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Pd-Catalyzed Arylation Reactions with Phenol Diazonium Salts: Application in the Synthesis of Diarylheptanoids

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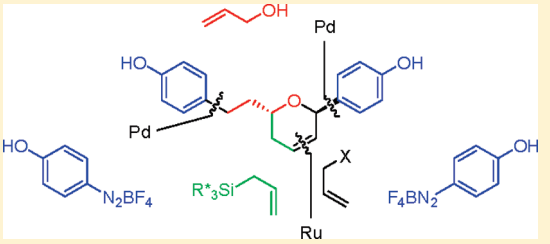
Supporting Information

ABSTRACT: The first total synthesis of the natural product (3*S*,7*R*)-5,6-dehydro-de-*O*-methyl centrolobine and various analogues is reported, using a highly regio- and diastereoselective Mizoroki−Heck reaction of phenol diazonium salts and enantiopure dihydropyrans. The assigned relative configuration was confirmed by single-crystal X-ray structure analysis, but a revision of the absolute configuration is proposed based on polarimetric measurement.



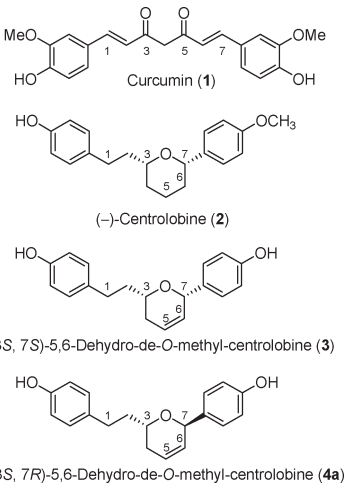
INTRODUCTION

Diarylheptanoids are natural products occurring in various plants.[1] They share an aliphatic C7 chain with aromatic substituents, often phenols, at the termini, and are very often bacteriostatic[2] or nematocidal[3] agents. Curcumin (**1**),[4] isolated from the rhizomes of *Curcuma longa*, is an example for an acyclic diarylheptanoid and was the only known diarylheptanoid for many decades. The second diarylheptanoid to be discovered was centrolobine (**2**),[5] which occurs in the heartwood of amazonian trees of *Centrolobium* sp. in both enantiomeric forms.[6,7] Since the discovery of centrolobine in 1964, numerous other diarylheptanoids, and in particular pyran-type diarylheptanoids, were isolated from various plants (Chart 1).

A particularly rich source of diarylheptanoid natural products is *Alpinia blepharocalyx*, which is used in traditional Chinese folk medicine for the treatment of gastrointestinal disorders and was thoroughly investigated by Kadota et al. over the past decade.[8] For example, they isolated and characterized (3*S*,7*S*)-5,6-dehydro-de-*O*-methyl centrolobine (**3**)[9] and its 7*R*-epimer **4a**[10] from this source, along with several dihydroxylated derivatives, dimers, and chalcone conjugates, which comprise the pyran core of **3** or **4a** (Chart 1).[10] Many of these compounds possess antiproliferative activity against human HT-1080 fibrosarcoma and murine colon 26-L5 carcinoma cells. For several structurally related compounds, antibacterial activities and antileishmanial activities were detected.[6,11]

Synthetic efforts in this field have mostly been directed at the synthesis of (−)-centrolobine. Various methods such as hetero-Diels−Alder reactions,[12] cross metathesis−reductive etherification sequences,[13,14] diastereoselective ring rearrangement metathesis,[15] Prins cyclizations,[16,17] and oxidative[18,19] or acid-catalyzed[20] intramolecular etherifications have been used as key steps. A common feature of these methods is the high *cis*-selectivity, which is required if centrolobine or other *cis*-configured pyran-type diarylheptanoids are the targets. The synthesis of *trans*-epimers has attracted considerably less attention,[18,21] probably because *trans*-centrolobines have not been isolated from natural sources.

Chart 1. Structures of Curcumin (1) and Pyran-Type Diarylheptanoids (2−4a)



We have recently devised a stereodivergent route to all stereoisomers of centrolobine that relies on an intermolecular Mizoroki−Heck reaction of cyclic enol ethers and a 4-methoxybenzene diazonium salt.[22] Mizoroki−Heck reactions with arene diazonium salts were first described by Matsuda et al.[23] but have remained largely unexplored for quite some time.[24] Over the past decade, contributions from several groups[25−40] have triggered a renaissance of Pd-catalyzed coupling reactions with diazonium salts.

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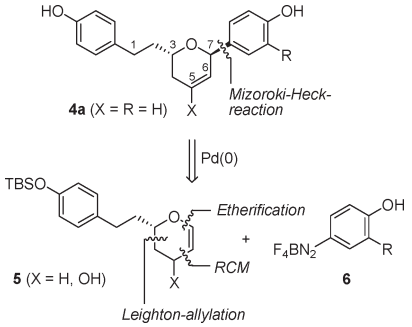
Scheme 1. Synthetic Plan for Dehydro-de-*O*-methyl centrolobines



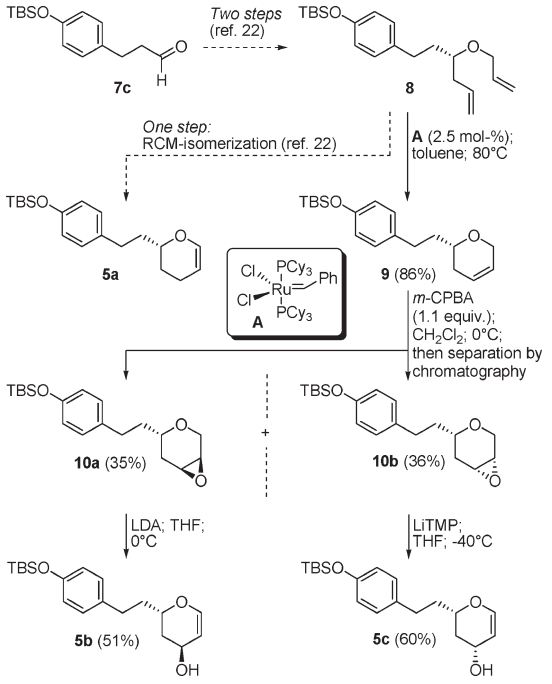
During our studies directed at the synthesis of pyran-type diarylheptanoids, we required a method for the introduction of phenols to access not only aryl methyl ethers such as centrolobine but also demethylated diarylheptanoids. A solution for this problem is the use of benzyl-protected arene diazonium salts, which we applied to the synthesis of *rac*-de-*O*-methyl centrolobine.[41] However, we experienced considerable difficulties with the final debenzylation step, which was often associated with a reductive cleavage of the tetrahydropyran ring and could not be achieved without concomitant hydrogenation of an endocyclic C−C double bond. For these reasons, we considered unprotected phenol diazonium salts as coupling reagents. We have recently discovered that these compounds are highly reactive electrophiles in the Mizoroki−Heck reaction with electron-deficient alkenes, such as acrylates and acrylic amides, with reactivities often exceeding those observed for their O-alkylated counterparts.[42]

In this contribution, we report the first stereoselective synthesis of the natural product (3*S*,7*R*)-5,6-dehydro-de-*O*-methyl centrolobine (**4a**) and several non-natural derivatives. A Pd-catalyzed Mizoroki−Heck reaction of cyclic enol ethers **5** and phenol diazonium salts **6** was envisaged as the key step (Scheme 1).

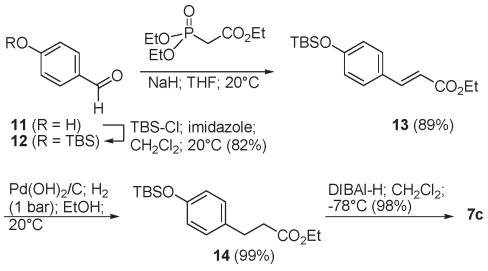
RESULTS AND DISCUSSION

Synthesis of Cyclic Enol Ethers 5. We synthesized three dihydropyrans **5a**−**c** from a common precursor **8** (Scheme 2). Allyl ether **8** was obtained in enantiomerically pure form as previously described by us,[22] using a Leighton allylation[43] of TBS-protected aldehyde **7c** and a Williamson etherification of the resulting homoallylic alcohol. Dihydropyran **5a** (X = H)[22] is available from **8** in one step using the tandem RCM isomerization sequence developed by Snapper et al.[44] and by us.[45−47] For the synthesis of diastereomers **5b** and **5c**, allyl ether **8** was cyclized in a ring closing metathesis reaction in the absence of isomerization-promoting additives. The resulting dihydropyran **9** was epoxidized with *m*-CPBA, giving two diastereomeric dihydropyran oxides **10a** and **10b** in a 1:1 ratio. These diastereomers are easily separable by chromatography and were then individually treated with Li amides to promote a rearrangement to allylic alcohols. This reaction has originally been investigated by Rickborn et al.[48−50] and was further investigated by us[51,52] and others,[53] extending the research to include the synthesis of cyclic enol ethers from dihydrofuran and dihydropyran oxides. We found that for the *trans*-isomer **10a** a highly regioselective rearrangement to **5b** was achieved with LDA, whereas partial

Scheme 2. Syntheses of Dihydropyrans 5a−c



Scheme 3. Synthesis of 7c via Olefination and Ester Reduction



deprotonation at the 4-position was observed upon treatment of the *cis*-diastereomer **10b** with this base, resulting in the formation of an undesired regioisomer. This insufficiency could be corrected by using the sterically more demanding base Li-2,2,6,6-tetramethylpiperidide (LiTMP), which gave **5c** as a single regioisomer.

Alternative Syntheses of TBS-Protected Aldehyde 7c. Aldehyde **7c** (Scheme 2) was originally synthesized from coumaric acid in four steps, following a literature procedure.[54] We found, however, that an alternative synthesis starting from 4-hydroxybenzaldehyde (**11**) is more convenient. This synthesis involves TBS protection of **11**, Horner−Wadsworth−Emmons olefination of **12**, hydrogenation of **13**,[55] and finally partial reduction of the ester **14** with DIBAl-H[54] to give **7c** in four steps and 70% overall yield (Scheme 3).

Although this synthesis works well and provides the required aldehyde **7c** in useful quantities, we thought that an alternative synthesis which uses the same precursor for both aryl substituents in diarylheptanoids such as **3** or **4a** might be overall more economical. Such a synthesis would require a Mizoroki−Heck reaction of a phenol diazonium salt **6a** (Scheme 1, R = H) and

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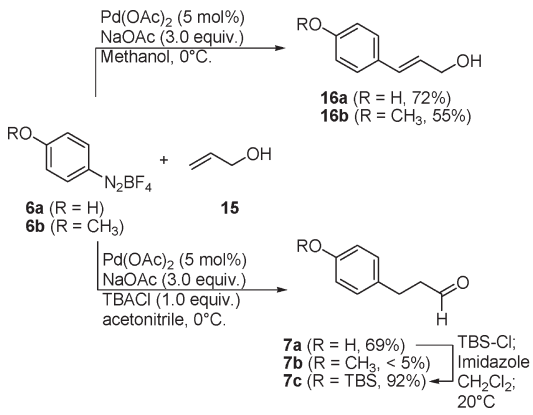
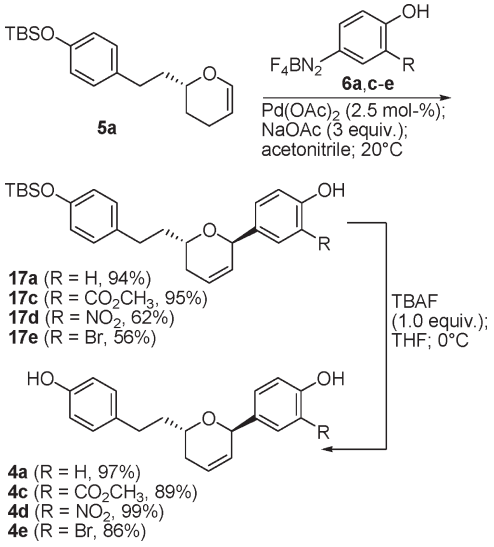
Scheme 4. Mizoroki–Heck Reaction of Diazonium Salts 6 and Allyl Alcohol (15)



Scheme 5. Synthesis of Diarylheptanoids 4



allyl alcohol (**15**). Mizoroki–Heck reactions of allylic alcohols and iodoarenes were investigated by Jefferey using two different catalyst systems:[56] with NBu_4Cl as an additive, aldehydes **7** are the preferred products because the Pd hydride species resulting from β-hydride elimination is stabilized by complexation of chloride and may efficiently catalyze a subsequent double bond migration. Conversely, the addition of Ag[57] or Tl salts[58] results in the preferred formation of alcohols **16** because the concentration of halide is lowered, which results in a destabilization of the Pd hydride species and consequently in a suppression of subsequent isomerization reactions. Mizoroki–Heck reactions of primary or secondary allylic alcohols and arene diazonium salts have also been investigated and normally give aldehydes or ketones, respectively, as the major products.[23,36,37,59,60] In particular, for simple allyl alcohol (**15**), however, the reaction suffers from low yields and insufficient selectivities, and in those cases where methanol was used as a solvent, partial or complete acetal formation was observed.[37,59] Encouraged by our good results for Mizoroki–Heck reactions of phenol diazonium salts and electron-deficient alkenes, we investigated the challenging substrate **15** using the previously established standard conditions. In contrast to the majority of Pd-catalyzed coupling reactions previously described in the literature, we found that for phenol diazonium salts better results are obtained in the presence of a base.[42] This might be attributed to the formation of a quinone diazide, which is presumably less sensitive to decomposition by attack of the nucleophilic solvent methanol. Thus, by using ligandless $Pd(OAc)_2$ as a precatalyst, NaOAc as a base, and methanol as a solvent, we obtained allylic alcohol **16a** from **6a** and **15** in 72% yield, along with 11% of aldehyde **7a**. Interestingly, 4-methoxybenzene diazonium salt **6b** reacts analogously with **15** to give **16b**, albeit in lower yield (Scheme 4). The reaction of **6b** and **15** had previously been investigated using a different precatalyst and base-free conditions, which is most likely the crucial difference. Under these conditions, a mixture of regioisomeric acetals was obtained.[37]

For the selective synthesis of aldehyde **7a**, tetrabutyl ammonium chloride (TBACl) was added to the reaction mixture, and the solvent methanol was replaced by acetonitrile. TBACl, to the best of our knowledge, has not been successfully used as an additive in Pd-catalyzed coupling reactions with arene diazonium salts. Interestingly, the reaction of **15** and **6b** failed completely in the presence of 1 equiv of TBACl, whereas aldehyde **7a** was isolated under these conditions in good yield and high selectivity. This example underlines once more the enhanced stability of phenol diazonium salts compared to other arene diazonium salts to nucleophiles. The required aldehyde **7c** was obtained from **7a** by silylation in high yield (Scheme 4).

Synthesis of 4a and Non-natural Analogues. For the synthesis of the natural product (3*S*,7*R*)-5,6-dehydro-de-*O*-methyl centrolobine (**4a**) and its non-natural analogues **4c–e**, the TBS-protected dihydropyran **5a** was reacted with phenol diazonium salts **6a** and **6c–e** using $Pd(OAc)_2$ as a precatalyst, basic conditions, and acetonitrile as a solvent (Scheme 5).

The mono-TBS-protected diarylheptanoids **17a** and **17c–e** were obtained in fair to excellent yields and diastereomeric ratios exceeding 19:1, as determined by ^1H NMR spectroscopy. Most importantly, subsequent double bond migration, which is known to be a problem in Pd-catalyzed arylations with iodoarenes,[61] is fully suppressed in these reactions. The synthesis of **4a** and its non-natural analogues **4c–e** was completed by deprotection with TBAF. All spectroscopical and physical data obtained for synthetic **4a** match those reported by Kadota et al. for the natural product,[10] except for the specific rotation. While these authors reported a value of $[\alpha]^{24}_D = -12.3$ (*c* 0.335, methanol), we found not only a different value but also a different sign for the specific rotation, that is, $[\alpha]^{24}_D = +48.7$ (*c* 0.37, methanol). We are confident that we actually synthesized (3*S*,7*R*)-configured **4a** because the assigned relative configuration was confirmed by single-crystal X-ray structure analysis of our synthetic material,[62] and the absolute configuration at stereocenter C3 (diarylheptanoid numbering, refer to Scheme 1) is a result of Leighton's well-established allylation method, using the (*S*,*S*)-configured reagent derived from cyclohexanediamine.[43] Furthermore, we previously used (*S*)-**8** to synthesize (−)-centrolobine, whose absolute configuration has been secured by total synthesis,[63] chiroptical methods,[64] and very recently by crystallographic methods.[19] Nevertheless, we tried to unambigously prove the assigned (3*S*,7*R*)-configuration of dextrorotatory *trans*-de-*O*-methyl-5,6-dehydrocentrolobines **4** by X-ray crystallography using anomalous scattering. The presence of heavy atoms is required for this method, and the bromo-analogue **4e** seemed to

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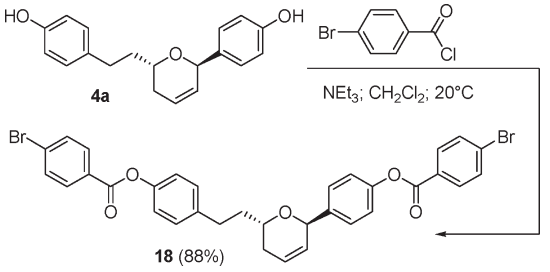
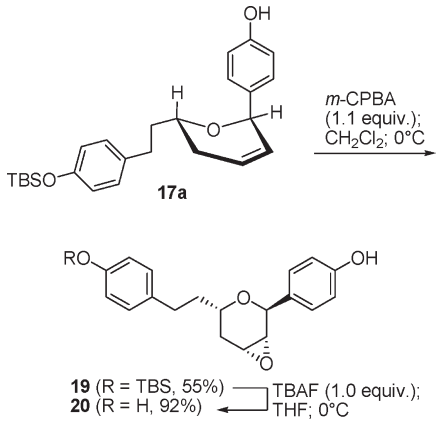
Scheme 6. Synthesis of a Bis-4-bromobenzoate Derivative 18



Scheme 7. Synthesis of a Non-natural Dihydropyran Oxide-Type Diarylheptanoid 20



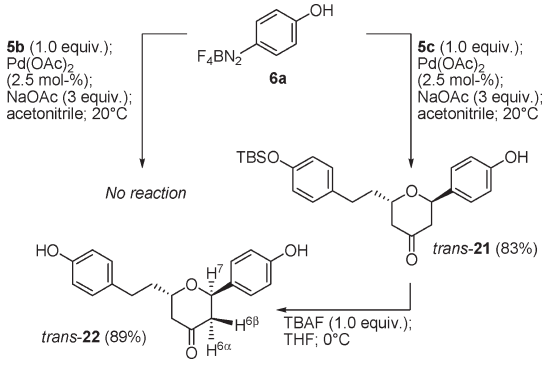
be a suitable derivative. Unfortunately, **4e** was repeatedly isolated as a viscous oil, and all attempts to obtain single crystals failed. Therefore, **4a** was converted into its bis-4-bromobenzoate **18**, which crystallized nicely. However, the crystals were of insufficient quality for single-crystal structure analysis (Scheme 6).

We cannot conclusively decide whether the (3*S*,7*R*)-configuration assigned to the natural product is correct or not. However, we are confident that (3*S*,7*R*)-**4a** is (+)-**4a**, hence (−)-**4a** must be (3*R*,7*S*)-**4a**. It should be noted that the originally assigned absolute configuration of naturally occurring (−)-**4a** has recently been challenged by Rogano and Rüedi, who also proposed a revision to (3*R*,7*S*)-**4a**, based on chiroptical comparison.[19]

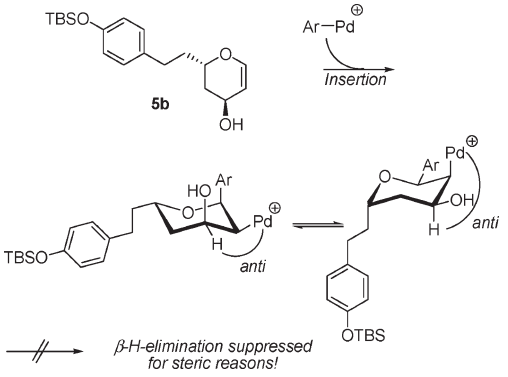
Apart from centrolobines (**2** and *ent*-**2**) and 5,6-dehydrocentrolobines (**3** or *ent*-**3**, **4a** or *ent*-**4a**), several pyran-type diarylheptanoids bearing oxygen substituents in the 5- or 6-position were isolated from various sources, including *Alpinia blepharocalyx*[10] and *Zingiber officinale*.[65] We synthesized a non-natural 5,6-dioxygenated diarylheptanoid **20** from **17a** by epoxidation with *m*-CPBA and subsequent desilylation. The phenol substituent at C7, which adopts predominantly a pseudoaxial orientation, efficiently directs the epoxidizing agent to the opposite face of the C−C double bond, resulting in a high *trans*-diastereoselectivity, while the sterically less demanding and more remote alkyl chain at C3 seems to have considerably less influence on the stereochemical outcome (Scheme 7).

With a view toward the synthesis of pyran-type diarylheptanoids which are oxygenated at C5 but not at C6, we investigated the Mizoroki−Heck reactions of dihydropyrans **5b** and **5c**. It is evident from the examples discussed above (Scheme 5) that a substituent at

Scheme 8. Pd-Catalyzed Arylation of 5b and 5c



Scheme 9. Attempted Arylation of 5b



C3 exerts a strong influence on the stereochemical course of the Pd-catalyzed arylation, and we were therefore intrigued by the opportunity to test the effect of a second substituent in close proximity to the reacting double bond. Using the conditions previously established for the arylation with phenol diazonium salts, the *cis*-configured dihydropyran **5c** was reacted with **6a**. This reaction yields exclusively tetrahydropyranone *trans*-**21** in good yield and high diastereoselectivity. Deprotection with TBAF in THF proceeded smoothly to *trans*-**22** without noticeable epimerization (Scheme 8).

Our assignment of a *trans*-configuration is based on a comparison with the spectroscopical data reported for a similar compound, which was previously synthesized by Clarke and Martin in the course of a synthesis of *rac*-centrolobine via a Maitland−Japp reaction. We observed for the signal of H7 a pseudotriplet at δ = 5.18 ppm with a coupling constant of 5.4 Hz, which matches the data reported by Clarke and Martin very well. These authors also isolated and characterized a *cis*-epimer, for which H7 appears as a doublet of doublets with $J(H6^{\alpha}\text{-}H7)$ of 10.7 Hz and $J(H6^{\beta}\text{-}H7)$ of 3.8 Hz.[66]

The reaction of the *trans*-configured diastereomer **5b** under otherwise identical conditions resulted in a quantitative recovery of the starting material. This failure can be understood by assuming a dominant directing effect of the substituent at C3, which directs the incoming σ-aryl-Pd complex to the opposite face of the C6−C7 double bond. Upon *cis*-insertion, however, the catalytic cycle stops because no β-hydrogen in the required *syn*-orientation is available and subsequent β-hydride elimination is therefore inhibited (Scheme 9).

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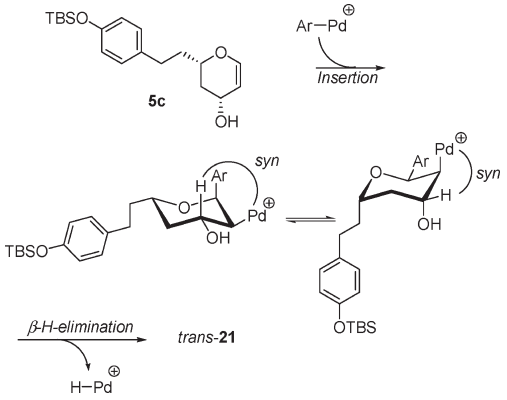
Scheme 10. Arylation of 5c



In contrast to **5b**, the *cis*-configured **5c** reacts with the σ-aryl-Pd complex to an insertion product with a favorable *syn*-orientation of Pd and β-hydrogen, and the catalytic cycle can proceed with the β-hydride elimination to an enol, which tautomerizes to the ketone *trans*-**21** (Scheme 10).

CONCLUSIONS

In summary, we report the first total synthesis of the diarylheptanoid *trans*-(+)-5,6-dehydro-de-*O*-methyl centrolobine, using a Pd-catalyzed coupling of a phenol diazonium salt as the key step. Our results suggest that the original assignment of the (3*S*,7*R*)-configuration to the naturally occurring laevorotatory compound should be revised to (3*R*,7*S*). Future work in this area will show whether or not this revision has implications on the assigned absolute configurations of other *trans*-configured pyran-type diarylheptanoids. From a methodology point of view, we could demonstrate that phenol diazonium salts are interesting and versatile reagents for Pd-catalyzed C−C bond-forming reactions. They are not only highly reactive arylating agents but also enable a considerable reduction of protecting group effort in target molecule synthesis.

EXPERIMENTAL SECTION

(*S*)-*tert*-Butyl(4-(2-(3,6-dihydro-2*H*-pyran-2-yl)ethyl)phenoxy)dimethylsilane (9). To a solution of **8** (1.00 g, 2.9 mmol) in toluene (10 mL) was added first generation Grubbs' catalyst **A** (60 mg, 2.5 mol %). The solution was heated to 80 °C for 2 h, cooled to ambient temperature, and all volatiles were evaporated. The residue was purified by chromatography on silica (eluent hexanes/MTBE 10:1) to give **9** (0.80 g, 2.5 mmol, 86%) as a colorless liquid: $[\alpha]^{24}_D = +20.7$ (*c* 0.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 5.80 (ddd, *J* = 10.7, 4.4, 2.2 Hz, 1H), 5.72 (dm, *J* = 10.2 Hz, 1H), 4.22−4.15 (2H), 3.46 (ddd, *J* = 13.3, 8.8, 4.4 Hz, 1H), 2.74 (ddd, *J* = 14.0, 9.4, 5.5 Hz, 1H), 2.63 (ddd, *J* = 13.8, 9.1, 7.2 Hz, 1H), 2.06−1.95 (2H), 1.94−1.65 (2H), 0.98 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6 (0), 134.8 (0), 129.3 (1), 126.4 (1), 124.3 (1), 119.8 (1), 72.7 (1), 65.9 (2), 37.7 (2), 31.1 (2), 30.9 (2), 25.7 (3), 18.2 (0), −4.4 (3); IR (neat) ν 2928 (w), 1508 (s), 1250 (s), 1091 (m); MS (ESI) *m*/*z* 319 ([M + H]$^+$,100), 297 (100), 281 (20), 221 (50); HRMS (ESI) *m*/*z* calcd for $C_{19}H_{31}O_2Si[M+H]^+$ 319.2093, found 319.2101.

Synthesis of Dihydropyran Oxides 10a,b. To a solution of **9** (0.75 g, 2.4 mmol) in CH_2Cl_2 (50 mL) was added *m*-CPBA (0.60 g, 2.4 mmol) at 0 °C. The resulting suspension was warmed to ambient temperature and stirred for 6 h. It was then washed with a saturated aqueous solution of Na_2SO_3 (20 mL), the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated. The resulting diastereomers were separated by column chromatography on silica (eluent hexanes/MTBE 3:1) to give **10a** (280 mg, 0.84 mmol, 35%) and **10b** (290 mg, 0.87 mmol, 36%) as colorless liquids. **Analytical data for (4-(2-((1*R*,4*S*,6*S*)-3,7-dioxabicyclo[4.1.0]heptan-4-yl)ethyl)phenoxy)-(*tert*-butyl)dimethylsilane (10a):** $[\alpha]^{24}_D = +13.4$ (*c* 0.35, CH_2Cl_2); ^{1}H NMR (300 MHz, $CD_3C(O)CD_3$) δ 7.06 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 4.19 (dd, *J* = 13.5, 4.1 Hz, 1H), 3.75 (d, *J* = 13.5 Hz, 1H), 3.31−3.17 (3H), 2.66 (ddd, *J* = 13.8, 8.4, 5.4 Hz, 1H), 2.53 (ddd, *J* = 13.9, 8.3, 8.3 Hz, 1H), 1.97 (ddd, *J* = 14.5, 2.3, 2.3 Hz, 1H), 1.69−1.56 (3H), 0.98 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CD_3C(O)CD_3$) δ 154.6 (0), 136.0 (0), 130.2 (1), 120.7 (1), 69.7 (1), 66.4 (2), 51.5 (1), 51.1 (1), 38.5 (2), 32.4 (2), 31.6 (2), 26.1 (3), 18.8 (0), −4.2 (3). **Analytical data for (4-(2-((1*S*,4*S*,6*R*)-3,7-dioxabicyclo-[4.1.0]heptan-4-yl)ethyl)phenoxy)-(*tert*-butyl)dimethylsilane (10b):** $[\alpha]^{24}_D = +17.6$ (*c* 0.34, CH_2Cl_2); ^{1}H NMR (300 MHz, $CD_3C(O)CD_3$) δ 7.06 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 4.07 (d, *J* = 13.3 Hz, 1H), 3.76 (dd, *J* = 13.3, 0.5 Hz, 1H), 3.31 (dd, *J* = 5.7, 4.2 Hz, 1H), 3.10 (m, 1H), 2.96 (d, *J* = 4.1 Hz, 1H), 2.69−2.48 (2H), 1.91 (ddd, *J* = 15.1, 5.8, 3.9 Hz, 1H), 1.66−1.55 (3H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CD_3C(O)CD_3$) δ 154.6 (0), 136.0 (0), 130.3 (1), 120.7 (1), 72.6 (1), 65.4 (2), 50.0 (1), 49.4 (1), 38.6 (2), 31.4 (2), 30.7 (2), 26.1 (3), 18.2 (0), −4.2 (3); IR (neat) ν 2931 (w), 2856 (w), 1608 (w), 1509 (s), 1252 (s); MS (EI) *m*/*z* 334 ([M]$^+$, 15), 264 (37), 219 (100); HRMS (EI) calcd for $C_{19}H_{30}O_3Si[M]^+$ 334.1964, found 334.1970. Anal. Calcd for $C_{19}H_{30}O_3Si$: C, 68.2; H, 9.0. Found: C, 67.9; H, 8.9.

(2*S*,4*S*)-2-(4-(*tert*-Butyldimethylsilyloxy)phenethyl)-3,4-dihydro-2*H*-pyran-4-ol (5b). To a solution of diisopropylamine (0.20 mL, 1.5 mmol) in THF (5.0 mL) was added BuLi (2.5 M solution in hexanes, 0.8 mL, 2.0 mmol) at 0 °C. The solution was stirred at this temperature for 1 h, and then a solution of **10a** (330 mg, 1.0 mmol) in THF (5.0 mL) was added dropwise at this temperature. Stirring was continued for 5 h, and a saturated solution of NH_4Cl (20 mL) was added. The organic layer was separated, and the aqueous layer was extracted with MTBE (150 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica (eluent hexanes/MTBE 1:1) to give **5b** (170 mg, 0.51 mmol, 51%) as a colorless liquid: $[\alpha]^{24}_D = -84.9$ (*c* 0.79, CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6) δ 6.98 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.39 (d, *J* = 6.1 Hz, 1H), 4.70 (m, 1H), 3.89−3.79 (2H), 2.75 (ddd, *J* = 13.9, 10.3, 5.4 Hz, 1H), 2.58 (ddd, *J* = 13.9, 10.0, 6.5 Hz, 1H), 1.81 (dddd, *J* = 13.7, 8.4, 8.4, 5.5 Hz, 1H), 1.68−1.54 (2H), 1.34 (ddd, *J* = 13.9, 12.2, 3.9 Hz, 1H), 1.01 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 154.6 (0), 147.3 (1), 135.4 (0), 130.1 (1), 120.7 (1), 103.8 (1), 71.0 (1), 60.1 (1), 37.9 (2), 37.7 (2), 31.5 (2), 26.3 (3), 18.8 (0), −4.0 (3); IR (neat) ν 3345 (w), 2928 (m), 2858 (m), 1639 (m), 1509 (s), 1241 (s); MS (EI) *m*/*z* 334 ([M]$^+$, 52), 221 (60), 181 (100); HRMS (EI) calcd for $C_{19}H_{30}O_3Si[M]^+$ 334.1959, found 334.1950. Anal. Calcd for $C_{19}H_{30}O_3Si$: C, 68.2; H, 9.0. Found: C, 68.0; H, 8.9.

(2*S*,4*R*)-2-(4-(*tert*-Butyldimethylsilyloxy)phenethyl)-3,4-dihydro-2*H*-pyran-4-ol (5c). To a solution of 2,2,6,6-tetramethylpiperidine (0.30 mL, 1.8 mmol) in THF (10 mL) was added a solution of BuLi (2.5 M solution in hexanes, 0.60 mL, 1.5 mmol) at −40 °C. The solution was stirred for 1 h, and then a solution of **10b** (340 mg, 1.0 mmol) in THF (10 mL) was added dropwise at −40 °C. Stirring was continued for 2 h, and the reaction was quenched by addition of a saturaed aqueous solution of NH_4Cl-Lösung (20 mL). The organic layer was separated, and the aqueous layer was extracted with MTBE (150 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica (eluent hexanes/MTBE 1:1) to give **5c** (200 mg, 0.60 mmol, 60%) as a colorless liquid: $[\alpha]^{24}_D = -9.4$ (*c* 0.33, CH_2Cl_2);

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^{1}H NMR (300 MHz, C_6D_6) δ 6.98 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H), 6.28 (dd, J = 6.2, 1.0 Hz, 1H), 4.59 (dt, J = 6.2, 1.9 Hz, 1H), 4.09 (m, 1H), 3.64 (dddd, J = 13.0, 10.9, 4.3, 2.0 Hz, 1H), 2.67 (ddd, J = 13.8, 9.4, 6.5 Hz, 1H), 2.55 (ddd, J = 13.8, 9.5, 6.9 Hz, 1H), 1.82 (dddd, J = 13.9, 8.6, 8.6, 5.4 Hz, 1H), 1.68 (ddt, J = 12.9, 6.5, 1.7 Hz, 1H), 1.54 (dddd, J = 14.0, 9.9, 6.9, 4.3 Hz, 1H), 1.40 (ddd, J = 13.0, 11.3, 9.2 Hz, 1H), 1.01 (s, 9H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, C_6D_6) δ 154.6 (0), 145.2 (1), 135.3 (0), 130.1 (1), 120.7 (1), 106.6 (1), 74.4 (1), 63.4 (1), 38.8 (2), 37.8 (2), 31.3 (2), 26.3 (3), 18.8 (0), −4.0 (3); IR (neat) ν 2928 (w), 2857 (w), 1640 (w), 1509 (s), 1251 (s); MS (EI) m/z 334 ([M]$^+$, 10), 264 (20), 221 (100); HRMS (EI) calcd for $C_{19}H_{30}O_3Si$[M]$^+$ 334.1964, found 334.1976. Anal. Calcd for $C_{19}H_{30}O_3Si$: C, 68.2; H, 9.0. Found: C, 67.6; H, 8.8.

4-(*tert*-Butyldimethylsilyloxy)benzaldehyde (12) (ref 55). To a solution of 4-hydroxybenzaldehyde (**11**, 4.00 g, 33.0 mmol) in CH_2Cl_2 (25 mL) was added imidazole (4.50 g, 66.0 mmol) at 0 °C, followed after 15 min by TBSCl (5.00 g, 33.0 mmol). The mixture was stirred for 12 h at ambient temperature, diluted with MTBE (10 mL), and washed with brine (25 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica (eluent cyclohexane/MTBE 10:1) to give **12** (6.40 g, 27.0 mmol, 82%) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.78 (d, J = 8.7 Hz, 2H), 6.94 (d, J = 8.5 Hz, 2H), 0.99 (s, 9H), 0.25 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.9 (1), 161.5 (0), 131.9 (1), 130.4 (1), 120.5 (0), 25.5 (3), 18.2 (0), −4.4 (3).

(*E*)-Ethyl-3-(4-(*tert*-butyldimethylsilyloxy)phenyl)acrylate (13) (ref 55). To a solution of triethylphosphonoacetate (5.7 mL, 29.0 mmol) in THF (50 mL) was added NaH (60% dispersion in mineral oil, 1.10 g, 29.0 mmol) at 0 °C. Stirring was continued for 15 min, and **12** (6.20 g, 26.0 mmol) was added. The resulting suspension was stirred for 12 h and washed with water (25 mL) and then with a saturated aqueous solution of $NaHCO_3$ (25 mL). The organic layer was separated, and the aqueous layer was extracted with MTBE (150 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica (eluent cyclohexane/MTBE 10:1) to give **13** (7.10 g, 23.0 mmol, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, J = 16.0 Hz, 1H), 7.41 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.30 (d, J = 16.0 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H), 0.98 (s, 9H), 0.22 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3 (0), 157.8 (0), 144.3 (0), 129.6 (1), 127.8 (1), 120.5 (1), 115.9 (1), 60.3 (2), 25.6 (3), 18.2 (0), 14.4 (3), −4.4 (3).

Ethyl-3-(4-(*tert*-butyldimethylsilyloxy)phenyl)propanoate (14) (ref 55). To a solution of **13** (7.10 g, 23.0 mmol) in ethanol (50 mL) was added $Pd(OH)_2$/C (10 wt %, 71 mg). The solution was saturated with hydrogen and stirred under an atmosphere of hydrogen (1 bar) for 12 h at ambient temperature. The suspension was filtered through Celite, and all volatiles were removed in vacuo. The residue was purified by chromatography on silica (eluent cyclohexane/MTBE 5:1) to give **14** (7.00 g, 23.0 mmol, 99%) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (d, J = 8.6 Hz, 2H), 6.75 (d, J = 7.1 Hz, 2H), 4.12 (q, J = 7.1 Hz, 2H), 2.88 (t, J = 7.8 Hz, 2H), 2.57 (t, J = 7.7 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0 (0), 154.0 (0), 133.2 (0), 129.1 (1), 120.0 (1), 60.3 (2), 36.2 (2), 30.2 (2), 25.7 (3), 18.2 (0), 14.2 (3), −4.5 (3); MS (ESI) m/z 309 ([M + H]$^+$, 55), 263 (50), 221 (100); HRMS (ESI) m/z calcd for $C_{17}H_{29}O_3Si$[M + H]$^+$ 309.1886, found 309.1859.

3-(4-(*tert*-Butyldimethylsilyloxy)phenyl)propanal (7c) (ref 54). To a solution of **14** (3.00 g, 9.7 mmol) in CH_2Cl_2 (50 mL) was slowly added DIBAl-H (1.1 M solution in cyclohexane, 10.5 mL, 11.6 mmol) at 78 °C. The reaction was quenched after 2 h by addition of methanol (20 mL) and warmed to ambient temperature. HCl (aqueous, 1 M, 20 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (100 mL), and the combined organic layers were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica (eluent hexanes/MTBE 5:1) to give **7c** (2.50 g, 9.5 mmol, 98%) as a colorless liquid. Alternatively, the title compound was synthesized from **7a**: To a solution of **7a** (0.64 g, 4.3 mmol) in CH_2Cl_2 (10 mL) was added imidazole (0.32 g, 4.7 mmol) at 0 °C. The mixture was stirred for 15 min, and TBSCl (0.71 g, 4.7 mmol) was added. It was allowed to warm to ambient temperature, and stirring was continued for 12 h. The resulting suspension was diluted with MTBE (25 mL) and washed with brine (10 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (40 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica (eluent cyclohexane/MTBE 5:1) to give **7c** (1.05 g, 4.0 mmol, 92%) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (t, J = 1.5 Hz, 1H), 7.04 (d, J = 8.6 Hz, 2H), 6.76 (d, J = 8.5 Hz, 2H), 2.92−2.87 (2H), 2.78−2.70 (2H), 0.98 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.8 (0), 154.0 (0), 132.9 (0), 129.1 (1), 120.1 (1), 45.5 (2), 27.3 (2), 25.7 (3), 18.2 (0), −4.5 (3); IR (neat) ν 2955 (w), 2929 (w), 2857(w), 1724 (m), 1509 (s), 1251 (s), 911 (s); MS (ESI) m/z 265 ([M + H]$^+$, 20), 221 (100); HRMS (ESI) m/z calcd for $C_{15}H_{25}O_2Si$[M+H]$^+$ 265.1624, found 265.1646. Anal. Calcd for $C_{15}H_{24}O_2Si$: C, 68.1; H, 9.2. Found: C, 67.9; H, 9.4.

3-(4-Hydroxyphenyl)propanal (7a) (ref 67). To a suspension of **6a** (208 mg, 1.0 mmol), allyl alcohol (**15**, 140 μL, 2.0 mmol), NaOAc (246 mg, 3.0 mmol), and TBACl (278 mg, 1.0 mmol) in CH_3CN (5.0 mL) was added $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) at 0 °C. The mixture was stirred for 6 h at this temperature, all volatiles were evaporated, and the residue was chromatographed on silica (eluent hexanes/MTBE 2:1) to give **7a** (104 mg; 0.7 mmol, 69%) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (t, J = 1.4 Hz, 1H), 7.06 (d, J = 8.5 Hz, 2H), 6.76 (d, J = 8.5 Hz, 2H), 4.85 (s, 1H), 2.93−2.85 (2H), 2.78−2.70 (2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.7 (1), 154.1 (0), 132.1 (0) 129.3 (1), 115.4 (1), 45.4 (2), 27.2 (2); IR (neat) ν 3368 (m), 1708 (s), 1612 (m), 1514 (s), 1444 (m), 1218 (s); MS (ESI) m/z 151 ([M + H]$^+$, 34), 133 (100); HRMS (ESI) calcd for $C_9H_{11}O_2$[M + H]$^+$ 151.0759, found 151.0758. Anal. Calcd for $C_9H_{10}O_2$: C, 72.0; H, 6.7. Found: C, 71.7; H, 6.7.

(*E*)-4-(3-Hydroxyprop-1-enyl)phenol (16a) (ref 68). To a suspension of **6a** (208 mg, 1.0 mmol), allyl alcohol (**15**, 140 μL, 2.0 mmol), and NaOAc (246 mg, 3.0 mmol) in methanol (5.0 mL) was added $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) at 0 °C. The reaction mixture was stirred at this temperature for 6 h and then evaporated. The residue was purified by chromatography on silica (eluent hexanes/MTBE 1:1) to give **16a** (108 mg, 0.72 mmol, 72%) as a colorless solid: mp 117−119 °C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.23 (d, J = 8.5 Hz, 2H), 6.73 (d, J = 8.6 Hz, 2H), 6.50 (d, J = 15.9 Hz, 1H), 6.16 (dt, J = 15.8, 5.9 Hz, 1H), 4.18 (dd, J = 5.9, 1.4 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD) δ 158.3, 132.0, 130.1, 128.8, 126.8, 116.4, 64.1; IR (neat) ν 3295 (w), 1605 (m), 1509 (s), 1246 (s); MS (ESI) m/z 151 ([M + H]$^+$, 100), 133 (60); HRMS (ESI) calcd for $C_9H_{11}O_2$[M + H]$^+$ 151.0759, found 151.0745. Anal. Calcd for $C_9H_{10}O_2$: C, 72.0; H, 6.7. Found: C, 71.5; H, 6.7.

(*E*)-3-(4-Methoxyphenyl)prop-2-en-1-ol (16b) (ref 69). To a suspension of **6b** (222 mg, 1.0 mmol), allyl alcohol (**15**, 140 μL, 2.0 mmol), and NaOAc (246 mg, 3.0 mmol) in methanol (5.0 mL) was added $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) at 0 °C. The reaction mixture was stirred at this temperature for 6 h, evaporated, and the residue was purified by chromatography on silica (eluent hexanes/MTBE 5:1) to give **16b** (90 mg, 0.55 mmol, 55%) as a colorless solid: mp 78−80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 6.55 (d, J = 15.9 Hz, 1H), 6.23 (dt, J = 15.9, 5.9 Hz, 1H), 4.29 (t, J = 4.5 Hz, 2H), 3.81 (s, 3H), 1.58 (s, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3 (0), 130.9 (1), 129.4 (0), 127.6 (1), 126.3 (1), 114.0 (1), 63.9 (2), 55.3 (3); IR (neat) ν 3359 (w), 2841 (w), 1605 (m), 1512 (m),

1245 (s); MS (ESI) m/z 165 ($[M + H]^+$, 12), 147 (100); HRMS (ESI) calcd for $C_{10}H_{13}O_2[M + H]^+$ 165.0916, found 165.0911. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.2; H, 7.4. Found: C, 72.9; H, 7.3.

4-((2*S*,6*R*)-6-(4-(*tert*-Butyldimethylsilyloxy)phenethyl)-5,6-dihydro-2*H*-pyran-2-yl)phenol (17a). To a solution of **5a** (100 mg, 0.31 mmol), **6a** (65 mg, 0.31 mmol), and NaOAc (76 mg, 0.93 mmol) in acetonitrile (5.0 mL) was added $Pd(OAc)_2$ (0.8 mg, 2.5 mol %). The mixture was stirred at ambient temperature until the evolution of gas had ceased (approximately 3 h), evaporated, and the residue was suspended in MTBE (10 mL). This suspension was filtered through Celite, all volatiles were removed in vacuo, and the residue was purified by chromatography on silica (eluent hexanes/MTBE 5:1) to give **17a** (120 mg, 0.29 mmol, 94%) as a colorless solid: mp 121−123 °C; $[\alpha]^{24}_D$ = +46.1 (c 1.05, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 6.75 (d, J = 8.5 Hz, 2H), 6.62 (d, J = 8.5 Hz, 2H), 6.03 (ddd, J = 10.3, 4.4, 2.2 Hz, 1H), 5.95 (m, 1H), 5.23 (br s, 1H), 5.01 (s, 1H), 3.48 (dddd, J = 4.0, 4.0, 8.6, 8.6 Hz, 1H), 2.62 (ddd, J = 13.8, 8.8, 5.1 Hz, 1H), 2.41 (ddd, J = 13.8, 8.2, 8.2 Hz, 1H), 2.02 (m, 2H), 1.82 (dddd, J = 13.8, 8.7, 8.6, 5.1 Hz, 1H), 1.62 (dddd, J = 12.5, 8.5, 8.5, 3.8 Hz, 1H), 0.97 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2 (0), 153.4 (0), 134.7 (0), 133.4 (0), 130.0 (1), 129.3 (1), 127.5 (1), 126.0 (1), 119.7 (1), 115.0 (1), 73.7 (1), 66.0 (1), 37.5 (2), 31.1 (2), 30.7 (2), 25.7 (3), 18.2 (0), −4.4 (3); IR (neat) ν 3267 (w), 2927 (w), 2856 (w), 1508 (s), 1250 (s), 1168 (m); MS (ESI) m/z 411 ($[M + H]^+$, 100), 393 (75), 221 (25); HRMS (ESI) calcd for $C_{25}H_{35}O_3Si[M + H]^+$ 411.2355, found 411.2200. Anal. Calcd for $C_{25}H_{34}O_3Si$: C, 73.1; H, 8.4. Found: C, 73.1; H, 8.5.

Methyl-5-((2*S*,6*R*)-6-(4-(*tert*-butyldimethylsilyloxy)phenethyl)-5,6-dihydro-2*H*-pyran-2-yl)-2-hydroxybenzoate (17c). As described above for **17a**, the title compound was obtained from **5a** (318 mg, 1.0 mmol) and **6c** (266 mg, 1.0 mmol) as a colorless liquid: yield 444 mg (95%); $[\alpha]^{24}_D$ = +60.3 (c 0.50, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.81 (s, 1H), 7.82 (d, J = 2.3 Hz, 1H), 7.55 (dd, J = 8.6, 2.3 Hz, 1H), 7.01 (d, J = 8.6 Hz, 1H), 6.75 (d, J = 8.4 Hz, 2H), 6.61 (d, J = 8.5 Hz, 2H), 6.07 (ddd, J = 10.3, 4.6, 2.2 Hz, 1H), 5.95 (dm, J = 10.2 Hz, 1H), 5.21 (br s, 1H), 3.95 (s, 3H), 3.43 (dddd, J = 8.6, 8.6, 4.0, 4.0 Hz, 1H), 2.64 (ddd, J = 13.8, 9.0, 4.7 Hz, 1H), 2.40 (ddd, J = 13.9, 8.2, 8.2 Hz, 1H), 2.09−1.98 (2H), 1.81 (dddd, J = 13.8, 8.7, 8.7, 5.1 Hz, 1H), 1.63 (dddd, J = 11.7, 8.1, 8.1, 3.3 Hz, 1H), 0.96 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6 (0), 161.3 (0), 153.5 (0), 136.2 (1), 134.6 (0), 132.1 (0), 129.7 (1), 129.2 (1), 127.0 (1), 126.6 (1), 119.6 (1), 117.6 (1), 111.8 (0), 73.4 (1), 66.1 (1), 52.3 (3), 37.4 (2), 31.1 (2), 30.7 (2), 25.7 (3), 18.2 (0), −4.5 (3); IR (neat) ν 2929 (w), 2857 (w), 1677 (m), 1509 (m), 1250 (s), 1208 (s), 1087 (m); MS (EI) m/z 468 (20), 411 (45), 379 (50), 207 (100), 163 (70); HRMS (EI) calcd for $C_{27}H_{36}O_5Si[M]^+$ 468.2332, found 468.2300. Anal. Calcd for $C_{27}H_{36}O_5Si$: C, 69.2; H, 7.7. Found: C, 68.9; H, 7.6.

4-((2*S*,6*R*)-6-(4-(*tert*-Butyldimethylsilyloxy)phenethyl)-5,6-dihydro-2*H*-pyran-2-yl)-2-nitrophenol (17d). As described above for **17a**, the title compound was obtained from **5a** (318 mg, 1.0 mmol) and **6d** (253 mg, 1.0 mmol) as a colorless liquid: yield 280 mg (62%); $[\alpha]^{24}_D$ = +87.2 (c 0.40, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.63 (s, 1H), 8.06 (d, J = 2.1 Hz, 1H), 7.69 (dd, J = 8.6, 2.1 Hz, 1H), 7.18 (d, J = 8.6 Hz, 1H), 6.81 (d, J = 8.4 Hz, 2H), 6.63 (d, J = 8.4 Hz, 2H), 6.12 (ddm, J = 9.9, 4.7 Hz, 1H), 5.96 (dm, J = 10.2 Hz, 1H), 5.23 (br s, 1H), 3.41 (dddd, J = 8.6, 8.6, 4.4, 4.4 Hz, 1H), 2.65 (ddd, J = 14.2, 9.2, 5.2 Hz, 1H), 2.42 (ddd, J = 13.9, 8.2, 8.2 Hz, 1H), 2.11−2.02 (2H), 1.84 (dddd, J = 14.0, 8.8, 8.8, 5.3 Hz, 1H), 1.76−1.61 (dddd, J = 13.4, 7.5, 7.5, 4.0 Hz, 1H), 0.97 (s, 9H), 0.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 153.6, 137.8, 134.3, 133.9, 133.0, 129.1, 127.4, 126.1, 124.3, 120.0, 119.7, 72.6, 66.6, 37.2, 30.9, 30.7, 25.7, 18.2, −4.5; IR (neat) ν 2928 (w), 2857 (w), 1628 (w), 1537 (m), 1509 (s), 1249 (s), 1170 (m); MS (EI) m/z 318 (25), 211 (50), 163 (40), 133 (70), 107 (100); HRMS (EI) calcd for $C_{25}H_{33}NO_5Si[M]^+$ 455.2128, found 455.2119. Anal. Calcd for $C_{25}H_{33}NO_5Si$: C, 65.9; H, 7.3. Found: C, 65.5; H, 7.5.

2-Bromo-4-((2*S*,6*R*)-6-(4-(*tert*-butyldimethylsilyloxy)phenethyl)-5,6-dihydro-2*H*-pyran-2-yl)-phenol (17e). As described above for **17a**, the title compound was obtained from **5a** (640 mg, 2.0 mmol) and **6e** (690 mg, 2.4 mmol) as a colorless liquid: yield 550 mg (56%); $[\alpha]^{24}_D$ = +51.4 (c 0.5, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 2.0 Hz, 1H), 7.28 (dd, J = 6.4, 2.0 Hz, 1H), 7.02 (d, J = 8.3 Hz, 1H), 6.77 (d, J = 8.5 Hz, 2H), 6.63 (d, J = 8.5 Hz, 2H), 6.05 (ddd, J = 10.1, 4.6, 2.2 Hz, 1H), 5.92 (dm, J = 10.1 Hz, 1H), 5.54 (br s, 1H), 5.19 (br s, 1H), 3.44 (dddd, J = 8.6, 8.6, 4.0, 4.0 Hz, 1H), 2.63 (ddd, J = 13.9, 8.8, 5.2 Hz, 1H), 2.42 (ddd, J = 13.8, 8.2, 8.2 Hz, 1H), 2.10−1.94 (2H), 1.81 (dddd, J = 13.8, 8.6, 8.6, 5.2 Hz, 1H), 1.64 (dddd, J = 12.5, 8.5, 8.5, 3.9 Hz, 1H), 0.97 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5 (0), 151.8 (0), 135.11 (0), 134.6 (0), 131.9 (1), 129.5 (1), 129.2 (1), 126.9 (1), 126.6 (1), 119.7 (1), 115.8 (1), 110.0 (0), 73.1 (1), 66.2 (1), 37.4 (2), 31.0 (2), 30.6 (2), 25.7 (3), 18.2 (0), −4.4 (3); IR (neat) ν 3263 (w), 2928 (m), 1606 (m), 1508 (s), 1251 (s), 1169 (m), 1059 (m); MS (ESI) m/z 491 (75), 489 ($[M + H]^+$, 80), 471 (100), 221 (30); HRMS (ESI) calcd for $C_{25}H_{34}BrO_3Si[M + H]^+$ 489.1415, found 489.1461. Anal. Calcd for $C_{25}H_{33}BrO_3Si$: C, 61.3; H, 6.8. Found: C, 61.2; H, 6.8.

(+)-2-*epi*-5,6-Dehydro-de-*O*-methylcentrolobine (4a). To a solution of **17a** (120 mg, 0.29 mmol) in THF (10 mL) was added TBAF-trihydrate (92 mg, 0.29 mmol) at 0 °C. The mixture was stirred for 1 h, washed with brine (5 mL), and the aqueous layer was extracted with ethyl acetate (30 mL). The combined organic layers were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica (eluent hexanes/MTBE 1:1) to give **4a** (84 mg, 0.28 mmol, 97%) as colorless crystals: mp 153−155 °C; $[\alpha]^{24}_D$ = +48.7 (c 0.37, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.21 (d, J = 8.5 Hz, 2H), 6.80 (d, J = 8.6 Hz, 2H), 6.62 (d, J = 8.6 Hz, 2H), 6.53 (d, J = 8.6 Hz, 2H), 6.01 (ddd, J = 10.2, 4.6, 2.1 Hz, 1H), 5.90 (dm, J = 10.2 Hz, 1H), 5.16 (br s, 1H), 3.48 (dddd, J = 8.7, 8.7, 4.1, 4.1 Hz, 1H), 2.51 (ddd, J = 13.2, 7.8, 5.2 Hz, 1H), 2.35 (ddd, J = 13.6, 8.1, 8.1 Hz, 1H), 2.05−1.90 (2H), 1.72 (dddd, J = 13.9, 8.8, 8.8, 5.2 Hz, 1H), 1.56 (dddd, J = 12.0, 8.3, 8.3, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 158.5 (0), 156.2 (0), 134.2 (0), 133.0 (0), 131.3 (1), 130.6 (1), 128.8 (1), 127.0 (1), 116.1 (1), 116.1 (1), 75.6 (1), 66.9 (1), 39.0 (2), 32.4 (2), 31.6 (2); IR (neat) ν 3290 (m), 2923 (w), 1612 (m), 1512 (s), 1233 (m); MS (ESI) m/z 297 ($[M + H]^+$, 60), 279 (100), 133 (35), 107 (40); HRMS (ESI) calcd for $C_{19}H_{21}O_3[M + H]^+$ 297.1491, found 297.1499. Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.0; H, 6.8. Found: C, 76.7; H, 6.8.

Methyl-2-hydroxy-5-((2*S*,6*R*)-6-(4-hydroxyphenethyl)-5,6-dihydro-2*H*-pyran-2-yl)benzoate (4c). As described above for **4a**, the title compound was obtained from **17c** (130 mg, 0.28 mmol) as a colorless liquid: yield 90 mg (89%); $[\alpha]^{24}_D$ = +87.4 (c 0.36, CH_2Cl_2); ^{1}H NMR (300 MHz, CD_3OD) δ 7.80 (d, J = 2.2 Hz, 1H), 7.54 (dd, J = 8.6, 2.3 Hz, 1H), 6.98 (d, J = 8.6 Hz, 2H), 6.61 (d, J = 8.5 Hz, 2H), 6.50 (d, J = 8.6 Hz, 2H), 6.06 (ddd, J = 9.4, 4.7, 2.2 Hz, 1H), 5.91 (dm, J = 10.3 Hz, 1H), 5.17 (br s, 1H), 3.93 (s, 3H), 3.40 (dddd, J = 8.6, 8.6, 4.0, 4.0 Hz, 1H), 2.52 (ddd, J = 13.4, 7.7, 5.2 Hz, 1H), 2.34 (ddd, J = 13.8, 7.7, 7.7 Hz, 1H), 2.03−1.94 (2H), 1.72 (dddd, J = 14.0, 8.9, 8.9, 5.2 Hz, 1H), 1.60 (ddm, J = 8.4, 3.6 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD, APT) δ 171.8 (0), 162.6 (0), 156.3 (0), 137.6 (1), 133.9 (0), 133.4 (0), 131.0 (1), 128.1 (1), 127.8 (1), 118.7 (1), 116.0 (1),113.2 (0), 75.1 (1), 67.0 (1), 53.1 (3), 38.6 (2), 32.3 (2), 31.5 (2); IR (neat) ν 3287 (w), 2925 (w), 1674 (m), 1514 (m), 1440 (m), 1208 (s), 1088 (m); MS (EI) m/z 354 ($[M]^+$, 32), 216 (45), 179 (36), 147 (37), 107 (100); HRMS (EI) calcd for $C_{21}H_{22}O_5[M]^+$ 354.1462, found 354.1440. Anal. Calcd for $C_{21}H_{22}O_5$: C, 71.2; H, 6.3. Found: C, 71.4; H, 6.3.

4-((2*S*,6*R*)-6-(4-Hydroxyphenethyl)-5,6-dihydro-2*H*-pyran-2-yl)-2-nitrophenol (4d). As described above for **4a**, the title compound was obtained from **17d** (130 mg, 0.28 mmol) as a yellowish liquid: yield 95 mg (99%); $[\alpha]^{24}_D$ = +121.3 (c 0.62, CH_2Cl_2); ^{1}H NMR (300 MHz, CD_3OD) δ 7.97 (d, J = 2.1 Hz, 1H), 7.63 (dd, J = 8.6, 2.1 Hz, 1H), 7.14 (d, J = 8.6 Hz, 1H), 6.67 (d, J = 8.4 Hz, 2H), 6.52 (d, J = 8.5 Hz, 2H), 6.08 (dm, J = 10.2 Hz, 1H), 5.93 (dm, J = 10.3 Hz, 1H), 5.18

(br s, 1H), 3.37 (dddd, J = 8.6, 8.6, 4.4, 4.4 Hz, 1H), 2.54 (ddd, J = 13.5, 8.1, 5.2 Hz, 1H), 2.35 (ddd, J = 13.9, 8.1, 8.1 Hz, 1H), 2.05−1.95 (2H), 1.81−1.54 (2H); ^{13}C NMR (75 MHz, CD_3OD) δ 156.3 (0), 155.3 (0), 138.5 (1), 135.2 (0), 134.8 (0), 133.8 (0), 130.3 (1), 128.3 (1), 127.5 (1), 125.5 (1), 121.1 (1), 116.0 (0), 74.2 (1), 67.5 (1), 38.4 (2), 32.1 (2), 31.5 (2); IR (neat) ν 3303 (w), 2925 (w), 1628 (m), 1537 (s), 1514 (s), 1317 (m), 1245 (s), 1172 (s); MS (EI) m/z 341 ([M]$^+$, 18), 323 (13), 107 (100); HRMS (EI) calcd for $C_{19}H_{19}NO_5$[M]$^+$ 341.1258, found 341.1260.

2-Bromo-4-((2*S*,6*R*)-6-(4-hydroxyphenethyl)-5,6-dihydro-2*H*-pyran-2-yl)phenol (4e). As described above for **4a**, the title compound was obtained from **17e** (180 mg, 0.37 mmol) as a colorless oil: yield 120 mg (86%); $[\alpha]^{24}_D$ = +91.3 (c 0.375, CH_2Cl_2); ^{1}H NMR (300 MHz, CD_3OD) δ 7.46 (d, J = 2.1 Hz, 1H), 7.19 (dd, J = 8.3, 2.0 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 6.64 (d, J = 8.5 Hz, 2H), 6.54 (d, J = 8.6 Hz, 2H), 6.05 (ddd, J = 10.1, 4.6, 2.2 Hz, 1H), 5.90 (dm, J = 10.3 Hz, 1H), 5.15 (br s, 1H), 3.43 (dddd, J = 8.7, 8.7, 4.0, 4.0 Hz, 1H), 2.53 (ddd, J = 13.0, 7.5, 5.2 Hz, 1H), 2.37 (ddd, J = 13.6, 8.5, 8.5 Hz, 1H), 2.08−1.90 (2H), 1.73 (dddd, J = 14.0, 8.9, 8.9, 5.2 Hz, 1H), 1.59 (dddd, J = 12.2, 8.6, 8.6, 3.5 Hz, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 156.1 (0), 155.1 (0), 134.9 (0), 134.4 (1), 134.0 (0), 130.5 (1), 130.2 (1), 128.0 (1), 127.5 (1), 117.1 (1), 116.1 (1), 110.7 (0), 74.8 (1), 67.0 (1), 38.7 (2), 32.2 (2), 31.5 (2); IR (neat) ν 3278 (m), 2924 (m), 1603 (m), 1513 (s), 1221 (s), 1171 (s), 1042 (s); MS (EI) m/z 374 ([M]$^+$, 13), 236 (17), 199 (22), 145 (29), 107 (100); HRMS (EI) calcd for $C_{19}H_{19}BrO_3$[M]$^+$ 374.0518, found 374.0517. Anal. Calcd for $C_{19}H_{19}BrO_3$: C, 60.8; H, 5.1. Found: C, 61.1; H, 5.2.

(2*S*,6*R*)-2-(4-(4′-Bromophenylcarboxy)phenethyl)-6-(4-(4′′-bromophenylcarboxy)phenyl)-3,6-dihydro-2*H*-pyran (18). To a solution of **4a** (30 mg, 0.10 mmol) in CH_2Cl_2 (5.0 mL) were added Et_3N (42.0 μL, 0.30 mmol) and 4-bromobenzoyl chloride (66 mg, 0.30 mmol). The reaction mixture was stirred at ambient temperature for 12 h. All volatiles were evaporated, and the residue was purified by chromatography on silica (eluent hexanes/MTBE 1:1) to give **18** (58 mg, 0.09 mmol, 88%) as colorless crystals: mp 160−168 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 2H), 7.99 (d, J = 8.6 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 7.61 (d, J = 8.7 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.6 Hz, 2H), 7.00 (d, J = 8.7 Hz, 2H), 6.95 (d, J = 8.7 Hz, 2H), 6.08 (ddd, J = 10.2, 4.7, 2.3 Hz, 1H), 5.31 (s, 1H), 5.99 (dm, J = 10.3 Hz, 1H), 3.51 (m, 1H), 2.74 (ddd, J = 13.5, 8.3, 5.1 Hz, 1H), 2.56 (dt, J = 13.8, 8.2 Hz, 1H), 2.17−1.99 (2H), 1.94−1.81 (1H), 1.76−1.64 (1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5 (0), 164.4 (0), 150.3 (0), 148.7 (0), 139.7 (0), 138.8 (0), 132.4 (1), 131.9 (1), 131.9 (1), 131.7 (1), 131.6 (0), 131.6 (1), 131.6 (1), 131.1 (0), 129.7 (1), 129.5 (1), 127.1 (0), 126.3 (0), 121.4 (1), 121.2 (1), 73.7 (1), 65.9 (1), 37.2 (2), 31.1 (2), 30.8 (2); MS (ESI) m/z 662 (10), 457 (21), 359 (59), 341 (100), 313 (54); HRMS (ESI) calcd for $C_{33}H_{26}Br_2O_5$[M + H]$^+$ 661.0225, found 661.0210.

Dihydropyran Oxide 19. To a solution of **17a** (120 mg, 0.29 mmol) in CH_2Cl_2 (10 mL) was added *m*-CPBA (110 mg, 0.32 mmol) at 0 °C. The reaction mixture was allowed to warm to ambient temperature and stirred for 12 h. It was washed with a saturated aqueous solution of Na_2SO_3 (2 mL), and the aqueous layer was extracted with CH_2Cl_2 (30 mL). The combined organic extracts were dried with $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica (eluent hexanes/MTBE 1:1) to give **19** (70 mg, 0.16 mmol, 55%) as a colorless oil: $[\alpha]^{24}_D$ = +7.7 (c 0.19, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 6.69 (d, J = 8.5 Hz, 2H), 6.61 (d, J = 8.5 Hz, 2H), 5.81 (s, 1H, OH), 5.19 (s, 1H), 3.53 (dd, J = 6.2, 3.3 Hz, 1H), 3.43 (d, J = 3.9, 0.5 Hz, 1H), 3.29 (ddd, J = 11.5, 8.2, 3.6 Hz, 1H), 2.55 (ddd, J = 13.8, 8.6, 5.1 Hz, 1H), 2.30 (dt, J = 13.9, 8.1 Hz, 1H), 1.88 (dd, J = 7.5, 3.0 Hz, 2H), 1.72 (dddd, J = 13.7, 8.4, 8.4, 5.1 Hz, 1H), 1.49 (dddd, J = 12.0, 8.3, 8.3, 3.6 Hz, 1H), 0.97 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9 (0), 153.4 (0), 134.4 (0), 130.0 (0), 129.2 (1), 119.7 (1), 115.4 (1), 71.9 (1), 63.2 (1), 51.1 (1), 50.6 (1), 37.5 (2), 30.4 (2), 29.3 (2), 25.7 (3), 18.2 (0), −4.5 (3); MS (EI) m/z 426 ([M]$^+$, 37), 369 (38), 221 (86), 121 (100); HRMS (EI) calcd for $C_{25}H_{34}O_4Si$ [M]$^+$ 426.2221, found 426.2212.

4-((1*R*,2*S*,4*S*,6*R*)-4-(4-Hydroxyphenethyl)-3,7-dioxabicyclo[4.1.0]heptan-2-yl)-phenol (20). As described above for **4a**, the title compound was obtained from **19** (50 mg, 0.12 mmol) as a colorless liquid: yield 34 mg (92%); $[\alpha]^{24}_D$ = −18.3 (c 0.22, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ 7.31 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 6.55 (d, J = 8.8 Hz, 2H), 6.51 (d, J = 8.8 Hz, 2H), 5.05 (s, 1H), 3.53−3.45 (m, 1H), 3.38 (d, J = 4.0 Hz, 1H), 2.42 (ddd, J = 12.9, 7.4, 5.2 Hz, 1H), 2.23 (m, 1H), 1.86 (dt, J = 15.3, 4.9 Hz, 1H), 1.71 (dd, J = 15.2, 11.0 Hz, 1H), 1.64−1.35 (2H); ^{13}C NMR (300 MHz, CD_3OD) δ 159.0 (0), 156.2 (0), 134.0 (0), 131.5 (1), 130.5 (1), 129.6 (0), 116.5 (1), 116.1 (1), 73.9 (1), 63.9 (1), 52.4 (1), 52.0 (1), 39.1 (2), 31.3 (2), 30.7 (2); IR (neat) ν 3313 (w), 2915 (w), 1612 (m), 1514 (s), 1445 (m), 1225 (s), 1145 (s); MS (EI) m/z 312 ([M]$^+$, 3), 147 (14), 133 (22), 120 (47), 107 (100); HRMS (EI) calcd for $C_{19}H_{20}O_4$[M]$^+$ 312.1356, found 312.1382.

(3*S*,7*R*)-3-(4-(*tert*-Butyldimethylsilyloxy)phenethyl)-7-(4-hydroxyphenyl)tetrahydropyran-5-one (*trans*-21). As described above for **17a**, the title compound was obtained from **5c** (180 mg, 0.54 mmol) and **6a** (125 mg, 0.60 mmol) as a colorless oil: yield 192 mg (83%); $[\alpha]^{24}_D$ = −13.4 (c 0.43, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.3 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 6.70 (d, J = 8.3 Hz, 2H), 5.41 (s, 1H), 5.23 (t, J = 5.5 Hz, 1H), 3.90 (dddd, J = 8.6, 8.6, 4.3, 4.3 Hz, 1H), 2.84−2.77 (2H), 2.70 (ddd, J = 14.5, 9.8, 5.2 Hz, 1H), 2.59−2.43 (2H), 2.36 (dd, J = 14.4, 7.8 Hz, 1H), 1.96 (dddd, J = 14.3, 9.4, 9.4, 5.3 Hz, 1H), 1.77−1.60 (m, 2H), 0.97 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.8 (0), 155.6 (0), 153.7 (0), 133.9 (0), 132.1 (0), 129.1 (1), 128.6 (1), 119.9 (1), 115.4 (1), 73.4 (1), 70.8 (1), 47.3 (2), 45.9 (2), 36.7 (2), 30.7 (2), 25.7 (3), 18.2 (0), −4.5 (3); IR (neat) ν 2929 (w), 2857 (w), 1712 (m), 1611 (w), 1509 (m), 1251 (s); MS (EI) m/z 426 ([M]$^+$, 24), 369 (55), 283 (72), 163 (100); HRMS (EI) calcd for $C_{25}H_{34}O_4Si$[M]$^+$ 426.2221, found 426.2221. Anal. Calcd for $C_{25}H_{34}O_4Si$: C, 70.4; H, 8.0. Found: C, 69.8; H, 7.9.

(3*S*,7*R*)-3-(4-Hydroxyphenethyl)-7-(4-hydroxyphenyl)tetrahydropyran-5-one (*trans*-22). As described above for **4a**, the title compound was obtained from *trans*-**21** (150 mg, 0.35 mmol) as a viscous colorless syrup: yield 96 mg (89%); $[\alpha]^{24}_D$ = −23.8 (c 0.71, CH_2Cl_2); ^{1}H NMR (300 MHz, CD_3OD) δ 7.19 (d, J = 8.6 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 8.6 Hz, 2H), 6.63 (d, J = 8.5 Hz, 2H), 5.18 (t, J = 5.6 Hz, 1H), 3.87 (dddd, J = 8.6, 8.6, 4.3, 4.3 Hz, 1H), 2.86−2.69 (2H), 2.62 (ddd, J = 14.1, 9.1, 5.2 Hz, 1H), 2.54−2.40 (2H), 2.34 (dd, J = 14.5, 7.7 Hz, 1H), 1.91 (dddd, J = 13.6, 8.9, 8.9, 4.2 Hz, 1H), 1.73−1.55 (m, 1H); ^{13}C NMR (75 MHz, CD_3OD) δ 210.3 (0), 158.6 (0), 156.5 (0), 133.8 (0), 132.7 (0), 130.5 (1), 129.7 (1), 116.4 (1), 116.2 (1), 74.9 (1), 72.0 (1), 48.1 (2), 47.0 (2), 38.1 (2), 31.8 (2); IR (neat) ν 3336 (w), 2926 (w), 2488 (w), 1698 (m), 1612 (m), 1512 (s), 1225 (s), 1172 (s), 1061 (m); MS (EI) m/z 312 ([M]$^+$, 23), 220 (65), 146 (62), 107 (100); HRMS (EI) calcd for $C_{19}H_{20}O_4$[M]$^+$ 312.1362, found 312.1365.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, analytical data, copies of ^{1}H and ^{13}C NMR spectra. Crystallographic details for compound **4a** (CCDC-811748). This material is available free of charge via the Internet at http://pubs.acs.org.

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