude product was purified by column chromatography (silica gel, 30% EtOAc in hexane) to give **4**,**I** (0.376 g, 74%). The opposite diastereomer **4**,**II** can be obtained selectively by thermal epimerization of **4,I** in toluene at 135 °C for 24 h according to the procedure described below.

Data for (a*R,7*S**)-diastereomer 4,I:** yellow crystals; mp 155.5−156.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (t, 3H, *J* = 7.4 Hz), 1.60−1.69 (m, 2H), 2.26 (td, 1H, *J* = 13.8, 5.5 Hz), 2.35−2.41 (m, 2H), 2.47 (td, 1H, *J* = 13.1, 6.5 Hz), 2.61−2.70 (m, 2H), 2.93 (s, 3H), 3.72 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 4.81 (s, 1H), 5.03 (d, 1H, *J* = 6.5 Hz), 6.59 (s, 1H), 6.63 (s, 1H,), 6.70 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 23.2, 31.0, 32.8, 39.7, 55.7, 56.1, 61.2, 62.0, 74.1, 108.6, 116.1, 122.8, 122.9, 124.9, 132.6, 137.5, 140.2, 145.5, 147.0, 149.1, 152.3; IR (mixture of diastereomers) (KBr, cm^{-1}) 3388 (vs, OH), 2936 (m), 1603 (m), 1423 (s), 1113 (s); mass spectrum (EI) *m*/*z* (rel intens) 388 M^+ (42), 356 M^+ − MeOH (100), 341 M^+ − MeOH − Me (11), 327 (21), 281 (6); HRMS (EI) *m*/*z* calcd for $C_{22}H_{28}O_6$ 388.1886, found 388.1881. Anal. Calcd for $C_{22}H_{28}O_6$ (mixture of diastereomers): C, 68.02; H, 7.27. Found: C, 67.92; H, 7.43.

Data for (a*S,7*S**)-diastereomer 4,II:** yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (t, 3H, *J* = 7.4 Hz), 1.60−1.72 (m, 2H), 2.08−2.15 (m, 1H), 2.27−2.41 (m, 2H), 2.44 (dd, 1H, *J* = 11.4, 5.2 Hz), 2.66 (t, 2H, *J* = 7.6 Hz), 3.40 (s, 3H), 3.69 (s, 3H), 3.909 (s, 3H), 3.912 (s, 3H), 4.07 (dd, 1H, *J* = 11.4, 6.2 Hz), 6.45 (s, 1H), 6.64 (s, 1H), 6.72 (s, 1H), 8.52 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 23.1, 30.4, 32.6, 37.0, 56.0, 58.2, 61.3, 61.9, 83.2, 109.0, 117.8, 118.0, 121.2, 122.2, 132.4, 136.4, 140.7, 143.9, 148.1, 149.3, 152.9; IR (mixture of diastereomers) (KBr, cm^{-1}) 3388 (vs, OH), 2936 (m), 1603 (m), 1423 (s), 1113 (s); mass spectrum (EI) *m*/*z* (rel intens) 388 M^+ (77), 356 M^+ − MeOH (100), 341 M^+ − MeOH − Me (15), 327 (27), 313 (19), 281 (9); HRMS (EI) *m*/*z* calcd for $C_{22}H_{28}O_6$ 388.1886, found 388.1886. Anal. Calcd for $C_{22}H_{28}O_6$ (mixture of diastereomers): C, 68.02; H, 7.27. Found: C, 67.92; H, 7.43.

Thermal Epimerization of Hydroquinones 4. Separate solutions of individual diastereomers **4,I** and **4,II** in dry toluene (10 mg/mL) were placed in Schlenk flasks, deoxygenated by the freeze−pump−thaw method (−196 °C/25 °C, three cycles), and then the flasks were back-filled with Ar at room temperature, sealed, and placed in an oil heating bath side by side. The solutions were stirred at 135 °C for 24 h. TLC and HPLC analysis of the mixtures showed that the same diastereomeric ratio had been achieved in both tubes. Then the solutions were mixed together, the toluene was removed in vacuo, and the diastereomeric ratio (**I**:**II**) was found by ^{1}H NMR to be 3:97. After that the mixture was purified chromatographically on silica gel, diastereomers **I** + **II** were collected, and the average material recovery was determined (92%).

(a*R,7*S**)-8-Acetoxy-11-hydroxy-1,2,3,7-tetramethoxy-10-propyl-5,6-dihydro-5H-dibenzo[*a*,*c*]cycloheptene (5,I) and (a*S**,7*S**)-11-Acetoxy-8-hydroxy-1,2,3,7-tetramethoxy-10-propyl-5,6-dihydro-5H-dibenzo[*a*,*c*]cycloheptene (6,II).** To a stirred solution of the selected diastereomer (**I** or **II**) of **4** (1 equiv) in dry CH_2Cl_2 (~0.2 M) under nitrogen was added Ac_2O (3 equiv), and this was followed by the dropwise addition of pyridine (3 equiv). The mixture was stirred at room temperature and monitored by TLC for the disappearance of the starting material (1 h and 40 min for isomer **I**, 36 h for isomer **II**). Then the mixture was quenched with water, the product was extracted with ether, and the organic layer was washed once with 10% HCl and once with water and then dried over $MgSO_4$. After the removal of the solvent, the residue was purified by column chromatography (silica gel, 20% EtOAc in hexane).

Data for (a*R,7*S**)-5,I:** yield 87%; yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.99 (t, 3H, *J* = 7.3 Hz), 1.63−1.74 (m, 2H),

2.21 (td, 1H, J = 14.0, 5.6 Hz), 2.32 (s, 3H), 2.32−2.41 (m, 2H), 2.47 (td, 1H, J = 13.4, 6.4 Hz), 2.66−2.76 (m, 2H), 2.88 (s, 3H), 3.75 (s, 3H), 3.885 (s, 3H), 3.892 (s, 3H), 4.54 (d, 1H, J = 6.4 Hz), 6.63 (s, 1H), 6.84 (s, 1H), 6.96 (s, 1H, OH, exchange with D_2O); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 20.7, 22.8, 30.8, 32.7, 40.0, 55.7, 56.5, 61.1, 62.0, 75.3, 108.7, 122.1, 122.3, 124.1, 128.7, 132.9, 137.4, 140.4, 142.2, 149.2, 149.8, 152.6, 169.9; IR (KBr, cm^{-1}) 3375 (s, OH), 2936 (s), 1762 (s, CO), 1603 (m), 1455 (s), 1208 (s); mass spectrum (EI) m/z (rel intens) 430 M^+ (44), 388 $M^+ - CH_2CO$ (16), 356 $M^+ - CH_2CO - MeOH$ (66), 327 (10), 84 (84), 49 (100); HRMS (EI) m/z calcd for $C_{24}H_{30}O_7$ 430.1992, found 430.1992. Anal. Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. Found: C, 66.90; H, 6.98.

Data for (a*S,7*S**)-6,II:** yield 70%; yellow oil or amorphous solid; ^1H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, 3H, J = 7.4 Hz), 1.58−1.69 (m, 2H), 1.89−2.00 (br.s, 3H), 2.01−2.08 (m, 1H), 2.29−2.42 (m, 3H), 2.43−2.49 (m, 2H), 3.43 (s, 3H), 3.59−3.70 (br.s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 4.12 (dd, 1H, J = 11.4, 5.6 Hz), 6.54 (s, 1H), 6.75 (s, 1H), 8.84 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 20.5, 22.8, 29.6, 32.3, 36.7, 55.8, 58.4, 60.9, 60.9, 83.3, 107.2, 117.1, 118.7, 120.1, 127.7, 134.7, 135.8, 139.3, 140.3, 150.8, 152.3, 153.1, 169.0; IR (KBr, cm^{-1}) 3328 (s, OH), 2937 (s), 1760 (s, CO), 1597 (m), 1455 (s), 1190 (s); mass spectrum (EI) m/z (rel intens) 430 M^+ (55), 388 $M^+ - CH_2CO$ (90), 356 $M^+ - CH_2CO - MeOH$ (100), 341 (11), 324 (26), 309 (15), 281 (9); HRMS (EI) m/z calcd for $C_{24}H_{30}O_7$ 430.1992, found 430.1988.

8-Acyloxy-1,2,3,7,11-pentamethoxy-9-propyl-5,6-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptenes, R² = COCH₃ (7), COCMe₃ (8). To a stirred suspension of (a*S**,7*S**)-**2,II** (R, R^1 = Me)[9] (0.1 g, 0.249 mmol) in 2 mL of anhydrous ether under nitrogen was added $(RCO)_2O$ (1.81 mmol) in one portion. Then 10−12 mg of anhydrous $FeCl_3$ was added quickly as a solid. The reaction was monitored by TLC for the disappearance of the starting material (1 h for R = $COCH_3$, 3.5 h for R = $COCMe_3$). The reaction was quenched with 2 mL of the saturated Na_2HPO_4 solution, stirred for 1 h, and then extracted twice with ether, and then the organic layers were combined and dried over $MgSO_4$.

Compound 7,II, R = COCH₃. Solvent was removed in vacuo to give (a*S**,7*S**)-**7**,**II** (0.11 g, 99%): colorless crystals; mp 101.5−102.5 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 1.01 (t, 3H, J = 7.4 Hz), 1.60−1.74 (m, 2H), 2.05−2.19 (m, 2H), 2.26 (s, 3H), 2.35−2.40 (m, 2H), 2.54 (t, 2H, J = 7.6 Hz), 3.29 (s, 3H), 3.74 (s, 3H), 3.76 (s, 3 H), 3.89 (s, 6H), 4.02 (dd, 1H, J = 10.9, 7.0 Hz), 6.56 (s, 1H), 6.80 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.2, 20.7, 23.2, 30.1, 33.0, 36.8, 55.8, 55.9, 57.8, 60.7, 60.8, 81.4, 106.6, 111.1, 119.8, 122.1, 130.0, 135.3, 135.7, 138.8, 140.2, 151.4, 153.0, 153.6, 170.6; IR (mixture of diastereomers) (KBr, cm^{-1}) 2938 (s), 1761 (s, CO), 1465 (s), 1207 (s), 1120 (m); mass spectrum (EI) m/z (rel intens) 444 M^+ (75), 402 (6), 370 (100), 355 (13), 339 (17), 324 (9), 295 (7); HRMS (EI) m/z calcd for $C_{25}H_{32}O_7$ 444.2148, found 444.2151. Anal. Calcd for $C_{25}H_{32}O_7$ (mixture of diastereomers): C, 67.55; H, 7.26. Found: C, 67.52; H, 7.39.

Compound 7,I, R = COCH₃. The (a*R**,7*S**)-diastereomer **7,I** can be obtained from **7,II** by thermal epimerization (165 °C, 30 h) according to the procedure described below: colorless crystals; mp 157.5−158.0 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 1.02 (t, 3H, J = 7.4 Hz), 1.64−1.73 (m, 2H,), 2.13−2.61 (m, 4H), 2.34 (s, 3H), 2.49 (t, 2H, J = 7.8 Hz), 2.87 (s, 3H), 3.79 (s, 3H), 3.82 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 4.51 (d, 1H, J = 5.9 Hz), 6.54 (s, 1H), 6.84 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.3, 20.6, 22.9, 30.2, 33.0, 39.5, 55.5, 55.9, 56.0, 60.5, 60.8, 75.0, 106.1, 111.7, 121.4, 123.6, 131.1, 133.7, 135.8, 140.0, 140.8, 151.6, 152.4, 154.5, 168.9.; IR (mixture of diastereomers) (KBr, cm^{-1}) 2938 (s), 1761 (s, CO), 1465 (s), 1207 (s), 1120 (m); mass spectrum (EI) m/z (rel intens) 444 M^+ (82), 402 (6), 370 (100), 355 (14), 339 (19), 324 (11), 295 (9); HRMS (EI) m/z calcd for $C_{25}H_{32}O_7$ 444.2148, found 444.2152. Anal. Calcd for $C_{25}H_{32}O_7$ (mixture of diastereomers): C, 67.55; H, 7.26. Found: C, 67.52; H, 7.39.

Compound 8,II, R = COCMe₃. The solvent was removed in vacuo, and the residue was dried by warming under high vacuum until a constant mass was reached, giving (a*S**,7*S**)-**8**,**II** (0.12 g, 99%): yellow oil; ^1H NMR (600 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 7.3 Hz), 1.37 (s, 9H), 1.58−1.71 (m, 2H), 2.03−2.10 (m, 1H), 2.10−2.18 (m, 1H), 2.35−2.40 (m, 2H), 2.47−2.52 (m, 2H), 3.25 (s, 3H), 3.73 (s, 3H), 3.75 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 4.02 (dd, 1H, J = 11.1, 6.9 Hz), 6.56 (s, 1H), 6.78 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.1, 23.6, 27.4, 30.4, 33.3, 36.7, 39.1, 55.9, 56.0, 57.9, 60.8, 60.9, 81.9, 106.7, 111.4, 120.0, 122.3, 130.8, 135.3, 135.9, 139.3, 140.2, 151.5, 153.0, 153.5, 177.8; IR (mixture of diastereomers) (KBr, cm^{-1}) 2932 (s), 1749 (s, CO), 1466 (s), 1233 (m), 1115 (m); mass spectrum (EI) m/z (rel intens) 486 M^+ (15), 416 (5), 386 $M^+ - COCMe_3 - Me$ (4), 370 $M^+ - COCMe_3 - MeO$ (23), 339 (4), 292 (11), 149 (8), 57 (100). Anal. Calcd for $C_{28}H_{38}O_7$ (mixture of diastereomers): C, 69.11; H, 7.87. Found: C, 69.06; H, 7.87.

Compound 8,I, R = COCMe₃. The (a*R**,7*S**)-diastereomer **8**,**I** can be obtained from **8,II** by thermal epimerization (165 °C, 30 h) according to the procedure described below: colorless crystals; mp 150.9−151.3 °C; ^1H NMR (300 MHz, 100 °C, DMSO-d_6) δ 0.97 (t, 3H, J = 7.4 Hz), 1.38 (s, 9H), 1.56−1.70 (m, 2H), 2.05−2.14 (m, 2H), 2.19−2.38 (m, 2H), 2.41−2.48 (m, 2H), 2.77 (s, 3H,), 3.65 (s, 3H), 3.71 (s, 3H), 3.75 (s, 3H), 3.81 (s, 3H), 4.37−4.40 (m, 1H), 6.57 (s, 1H), 6.93 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 23.3, 27.2, 30.3, 33.0, 39.1, 55.9, 60.6, 74.9, 106.2, 112.2, 121.6, 123.8, 131.3, 133.6, 135., 140.1, 140.8, 151.7, 152.3, 154.4, 177.8; one CH_2 could not be located; on the basis of integration, signals at 55.9 and 60.6 ppm may contain three and two CH_3 groups, respectively; IR (mixture of diastereomers) (KBr, cm^{-1}) 2932 (s), 1749 (s, CO), 1466 (s), 1233 (m), 1115 (m); mass spectrum (EI) m/z (rel intens) 486 M^+ (13), 386 $M^+ - COCMe_3 - Me$ (100), 370 $M^+ - COCMe_3 - MeO$ (16), 355 (15), 339 (15), 323 (9), 192 (5); Anal. Calcd for $C_{28}H_{38}O_7$ (mixture of diastereomers): C, 69.11; H, 7.87. Found: C, 69.06; H, 7.87.

1,2,3,7,8,11-Hexamethoxy-9-propyl-5,6-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptenes (9). To a stirred solution of (a*S**,7*S**)-**2a,II** (R, R^1 = Me) (0.05 g, 0.124 mmol) in 2 mL of dry THF under nitrogen was added NaH (0.015 g, 0.622 mmol), and the resulting suspension was refluxed for 3 h. Then MeI (0.088 g, 0.622 mmol) was added in one portion, and the mixture was stirred at 65 °C for 4 h. The reaction mixture was cooled to room temperature, carefully quenched with 5 mL of water, and acidified with 10% HCl solution. The product was extracted twice with ether, and then the combined organic layers were separated and dried over $CaCl_2$. The solvent was removed, and the residue was purified chromatographically (silica gel, 15% EtOAc in hexane) to give (a*S**,7*S**)-**9**,**II** (0.045 g, 87%) as a colorless oil: ^1H NMR (600 MHz, $CDCl_3$) δ 1.04 (t, 3H, J = 7.4 Hz), 1.64−1.77 (m, 2H), 2.08−2.17 (m, 1H), 2.30−2.39 (m, 2H), 2.40−2.47 (m, 1H), 2.60 (ddd, 1H, J = 13.7, 9.6, 6.0 Hz), 2.75 (ddd, 1H, J = 13.7, 9.9, 6.1 Hz), 3.32 (s, 3H), 3.70 (s, 3H), 3.74 (s, 3H), 3.77 (s, 3H), 3.892 (s, 3H), 3.895 (s, 3H), 4.06 (dd, 1H, J = 11.8, 5.9 Hz), 6.56 (s, 1H), 6.77 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 24.0, 30.4, 32.5, 38.9, 55.9, 56.1, 58.2, 60.7, 60.9, 62.5, 81.3, 106.6, 111.4, 120.8, 122.1, 130., 135.2, 136.9, 140.4, 149.1, 151.5, 152.1, 152.9; IR (mixture of diastereomers) (KBr, cm^{-1}) 2937 (s), 1600 (m), 1465 (s), 1238 (s), 1093 (s); mass spectrum (EI) m/z (rel intens) 416 M^+ (100), 385 $M^+ - MeO$ (11), 369 $M^+ - MeOH - Me$ (11), 353 (7), 339 (7), 167 (9), 149 (29), 57 (11). Anal. Calcd for $C_{24}H_{32}O_6$ (mixture of diastereomers): C, 69.21; H, 7.74. Found: C, 69.03; H, 7.81.

The (a*R**,7*S**)-diastereomer **9**,**I** can be obtained from **9,II** by thermal epimerization (160 °C, 20 h) according to the procedure described below: colorless crystals; mp 126.6−127.0 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05 (t, 3H, J = 7.4 Hz), 1.67−1.81 (m, 2H), 2.22−2.55 (m, 4H), 2.60−2.76 (m, 2H), 2.92 (s, 3H), 3.72 (s, 3H), 3.77 (s, 3H), 3.81 (s, 3H), 3.85 (s, 3H), 3.87 (s, 3H), 4.95 (dd, 1H, J = 5.3, 1.8 Hz), 6.55 (s, 1H), 6.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 23.8, 30.4, 32.1, 40.3, 55.5, 55.85, 55.93, 60.5, 60.7, 62.0, 74.4, 106.1, 111 0.8, 121.9,

123.5, 131.7, 134.6, 135.6, 140.0, 150.0, 151.6, 152.1, 153.0; IR (mixture of diastereomers) (KBr, cm^{-1}) 2937 (s), 1600 (m), 1465 (s), 1238 (s), 1093 (s); mass spectrum (EI) *m*/*z* (rel intens) 416 M^+ (100), 385 $M^+ - MeO$ (8), 369 $M^+ - MeOH - Me$ (8), 254 (27), 239 (8), 200 (8), 149 (16), 57 (34). Anal. Calcd for $C_{24}H_{32}O_6$ (mixture of diastereomers): C, 69.21; H, 7.74. Found: C, 69.03; H, 7.81.

7,11-Dialkoxy-1,2,3-trimethoxy-9-propyl-8-trialkylsiloxyl-5,6-dihydro-5*H*-dibenzo[*a*,*c*]cycloheptenes 10−12. General Procedure Illustrated for 12a. To a stirred solution of the proper (a*S**,7*S**)-phenol **2,II** (1 equiv) in dry THF (∼0.065 M) under nitrogen was added NaH (3 equiv) as a 60% suspension in mineral oil, and the mixture was refluxed for 3 h. Then it was treated with the desired silyl chloride (PG)Cl (3 equiv) under the conditions indicated in Scheme 3. The progress of the reaction was monitored by TLC. After the protection was complete, the mixture was carefully quenched with saturated aqueous $NaHCO_3$ at room temperature, the product was extracted twice with ether, and then the organic layers were separated and dried over $CaCl_2$. The solvent was removed, and the residue was purified on a short column (silica gel, 15% EtOAc in hexane). The products and yields are given in Scheme 3.

Compound 12a,II. Protection Conditions. (TIPS)Cl was added, and the mixture was refluxed for 3 h (9 h if $R^1 = t$-Bu). Purification provided the TIPS-protected (a*S**,7*S**)-phenol **12a,II** (R, R^1 = Me) in 97% yield as colorless crystals: mp 139.4−140.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.97 (t, 3H, J = 7.3 Hz), 1.12 (d, 9H, J = 7.5 Hz), 1.13 (d, 9H, J = 7.5 Hz), 1.39 (sept., 3H, J = 7.5 Hz), 1.57−1.68 (m, 2H), 2.19−2.25 (m, 2H), 2.34−2.43 (m, 3H), 2.88 (ddd, 1H, J = 13.7, 9.5, 6.1 Hz), 3.23 (s, 3H), 3.58 (s, 3H), 3.70 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 4.01 (dd, 1H, J = 9.9, 8.7 Hz), 6.55 (s, 1H), 6.70 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 14.6, 18.3, 18.4, 24.3, 30.7, 33.6, 37.9, 55.9, 56.3, 57.7, 60.5, 61.0, 82.1, 106.8, 111.5, 121.3, 122.2, 127.6, 133.9, 135.4, 140.4, 144.9, 150.4, 151.6, 152.7; IR (mixture of diastereomers) (KBr, cm^{-1}) 2935 (s), 1599 (m), 1462 (s), 1239 (s), 1105 (s); mass spectrum (EI) *m*/*z* (rel intens) 558 M^+ (76), 526 $M^+ - MeOH$ (15), 515 $M^+ - i$-Pr (33), 483 $M^+ - MeOH - i$-Pr (100), 468 $M^+ - MeOH - i$-Pr − Me (37), 452 (14), 370 $M^+ - MeO - Si(i\text{-Pr})_3$ (28), 149 (9), 89 (15), 75 (13). Anal. Calcd for $C_{32}H_{50}O_6Si$ (mixture of diastereomers): C, 68.78; H, 9.02. Found: C, 68.84; H, 9.05.

Compound 12a,I. The (a*R**,7*S**)-diastereomers **12,I** can be obtained from **12a,II** by thermal epimerization (160 °C, 20 h) according to the procedure described below. This gave **12a,I** in 98% yield as a 98:2 mixture of diastereomers **I** and **II** as colorless crystals: mp 150.9−152.6 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.00 (t, 3H, J = 7.5 Hz), 1.14 (d, 9H, J = 7.6 Hz), 1.15 (d, 9H, J = 7.5 Hz), 1.30 (sept., 3H, J = 7.6 Hz), 1.61−1.73 (m, 2H), 2.23 (td, 1H, J = 14.1, 5.3 Hz), 2.30−2.37 (m, 2H), 2.47−2.54 (m, 2H), 2.77 (ddd, 1H, J = 14.0, 9.6, 6.5 Hz), 2.89 (s, 3H), 3.67 (s, 3H), 3.72 (s, 3H), 3.87 (s, 6H), 4.92 (d, 1H, J = 6.3 Hz), 6.52 (s, 1H), 6.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 14.4, 18.20, 18.23, 23.8, 30.7, 33.3, 39.1, 55.5, 55.6, 56.3, 60.6, 60.7, 74.2, 106.1, 112.3, 122.7, 123.6, 129.2, 131.6, 135.3, 140.3, 146.3, 151.3, 151.9, 152.0; IR (mixture of diastereomers) (KBr, cm^{-1}) 2935 (s), 1599 (m), 1462 (s), 1239 (s), 1105 (s); mass spectrum (EI) *m*/*z* (rel intens) 558 M^+ (87), 515 $M^+ - i$-Pr (32), 483 $M^+ - MeOH - i$-Pr (100), 468 $M^+ - MeOH - i$-Pr − Me (40), 452 (14), 370 $M^+ - MeO - Si(i\text{-Pr})_3$ (22), 159 (29), 133 (18), 91 (15). Anal. Calcd for $C_{32}H_{50}O_6Si$: C, 68.78; H, 9.02. Found: C, 68.84; H, 9.05.

(a*R,7*S**)-7,11-Dialkoxy-8-hydroxy-1,2,3-trimethoxy-9-propyl-5,6-dihydro-5H-dibenzo[*a*,*c*]cycloheptenes 2,I. General Procedure illustrated for 2a,I.** To a solution of the proper TIPS-protected (a*R**,7*S**)-phenol **12,I** (1 equiv) in THF (∼0.05 M) was added TBAF·$3H_2O$ (1.25 equiv) in one portion. The mixture was stirred for 0.5 h and monitored by TLC for the disappearance of the starting material. After the reaction was complete, the solvent was removed in vacuo, and the residue was purified on a short column (silica gel, 25% EtOAc in hexane). The products and yields are given in Scheme 4.

Data for phenol 2a,I (R, R^1 = Me): yield 93%; colorless crystals; mp 158.5−159.5 °C; ^{1}H NMR (500 MHz, acetone-d_6) δ 0.99 (t, 3H, J = 7.3 Hz), 1.64−1.73 (m, 2H), 2.11−2.23 (m, 2H), 2.29−2.35 (m, 2H), 2.69 (dd, 2H, J = 9.1, 6.6 Hz), 2.81 (s, 3H), 3.67 (s, 3H), 3.70 (s, 3H), 3.75 (s, 3H), 3.81 (s, 3H), 5.11 (dd, 1H, J = 6.0, 1.4 Hz), 6.55 (s, 1H), 6.77 (s, 1H, OH), 6.80 (s, 1H); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (t, 3H, J = 7.4 Hz), 1.65−1.78 (m, 2H), 2.18−2.40 (m, 3H), 2.42−2.53 (m, 1H), 2.53−2.67 (m, 2H), 2.92 (s, 3H), 3.72 (s, 3H), 3.78 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 4.42 (s, 1H, OH), 5.05−5.11 (br s, 1H), 6.53 (s, 1H), 6.71−6.77 (br s, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 14.3, 24.0, 31.2, 33.5, 40.0, 55.6, 56.1, 56.3, 60.5, 60.7, 74.6, 107.4, 113.2, 123.9, 124.8, 128.0, 129.7, 136.5, 141.3, 146.6, 151.8, 152.7, 153.1; IR (KBr, cm^{-1}) 3458 (s, OH), 3215 (s, OH), 2934 (s), 1600 (m), 1477 (s), 1225 (s); mass spectrum (EI) *m*/*z* (rel intens) 402 M^+ (31), 370 $M^+ - MeOH$ (100), 355 (12), 339 (20), 324 (11), 295 (5), 185 (10); HRMS (EI) *m*/*z* calcd for $C_{23}H_{30}O_6$ 402.2042, found 402.2056. Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.64; H, 7.51. Found: C, 68.49; H, 7.78.

Thermal Epimerization of Phenols 2 and Their Derivatives 7−12. General Procedure Illustrated for 12a. The solutions of pure diastereomers of **2**, **4**, or **7−12** (**I** (a*R**,7*S**) and **II** (a*S**,7*S**)) in dry toluene (10 mg/mL) were sealed in separate tubes under Ar. The tubes were placed in an oil heating bath side by side, and then the solutions were stirred under the conditions indicated in Tables 1 and 2. The progress of epimerization was monitored by TLC and HPLC, and the reaction was stopped as soon as the same diastereomeric ratio had been achieved in both tubes. Then the solutions were mixed together, toluene was removed in vacuo, and the ratio was measured by ^{1}H NMR. After that the mixture was purified chromatographically on the silica gel, diastereomers **I** + **II** were collected, and the average material recovery was determined. The results are presented in Tables 1 and 2. For diastereomers **12a,I** and **12a,II**, the epimerization was complete in 20 h at 160 °C and gave a 98% recovery as a 98:2 mixture of diastereomers **12a,I** and **12a,II**.

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Supporting Information Available: Full experimental details and characterization data for compounds **2**,**I** and **4**−**12** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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