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Synthesis of the Cores of Hypocrellin and Shiraiachrome: Diastereoselective 1,8-Diketone Aldol Cyclization

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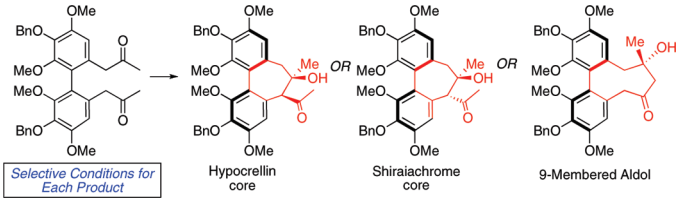
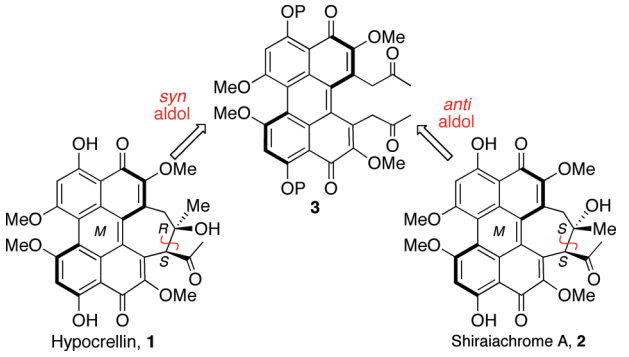


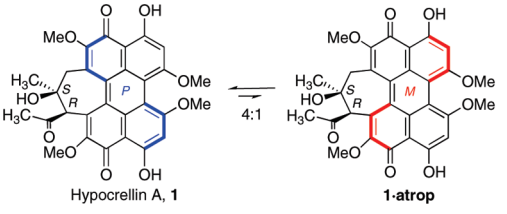
Intramolecular 1,8-diketone aldol reactions were studied as a tool for the construction of the seven-membered rings of hypocrellin and shiraiachrome. Conditions were identified to obtain the relative stereochemistries present in the two natural products with excellent diastereoselectivity. In addition, a nine-membered ring congener, which has yet to be observed in nature, formed with high selectivity when a hindered amine was used in conjunction with silazide bases.

Introduction

Hypocrellin (**1**) and shiraiachrome (**2**) are members of the perylenequinone class of natural products that also includes the elsinochromes, the calphostins, and cercosporin (Scheme 1).[1] The novel helically chiral structures of **1** and **2** are each comprised of an oxidized pentacyclic core as well as a seven-membered carbocyclic ring. Our interest in hypocrellin, isolated from *Hypocrella bambusae*,[2] largely stems from its potential use as a photoactivated therapeutic agent.[3] Existing as a 4:1 mixture of rapidly interconverting atropisomers (eq 1),[4] hypocrellin displays potent light-induced activity against bladder, brain, prostate, and leukemia cell lines[5] as well as antiviral[6] and immunotherapeutic properties.[7]

SCHEME 1. Retrosynthesis of Hypocrellin, Shiraiachrome, and Elsinochrome





(1)

Scheme 1 illustrates our retrosynthetic analysis of hypocrellin and shiraiachrome A with respect to the ancillary

(1) For reviews see: (a) Weiss, U.; Merlini, L.; Nasini, G. *Prog. Chem. Org. Nat. Prod.* **1987**, *52*, 1–71. (b) Bringmann, G.; Günther, C.; Ochse, M.; Schupp, O.; Tasler, S. *Prog. Chem. Org. Nat. Prod.* **2001**, *82*, 1–249.
(2) Chen, W. S.; Chen, Y. T.; Wang, X. Y.; Friedrichs, E.; Puff, H.; Breitmaier, E. *Liebigs Ann. Chem.* **1981**, 1880–1885.
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(4) Mazzini, S.; Merlini, L.; Mondelli, R.; Scagloni, L. *J. Chem. Soc., Perkin Trans. 2* **2001**, 409–416.
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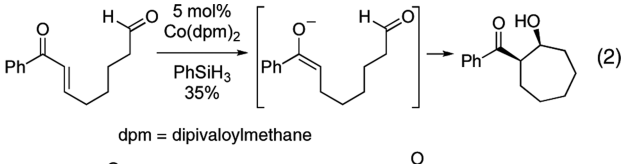
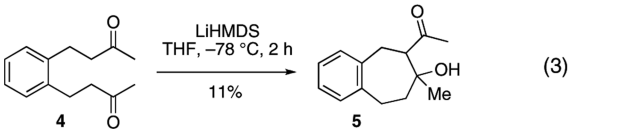
rings. From a common precursor (**3**), the seven-membered ring will be generated via an intramolecular aldol cyclization using the axial configuration as a stereochemical relay. While there is precedent for highly diastereoselective aldol reactions involving ketone electrophiles,[8] there are no instances involving acyclic 1,8-diketone substrates. In this paper, we describe model studies to evaluate the feasibility and stereochemical outcome of such an aldol reaction.

Results and Discussion

To the best of our knowledge, the type of 1,8-diketone aldol reaction that we proposed to use had not been employed previously outside of bridged or macrocyclic architectures.[9] In fact, aldol cyclizations of 1,8-dicarbonyls to form seven-membered rings are quite rare. A linear 1,8-dicarbonyl substrate (eq 2) that does yield the seven-membered ring aldol product proceeds in low yield (35%) even with a more reactive aldehyde electrophile.[10] In order to probe this type of ring-forming process further, we subjected 1,8-diketone **4**[11] to LHMDS and were encouraged by the formation of the seven-membered aldol product **5**, albeit in low yield (eq 3). We postulated that the insertion of two further sp^2 centers into the tether between the ketones (i.e., **3**) would constrain the reacting groups in closer proximity and facilitate such a process.



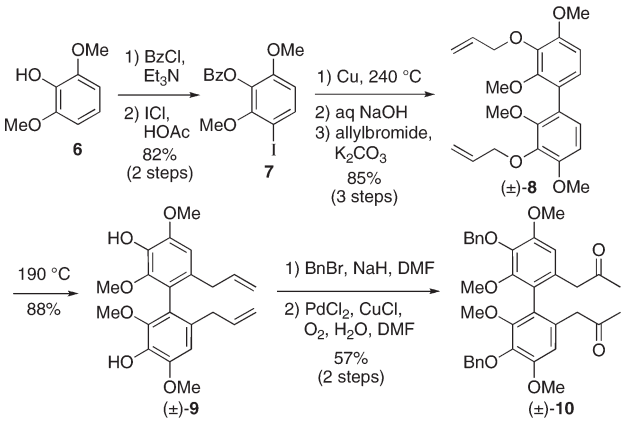
dpm = dipivaloylmethane



We selected readily accessible racemic **10** as a model system to study the key transformation (Scheme 2). Importantly, the tether contains four sp^2 centers permitting an evaluation of conformational rigidity on the process. Commercially available phenol **6** was protected as the benzoate and then iodinated to provide **7**. Ullman coupling followed by deprotection afforded the racemic axially chiral biphenol, which was allylated to yield **8**. Subsequent tandem Claisen–Cope rearrangement under thermal conditions provided **9**.[12] Further benzylation and regioselective Wacker oxidation afforded the desired 1,8-diketone **10**.

With **10** in hand, conditions were explored to achieve the key intramolecular aldol transformation. On the basis of transition structure calculations, the *Z*-enolate (**11Z**) was expected to provide the *syn*-aldol product with the relative configuration of hypocrellin, **1** (Scheme 3, **12a**).[13]

SCHEME 2. Synthesis of a 1,8-Diketone Model Substrate



No reaction was observed under Lewis acid aldol conditions (entries 1 and 2, Table 1). LDA did provide the product, but as a complex mixture (entry 3). On the other hand, silazide bases[14] yielded only two diastereomers in all trials. The nature of the enolate cation affected the stereoselectivity with lithium enolates proving superior (entries 4–6). Warmer temperatures (entry 7) resulted in lower selectivity, but attempts to achieve a thermodynamic product ratio by further warming resulted in complex mixtures. Addition of HMPA gave further improvement (entries 8 and 9), but the optimal selectivity was obtained with $Li(SiPhMe_2)_2$[14b] furnishing **12** as a 18:1 diastereomeric ratio and 100% conversion (entry 10).

Determination of the relative configuration proved difficult. With no vicinal protons, coupling constants could not be used. Analysis of the lowest energy conformational families obtained with MM2*[15] indicated a lack of characteristic NOEs to distinguish among all the four diastereomers without pure samples of each. Ultimately, debenzylation to **13a** and cocrystallization with methyl phenyl sulfoxide afforded suitable crystals (Figure 1). Pleasingly, the relative stereochemistry of **12a** *matches that of the major atropisomer* of hypocrellin.[16]

Buoyed by this success, we turned again to transition structure calculations which indicated that the *E*-enolate (**11E**) should provide the *anti*-aldol product **12c** (Scheme 3)[13] corresponding to the relative stereochemistry of shiraiachrome A (**2**). Following a report by Collum, we utilized hindered bases with LiHMDS to initiate formation of the *E*-enolate.[17] These conditions in this system, however, produced a nine-membered ring product (**12f**) (Table 1, entries 11–13). Presumably, the very large bases create hindered LiHMDS adducts that cause enolization to the less hindered position (**11A**, see below) even though it is substantially less acidic. In line with this

(8) Selected examples: (a) Baciagaluppo, J. A.; Colombo, M. I.; Cravero, R. M.; González-Sierra, M.; Preite, M. D.; Zinczuk, J.; Rúveda, E. A. *Tetrahedron: Asymmetry* **1994**, *5*, 1877–1880. (b) Jung, M. E.; Johnson, T. W. *J. Am. Chem. Soc.* **1997**, *119*, 12412–12413. (c) Kaji, Y.; Koami, T.; Nakamura, A.; Fujimoto, Y. *Chem. Pharm. Bull.* **2000**, *48*, 1480–1483.

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(13) See the Supporting Information.

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SCHEME 3. Intramolecular 1,8-Diketone Aldol Cyclization

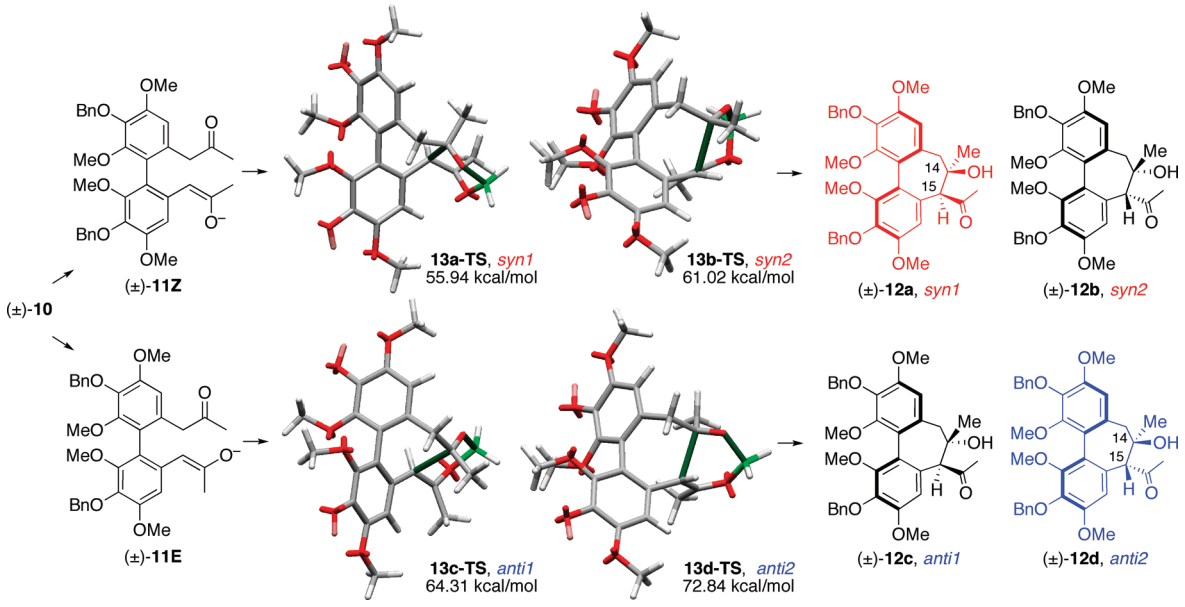
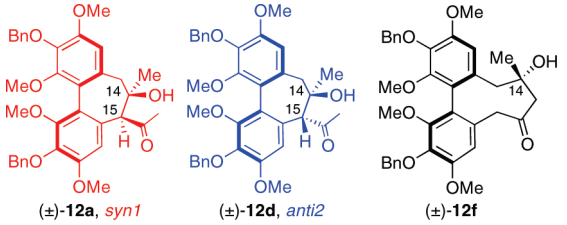


TABLE 1. Intramolecular Diketone Aldol Cyclization[a]



entry	reagents	solvent	*T* (°C)	time (h)	conv[b] (%)	12a:d:f[c]
1	$TiCl_4$, NEt_3	CH_2Cl_2	−78	2		ND
2	Cy_2BCl, NEt_3	THF	25	2		ND
3	LDA	THF	−78	1	> 30	ND[d]
4	KHMDS	THF	−78	1	77	2:1:0
5	NaHMDS	THF	−78	1	78	3:1:0
6	LiHMDS	THF	−78	1	95	5:1:0
7	LiHMDS	THF	−40	1	100	4:1:0
8	LiHMDS	THF/HMPA (5 vol%)	−78	1	95	7:1:0
9	LiHMDS	THF/HMPA (2 equiv)	−78	1	97	8:1:0
10	**$Li(SiPhMe_2)_2$**	**THF**	**−78**	**1**	**100 (70)**	**18:1:0**
11	LiHMDS	$PhCH_3/Et_3N$ (80 equiv)	−78	2	85	1:3:13
12	LiHMDS	$PhCH_3/i\text{-}Pr_2EtN$ (80 equiv)	−78	2	80	1:2:14
13	**LiHMDS**	**$PhCH_3/Ph_3N$ (80 equiv)**	**−78**	**2**	87 (67)	**1:5:55**
14	LiTMP	THF	−78	2	90	1:7:27
15	**LiTMP**	**THF/LiBr**	**−78**	**2**	90 (71)	**3:10:1**

[a]All reactions were carried out in a 3 μM concentration and quenched with saturated NH_4Cl (aq). [b]Conversion was determined by 500 MHz ^1H NMR. Isolated yields of the major isomer are in parentheses. [c]Ratios were determined by integration of the characteristic aromatic protons (**12a**: 6.32, 6.56 ppm; **12d**: 6.45, 6.66 ppm; **12f**: 6.60, 6.65 ppm). [d]Complex mixture of products.

hypothesis, progressively larger bases (Ph_3N > *i*-Pr_2EtN > Et_3N) provided greater amounts of **12f**. With Ph_3N, **12f** accounted for 90% of the product (entry 13).

Thus, attention turned to the tetramethylpiperide (TMP) bases[18] to generate the *E*-enolate and the shiraiachrome diastereomer. While LiTMP alone provided the nine-membered aldol product (Table 1, entry 14), LiTMP·HBr provided **12d**, which had been observed as the minor diastereomer in the $Li(SiPhMe_2)_2$ reaction (entry 10), as the major product (entry 15).

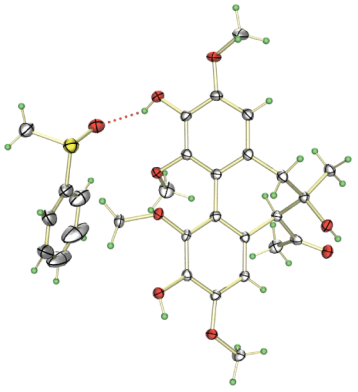


FIGURE 1. Crystal structure of **13a** (debenzylated **12a**) cocrystallized with MePhS=O (30% thermal ellipsoids).

To determine the structure of **12d**, several experiments were undertaken on the debenzylated versions of **12a**−**d** (**13a**−**d**) (Figure 2). First, a comparison of the crystal structure of **13a** to the MM2*-calculated structure showed remarkable agreement,[13] indicating that calculations could be used to estimate distances and dihedral angles. Second, **13d** was established as an *anti* diastereomer from the chemical shifts of the C15-H. In **13a** (Figure 2), the C15−H (3.40 ppm) is *trans* to the C14-OH in **13a**. The observation of a higher chemical shift of 3.60 ppm for the C15-H of the new compound implied a closer proximity of the C15-H to the C14-OH (i.e., a *cis* relationship), narrowing the field to

(18) Collum, D. B.; Hall, P. L.; Gilchrist, J. H. *J. Am. Chem. Soc.* **1991**, *113*, 9571–9574.

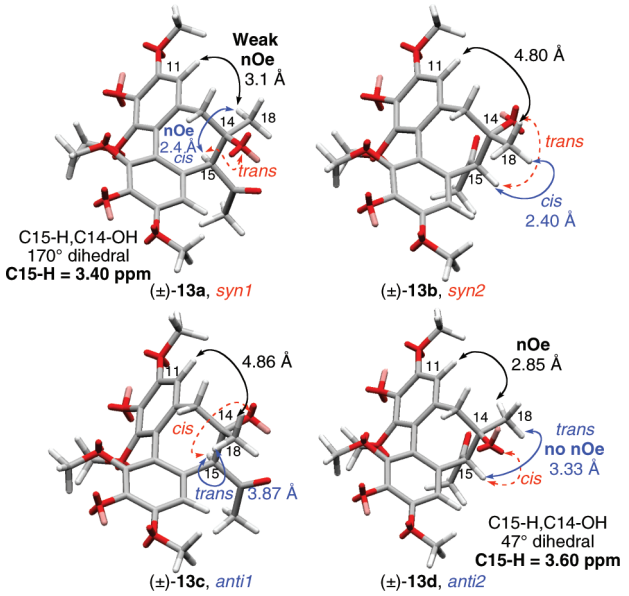


FIGURE 2. Assignment of the relative stereochemistry by examination of the compounds (**13a**−**d**) arising from debenzylation of **12a**−**d** (X-ray distances and angles for **13a**; calculated for **13b**−**d**).

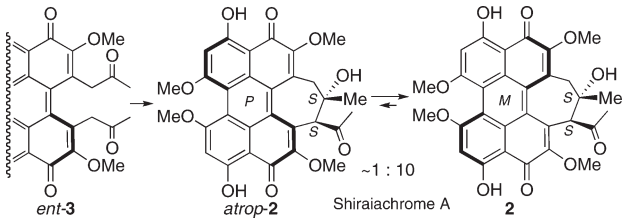
13c or **13d**. Third, NOE experiments were performed on **13a** and on the debenzylated form of the *E*-enolate product (Figure 2). For **13a**, NOEs between H11 and H18 and H15 and H18 were observed, consistent with the distances from the crystal and calculated structures. For the *E*-enolate product, lack of an H15−H18 NOE indicates a *trans* array confirming an *anti*-aldol adduct (**13c** or **13d**). The strong NOE between H11 and H18, however, is only consistent with **13d**, implying that **12d** is the major product with LiTMP·HBr (Table 1, entry 15). This result was not in accord with our expectations that **12c** would predominate (see TS calculations in Scheme 3).

Overall, the results indicate that the biaryl stereochemistry controls the facial approach to the ketone electrophile, thereby establishing the C14 stereocenter (see Scheme 3). On the other hand, the enolization method controls the relative configuration between C14 and C15 (*syn*-aldol for **12a** and *anti*-aldol for **12d**).

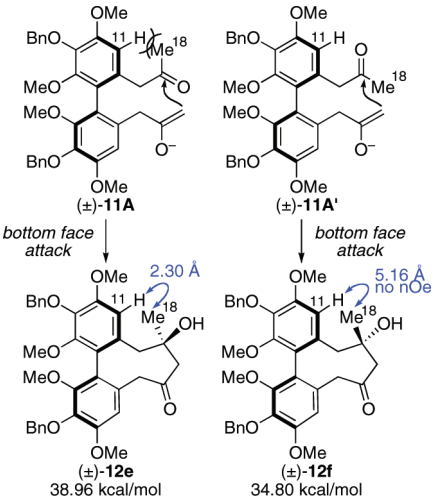
These results support the use of **3** (Scheme 1) with Li(SiPhMe$_2$)$_2$ to produce hypocrellin (**1**), a tactic which has proved successful.[16] On the other hand, the results also indicate that LiTMP·HBr would not produce shiraiachrome A (**2**) from **3**, raising the interesting question of how one might access **2**. We propose that *ent*-**3** would provide the enantiomeric array of that illustrated in **12d** (Scheme 3) yielding *atrop*-**2** which would only equilibrate with the major form **2**[4] after formation of the seven-membered ring that lowers the atropisomerization energy barrier (Scheme 4).[16]

With the above results in hand for **12a** and **12d**, the stereochemistry of the nine-membered ring product was expected to arise from a similar facial attack on the carbonyl controlled by the biaryl axis (i.e., **12e**, Scheme 5). However, experiments show no H11−H18 NOE, pointing to **12f** as the product. This result may be explained by the biaryl stereochemistry controlling the approach to the carbonyl in lower energy conformational isomer **11A**′ where steric interactions between H11 and C18 are minimized relative to **11A**. It is

SCHEME 4. Shiraiachrome Synthesis Plan



SCHEME 5. Stereochemistry of 12f



unlikely that this result is due to formation of a mixture of **12e** and **12f** followed by a thermodynamic equilibration, due to the high atropisomeric stability of these compounds.[1b]

Conclusions

The high yields observed in the 1,8-diketone aldol reaction of model system **10** were unexpected in light of past precedent which indicates that a bridged scaffold is necessary to effect an efficient aldol reaction between ketone centers in a 1,8-relationship. Furthermore, the transannular aldol reaction is expected to induce significant dihedral strain since the biaryl angle becomes compressed going from **10** (88° calcd) to **12a/12d** (55° X-ray). Since the biaryl angle in **3** (31° calcd, Scheme 1) positions the reacting groups in even closer proximity, formation of **1** or **2** (23−24° X-ray) does not require much movement and was expected to occur even more readily. Thus, these results strongly supported the proposed aldol pathway that was subsequently employed to form the natural products hypocrellin (**1**) and shiraiachrome (**2**) following the plan outlined in Scheme 1.[16]

In conclusion, we have developed an efficient method for installing the seven-membered ring of hypocrellin (**1**) or shiraiachrome A (**2**) stereoselectively via intramolecular 1,8-diketone aldol cyclizations. Furthermore, use of hindered bases (Ph$_3$N) in conjunction with LiHMDS furnished a nine-membered aldol product via the acetate enolate, which provides an avenue to interesting nonnatural perylenequinones for further study.

Experimental Section

1-[4,6,2′,4′-Tetramethoxy-5,3′dibenzyloxy-6′-(2-oxopropyl)biphenyl-2-yl]propan-2-one (12). A solution of the diol **9** (275 mg,

0.71 mmol) in DMF (20 mL) was cooled to 0 °C. NaH (60% in oil, 140 mg, 3.6 mmol) was added and the mixture stirred for 15 min. Benzyl bromide (0.43 mL, 3.56 mmol) and *n*-Bu_4NI (26 mg, 0.071 mmol) were added at 25 °C and the reaction stirred for 1 h. The mixture was acidified with 1 M HCl, diluted with EtOAc, washed with H_2O (6×) and brine, and dried (Na_2SO_4). The concentrate was chromatographed (40% EtOAc/hexanes) to afford 1-[4,6,2′,4′-tetramethoxy-5,3′dibenzyloxy-6′-allylbiphenyl-2-yl]propan-2-ene as a yellow resin (281 mg, 70%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 6.9 Hz, 4H), 7.35 (t, J = 6.9 Hz, 4H), 7.29 (t, J = 7.2 Hz, 2H), 6.62 (s, 2H), 5.84−5.76 (m, 2H), 5.08 (d, J = 11.1 Hz, 2H), 5.05 (d, J = 11.1 Hz, 2H) 5.01−4.98 (m, 2H), 4.98−4.96 (m, 2H), 3.88 (s, 6H), 3.67 (s, 6H), 3.03−2.93 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 152.1, 139.2, 138.1, 137.3, 135.1, 128.6, 128.4, 128.1, 123.2, 116.1, 107.9, 75.2, 60.9, 56.1, 37.9; IR (film) 2930, 2856, 1594, 1455 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{36}H_{38}O_6Na^+$ (MNa^+) 589.2566, found 589.2571.

To a solution of $PdCl_2$ (1.3 g, 7.1 mmol) and CuCl (3.5 g, 3.5 mmol) stirred in a DMF/H_2O mixture (7:1 v:v, 50 mL) at room temperature for 30 min was added 1-[4,6,2′,4′-tetramethoxy-5,3′dibenzyloxy-6′-allylbiphenyl-2-yl]propan-2-ene (1.0 g, 1.8 mmol). After being stirred under oxygen 18 h, the reaction mixture was acidified with 1 M HCl, diluted with EtOAc, washed with H_2O (6×) and brine, and dried (Na_2SO_4). The corresponding concentrate was chromatographed (20−50% EtOAc/hexanes) to afford **10** (520 mg, 50%) as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 7.4 Hz, 4H), 7.29 (t, J = 7.1 Hz, 4H), 7.23 (t, J = 6.6 Hz, 2H), 6.58 (s, 2H), 5.07 (s, 4H), 3.88 (s, 6H), 3.60 (s, 6H), 3.35 (d, J = 16.7 Hz, 2H), 3.30 (d, J = 16.7 Hz, 2H), 1.94 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.6, 153.4, 152.0, 139.7, 138.0, 130.5, 128.6, 128.5, 128.1, 123.2, 109.5, 75.2, 60.8, 56.1, 47.9, 29.9; IR (film) 2937, 1710, 1594 1455 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{36}H_{38}O_8Na^+$ (MNa^+) 621.2464, found 621.2463.

(*R*$_a$*,*R,*S**)-1-(6-Hydroxy-1,3,10,11-tetramethoxy-2,9-dibenzyloxy-6-methyl-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-yl)ethanone (12a).** A solution of **10** (15 mg, 0.033 mmol) in THF (20 mL) was cooled to −78 °C under argon. Lithium tetramethyldiphenyl disilylamide (34 μL, 0.040 mmol, 1.2 M in THF) was added and the mixture stirred for 1 h. The mixture was quenched with saturated NH_4Cl, extracted with EtOAc, washed with brine, dried (Na_2SO_4), and concentrated. Analysis of this material (500 MHz ^{1}H NMR) indicated 100% conversion and an 18:1 diastereomeric ratio of **12a**:**12d**. The concentrate was chromatographed which separated the diastereomers (30% EtOAc/hexanes) to afford **12a** (11 mg, 70%) as a yellow resin: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50, (d, J = 7.4 Hz, 4H), 7.39−7.35 (m, 4H), 7.32−7.29 (m, 2H), 6.56 (s, 1H), 6.32 (s, 1H), 5.02−5.18 (m, 4H), 3.88 (s, 3H), 3.84 (s, 3H), 3.74 (s, 3H), 3.66 (s, 3H), 3.39 (s, 1H), 2.38 (d, J = 13.0 Hz, 1H), 2.32 (d, J = 13.0 Hz, 1H), 2.17 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 213.6, 153.5, 153.4, 152.5, 152.3, 141.1, 140.2, 138.2, 138.1, 133.2, 130.1, 128.7, 128.6, 128.5, 128.4, 128.1, 128.0, 123.9, 121.8, 108.7, 105.9, 80.8, 75.4, 75.3, 61.2, 61.1, 60.3, 60.2, 56.3, 46.9, 32.4, 26.9; IR (film) 3497, 2937, 1698, 1598 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{36}H_{38}O_8Na^+$ (MNa^+) 621.2464, found 621.2449.

(*R*$_a$*,*R,*S**)-1-(6-Hydroxy-1,3,10,11-tetramethoxy-2,9-hydroxy-6-methyl-6,7-dihydro-5*H*-dibenzo[*a*,*c*]cyclohepten-5-yl)ethanone (13a).** To a solution of **12a** (single isomer, 69 mg, 0.12 mmol) in a MeOH/THF mixture (1:1 v/v, 10 mL) was added 10% Pd/C (130 mg, 1.2 mmol). A hydrogen balloon was added, and the reaction mixture was stirred for 20 min. The mixture was filtered through silica (10% MeOH/CH_2Cl_2) to afford **13a** as a colorless oil (51 mg, 100%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (s, 3H), 2.13 (s, 3H), 2.30 (d, J = 13.1 Hz, 1H), 2.36 (d, J = 13.1 Hz, 1H), 3.41 (s, 1H), 3.52 (s, 3H), 3.67 (s, 3H), 3.90 (s, 3H), 3.94 (s, 3H), 4.52 (s, 1H), 5.63 (s, 1H), 5.66 (s, 1H), 6.33 (s, 1H), 6.56 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 31.9, 46.4, 56.2, 56.3, 59.8, 60.3, 60.4, 80.7, 104.9, 107.7, 120.6, 122.9, 125.4, 128.3, 137.4, 138.2, 145.3, 145.5, 147.0, 147.1, 213.4; IR (thin film) 3439, 2937, 1695, 1610 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{26}O_8Na$ (MNa^+) 441.1525, found 441.1544.

To a solution of **13a** (23 mg, 0.061 mmol) in a benzene/hexane mixture (1:1 v/v, 0.40 mL) was added racemic phenylmethyl sulfoxide (17 mg, 0.12 mmol). The mixture was stirred at room temperature for 12 h. The precipitate was recrystallized from CH_2Cl_2/hexane (1:1 v/v, 1 mL) to afford the cocrystal product. A crystal structure was obtained, securing the relative configuration (see the Supporting Information).

(*R*$_a$*,*R,*R**)-1-(6-Hydroxy-1,3,9,11-tetramethoxy-2,10-dibenzyloxy-6-methyl-5*H*-dibenzo[*a*,*c*]cycloheptan-5-yl)ethanone (12d).** To a stirring solution of **10** (90 mg, 0.15 mmol) in THF (16.0 mL) at −78 °C under Ar was added the LiTMP−LiBr complex (15.0 mL, 0.8 M LiTMP, 0.75 mmol). After being stirred for 2 h at −78 °C, the mixture was quenched with satd NH_4Cl, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The concentrate was chromatographed (2% MeOH in 1:1 Et_2O/hexanes), yielding **12d** (64 mg, 71%) as pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53, (d, J = 7.2 Hz, 2H), 7.49 (d, J = 7.2 Hz, 2H), 7.38−7.34 (m, 4H), 7.32−7.29 (m, 2H), 6.65 (s, 1H), 6.44 (s, 1H), 5.16 (d, J = 11.0 Hz, 1H), 5.15 (d, J = 11.0 Hz, 1H), 5.07 (d, J = 10.1 Hz, 1H), 5.06 (d, J = 10.1 Hz, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.72 (s, 3H), 3.66 (s, 3H), 3.58 (s, 1H), 2.81 (s, 1H), 2.44 (d, J = 14.0 Hz, 1H), 2.18 (d, J = 14.0 Hz, 1H), 2.13 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 210.4, 153.7, 153.4, 152.5, 152.3, 140.9, 140.2, 138.1, 137.9, 133.1, 131.3, 128.6, 128.5, 128.4, 128.11, 128.05, 124.2, 121.7, 108.7, 106.0, 81.4, 75.4, 75.3, 63.7, 61.2, 61.1, 56.5, 56.2, 48.0, 31.4, 29.9, 24.0; IR (film) 3250 (br), 2943, 2881, 2835, 1715, 1599, 1460, 1413, 1104, 749 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{36}H_{38}O_8Na^+$ (MNa^+) 621.2462, found 621.2451.

(*R*$_a$*, *S)-1,3,11,13-Tetramethoxy-2,12-dibenzyloxy-8-methyl-8-hydroxy-5,7,9-trihydro-7*H*-dibenzo[*a*,*c*]cyclononen-6-one (12f).** To a stirring solution of **10** (90 mg, 0.15 mmol) and Ph_3N (1.5 g, 6.0 mmol) in $PhCH_3$ (20 mL) at −78 °C under Ar was added lithium hexamethyl disilylamide (5.0 mL, 1.0 M in $PhCH_3$, 5.0 mmol). After being stirred at −78 °C for 2 h, the mixture was quenched with satd NH_4Cl, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The concentrate was chromatographed (2% MeOH in 1:1 Et_2O/hexanes), yielding **12f** (60 mg, 67%) as pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, J = 7.4 Hz, 4H), 7.37−7.32 (m, 4H), 7.30−7.28 (m, 2H), 6.65 (s, 1H), 6.60 (s, 1H), 5.13 (d, J = 11.1 Hz, 1H), 5.09 (d, J = 11.1 Hz, 1H), 5.04 (d, J = 11.1 Hz, 1H), 5.01 (d, J = 11.1 Hz, 1H), 4.06 (s, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.70 (s, 3H), 3.64 (s, 3H), 3.32 (d, J = 16.6 Hz, 1H), 3.16 (d, J = 16.6 Hz, 1H), 2.53 (d, J = 13.8 Hz, 1H), 2.50 (d, J = 13.8 Hz, 1H), 2.30 (d, J = 13.2 Hz, 1H), 1.91 (d, J = 13.2 Hz, 1H), 1.19 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 211.0, 154.0, 153.8, 152.1, 151.41, 140.3, 140.0, 138.0, 137.7, 133.1, 131.7, 128.7, 128.5, 128.4, 128.2, 128.0, 124.7, 123.3, 110.4, 109.8, 77.6, 75.6, 75.0, 74.7, 61.0, 60.9, 56.23, 56.16, 52.7, 48.2, 46.0, 31.4; IR (film) 3247 (br), 2927, 2858, 1730, 1692, 1599,1460, 1406, 1097, 1027, 749 cm^{-1}; HRMS (ESI$^+$) calcd for $C_{36}H_{38}O_8Na^+$ (MNa^+) 621.2462, found 621.2416.

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Supporting Information Available: Additional experimental descriptions, NMR spectra, calculated structures, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.