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Diastereoselective Synthesis of Complex *cis*-Hexahydroindanes by Reductive Alkylation

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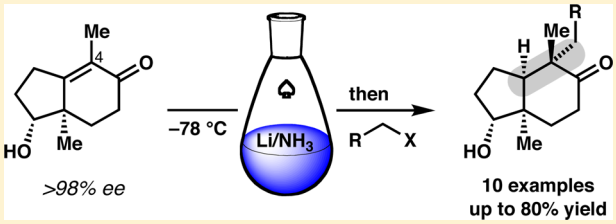
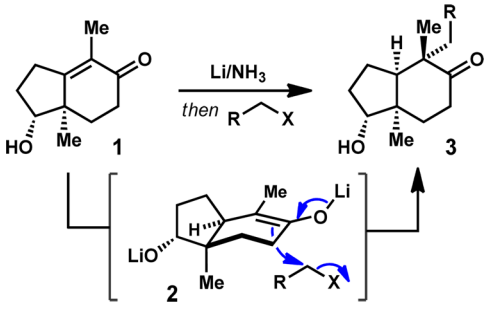
Supporting Information

ABSTRACT: An efficient and operationally simple approach to complex *cis*-hexahydroindanes is reported. Upon Birch reduction of unprotected, C4-alkylated tetrahydroindanols and electrophilic trapping of the tetrasubstituted enolate, *cis*-fused products are formed with a new stereogenic quaternary carbon. The reaction is convergent, completely diastereoselective, and shows a broad scope with regard to the electrophile.



Success in preparing any complex molecule relies on our ability to generate C−C bonds in a direct and stereocontrolled fashion. Multi-bond-forming reactions, as well as those giving rise to contiguous chiral carbon atoms, continue to be of high value in synthetic planning.[1,2] Recently, in the course of designing an approach to the family of *cis*-fused, biologically active sesquiterpene quinones,[3−6] we had occasion to test dissolving metal reduction on an unprotected lower homologue of the Wieland Miescher ketone (see **1**, Scheme 1). In ene-

Scheme 1. Projected Conformational Bias in a Stereoselective Birch Alkylation of Tetrahydroindanol 1



decalone ([4.4.0]-bicyclic) settings, Birch alkylation[7] serves well to forge a thermodynamically favored *trans* ring fusion.[8−14] However, two known cases of dissolving metal reduction on tetrahydroindane ([4.3.0]-bicyclic) substrates have shown a kinetic[15] preference for a *cis* ring juncture.[16,17] Interestingly, in neither case was the potential for diastereoselective alkylation at the resulting metal enolate explored. We surmised that upon hydrogen atom abstraction by the radical anion to give **2**, face-selective quaternization of the α-carbon would be facilitated by the cup-shaped nature of the intermediate (→**3**, Scheme 1).[18]

Herein, we report a data set consistent with this logic. Specifically, we widen the literature precedent to include 10 examples of *cis*-hexahydroindanone synthesis, each attesting to a high level of diastereochemical control over formation of the fully substituted α-carbon. In addition, initial work at further transforming the products has revealed a facile transannular acyloin-type rearrangement[19] made possible by the densely adorned nature of the tetrahydroindane scaffold.

We began our study by refining a multigram scale entry to chiral tetrasubstituted enone **1**. The efficiency of a known[20] D-phenylalanine-catalyzed Hajos-Parrish synthesis of C4-alkyl tetrahydroindanones has been improved by minimizing solvent and sonicating the reaction mixture.[21] Enantiomeric excess is high (92%) under these conditions, but we sought to obtain the substrate in optically pure form. As detailed below, enantioenrichment by recrystallization (92→98% ee) is possible for the α-alcohol (**1**) obtained by stereoselective borohydride reduction of the diketone.[22] As shown below in entry 1 of Table 1, dissolution of this material in Li−NH_3/THF at −78 °C and trapping with benzyl bromide provides ketocarbinol **4** as a single diastereomer in 70% yield. No epimeric product could be detected; the only byproducts derive from protonation or O-alkylation of the tetrasubstituted enolate. Relative configuration in the major product has been confirmed via X-ray analysis for single crystals of racemic **4** (Supporting Information). This result supports the prior findings of Lhomett and Paquette[16,17] and additionally highlights an inherent preference for convex approach of the electrophile during alkylation of the putative lithium enolate.

Remaining entries in the table suggest that the reaction is a general solution to building various complex *cis*-hydroindanes. For instance, the same high level of 1,2-induction occurs for prenylation (entry 2), and the product **5** contains a key stereotriad found in the *Clerodane* diterpene core.[18,23,24] Entry 3 reveals that *ortho* substitution is well-tolerated in a synthesis of **7**, and reaction efficiency remains high with a deactivating chlorine substituent (entry 4). The latter result is also of interest in that no competitive dehalogenation of the arene occurs (53% of **10**). We also find that higher yields are possible

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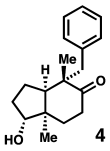
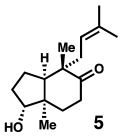
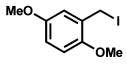
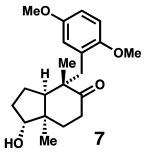
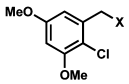
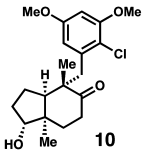
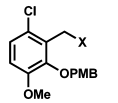
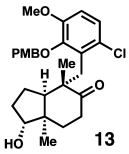
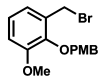
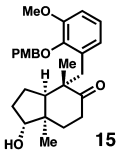
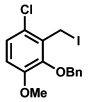
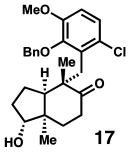
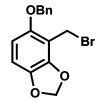
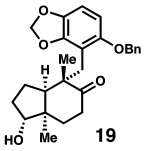
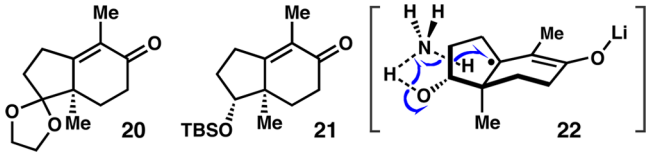
Table 1. Scope of the Birch Reductive Alkylation with Tetrahydroindanol 1[a]

Entry	Electrophile	Product	Yield (%)[b]
1		 **4**	70
2		 **5**	76[c]
3	 **6**	 **7**	78
4	 X = Br **8**	 **10**	53
5	X = I **9**		81
6	 X = Br **11**	 **13**	44
7	X = I **12**		79
8	 **14**	 **15**	53
9	 **16**	 **17**	79
10	 **18**	 **19**	63

[a]Conditions: 3 equiv of Li in NH_3, −78 to −33 °C, 1 h; then −78 °C, 5 equiv of RCH_2X. [b]After column chromatography. [c]Inseparable 14:1 mixture favoring **5**.

with recourse to benzylic iodides as electrophiles (81% of **10**; see entries 3 and 5 versus 4). The closing five entries (6−10) of Table 1 are noteworthy due to the hindered nature of each trapping agent as well as the observed retention of both benzyl and 4-methoxybenzyl ethers under the reaction conditions. All transformations have proven reproducible and robust, with no noticeable diminution in purified yield on scales ranging from 0.2 to 5 mmol (~1 g) of substrate **1**. The recommendation for 5.0 equiv of each electrophile (Table 1) is based on extensive optimization to maximize the yield of product. In certain cases, this is a disadvantage since the electrophile can be more valuable than enone **1**. Reducing the amount of trapping agent still results in a clean transformation, but the product is obtained in lower yield. For instance, if only 2.0 equiv of the complex electrophile **18** is utilized in entry 10, **19** is recovered in 53% yield, corresponding to a 10% decrease in efficiency. To an extent, this is explained by the presence of small amounts of the very nonpolar 1,2-diarylethane in unpurified reaction mixtures. The byproduct derives from background reductive dimerization induced by the minor 0.5 molar equiv excess of lithium (3 equiv total) used to ensure complete two-electron reduction of the enone.[25]

Some additional findings on the enone functionalization warrant mention. First, the noncommercial electrophiles shown in Table 1 (for entries 3−10) are readily available on multigram scale by the fully optimized procedures provided in the Experimental Section. Second, attempts to replicate these results with the ethylene ketal **20**[16] under the standard Birch conditions of Table 1 gave *cis*-fused products but with a noticeable reduction in yield. A greater steric hindrance by the protecting group may account for this, but there is also a clear benefit to having a stoichiometric proton source internal to the enone substrate (α-hydroxyl in **1**). Further evidence for this assertion comes in the form of a 10−15% reduction in chemical yield for *cis*-fused products when the TBS ether **21**[22] is used as the starting material. Even though the identity of the protecting group does not change the stereochemical outcome, the greater efficiencies observed with the free cyclopentanol are intriguing. Two equivalents of lithium is required for this reaction, and 3 equiv (a 0.5 molar excess) was utilized in practice because of the oxide layer in commercial samples of Li wire and the need to prevent premature bleaching of the deep blue reaction mixtures prior to addition of the electrophile. At least 4 equiv of the metal would be needed if the internal hydroxylic proton was immediately lost to reduction in the form of dihydrogen. These considerations imply that enone reduction is much faster than formation of the lithium alkoxide. At this point, we cannot rule out the possibility that the more efficient reactions observed for tetrahydroindanol **1** benefit from intramolecular hydrogen atom abstraction by the radical anion formed via kinetically favored, one-electron reduction of the enone. Simple models do not convincingly demonstrate that the cyclopentyl carbinol is close enough in proximity to the β-carbon to allow for internal delivery, but with the potential for participation by a molecule of solvent (NH_3; see **22**), the process is likely facilitated relative to intermolecular alternatives.[26]



Finally, further transformation of the hexahydroindanol products is successful in spite of steric crowding imposed by the new quaternary center. We document here an interesting reaction outcome that, though unforeseen, can now be expected from the entire class of 5,6-bicyclic derivatives synthesized. As shown in Scheme 2, unprotected **10** does furnish an ene-carbinol under the very forcing yet precedented Wittig conditions[27] provided (→**23**, methyltriphenyl-

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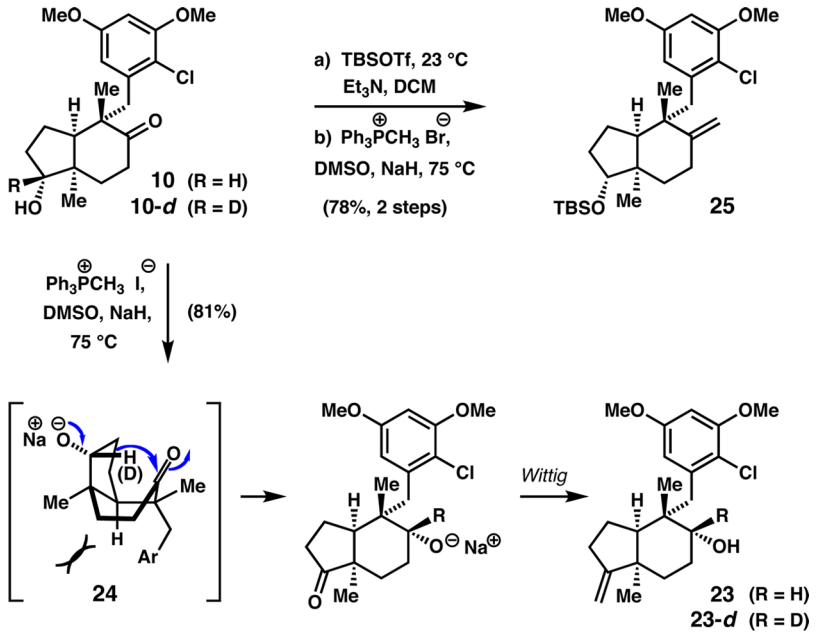
Scheme 2. Further Transformation Reveals a Remarkably Facile and Unexpected Rearrangement



phosphonium iodide, dimsyl sodium, 75 °C), but it is the exclusive result of transannular hydride migration and subsequent cyclo*pentanone* methylenation. This type of internal redox event finds precedent in Prelog's work[28] with less substituted *cis*-fused hydroxy hydroindanones as well as bridged bicyclic settings that are conformationally locked.[29−31] In the present case, the positioning of two quaternary carbons 1,3 within the cyclohexanone leads to a *syn*-pentane interaction in either chair conformer. This renders the stereoelectronically favorable boat conformation (see **24**, Scheme 2) accessible under the reaction conditions. Adding validity to this assertion are the facts that (1) TOCSY NMR data rigorously establish the connectivity pictured in **23**, and an X-ray structure[32] of the methylene cyclopentane has been secured; (2) the isotopically labeled starting material **10-*d*** (prepared by diketone reduction with $NaBD_4$)[33] selectively translocates deuterium to the anticipated position in product **23-*d*** under identical reaction conditions; (3) the corresponding cyclohexanone and cyclopentanone sodium alkoxides are in equilibrium by NMR when exposed to base in the absence of the Wittig salt;[34] and (4) as shown in Scheme 2, preventing alkoxide formation via TBS protection leads to the initially targeted exocyclic methylene cyclohexane **25** in good yield.

To conclude, a concise entry to complex *cis*-hexahydroindanols has been developed. Lithium−ammonia reduction of the corresponding tetrahydroindanol generates a *cis*-fused enolate that has been functionalized with a range of hindered electrophiles in high yield with perfect stereocontrol. We hope that our findings encourage other synthetic chemists to capitalize on the simplicity of the dissolving metal conditions in building other fused 5,6-bicyclic structures with a *cis* juncture.

■ EXPERIMENTAL SECTION

All reactions were carried out in flame-dried glassware under an atmosphere of dry argon[35] using standard Schlenk and vacuum line techniques. Enone **1** and other starting materials made by literature protocols are noted as such in the procedure in which they first appear. High-resolution mass spectral data were obtained with a TOF detector with data acquisition in real time (DART).

General Procedure for Reductive Alkylation. A two-neck 250 mL round-bottom flask equipped with a coldfinger condenser and magnetic stir bar was charged with lithium wire (58.0 mg, 8.36 mmol, 3.00 equiv), evacuated, and flame-dried again. After backfilling with argon, the apparatus was cooled to −78 °C, and ammonia (36 mL) was freshly distilled from sodium metal into the reaction flask, forming a deep blue solution. A solution of enone **1**[21,22,36] (499 mg, 2.77 mmol, 1.00 equiv) in 20 mL of THF was added over 30 min, at which point the mixture was warmed to a gentle reflux and stirred for 1 h. The solution was then recooled to −78 °C and diluted with 14 mL of THF. In a separate flask, a solution of the electrophile (13.9 mmol, 5.00 equiv) in 15 mL of THF was precooled to −78 °C and added as rapidly as possible to the blue solution via syringe. Immediately, the deep blue color bleached to white, and stirring was continued at −78 °C for 8 h. The reaction mixture was then allowed to gradually warm to room temperature with concomitant evaporation of ammonia. The basic solution was acidified by the addition of 200 mL of saturated NH_4Cl, and the product was extracted with Et_2O (3 × 75 mL). The combined organics were washed with H_2O (200 mL) and saturated NaCl (200 mL), dried over Na_2SO_4, filtered, and concentrated. Purification was achieved by column chromatography on silica gel.

(1*R*,3a*R*,4*S*,7a*R*)-4-Benzyl-1-hydroxy-4,7a-dimethylhexahydro-1*H*-inden-5(6*H*)-one (4). From enone **1** (50.0 mg, 0.277 mmol, 1.00 equiv) and benzyl bromide (165 μL, 1.39 mmol, 5.00 equiv), **4** was recovered as a white solid (52.6 mg, 69.7%): mp 117−120 °C. X-ray quality single crystals were obtained by crystallization from hot ethyl acetate and hexanes (1:2 v/v): R_f = 0.45 (45% ethyl acetate in hexanes); $[\alpha]_D^{20}$ = −1.49 (*c* 1.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26−7.17 (m, 3H), 7.03−7.00 (m, 2H), 3.84−3.79 (m, 1H), 3.28 (d, *J* = 13.7 Hz, 1H), 2.82−2.73 (m, 2H), 2.35 (ddd, *J* = 16.4, 6.4, 5.4 Hz, 1H), 2.18 (dd, *J* = 10.7, 8.5 Hz, 1H), 2.07−2.00 (m, 1H), 1.90−1.76 (m, 3H), 1.56−1.46 (m, 2H), 1.35 (s, 3H), 1.28−1.15 (m, 1H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 215.9, 137.5, 130.2, 128.2, 126.6, 81.6, 53.5, 52.3, 44.5, 43.2, 35.6, 32.4, 31.2, 26.4, 23.5, 20.7; IR (neat) 3473, 2959, 2871, 1701, 1452, 1090, 979, 753, 701 cm^{-1}; HRMS (ESI+) calcd for $C_{18}H_{25}O_2$ $[M + H]^+$ 273.1855; found 273.1857.

(1*R*,3a*R*,4*S*,7a*R*)-1-Hydroxy-4,7a-dimethyl-4-(3-methylbut-2-en-1-yl)hexahydro-1*H*-inden-5(6*H*)one (5). From racemic enone **1** (100 mg, 0.555 mmol, 1.00 equiv) and prenyl bromide (330 μL, 2.78 mmol, 5.00 equiv), **5** was recovered as a colorless oil (106 mg, 76.0%). The product was a 14:1 mixture with the uncharacterized minor α-epimer as determined by ^{1}H NMR. Analytically pure material was

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obtained by combining only the later eluting fractions: R_f = 0.35 (40% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.02−4.96 (m, 1H), 3.75 (ddd, J = 5.4, 5.4, 5.4 Hz, 1H), 2.65−2.57 (m, 1H), 2.49 (dd, J = 14.7, 7.3 Hz, 1H), 2.27, 2.14 (m, 3H), 2.06−1.98 (m, 1H), 1.86 (dddd, J = 16.4, 8.3, 8.3, 2.4 Hz, 1H), 1.74−1.68 (m, 5H), 1.60 (s, 3H), 1.53−1.45 (m, 2H), 1.30 (s, 3H), 1.20−1.12 (m, 1H), 0.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 216.7, 134.4, 119.2, 81.7, 52.7, 51.6, 43.2, 36.7, 35.1, 32.4, 31.2, 26.8, 26.1, 23.2, 20.6, 18.2; IR (neat) 2441, 2961, 2928, 2872, 1699, 1451, 1376, 1052, 978 cm^{-1}; HRMS (ESI+) calcd for $C_{16}H_{27}O_2$ $[M + H]^+$ 251.2011; found 251.2014.

2-(Iodomethyl)-1,4-dimethoxybenzene (6). From 2-(bromomethyl)-1,4-dimethoxybenzene[37] (1.18 g, 5.09 mmol, 1.00 equiv), **6** was obtained by treatment with NaI (1.53 g, 10.2 mmol, 2.00 equiv) in 8.5 mL of distilled acetone (12 h, 23 °C). The mixture was filtered through Celite, concentrated, dissolved in 20 mL of CH_2Cl_2, and washed with 15 mL of 50% $Na_2S_2O_3$. Drying, filtration, and concentration provided **6** as a yellow solid (1.39 g, 97.8%): mp 62−64 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.86 (d, J = 2.9 Hz, 1H), 6.80−6.74 (m, 2H), 4.45 (s, 2H), 3.86 (s, 3H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.4, 151.5, 128.4, 115.7, 114.6, 112.2, 56.1, 55.9, 1.3; IR (neat) 3040, 2942, 2831, 1498, 1462, 1223, 1154, 1040, 800, 700, 507 cm^{-1}; HRMS (ESI+) calcd for $C_9H_{12}IO_2$ $[M + H]^+$ 278.9882; found 278.9882.

(1*R*,3a*R*,4*S*,7a*R*)-4-(2,5-dimethoxybenzyl)-1-hydroxy-4,7a-dimethylhexahydro-1*H*-inden-5(6*H*)-one (7). From enone **1** (50.0 mg, 0.277 mmol, 1.00 equiv) and iodide **6** (540 mg, 1.94 mmol, 7.00 equiv),[38] **7** was recovered as a white solid (71.6 mg, 77.8%): mp 104−106 °C; R_f = 0.38 (60% ethyl acetate in hexanes); $[\alpha]_D^{20}$ = −20.20 (c 1.72, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.72−6.66 (m, 2H), 6.58 (d, J = 3.2 Hz, 1H), 3.81 (dd, J = 12.3, 6.1 Hz, 1H), 3.73 (s, 3H), 3.70 (d, J = 13.4 Hz, 1H), 3.64 (s, 3H), 2.87 (ddd, J = 16.7, 8.3, 5.4 Hz, 1H), 2.38 (d, J = 13.4 Hz, 1H), 2.22 (ddd, J = 16.6, 8.5, 5.4 Hz, 1H), 2.12 (dd, J = 12.0, 8.3 Hz, 1H), 2.04−1.95 (m, 2H), 1.85 (dddd, J = 15.6, 7.8, 7.8, 2.0 Hz, 1H), 1.79−1.71 (m, 2H), 1.52−1.43 (m, 1H), 1.35 (s, 3H), 1.15−1.04 (m, 1H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 214.7, 152.9, 151.8, 127.0, 119.1, 111.8, 110.8, 81.2, 56.2, 55.8, 55.1, 51.8, 42.6, 40.5, 35.2, 32.2, 31.4, 27.3, 24.1, 20.3; IR (neat) 3449, 2956, 1699, 1501, 1464, 1224, 1049, 802, 713 cm^{-1}; HRMS (ESI+) calcd for $C_{20}H_{29}O_4$ $[M + H]^+$ 333.2066; found 333.2069.

1-(Bromomethyl)-2-chloro-3,5-dimethoxybenzene (8). Commericially available (3,5-dimethoxyphenyl)methanol (10.4 g, 62.0 mmol, 1.0 equiv) was chlorinated in 310 mL of CCl_4 (reflux, 48 h) with *N*-chlorosuccinimide (7.86 g, 58.9 mmol, 0.950 equiv). After conventional aqueous workup, the chloro-alcohol was recrystallized to afford a white solid (9.00 g, 71.7%) from Et_2O/hexanes (5:1 v/v): mp 88−90 °C. Bromide **8** was obtained as a white solid (3.0 g, 82%) from 2.80 g (13.8 mmol, 1.00 equiv) of the chloro-alcohol by exposure to PBr_3 (0.49 mL, 5.1 mmol, 0.37 equiv) in 46 mL of benzene: mp 100−102 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.58 (d, J = 2.8 Hz, 1H), 6.48 (d, J = 2.8 Hz, 1H), 4.57 (s, 2H), 3.88 (s, 3H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.9, 156.3, 136.9, 114.6, 106.7, 100.3, 56.4, 55.7, 31.1; IR (neat) 3097, 2975, 1585, 1470, 1432, 1334, 1200, 1165, 1082, 1030, 951, 819, 721, 673, 610 cm^{-1}; HRMS (ESI+) calcd for $C_9H_{11}{}^{79}Br^{37}ClO_2$ $[M + H]^+$ 266.9601; found 266.9601.

2-Chloro-1-(iodomethyl)-3,5-dimethoxybenzene (9). From benzyl bromide **8** (502 mg, 1.89 mmol, 1.00 equiv) and NaI (566 mg, 3.78 mmol, 2.00 equiv) in 3.2 mL of distilled acetone (12 h, 23 °C) using the workup described for **6**, concentration gave **9** as a white solid (539 mg, 91.3%): mp 127−129 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.54 (d, J = 2.7 Hz, 1H), 6.44 (d, J = 2.7 Hz, 1H), 4.50 (s, 2H), 3.87 (s, 3H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.9, 156.4, 138.3, 114.2, 106.0, 99.9, 56.4, 55.7, 3.1; IR (neat) 3058, 2939, 1586, 1469, 1418, 1332, 1204, 1156, 1076, 1030, 951, 818, 675 cm^{-1}; HRMS (ESI+) calcd for $C_9H_{11}ClIO_2$ $[M + H]^+$ 312.9492; found 312.9490.

(1*R*,3a*R*,4*S*,7a*R*)-4-(2-Chloro-3,5-dimethoxybenzyl)-1-hydroxy-4,7a-dimethylhexahydro-1*H*-inden-5(6*H*)-one (10). From enone **1** (56.2 mg, 0.312 mmol, 1.00 equiv) and iodide **9** (488 mg, 1.56 mmol, 5.00 equiv),[38] **10** was recovered as a white solid (92.6 mg, 80.9%): mp 165−168 °C; R_f = 0.33 (60% ethyl acetate in hexanes); $[\alpha]_D^{20}$ = −27.64 (c 1.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.37 (d, J = 2.7 Hz, 1H), 6.15 (d, J = 2.7 Hz, 1H), 3.86−3.79 (m, 4H), 3.74 (s, 3H), 3.51 (d, J = 13.9 Hz, 1H), 3.0 (d, J = 13.9 Hz, 1H), 2.87 (ddd, J = 15.2, 9.3, 5.6 Hz, 1H), 2.38−2.30 (m, 1H), 2.22 (dd, J = 11.0, 8.3 Hz, 1H), 2.07−1.99 (m, 1H), 1.97−1.76 (m, 3H), 1.34 (s, 3H), 1.17 (dddd, J = 9.3, 9.3, 9.3, 9.3 Hz, 1H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 215.4, 158.2, 155.9, 137.5, 115.6, 108.0, 98.3, 81.4, 56.3, 55.8, 55.6, 52.3, 42.9, 41.5, 35.4, 32.6, 31.4, 26.8, 23.7, 19.7; IR (neat) 3448, 2958, 2878, 1697, 1590, 1455, 1330, 1203, 1163, 1084, 979, 753 cm^{-1}; HRMS (ESI+) calcd for $C_{20}H_{28}ClO_4$ $[M + H]^+$ 367.1676; found 367.1684.

2-(Bromomethyl)-1-chloro-4-methoxy-3-(4-methoxybenzyloxy)benzene (11). Starting from PMB-protected *o*-vanillin,[39] (3-methoxy-2-(4-methoxybenzyloxy)phenyl)methanol is available from aldehyde reduction ($NaBH_4$, EtOH, 10 min, 23 °C, 96%). The resulting white solid (11.4 g, 41.7 mmol, 1.00 equiv), mp 67−70 °C, was used without purification. Chlorination at the 6 position by treatment with 1,3-dichloro-5,5-dimethylhydantoin (9.86 g, 50.0 mmol, 1.20 equiv) in 83 mL of CH_2Cl_2 (20 h, 4 °C) and conventional aqueous workup (as described for **6**) left a residue that was purified by flash chromatography to give a white solid (9.13 g, 70.9%): mp 76−78 °C; R_f = 0.29 (30% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 8.3 Hz, 2H), 6.84 (d, J = 8.8 Hz, 1H), 5.03 (s, 2H), 4.69 (d, J = 6.8 Hz, 2H), 3.89 (s, 3H), 3.81 (s, 3H), 2.08 (t, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.9, 151.9, 147.3, 132.9, 130.5, 129.3, 125.9, 124.9, 114.1, 112.9, 75.6, 58.3, 56.2, 55.4; IR (neat) 3440, 2958, 2897, 2837, 1612, 1514, 1473, 1440, 1271, 1250, 1175, 1013 cm^{-1}; HRMS (ESI+) calcd for $C_{16}H_{16}ClO_4$ $[M - H]^+$ 307.0737; found 307.0744. The benzyl alcohol (623 mg, 2.02 mmol, 1.00 equiv), CBr_4 (872 mg, 2.64 mmol, 1.30 equiv), and PPh_3 (689 mg, 2.63 mmol, 1.30 equiv) were dissolved in 4.0 mL of THF at 0 °C and warmed to 23 °C after 10 min. After diluting with water (20 mL) and extracting with CH_2Cl_2 (3 × 20 mL), the combined organic layers were dried, filtered, and concentrated. Purification by flash chromatography gave **11** as a white solid (785 mg, quantitative): mp 80−84 °C; R_f = 0.52 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45 (d, J = 8.6 Hz, 2H), 7.11 (d, J = 8.8 Hz, 1H), 6.93 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.8 Hz, 1H), 5.10 (s, 2H), 4.63 (s, 2H), 3.89 (s, 3H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.8, 151.9, 147.4, 130.5, 130.4, 129.4, 126.3, 125.0, 114.0, 113.4, 74.9, 56.2, 55.4, 25.6; IR (neat) 3002, 2959, 2836, 1612, 1583, 1514, 1474, 1272, 1250, 1174, 1076, 974, 804 cm^{-1}; HRMS (ESI+) calcd for $C_{16}H_{15}BrClO_3$ $[M - H]^+$ 368.9893; found 368.9878.

1-Chloro-2-(iodomethyl)-4-methoxy-3-(4-methoxybenzyloxy)benzene (12). From benzyl bromide **11** (483 mg, 1.30 mmol, 1.00 equiv) by treatment with NaI (390 mg, 2.60 mmol, 2.00 equiv) in 2.2 mL of distilled acetone (12 h, 23 °C), **12** was obtained. The workup was by direct analogy to that of **6**, affording **12** as a pale yellow solid (542 mg, 99.6%): mp 85−88 °C; R_f = 0.52 (33% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.47 (d, J = 8.8 Hz, 2H), 7.07 (d, J = 8.8 Hz, 1H) 6.94 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.8 Hz, 1H), 5.15 (s, 2H), 4.52 (s, 2H), 3.88 (s, 3H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.8, 151.9, 146.8, 131.8, 130.3, 129.5, 125.9, 125.0, 114.0, 112.9, 73.8, 56.2, 55.4, −2.4; IR (neat) 2935, 2835, 1612, 1514, 1473, 1370, 1272, 1250, 1174, 1107, 1071, 1034, 972, 801 cm^{-1}; HRMS (ESI+) calcd for $C_{16}H_{15}ClIO_3$ $[M + H]^+$ 416.9754; found 416.9753.

(1*R*,3a*R*,4*S*,7a*R*)-4-(6-Chloro-3-methoxy-2-((4-methoxybenzyl)oxy)benzyl)-1-hydroxy-4,7a-dimethylhexahydro-1*H*-inden-5(6*H*)-one (13). From racemic enone **1** (65.6 mg, 0.366 mmol, 1.00 equiv) and iodide **12** (766 mg, 1.83 mmol, 5.00 equiv),[38] **13** was recovered as a white solid (136 mg, 78.6%): mp 50−56 °C; R_f = 0.25 (50% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 8.8 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 6.75 (d, J = 8.8 Hz, 1H), 4.98 (d, J = 11.2 Hz, 1H), 4.82 (d, J = 11.0 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.72 (dd, J = 6.1, 6.1 Hz, 1H), 3.39 (d, J = 13.2 Hz, 1H), 2.84 (d, J = 13.7 Hz, 1H), 2.67 (ddd, J = 13.7, 7.8, 5.6 Hz, 1H), 2.09 (dd, J = 11.7, 8.0 Hz, 1H), 2.05−1.91

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(m, 2H), 1.78 (ddd, J = 15.4, 7.8, 2.0 Hz, 1H), 1.74−1.67 (m, 1H), 1.58−1.48 (m, 2H), 1.47−1.38 (m, 1H), 1.18 (s, 3H), 1.05−0.92 (m, 1H), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 214.8, 159.8, 151.2, 147.9, 130.6, 130.5, 129.8, 127.2, 124.30, 113.9, 111.9, 81.1, 74.8, 57.0, 56.1, 55.4, 51.8, 42.3, 37.2, 35.0, 32.3, 31.5, 27.2, 23.9, 19.1; IR (neat) 3471, 2859, 2872, 1700, 1612, 1514, 1466, 1276, 1251, 1143, 940 cm^{-1}; HRMS (ESI+) calcd for $C_{27}H_{33}ClO_5$ [M − OH]$^+$ 455.1989; found 455.1982.

1-(Bromomethyl)-3-methoxy-2-(4-methoxybenzyloxy)-benzene (14). From the same alcohol above with conditions detailed for **11** (CBr_4, PPh_3, THF, 0 °C, 10 min). Purification by flash chromatography gave **14** as a white solid (834 mg, 89.2%): mp 50−52 °C; R_f = 0.42 (20% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.45 (d, J = 8.6 Hz, 2H), 7.05 (d, J = 7.8 Hz, 1H), 6.97 (dd, J = 7.5, 1.2 Hz, 1H), 6.95−6.89 (m, 3H), 5.10 (s, 2H), 4.50 (s, 2H), 3.90 (s, 3H), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.7, 153.1, 146.3, 132.4, 130.3, 129.9, 124.4, 122.8, 114.0, 113.2, 74.5, 56.0, 55.4, 28.6; IR (neat) 2957, 2936, 2836, 1612, 1586, 1514, 1479, 1374, 1271, 1250, 1174, 1070 cm^{-1}; HRMS (ESI+) calcd for $C_{16}H_{16}BrO_3$ [M − H]$^+$ 335.0283; found 335.0271.

(1*R*,3a*R*,4*S*,7a*R*)-1-Hydroxy-4-(3-methoxy-2-((4-methoxybenzyl)oxy)benzyl)-4,7a-dimethylhexahydro-1*H*-inden-5(6*H*)-one (15). From racemic enone **1** (51.0 mg, 0.283 mmol, 1.00 equiv) and bromide **14** (473 mg, 1.40 mmol, 5.00 equiv),[38] **15** was recovered as a sticky foam (65.4 mg, 52.7%): R_f = 0.26 (50% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.31 (d, J = 8.8 Hz, 2H), 6.92 (dd, J = 8.1, 8.1 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 6.80 (dd, J = 8.3, 1.5 Hz, 1H), 6.56 (dd, J = 7.8, 1.5 Hz, 1H), 4.98 (d, J = 11.0 Hz, 1H), 4.83 (d, J = 11.0 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.73 (ddd, J = 5.6, 5.6, 5.6 Hz, 1H), 3.36 (d, J = 13.4 Hz, 1H), 2.70 (ddd, J = 14.5, 8.8, 5.6 Hz, 1H), 2.50 (d, J = 13.4 Hz, 1H), 2.12 (ddd, J = 10.0, 7.6, 5.4 Hz, 1H), 2.07−2.02 (m, 1H), 2.0−1.92 (m, 1H), 1.80 (dddd, J = 16.1, 8.3, 8.3, 2.4 Hz, 1H), 1.76−1.69 (m, 1H), 1.62−1.56 (m, 2H), 1.47−1.40 (m, 1H), 1.19 (s, 3H), 1.11−1.02 (m, 1H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 215.4, 159.6, 152.6, 146.8, 131.7, 130.4, 130.2, 123.8, 123.2, 113.9, 111.2, 81.4, 74.6, 55.9, 55.6, 55.4, 52.1, 42.7, 39.0, 35.2, 32.3, 31.4, 27.0, 23.8, 20.3; IR (neat) 3431, 2956, 2836, 1700, 1611, 1584, 1514, 1474, 1302, 1250, 1174, 1083 cm^{-1}; HRMS (ESI+) calcd for $C_{27}H_{34}O_5$ [M + H]$^+$ 439.2484; found 439.2489.

2-(Benzyloxy)-4-chloro-3-(iodomethyl)-1-methoxybenzene (16). From (2-(benzyloxy)-3-methoxyphenyl)methanol[40] with the same aryl chlorination (92%), bromination (88%), and iodination procedures described above for **12**, concentration gave **16** as a pale yellow solid that was used without purification (38.0 g, 98.1%): mp 72−75 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.56−7.52 (m, 2H), 7.43−7.34 (m, 3H), 7.08 (d, J = 8.8 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 5.22 (s, 2H), 4.55 (s, 2H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.9, 146.8, 137.3, 131.8, 128.6, 128.4, 128.3, 125.9, 125.1, 112.8, 74.0, 56.2, −2.7; IR (neat) 3006, 2974, 2839, 1575, 1471, 1460, 1430, 1366, 1267, 1223, 1099, 1064, 964, 883, 797, 747, 693 cm^{-1}; HRMS (ESI+) calcd for $C_{15}H_{18}ClINO_2$ [M + NH_4]$^+$ 406.0071; found 406.0075.

(1*R*,3a*R*,4*S*,7a*R*)-4-(2-(Benzyloxy)-6-chloro-3-methoxybenzyl)-1-hydroxy-4,7a-dimethylhexahydro-1*H*-inden-5(6*H*)-one (17). From enone **1** (499 mg, 2.77 mmol, 1.00 equiv) and iodide **16** (5.40 g, 13.9 mmol, 5.00 equiv), **17** was recovered as a white solid (968 mg, 78.9%): mp 45−50 °C; R_f = 0.33 (50% ethyl acetate in hexanes); $[\alpha]_D^{20}$ = −32.50 (c 0.86, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.31 (m, 5H), 7.05 (d, J = 8.8 Hz, 1H), 6.76 (d, J = 8.8 Hz, 1H), 5.04 (d, J = 11.2 Hz, 1H), 4.89 (d, J = 11.5 Hz, 1H), 3.83 (s, 3H), 3.71 (ddd, J = 6.1, 6.1, 6.1 Hz, 1H), 3.42 (d, J = 13.7 Hz, 1H), 2.87 (d, J = 13.7 Hz, 1H), 2.65 (dddd, J = 13.7, 5.4, 5.4, 5.4 Hz, 1H), 2.10 (dd, J = 11.7, 8.1 Hz, 1H), 2.04−1.90 (m, 2H), 1.83−1.74 (m, 1H), 1.73−1.62 (m, 1H), 1.56−1.47 (m, 2H), 1.47−1.38 (m, 1H), 1.17 (s, 3H), 1.08−0.93 (m, 1H), 0.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 214.8, 151.1, 147.9, 137.6, 130.4, 128.8, 128.6, 128.3, 127.2, 124.4, 111.9, 81.0, 75.2, 57.0, 56.1, 51.8, 42.3, 37.2, 35.0, 32.3, 31.5, 27.2, 23.9, 19.1; IR (neat) 3430, 2956, 2872, 1697, 1576, 1463, 1375, 1275, 1214, 1077, 974, 798, 749, 697 cm^{-1}; HRMS (ESI+) calcd for $C_{26}H_{32}ClO_4$ [M + H]$^+$ 443.1989; found 443.2005.

5-(Benzyloxy)-4-(bromomethyl)benzo[*d*][1,3]dioxole (18). Commercial sesamol was converted to (5-(benzyloxy)benzo[*d*][1,3]-dioxol-4-yl)methanol by a routine sequence involving benzylation (BnBr, K_2CO_3, DMF, 23 °C, 99%), formylation (*n*-BuLi, THF, −78 °C; DMF, 70%), and reduction ($NaBH_4$, 9:1 THF/H_2O, 23 °C, 90%). To this alcohol (3.50 g, 13.5 mmol, 1.00 equiv) in 80 mL of Et_2O was added pyridine (54.2 μL, 0.678 mmol, 0.0500 equiv). PBr_3 (1.28 mL, 13.6 mmol, 1.00 equiv) was introduced over 35 min by syringe pump. The resulting cloudy mixture was stirred for 40 min, quenched with H_2O (50 mL), and extracted with Et_2O (3 × 50 mL). The combined organics were washed with H_2O (50 mL) and saturated NaCl (50 mL), dried over $MgSO_4$, filtered, and concentrated to give **18** as a white solid (4.32 g, 99.3%): mp 91−93 °C; R_f = 0.55 (30% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.49−7.46 (m, 2H), 7.42−7.38 (m, 2H), 7.35−7.33 (m, 1H), 6.67 (d, J = 8.4 Hz, 1H), 6.33 (d, J = 8.4 Hz, 1H), 6.01 (s, 2H), 5.08 (s, 2H), 4.59 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.9, 147.1, 141.8, 137.0, 128.7, 128.0, 127.3, 110.2, 107.9, 104.1, 101.9, 71.1, 22.2; IR (neat) 3031, 2777, 1644, 1462, 1243, 1160, 1058, 924, 737 cm^{-1}. HRMS (ESI+) calcd for $C_{15}H_{14}BrO_3$ [M + H]$^+$ 321.0126; found 321.0117.

(1*R*,3a*R*,4*S*,7a*R*)-4-((5-(Benzyloxy)benzo[*d*][1,3]dioxol-4-yl)-methyl)-1-hydroxy-4,7a-dimethylhexahydro-1*H*-inden-5(6H)-one (19). From racemic enone **1** (49.2 mg, 0.273 mmol, 1.00 equiv) and bromide **18** (437 mg, 1.36 mmol, 5.00 equiv), **19** was recovered as a white solid (72.8 mg, 63.1%): mp 150−152 °C; R_f = 0.32 (60% ethyl acetate in hexanes); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41−7.36 (m, 4H), 7.35−7.29 (m, 1H), 6.67 (d, J = 8.5 Hz, 1H), 6.27 (d, J = 8.5 Hz, 1H), 5.87 (d, J = 1.5 Hz, 1H), 5.80 (d, J = 1.5 Hz, 1H), 4.93 (d, J = 11.5 Hz, 1H), 4.88 (d, J = 11.5 Hz, 1H), 3.74 (ddd, J = 6.1, 6.1, 6.1 Hz, 1H), 3.47 (d, J = 13.4 Hz, 1H), 2.69 (d, J = 13.4 Hz, 1H), 2.61 (ddd, J = 16.8, 8.5, 5.4 Hz, 1H), 2.13 (dd, J = 12.2, 8.3 Hz, 1H), 2.02−1.91 (m, 2H), 1.84 (dddd, J = 15.6, 7.8, 7.8, 2.0 Hz, 1H), 1.73 (ddd, J = 13.9, 8.0, 5.6 Hz, 1H), 1.54−1.40 (m, 3H), 1.28 (s, 3H), 1.10−1.00 (m, 1H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 215.1, 152.7, 147.6, 141.1, 137.2, 128.6, 128.1, 128.0, 109.9, 105.9, 103.3, 100.8, 81.1, 71.0, 56.3, 52.2, 42.4, 35.1, 33.7, 32.1, 31.3, 27.4, 24.0, 19.9; IR (neat) 3440, 2958, 2979, 1697, 1458, 1377, 1243, 1102, 1052, 930, 735 cm^{-1}; HRMS (ESI+) calcd for $C_{26}H_{31}O_5$ [M + H]$^+$ 423.2172; found 423.2174.

(3a*R*,4*S*,5*R*,7a*R*)-4-(2-Chloro-3,5-dimethoxybenzyl)-4,7a-dimethyl-1-methyleneoctahydro-1*H*-inden-5-ol (23). A dimsyl sodium solution was prepared from NaH (35.1 mg, 1.46 mmol, 7.00 equiv) and 1.5 mL of dry DMSO in a two-neck 25 mL round-bottom flask equipped with a magnetic stir bar by heating at 75 °C for 1 h.[41] At room temperature, a solution of Ph_3PCH_3I (764 mg, 1.88 mmol, 9.00 equiv) in 2.6 mL of DMSO was added over 30 min, turning the mixture bright yellow. After 30 min of additional stirring, a solution of racemic **10** (76.3 mg, 0.208 mmol, 1.00 equiv) in 0.58 mL of DMSO was added, and the reaction was heated at 75 °C for 16 h. The resulting amber solution was acidified with 5 mL of saturated NH_4Cl, diluted with H_2O (15 mL), and washed with Et_2O (3 × 15 mL). The combined organics were washed with H_2O (15 mL) and saturated NaCl (15 mL), dried over Na_2SO_4, filtered, and concentrated. Purification by flash chromatography gave **23** as a white solid (61 mg, 81%): mp 117−119 °C; R_f = 0.33 (60% Et_2O in pentane); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.69 (d, J = 2.7 Hz, 1H), 6.38 (d, J = 2.7 Hz, 1H), 4.75−4.71 (m, 2H), 3.86 (s, 3H), 3.78 (s, 3H), 3.61−3.57 (m, 1H), 2.97−2.89 (m, 2H), 2.57−2.47 (m, 1H), 2.42−2.32 (m, 1H), 2.09−1.90 (m, 2H), 1.82−1.65 (m, 4H), 1.57−1.50 (m, 1H), 1.49 (d, J = 4.6 Hz, 1H), 1.11 (s, 3H), 0.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 159.9, 158.1, 155.7, 139.2, 115.8, 109.0, 101.4, 97.6, 72.5, 56.3, 55.6, 51.7, 45.0, 42.0, 38.4, 31.3, 30.6, 27.8, 25.6, 23.3, 18.4; IR (neat) 3556, 2949, 1588, 1454, 1287, 1201, 1161, 1082, 1034, 907, 730, 632 cm^{-1}; HRMS (ESI+) calcd for $C_{21}H_{28}ClO_2$ [M − OH]$^+$ 347.1778; found 347.1766.

***tert*-Butyl(((1*R*,3a*S*,4*S*,7a*R*)-4-(2-Chloro-3,5-dimethoxybenzyl)-4,7a-dimethyl-5-methyleneoctahydro-1*H*-inden-1-yl)oxy)-dimethylsilane (25).** The secondary carbinol in **10** was protected as its TBS ether by standard means (Et_3N, TBSOTf, CH_2Cl_2, 3 h, −78 °C). Dimsyl sodium was then prepared as above from NaH (32.6 mg,

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1.36 mmol, 7.40 equiv) and 1.5 mL of dry DMSO.[41] At room temperature, a solution of Ph_3PCH_3Br (624 mg, 1.75 mmol, 9.50 equiv) in 2.4 mL of DMSO was added over 30 min, turning the mixture bright yellow. After 30 more minutes of stirring, a solution of the TBS ether (93.4 mg, 0.184 mmol, 1.00 equiv) in 0.56 mL of DMSO and 0.50 mL of THF was added, and the reaction was heated at 75 °C for 16 h. The resulting amber solution was worked up by analogy to **23**, giving **25** as a white solid (95.0 mg, quantitative): mp 97−98 °C; R_f = 0.33 in 50% Et_2O in pentane; $[\alpha]_D^{20}$ = +32.36 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.35 (d, *J* = 2.7 Hz, 1H), 6.21 (d, *J* = 2.7 Hz, 1H), 4.93 (s, 1H), 4.42 (s, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.55 (dd, *J* = 5.9, 1.5 Hz, 1H), 3.25 (d, *J* = 13.5 Hz, 1H), 3.01 (d, *J* = 13.4 Hz, 1H), 2.71 (ddd, *J* = 13.7, 13.7, 5.4 Hz, 1H), 2.24−2.18 (m, 1H), 2.09−2.02 (m, 1H), 1.98−1.89 (m, 1H), 1.84−1.74 (m, 1H), 1.47−1.22 (m, 7H), 0.92 (s, 9H), 0.81 (s, 3H), 0.5 (s, 3H), 0.4 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 157.5, 155.4, 151.3, 139.5, 115.8, 112.0, 108.0, 97.8, 84.3, 56.3, 55.4, 55.0, 46.0, 44.3, 41.5, 33.8, 31.6, 29.9, 26.7, 26.1, 23.3, 22.4, 18.3, −4.3, −4.7; IR (neat) 2953, 2930, 2856, 1590, 1455, 1371, 1285, 1255, 1202, 1163, 1074, 1004, 833, 722 cm^{-1}; HRMS (ESI+) calcd for $C_{27}H_{44}ClO_3Si$ $[M + H]^+$ 479.2748; found 479.2733.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray crystallographic data for compound **4** (CCDC reference number 911293) and copies of the ^{1}H and ^{13}C NMR spectra for all numbered compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(34) At 75 °C, the temperature at which Wittig reaction is successful, the ratio of cyclopentanone to cyclohexanone products is 6:1 according to ^{1}H NMR spectroscopy in the case of structure **19**. Upon cooling to 23 °C and performing an aqueous workup, the ratio does not change.

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