Title	Asymmetric syntheses of diarylheptanoid natural products (-)-centrolobine and (-)-de-O-methylcentrolobine via hetero-Diels–Alder reaction catalyzed by dirhodium(II) tetrakis[(R)-3-(benzene-fused-phthalimido)-2-piperidinonate]
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Asymmetric syntheses of diarylheptanoid natural products, (–)-centrolobine and (–)-de-*O*-methylcentrolobine *via* hetero-Diels–Alder reaction catalyzed by dirhodium(II) tetrakis[(*R*)-3-(benzene-fused-phthalimido)-2-piperidinonate]

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Abstract—Catalytic asymmetric syntheses of (–)-centrolobine and (–)-de-*O*-methylcentrolobine have been achieved, incorporating a hetero-Diels–Alder (HDA) reaction between 4-aryl-2-silyloxy-1,3-butadienes and phenylpropargyl aldehyde derivatives as a key step. The HDA reaction using dirhodium(II) tetrakis[(*R*)-3-(benzene-fused-phthalimido)-2-piperidinonate], Rh₂(*R*-BPTPI)₄, as a chiral Lewis acid catalyst provides exclusively *cis*-2,6-disubstituted tetrahydropyran-4-ones in up to 93% ee.

1. Introduction

Diarylheptanoid natural products containing a tetrahydropyran ring, such as centrolobine,¹ de-*O*-methylcentrolobine,^{1c,2} calyxins³ and diospongins,⁴ exhibit a wide range of biological activity. Not surprisingly, therefore, these compounds have aroused considerable interest within the medicinal and synthetic chemistry communities.^{5–7}

R = Me: (–)-centrolobine (**1**)
R = H: (–)-de-*O*-methylcentrolobine (**2**)

(–)-Centrolobine (**1**) is an antibiotic isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosimum potabile* in the amazon rain forest.¹ (–)-De-*O*-methylcentrolobine (**2**), isolated from the same heartwood of *Centrolobium robustum*, displays a good antileishmanial activity.^{1c,2} Solladie and co-workers accomplished the first asymmetric total synthesis of (–)-centrolobine (**1**) in 2002,

which also established the absolute configuration of **1**.⁸ Since then, a number of groups have achieved the synthesis of **1** in both racemic⁹ and optically active forms.¹⁰ A variety of approaches starting with optically active building blocks, obtained by well-established asymmetric reactions or the chiral pool method, have been devised to provide access to the *cis*-2,6-disubstituted tetrahydropyran rings. These include the Prins and related cyclizations,^{10a,g,h} reductive etherifications,^{8,10b} one-pot cross metathesis-hydrogenation-lactonization procedure,^{10c} radical cyclization,^{10d} nucleophilic addition-stereoselective reduction protocol,^{10e} intramolecular oxy-Michael reaction,^{10f} diastereoselective ring rearrangement metathesis-isomerization sequence¹⁰ⁱ and FeCl₃-mediated cyclization of 1,5-diol.^{10j}

The hetero-Diels–Alder (HDA) reaction¹¹ between dienes and carbonyl compounds is one of the most straightforward methods for constructing tetrahydropyran derivatives, because of setting up to three new stereocenters in a single step. Jacobsen and co-workers recently developed highly enantio- and diastereoselective HDA reactions between monooxygenated 1,3-dienes and simple aldehydes catalyzed by tridentate Schiff base Cr(III) complexes.¹² The Jacobsen catalytic asymmetric HDA reaction has found numerous applications in total syntheses of tetrahydropyran-containing natural products.¹³ However, the HDA reaction has not yet been adapted to the diarylheptanoid tetrahydropyran system.¹⁴ We recently reported that dirhodium(II) tetrakis[(*S*)-3-(benzene-fused-phthalimido)-2-piperidinonate], Rh₂(*S*-BPTPI)₄, is a highly efficient Lewis acid catalyst for *endo*- and enantioselective

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Centrolobine; (–)-De-*O*-methylcentrolobine; Chiral Rh(II) catalyst.

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HDA reactions of a diverse range of aldehydes with Danishefsky-type dienes as well as with monooxygenated dienes, in which up to 99% ee and turnover numbers as high as 48,000 are achieved (Eq. 1).^{15,16} In order to demonstrate the utility of this catalytic methodology, we now addressed asymmetric syntheses of (–)-centrolobine (**1**) and (–)-de-*O*-methylcentrolobine (**2**), focusing on the Rh₂(*R*-BPTPI)₄-catalyzed HDA reaction between 4-aryl-2-silyloxy-1,3-butadienes and phenylpropargyl aldehyde derivatives.

2. Results and Discussion

2.1. Synthetic plan

Our synthetic strategy for **1** and **2** based on the HDA reaction is outlined retrosynthetically in Scheme 1. With the high reactivity of phenylpropargyl aldehyde as a dienophile previously identified,¹⁵ we envisioned that the Rh₂(*R*-BPTPI)₄-catalyzed HDA reaction between 4-aryl-2-triethylsilyloxy-1,3-butadienes **4** and phenylpropargyl aldehyde derivatives **5** would provide *cis*-(2*R*,6*S*)-disubstituted tetrahydropyran-4-ones **3** as the key intermediates. The appropriately protected intermediates **3** could be uneventfully transformed into **1** and **2** via catalytic hydrogenation of the triple bond and removal of the carbonyl group. As for this type of HDA reaction, Baldoli and co-workers reported a ZnCl₂-promoted stereoselective HDA reaction of 4-(2-methoxyphenyl)-2-trimethylsilyloxy-1,3-butadiene with enantiopure 2-chlorobenzaldehyde-Cr(CO)₃ complex.¹⁷ However, to the best of our knowledge, no examples of an HDA reaction between monooxygenated dienes bearing phenyl groups at C4 and aldehydes have been reported.¹⁸ In this respect, Wessjohann and co-workers reported that the BF₃·OEt₂-mediated reaction of 2-*tert*-butyldimethylsilyloxy-1,3-butadiene derivative, which has an aromatic ring conjugated to the diene system, with crotonaldehyde and cinnamaldehyde gave the classical Diels–Alder cycloadducts as the sole products, rather than the expected HDA products.¹⁹ Consequently, the development of the HDA reaction between 4-aryl-2-

silyloxy-1,3-butadienes and phenylpropargyl aldehydes has become a challenging objective.

Scheme 1. Retrosynthetic analysis of (–)-centrolobine and (–)-de-*O*-methylcentrolobine.

2.2. Preparation of dienes and aldehydes for the HDA reaction

At the outset of our studies, we expected that 4-(4-methoxyphenyl)-2-triethylsilyloxy-1,3-butadiene (**4a**) and 4-(4-benzyloxyphenyl)-2-triethylsilyloxy-1,3-butadiene (**4b**) would serve as the diene components for the synthesis of **1** and **2**, respectively. The dienes **4a** and **4b** were prepared by the reaction of readily available α,β-unsaturated ketones **6a**²⁰ and **6b**²¹ with Et₃SiOTf in the presence of Et₃N in CH₂Cl₂ at 0 °C (Scheme 2). 4-Phenyl-2-triethylsilyloxy-1,3-butadiene (**4c**) as a model diene was also prepared from benzalacetone (**6c**) under the same conditions.

Scheme 2. Preparation of dienes **4a–c**.

Phenylpropargyl aldehydes **5a** and **5b**, bearing *tert*-butyldimethylsilyloxy and methanesulfonyloxy groups at the *para* position on the benzene ring, were prepared by the Sonogashira coupling²² of propargyl alcohol with iodophenol derivatives **7a**²³ and **7b**,²⁴ and subsequent Dess–Martin oxidation (Scheme 3).

Scheme 3. Reagents and conditions: (a) propargyl alcohol, $\text{PdCl}_2(\text{PPh}_3)_2$ (0.5 mol %), CuI (1 mol %), Et_3N , 23 °C; (b) Dess-Martin periodinane, CH_2Cl_2 , 0 °C.

2.3. Enantioselective HDA reaction

On the basis of our previous work,¹⁵ we initially evaluated the HDA reaction between 4-(4-methoxyphenyl)-2-triethylsilyloxy-1,3-butadiene (**4a**) (1.5 equiv.) and phenylpropargyl aldehyde (**5c**) as a model system using 1 mol % of $\text{Rh}_2(R\text{-BPTPI})_4$. The reaction in dichloromethane at room temperature proceeded in 48 h, and, after treatment with TBAF, gave the *cis*-2,6-disubstituted tetrahydropyran-4-one **3a** as the sole product in 83% yield with 91% ee (Table 1, entry 1). The *cis* stereochemistry of **3a** was

established by the ^1H NOE between C2-H and C6-H (Figure 1). Encouraged by this result, we next examined the reaction with *p*-*tert*-butyldimethylsilyloxy-substituted phenylpropargyl aldehyde **5a**. However, the introduction of this substituent was found to be detrimental as the reaction did not proceed under the foregoing conditions. Even when 5 mol % of the catalyst was used in refluxing dichloromethane, only 15% yield of **3b** was isolated, though perfect *cis*-selectivity and 87% ee were observed (entry 2). Thus, we were gratified to find that the HDA reaction of **4a** with aldehyde **5b** bearing a methanesulfonyloxy substituent as the electron-withdrawing group proceeded smoothly to completion within 12 h, and, after desilylation, gave exclusively the *cis*-2,6-disubstituted tetrahydropyran-4-one **3c** for the synthesis of (–)-centrolobine (**1**) in 87% yield with 93% ee (entry 3). The HDA reaction of *p*-benzyloxy-substituted diene **4b** with aldehyde **5b** also worked well, providing tetrahydropyran-4-one **3d** for the synthesis of (–)-*O*-methylcentrolobine (**2**) in 84% yield with 90% ee (entry 4). The absolute stereochemistry of **3c** and **3d** was established as (2*R*,6*S*) by their transformation into **1** and **2**, respectively (*vide infra*).

Table 1. Enantioselective hetero-Diels–Alder reactions catalyzed by $\text{Rh}_2(R\text{-BPTPI})_4$

Entry	4	R ¹	5	R ²	Temp, °C	Time, h	Tetrahydropyran-4-one	Yield, % ^a	% Ee
1	4a	OMe	5c	H	23	48	3a	83	91 ^{b,c}
2 ^d	4a	OMe	5a	OTBS	Reflux	48	3b (R ² = OH) ^e	15	87 ^{b,c}
3	4a	OMe	5b	OMs	23	12	3c	87	93 ^f
4	4b	OBn	5b	OMs	23	12	3d	84	90 ^f

^a Isolated yield.

^b Determined by HPLC (Daicel Chiralcel OD-H).

^c The absolute stereochemistry was not determined.

^d 5 mol % of $\text{Rh}_2(R\text{-BPTPI})_4$ was used.

^e Only phenol product was obtained due to the concomitant desilylation.

^f Determined by HPLC (Daicel Chiralpak AD-H).

Figure 1. NOE experiments of **3a**.

For comparison, the HDA reaction between 4-phenyl-2-triethylsilyloxy-1,3-butadiene (**4c**) and aldehyde **5b** in the presence of $\text{Rh}_2(R\text{-BPTPI})_4$ was then attempted. However, the reaction did not proceed at all (Eq. 2). These results suggest that the combination of an increase in the HOMO energy of silyoxydienes **4** and a decrease in the LUMO energy of phenylpropargyl aldehydes **5** by means of the *para*-substitutions on the benzene ring is crucial for the success of this type of HDA reaction.

As an alternative approach to *cis*-2,6-disubstituted tetrahydropyran-4-ones, we finally investigated the HDA reaction between 4-methanesulfonyloxybenzaldehyde (**8**) and 6-(4-benzyloxyphenyl)-2-triethylsilyloxy-1,3-hexadien-5-yne (**9**)²⁵ (Eq. 3). However, no reaction occurred. This observation again indicates that the sterically less-demanding and electron-deficient phenylpropargyl aldehydes are particularly suitable dienophiles for the $\text{Rh}_2(R\text{-BPTPI})_4$ -catalyzed HDA reaction with monooxygenated dienes.

2.4. Syntheses of (–)-centrolobine and (–)-de-O-methylcentrolobine

With the efficient construction of *cis*-2,6-disubstituted tetrahydropyran-4-ones **3c** and **3d** realized, the stage was now set for the completion of asymmetric syntheses of (–)-centrolobine (**1**) and (–)-de-O-methylcentrolobine (**2**). The synthesis of **1** from tetrahydropyran-4-one **3c** is illustrated in Scheme 4. A single recrystallization of **3c** with 93% ee from ethanol produced optically pure material, mp 134–135 °C, $[\alpha]_D^{22}$ –4.95° (*c* 1.02, CHCl_3) in 76% yield. Catalytic hydrogenation of the triple bond provided **10** in 96% yield. Tosylhydrazide formation of ketone **10** with *p*-toluenesulfonyl hydrazine was followed by reduction with NaBH_3CN in the presence of *p*-TsOH to produce tetrahydropyran **12** in 75% yield.²⁷ Finally, removal of the methanesulfonyl group with K_2CO_3 in MeOH completed the asymmetric synthesis of (–)-centrolobine (**1**), mp 85.0–85.5 °C (lit.,^{1c} mp 84–86 °C), $[\alpha]_D^{21}$ –93.7° (*c* 1.02, CHCl_3) [lit.,^{1d} $[\alpha]_D$ –92.2° (*c* 1, CHCl_3)], which also established the preferred absolute stereochemistry of cycloadduct **3c** as (2*R*,6*S*). The synthetic material **1** exhibited identical spectroscopic data with those reported for natural (–)-centrolobine (IR, ¹H NMR, ¹³C NMR, HRMS).¹

Consequently, the stereochemical outcome of the present HDA reaction can be rationalized on the basis of the absolute stereochemical model we previously proposed,¹⁵ which contains a hydrogen bond between the formyl hydrogen atom and the carboxamidate oxygen atom²⁸ in rhodium catalyst-aldehyde complexes (Figure 2). The approach of dienes **4** in an *endo* mode to avoid intrusion into the rhodium framework leads to the observed cycloadducts **3** with a 2,6-*cis*-arrangement of substituents.

Scheme 4. Reagents and conditions: (a) H_2 , 10% Pd/C, EtOAc, 2 h (for **3c**) or 4 h (for **3d**); (b) TsNHNH_2 , MeOH, reflux, 2 h; (c) NaBH_3CN , TsOH, DMF-sulfolane (1:1), 110 °C, 1 h; (d) K_2CO_3 , MeOH, reflux, 3 h.

Figure 2. Plausible stereochemical pathway.

We then proceeded to the asymmetric synthesis of (–)-de-*O*-methylcentrolobine (**2**) from tetrahydropyran-4-one **3d** (Scheme 4). Recrystallization of **3d** with 90% ee from ethanol resulted in the production of an optically pure sample, mp 135–136 °C, $[\alpha]_{\text{D}}^{20} -4.76^\circ$ (*c* 3.20, CH₃CN) in 73% yield. Sequential catalytic hydrogenation of the triple bond and hydrogenolysis of the benzyl ether in a single flask furnished tetrahydropyran-4-one **11** in 97% yield. The conversion of **11** to **2** was conducted in the same manner as that of **10** to **1**. The synthetic material **2** was spectroscopically (IR, ¹H NMR, ¹³C NMR, HRMS) identical with natural (–)-de-*O*-methylcentrolobine,^{2a} and also had an optical rotation, $[\alpha]_{\text{D}}^{22} -96.1^\circ$ (*c* 1.02, MeOH), in good agreement with the literature value [lit.,^{2a} $[\alpha]_{\text{D}}^{25} -95.1^\circ$ (*c* 0.9, MeOH)]. Thus, the preferred absolute stereochemistry of cycloadduct **3d** was established as (2*R*,6*S*).

3. Conclusion

We have developed a highly enantio- and diastereoselective HDA reaction between 4-aryl-2-silyloxy-1,3-butadienes and phenylpropargyl aldehyde derivatives using Rh₂(*R*-BPTPI)₄ as a chiral Lewis acid catalyst, which provides a straightforward entry to *cis*-(2*R*,6*S*)-2-arylethynyl-6-aryl-tetrahydropyran-4-ones. This represents the first example of an HDA reaction of 4-aryl-2-silyloxy-1,3-butadienes with aldehydes. Using this catalytic methodology, we have achieved the asymmetric synthesis of (–)-centrolobine in 7 steps and 41% overall yield from 4-iodophenyl methanesulfonate (**7b**), and the first asymmetric synthesis of (–)-de-*O*-methylcentrolobine in 8 steps and 39% overall yield from **7b**. Further application of this methodology to catalytic asymmetric synthesis of other diarylheptanoid natural products is currently in progress.

4. Experimental

4.1. General

Melting points were determined on a Büchi 535 digital melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-5300 spectrometer and absorbance bands are reported in wavenumber (cm^{–1}). ¹H NMR spectra were recorded on JEOL JNM-EX 270 (270 MHz) spectrometer and JEOL JNM-AL 400 (400 MHz) spectrometer. Chemical shifts are reported relative to internal standard (tetramethylsilane; δ_{H} 0.00, CDCl₃; δ_{H} 7.26 or acetone-*d*₆; δ_{H} 2.04). Data are presented as follows: chemical shift (δ , ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant and integration. ¹³C NMR spectra were recorded on JEOL JNM-AL 400 (100 MHz) spectrometer. The following internal references were used (CDCl₃; δ 77.0 or acetone-*d*₆; δ 29.8). Optical rotations were measured on a JASCO P-1030 digital polarimeter at the sodium D line (589 nm). EI-MS spectra were obtained on a JEOL JMS-FABmate spectrometer, operating with ionization energy of

70 eV. FAB-MS spectra were obtained on a JEOL JMS-HX 110 spectrometer.

Column chromatography was carried out on Kanto silica gel 60 N (63–210 mesh) or Wakogel® C-200 (75–150 μm). Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F₂₅₄ plates with visualization by ultraviolet, anisaldehyde stain solution or phosphomolybdic acid stain solution. Analytical high performance liquid chromatography (HPLC) was performed on a JASCO PU-1580 intelligent HPLC pump with JASCO UV-1575 intelligent UV/VIS detector. Detection was performed at 254 nm. Chiralcel OD-H and Chiralpak AD-H columns (0.46 cm $\times$ 25 cm) from Daicel were used. Retention times (*t_R*) and peak ratios were determined with JASCO-Borwin analysis system.

All non-aqueous reactions were carried out in flame-dried glassware under argon atmosphere unless otherwise noted. Reagents and solvents were purified by standard means. Dehydrated CH₂Cl₂ was purchased from Kanto Chemical Co., Inc. Rh₂(*R*-BPTPI)₄·3H₂O was prepared from D-ornithine according to the literature procedure of Rh₂(*S*-BPTPI)₄·3H₂O.¹⁵

4.2. Preparation of dienes

4.2.1. *trans*-4-(4-Methoxyphenyl)-2-triethylsilyloxy-1,3-butadiene (4a). To a solution of *trans*-4-(4-methoxyphenyl)-3-buten-2-one (**6a**)²⁰ (1.5 g, 8.5 mmol) and Et₃N (2.4 mL, 17 mmol) in CH₂Cl₂ (20 mL) was added triethylsilyl trifluoromethanesulfonate (1.9 mL, 8.5 mmol) at 0 °C. After stirring at this temperature for 0.5 h, the reaction was quenched with saturated NaHCO₃ solution (10 mL), and the whole was extracted with EtOAc (2 $\times$ 30 mL). The combined organic layers were washed with brine (2 $\times$ 10 mL), and dried over anhydrous Na₂SO₄. Filtration and evaporation *in vacuo* followed by column chromatography (Wakogel® C-200, 100:1 hexane/EtOAc with 2% Et₃N) provided **4a** (2.17 g, 88%) as a colorless oil: TLC *R_f* = 0.40 (19:1 hexane/EtOAc); IR (film) 1634, 1606, 1588, 1510, 1252, 1026 cm^{–1}; ¹H NMR (270 MHz, CDCl₃) δ 0.77 (q, *J* = 7.9 Hz, 6H, SiCH₂CH₃), 1.03 (t, *J* = 7.9 Hz, 9H, SiCH₂CH₃), 3.81 (s, 3H, OCH₃), 4.38 (s, 1H, C1-*H*), 4.39 (s, 1H, C1-*H*), 6.46 (d, *J* = 15.5 Hz, 1H, C3-*H*), 6.82 (d, *J* = 15.5 Hz, 1H, C4-*H*), 6.83–6.89 (m, 2H, *Ar*), 7.33–7.38 (m, 2H, *Ar*); ¹³C NMR (100 MHz, CDCl₃) δ 5.0 (CH₂), 6.8 (CH₃), 55.2 (CH₃), 95.3 (CH₂), 113.9 (CH), 124.2 (CH), 127.9 (CH), 128.5 (CH), 129.5 (C), 155.2 (C), 159.1 (C); FAB-HRMS *m/z* calcd for C₁₇H₂₇O₂Si (M+H)⁺ 291.1775, found 291.1781. Anal. Calcd for C₁₇H₂₆O₂Si: C, 70.29; H, 9.02. Found: C, 70.04; H, 9.06.

4.2.2. *trans*-4-(4-Benzyloxyphenyl)-2-triethylsilyloxy-1,3-butadiene (4b). Following the procedure for the preparation of **4a**, starting from *trans*-4-(4-benzyloxyphenyl)-3-buten-2-one (**6b**)²¹ (1.3 g, 5.0 mmol), Et₃N (1.4 mL, 10 mmol) and triethylsilyl trifluoromethanesulfonate (1.1 mL, 5.0 mmol), **4b** (1.56 g, 85%) was obtained as a colorless oil: TLC *R_f* = 0.33 (19:1 hexane/EtOAc); IR (film) 1632, 1605, 1588, 1508, 1241,

1020 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 0.76 (q, J = 7.6 Hz, 6H, SiCH_2CH_3), 1.03 (t, J = 7.6 Hz, 9H, SiCH_2CH_3), 4.38 (s, 1H, C1-*H*), 4.39 (s, 1H, C1-*H*), 5.07 (s, 2H, PhCH_2O), 6.46 (d, J = 15.8 Hz, 1H, C3-*H*), 6.81 (d, J = 15.8 Hz, 1H, C4-*H*), 6.91–6.95 (m, 2H, *Ar*), 7.30–7.45 (m, 7H, *Ar*); ^{13}C NMR (100 MHz, CDCl_3) δ 5.0 (CH_2), 6.8 (CH_3), 69.9 (CH_2), 95.4 (CH_2), 114.8 (CH), 124.3 (CH), 127.3 (CH), 127.8 (CH), 127.9 (CH), 128.4 (CH), 129.7 (C); 136.7 (C), 155.2 (C), 158.3 (C); FAB-HRMS m/z calcd for $\text{C}_{23}\text{H}_{31}\text{O}_2\text{Si}$ ($\text{M}+\text{H}$) $^+$ 367.2093, found 367.2090. Anal. Calcd for $\text{C}_{23}\text{H}_{30}\text{O}_2\text{Si}$: C, 75.36; H, 8.25. Found: C, 75.25; H, 8.27.

4.2.3. *trans*-4-Phenyl-2-triethylsilyloxy-1,3-butadiene (4c). Following the procedure for the preparation of **4a**, starting from *trans*-4-phenyl-3-buten-2-one (**6c**) (730 mg, 5.0 mmol), Et_3N (1.4 mL, 10 mmol) and triethylsilyl trifluoromethanesulfonate (1.1 mL, 5.0 mmol), **4c** (1.08 g, 87%) was obtained as a colorless oil: TLC R_f = 0.35 (500:1 hexane/EtOAc); IR (film) 1588, 1328, 1023 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.77 (q, J = 7.7 Hz, 6H, SiCH_2CH_3), 1.03 (t, J = 7.7 Hz, 9H, SiCH_2CH_3), 4.42 (s, 1H, C1-*H*), 4.44 (s, 1H, C1-*H*), 6.58 (d, J = 15.9 Hz, 1H, C3-*H*), 6.87 (d, J = 15.9 Hz, 1H, C4-*H*), 7.20–7.26 (m, 1H, *Ar*), 7.29–7.34 (m, 2H, *Ar*), 7.41–7.43 (m, 2H, *Ar*); ^{13}C NMR (100 MHz, CDCl_3) δ 4.9 (CH_2), 6.7 (CH_3), 96.3 (CH_2), 126.4 (CH), 126.7 (CH), 127.6 (CH), 128.5 (CH), 129.1 (CH), 136.8 (C), 155.1 (C); EI-HRMS m/z calcd for $\text{C}_{16}\text{H}_{24}\text{O}_2\text{Si}$ (M) $^+$ 260.1596, found 260.1597. Anal. Calcd for $\text{C}_{16}\text{H}_{24}\text{OSi}$: C, 73.79; H, 9.29. Found: C, 73.59; H, 9.52.

4.2.4. Preparation of *trans*-6-(4-benzyloxyphenyl)-2-triethylsilyloxy-1,3-hexadien-5-yne (**9**)

4.2.4.1. (4-Benzyloxyphenyl)propynal. To a solutions of 3-(4-benzyloxyphenyl)-2-propyn-1-ol²⁶ (2.0 g, 8.4 mmol) and Et_3N (5.8 mL, 42 mmol) in CH_2Cl_2 (15 mL)–DMSO (15 mL) was added sulfur trioxide pyridine complex (3.3 g, 21 mmol) at 0 °C. After stirring at this temperature for 1 h, the mixture was diluted with EtOAc (20 mL), and poured into saturated aqueous NH_4Cl (20 mL). The whole was extracted with EtOAc (40 mL). The combined organic layers were washed with water (15 mL) and brine (3×15 mL), and dried over anhydrous Na_2SO_4 . Filtration and evaporation *in vacuo* followed by column chromatography (silica gel, 19:1 hexane/EtOAc) provided the title compound (1.90 g, 96%) as a pale yellow solid: mp 59.0–60.0 °C; TLC R_f = 0.30 (9:1 hexane/EtOAc); IR (film) 2174, 1643, 1596, 1505, 1254 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 5.11 (s, 2H, PhCH_2O), 6.97–7.00 (m, 2H, *Ar*), 7.34–7.43 (m, 5H, *Ar*), 7.55–7.58 (m, 2H, *Ar*), 9.39 (s, 1H, *CHO*); ^{13}C NMR (100 MHz, CDCl_3) δ 70.0 (CH_2), 88.7 (C), 96.4 (C), 111.2 (C), 115.2 (CH), 127.4 (CH), 128.2 (CH), 128.6 (CH), 135.4 (CH), 135.9 (C), 161.1 (C), 176.7 (C=O); EI-HRMS m/z calcd for $\text{C}_{16}\text{H}_{12}\text{O}_2$ (M) $^+$ 236.0837, found 236.0837. Anal. Calcd for $\text{C}_{16}\text{H}_{12}\text{O}_2$: C, 81.34; H, 5.12. Found: C, 81.23; H, 5.22.

4.2.4.2. *trans*-6-(4-Benzyloxyphenyl)-3-hexen-5-yn-2-one. To a solution of (4-benzyloxyphenyl)propynal (1.0 g, 4.2 mmol) in acetone (5 mL) was added 10% aqueous

NaOH (5 mL). After stirring at this temperature for 24 h, the reaction mixture was partitioned between EtOAc (30 mL) and water (10 mL). The organic layer was washed with water (5 mL) and brine (2×5 mL), and dried over anhydrous Na_2SO_4 . Filtration and evaporation *in vacuo* followed by column chromatography (silica gel, 9:1 hexane/EtOAc) provided the title compound (1.12 g, 96%) as a white solid; mp 100–101 °C; TLC R_f = 0.34 (4:1 hexane/EtOAc); IR (film) 2190, 1659, 1592, 1505, 1251 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.30 (s, 3H, COCH_3), 5.09 (s, 2H, PhCH_2O), 6.53 (d, J = 15.9 Hz, 1H, C3-*H*), 6.84 (d, J = 15.9 Hz, 1H, C4-*H*), 6.93–6.97 (m, 2H, *Ar*), 7.34–7.45 (m, 7H, *Ar*); ^{13}C NMR (100 MHz, CDCl_3) δ 27.5 (CH_3), 69.9 (CH_2), 86.0 (C), 100.3 (C), 114.3 (C), 115.0 (CH), 124.1 (CH), 127.4 (CH), 128.1 (CH), 128.6 (CH), 133.6 (CH), 136.2 (C), 136.9 (CH), 159.6 (C), 197.1 (C=O); EI-HRMS m/z calcd for $\text{C}_{19}\text{H}_{16}\text{O}_2$ (M) $^+$ 276.1150, found 276.1157. Anal. Calcd for $\text{C}_{19}\text{H}_{16}\text{O}_2$: C, 82.58; H, 5.84. Found: C, 82.76; H, 5.97.

4.2.4.3. *trans*-6-(4-Benzyloxyphenyl)-2-triethylsilyloxy-1,3-hexadien-5-yne (9**).** Following the procedure for the preparation of **4a**, starting from *trans*-6-(4-benzyloxyphenyl)-3-hexen-5-yn-2-one (550 mg, 2.0 mmol), Et_3N (0.56 mL, 4.0 mmol) and triethylsilyl trifluoromethanesulfonate (0.45 mL, 2.0 mmol), **9** (703 mg, 90%) was obtained as a colorless oil: TLC R_f = 0.32 (19:1 hexane/EtOAc); IR (film) 2193, 1602, 1578, 1507, 1322, 1243, 1018 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 0.74 (q, J = 8.2 Hz, 6H, SiCH_2CH_3), 1.01 (t, J = 8.2 Hz, 9H, SiCH_2CH_3), 4.38 (s, 1H, C1-*H*), 4.40 (s, 1H, C1-*H*), 5.06 (s, 2H, PhCH_2O), 6.15 (d, J = 15.4 Hz, 1H, C3-*H*), 6.46 (d, J = 15.4 Hz, 1H, C4-*H*), 6.90–6.93 (m, 2H, *Ar*), 7.31–7.43 (m, 7H, *Ar*); ^{13}C NMR (100 MHz, CDCl_3) δ 4.9 (CH_2), 6.7 (CH_3), 69.9 (CH_2), 87.4 (C), 92.7 (C), 97.1 (CH_2), 109.0 (CH), 114.8 (CH), 115.8 (CH), 127.4 (CH), 128.0 (CH), 128.6 (CH), 132.9 (CH), 136.5 (C), 137.9 (CH), 154.4 (C), 158.7 (C); EI-HRMS m/z calcd for $\text{C}_{25}\text{H}_{30}\text{O}_2\text{Si}$ (M) $^+$ 390.2015, found 390.2006. Anal. Calcd for $\text{C}_{25}\text{H}_{30}\text{O}_2\text{Si}$: C, 76.88; H, 7.74. Found: C, 76.91; H, 7.91.

4.3. Preparation of aldehydes

4.3.1. [4-(*tert*-Butyldimethylsilyloxy)phenyl]propynal (5a**).** To a stirred mixture of (4-*tert*-butyldimethylsilyloxy)iodobenzene (**7a**)²³ (2.0 g, 6.0 mmol), copper iodide (11 mg, 0.06 mmol, 1 mol %), $\text{PdCl}_2(\text{PPh}_3)_2$ (21 mg, 0.03 mmol, 0.5 mol %), and propargyl alcohol (0.70 mL, 12 mmol) was added Et_3N (6 mL) at 0 °C. After stirring at 23 °C for 2 h, the reaction mixture was diluted with EtOAc (20 mL), and filtered through a plug of Celite with EtOAc (10 mL). Filtration and concentration *in vacuo* followed by column chromatography (silica gel, 4:1 hexane/EtOAc) provided 3-[4-(*tert*-butyldimethylsilyloxy)phenyl]prop-2-yn-1-ol (1.49 g, 95%) as a pale yellow oil: TLC R_f = 0.32 (3:1 hexane/EtOAc); ^1H NMR (400 MHz, CDCl_3) δ 0.20 (s, 6H, $\text{Si}(\text{CH}_3)_2$), 0.97 (s, 9H, $\text{Si}(\text{CH}_3)_3$), 1.66 (t, 1H, J = 6.2 Hz, OH), 4.48 (d, 2H, J = 6.2 Hz, CH_2OH), 6.76–6.79 (m, 2H, *Ar*), 7.30–7.32 (m, 2H, *Ar*). To a solution of 3-[4-(*tert*-butyldimethylsilyloxy)phenyl]prop-2-yn-1-ol (790 mg, 3.0

mmol) in CH_2Cl_2 (10 mL) was added Dess–Martin periodinane (1.3 g, 3.0 mmol) at 0 °C. After stirring at this temperature for 3 h, the mixture was poured into an ice-cooled solution of saturated aqueous NaHCO_3 (5 mL) containing $\text{Na}_2\text{S}_2\text{O}_3 \cdot \text{H}_2\text{O}$ (0.5 g). The whole was extracted with EtOAc (50 mL). The combined organic layers were washed with water (2×5 mL) and brine (2×5 mL), and dried over anhydrous Na_2SO_4 . Filtration and evaporation *in vacuo* followed by column chromatography (silica gel, 39:1 hexane/EtOAc) provided **5a** (760 mg, 97%) as a pale yellow oil: TLC R_f = 0.37 (19:1 hexane/EtOAc); IR (film) 2244, 2184, 1659 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 0.23 (s, 6H, $\text{Si}(\text{CH}_3)_2$), 0.98 (s, 9H, $\text{Si}(\text{CH}_3)_3$), 6.84–6.86 (m, 2H, Ar), 7.50–7.52 (m, 2H, Ar), 9.39 (s, 1H, CHO); ^{13}C NMR (100 MHz, CDCl_3) δ -4.2 (CH_3), 18.3 (C), 25.6 (CH_3), 88.6 (C), 96.3 (C), 111.5 (C), 120.3 (CH), 135.1 (CH), 158.4 (C), 176.2 (C=O); EI-HRMS m/z calcd for $\text{C}_{15}\text{H}_{20}\text{O}_2\text{Si}$ (M)⁺ 260.1232, found 260.1232. Anal. Calcd for $\text{C}_{15}\text{H}_{20}\text{O}_2\text{Si}$: C, 69.19; H, 7.74. Found: C, 68.96; H, 8.00.

4.3.2. (4-Methanesulfonyloxyphenyl)propynal (**5b**).

Following the procedure of Sonogashira coupling of **7a**, starting from 4-iodophenyl methanesulfonate (**7b**)²⁴ (7.5 g, 25 mmol), copper iodide (47 mg, 0.25 mmol, 1 mol %), $\text{PdCl}_2(\text{PPh}_3)_2$ (88 mg, 0.13 mmol, 0.5 mol %), propargyl alcohol (2.9 mL, 50 mmol) and Et_3N (20 mL), 4-(3-hydroxy-1-propynyl)phenyl methanesulfonate (5.31 g, 94%) was obtained as a pale yellow solid: mp 56.0–56.5 °C; TLC R_f = 0.39 (1:2 hexane/EtOAc); ^1H NMR (270 MHz, CDCl_3) δ 1.71 (t, 1H, J = 6.3 Hz, OH), 3.16 (s, 3H, SO_2CH_3), 4.50 (d, 2H, J = 6.3 Hz, CH_2OH), 7.22–7.27 (m, 2H, Ar), 7.46–7.51 (m, 2H, Ar). Following the procedure of the Dess–Martin oxidation of 3-[4-(*tert*-butyldimethylsilyloxy)phenyl]prop-2-yn-1-ol, starting from 4-(3-hydroxy-1-propynyl)phenyl methanesulfonate (1.1 g, 5.0 mmol) and Dess–Martin periodinane (2.1 g, 5.0 mmol), **5b** (1.08 g, 96%) was obtained as a pale yellow solid: mp 84.5–85.0 °C; TLC R_f = 0.20 (2:1 hexane/EtOAc); IR (KBr) 2249, 2189, 1658, 1356, 1200, 1172, 1152 cm^{-1} ; ^1H NMR (270 MHz, CDCl_3) δ 3.20 (s, 3H, OCH_3), 7.32–7.37 (m, 2H, Ar), 7.64–7.70 (m, 2H, Ar), 9.43 (s, 1H, CHO); ^{13}C NMR (100 MHz, CDCl_3) δ 37.6 (CH_3), 88.5 (C), 92.7 (C), 118.2 (C), 122.3 (CH), 134.7 (CH), 150.5 (C), 176.4 (C=O); EI-HRMS m/z calcd for $\text{C}_{10}\text{H}_8\text{O}_4\text{S}$ (M)⁺ 224.0143, found 224.0144. Anal. Calcd for $\text{C}_{10}\text{H}_8\text{O}_4\text{S}$: C, 53.56; H, 3.60; S, 14.30. Found: C, 53.45; H, 3.61; S, 14.25.

4.4. HDA reaction

4.4.1. Typical procedure for the HDA reaction: (2*R*,6*S*)-2-(4-methanesulfonyloxyphenylethynyl)-6-(4-methoxyphenyl)tetrahydropyran-4-one (**3c**) (Table 1, Entry 3).

To a solution of (4-methanesulfonyloxyphenyl)propynal (**5b**) (450 mg, 2.0 mmol) in CH_2Cl_2 (3 mL) was added $\text{Rh}_2(\text{R-BPTPI})_4 \cdot 3\text{H}_2\text{O}$ (29 mg, 0.02 mmol, 1 mol %). Then the color of solution changed from pale yellow to brown. After stirring for 5 min, a solution of *trans*-4-(4-methoxyphenyl)-2-triethylsilyloxy-1,3-butadiene (**4a**) (870 mg, 3.0 mmol) in CH_2Cl_2 (1 mL) was added at 23 °C. After stirring at this temperature for 12 h, the reaction mixture turned into deep green solution. The whole mixture was

concentrated *in vacuo* furnished the deep green oil (1.3 g), which was purified by column chromatography (Wakogel® C-200, 4:1 hexane/EtOAc with 2% Et_3N) to give silyl enol ether (1.0 g) as a colorless oil. Subsequently, to a solution of the silyl enol ether in THF (4 mL) was added a solution of TBAF in THF (1.0 M, 2.0 mL, 2.0 mmol) at 23 °C. After stirring at this temperature for 0.5 h, the mixture was poured into a two-layer mixture of EtOAc (20 mL) and water (10 mL), and the whole was extracted with EtOAc (40 mL). The organic layer was washed with water (15 mL) and brine (2×15 mL), and dried over anhydrous Na_2SO_4 . Filtration and evaporation *in vacuo* furnished the crude product (800 mg) as a pale yellow oil, which was purified by column chromatography (silica gel, 3:2 hexane/EtOAc) to give **3c** (700 mg, 87%) as a pale yellow solid: mp 132–133 °C; TLC R_f = 0.25 (3:2 hexane/EtOAc); $[\alpha]_D^{22}$ -4.59° (*c* 1.01, CHCl_3) for 93% ee; IR (KBr) 2227, 1715, 1362, 1174, 1148 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.62–2.91 (m, 4H, CH_2COCH_2), 3.15 (s, 3H, SO_2CH_3), 3.81 (s, 3H, OCH_3), 4.66 (dd, J = 2.8, 11.5 Hz, 1H, C6-*H*), 4.77 (dd, J = 3.2, 11.7 Hz, 1H, C2-*H*), 6.90–6.94 (m, 2H, Ar), 7.22–7.27 (m, 2H, Ar), 7.32–7.36 (m, 2H, Ar), 7.48–7.52 (m, 2H, Ar); ^{13}C NMR (100 MHz, CDCl_3) δ 37.4 (CH_3), 47.4 (CH_2), 48.9 (CH_2), 55.2 (CH_3), 67.3 (CH), 78.4 (CH), 84.7 (C), 87.2 (C), 113.9 (CH), 121.2 (C), 121.9 (CH), 127.2 (CH), 131.7 (C), 133.3 (CH), 148.9 (C), 159.4 (C), 204.1 (C=O); EI-HRMS m/z calcd for $\text{C}_{21}\text{H}_{20}\text{O}_6\text{S}$ (M)⁺ 400.0980, found 400.0983. Anal. Calcd for $\text{C}_{21}\text{H}_{20}\text{O}_6\text{S}$: C, 62.99; H, 5.05; S, 8.01. Found: C, 62.86; H, 4.91; S, 7.99. The enantiomeric excess of **3c** was determined to be 93% by HPLC with a Chiralpak AD-H column (1:1 hexane/*i*-PrOH, 1.0 mL/min): t_R (major) = 18.2 min for (2*R*,6*S*)-enantiomer; t_R (minor) = 27.5 min for (2*S*,6*R*)-enantiomer. The preferred absolute configuration was established as (2*R*,6*S*) by transformation of **3c** into **1** (*vide infra*).

Recrystallization was performed by dissolving **3c** (700 mg, 1.8 mmol, 93 % ee) in 3 mL of hot EtOH. The pale yellow needles formed at room temperature after standing overnight, and were collected by suction, washed with 1 mL of ice cold EtOH and dried *in vacuo* to give optically pure **3c** (530 mg, 76%); mp 134–135 °C; $[\alpha]_D^{22}$ -4.95° (*c* 1.02, CHCl_3). The enantiopurity of **3c** was determined to be >99% ee by comparison of HPLC retention time with the racemic sample.

4.4.2. (2*R**,6*S**)-2-Phenylethynyl-6-(4-methoxyphenyl)tetrahydropyran-4-one (**3a**) (Table 1, Entry 1).

According to the typical procedure for HDA reaction, **3a** was prepared from diene **4a** (130 mg, 0.45 mmol), phenylpropargyl aldehyde (**5c**) (39 mg, 0.30 mmol), and $\text{Rh}_2(\text{R-BPTPI})_4 \cdot 3\text{H}_2\text{O}$ (4.3 mg, 0.003 mmol, 1 mol %) at 23 °C for 48 h. The crude product was purified by column chromatography (silica gel, 3:1 hexane/EtOAc) to provide **3a** (76 mg, 83%) as a pale yellow solid: mp 116–117 °C; TLC R_f = 0.29 (3:1 hexane/EtOAc); $[\alpha]_D^{23}$ -8.52° (*c* 1.02, CHCl_3) for 91% ee; IR (KBr) 2233, 1716 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.62–2.92 (m, 4H, CH_2COCH_2), 3.81 (s, 3H, OCH_3), 4.66 (dd, J = 2.6, 11.5 Hz, 1H, C6-*H*), 4.77 (dd, J = 3.0, 11.5 Hz, 1H, C2-*H*), 6.90–6.93 (m, 2H, Ar), 7.28–7.36 (m, 5H, Ar), 7.44–7.47 (m, 2H, Ar); ^{13}C

NMR (100 MHz, CDCl_3) δ 47.8 (CH_2), 49.1 (CH_2), 55.3 (CH_3), 67.7 (CH), 78.6 (CH), 86.0 (C), 86.4 (C), 114.0 (CH), 121.9 (C), 127.3 (CH), 128.2 (CH), 128.7 (CH), 131.8 (CH), 132.0 (C), 159.6 (C), 204.5 (C=O); EI-HRMS m/z calcd for $\text{C}_{20}\text{H}_{18}\text{O}_3$ (M^+) 306.1256, found 306.1258. Anal. Calcd for $\text{C}_{20}\text{H}_{18}\text{O}_3$: C, 78.41; H, 5.92. Found: C, 78.36; H, 5.99. The enantiomeric excess of **3a** was determined to be 91% by HPLC with a Chiralcel OD-H column (9:1 hexane/*i*-PrOH, 1.0 mL/min): t_R = 17.4 min for major enantiomer; t_R = 25.7 min for minor enantiomer. In order to assign the stereochemistry at C2 and C6, NOE studies were performed on **3a**. Irradiation of C2-H showed NOE with C6-H (15.9%) and C3-H (6.9%). Additionally, irradiation of C6-H exhibited NOE with C2-H (15.8%), C5-H (7.0%) and the *ortho* proton of the 4-methoxyphenyl group (6.5%). These data revealed *cis* relationship between C2-H and C6-H. The preferred absolute configuration of **3a** was not determined.

4.4.3. (2*R,6*S**)-2-(4-Hydroxyphenylethynyl)-6-(4-methoxyphenyl)tetrahydropyran-4-one (3b) (Table 1, Entry 2).** According to the typical procedure for HDA reaction, **3b** was prepared from diene **4a** (130 mg, 0.45 mmol), (4-*tert*-butyldimethylsilyloxyphenyl)propynal (**5a**) (78 mg, 0.30 mmol), and $\text{Rh}_2(\text{R-BPTPI})_4 \cdot 3\text{H}_2\text{O}$ (22 mg, 0.015 mmol, 5 mol %) at reflux for 48 h. The crude product was purified by column chromatography (silica gel, 2:1 hexane/EtOAc) to provide **3b** (14.0 mg, 15%) as a pale yellow solid: mp 149–150 °C; TLC R_f = 0.23 (1:1 hexane/EtOAc); $[\alpha]_D^{23}$ -4.07° (*c* 0.71, CHCl_3) for 87% ee; IR (KBr) 3382 (br), 2230, 1707 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.61–2.92 (m, 4H, CH_2COCH_2), 3.81 (s, 3H, OCH_3), 4.65 (dd, J = 2.6, 11.5 Hz, 1H, C6-*H*), 4.76 (dd, J = 3.0, 11.7 Hz, 1H, C2-*H*), 5.33 (br, 1H, OH), 6.74–6.78 (m, 2H, *Ar*), 6.89–6.83 (m, 2H, *Ar*), 7.32–7.36 (m, 4H, *Ar*); ^{13}C NMR (100 MHz, CDCl_3) δ 47.9 (CH_2), 49.1 (CH_2), 55.3 (CH_3), 67.8 (CH), 78.5 (CH), 84.5 (C), 86.5 (C), 113.8 (C), 114.0 (CH), 115.4 (CH), 127.4 (CH), 131.9 (C), 133.5 (CH), 156.4 (C), 159.5 (C), 205.3 (C=O); EI-HRMS m/z calcd for $\text{C}_{20}\text{H}_{18}\text{O}_4$ (M^+) 322.1205, found 322.1198. The enantiomeric excess of **3b** was determined to be 87% by HPLC with a Chiralcel OD-H column (1:1 hexane/*i*-PrOH, 1.0 mL/min): t_R = 7.2 min for major enantiomer; t_R = 10.4 min for minor enantiomer. The preferred absolute configuration of **3b** was not determined.

4.4.4. (2*R*,6*S*)-2-(4-Methanesulfonyloxyphenylethynyl)-6-(4-benzyloxyphenyl)tetrahydropyran-4-one (3d) (Table 1, Entry 4). According to the typical procedure for HDA reaction, **3d** was prepared from diene **4b** (550 mg, 1.5 mmol), (4-methanesulfonyloxyphenyl)propynal (**5b**) (220 mg, 1.0 mmol), and $\text{Rh}_2(\text{R-BPTPI})_4 \cdot 3\text{H}_2\text{O}$ (14 mg, 0.01 mmol, 1 mol %). The crude product was purified by column chromatography (silica gel, 3:1 hexane/EtOAc) to provide **3d** (400 mg, 84%) as a pale yellow solid: mp 134–135 °C; TLC R_f = 0.35 (1:1 hexane/EtOAc); $[\alpha]_D^{23}$ -4.16° (*c* 3.13, CH_3CN) for 90% ee; IR (KBr) 2232, 1720, 1352, 1172, 1152 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.60–2.91 (m, 4H, CH_2COCH_2), 3.15 (s, 3H, SO_2CH_3), 4.66 (dd, J = 2.7, 11.3 Hz, 1H, C6-*H*), 4.77 (dd, J = 3.2, 11.8 Hz, 1H, C2-*H*), 5.08 (s, 2H, PhCH_2O), 6.97–7.01 (m, 2H, *Ar*), 7.23–

7.26 (m, 2H, *Ar*), 7.31–7.43 (m, 7H, *Ar*), 7.49–7.52 (m, 2H, *Ar*); ^{13}C NMR (100 MHz, CDCl_3) δ 37.6 (CH_3), 47.5 (CH_2), 49.0 (CH_2), 67.5 (CH), 69.9 (CH_2), 78.5 (CH), 84.8 (C), 87.2 (C), 114.9 (CH), 121.3 (C), 122.0 (CH), 127.3 (CH), 127.4 (CH), 127.9 (CH), 128.5 (CH), 132.0 (C), 133.5 (CH), 136.6 (C), 149.0 (C), 158.7 (C), 204.3 (C=O); EI-HRMS m/z calcd for $\text{C}_{27}\text{H}_{24}\text{O}_6\text{S}$ (M^+) 476.1294, found 476.1296. Anal. Calcd for $\text{C}_{27}\text{H}_{24}\text{O}_6\text{S}$: C, 68.05; H, 5.08; S, 6.73. Found: C, 67.84; H, 5.07; S, 6.86. The enantiomeric excess of **3d** was determined to be 90% by HPLC with a Chiralpak AD-H column (1:1 hexane/*i*-PrOH, 1.0 mL/min): t_R (major) = 28.6 min for (2*R*,6*S*)-enantiomer; t_R (minor) = 39.8 min for (2*S*,6*R*)-enantiomer. The preferred absolute configuration was established as (2*R*,6*S*) by transformation of **3d** into **2** (*vide infra*).

Recrystallization was performed by dissolving **3d** (400 mg, 0.84 mmol, 90 % ee) in 2 mL of hot EtOH. The pale yellow needles formed at room temperature after standing overnight, and were collected by suction, washed with 1 mL of ice cold EtOH and dried *in vacuo* to give optically pure **3d** (290 mg, 73%); mp 135–136 °C; $[\alpha]_D^{20}$ -4.76° (*c* 3.20, CH_3CN). The enantiopurity of **3d** was determined to be >99% ee by comparison of HPLC retention time with the racemic sample.

4.5. Synthesis of (–)-centrolobine

4.5.1. (2*S*,6*S*)-6-[2-(4-Methanesulfonyloxyphenyl)ethyl]-2-(4-methoxyphenyl)tetrahydropyran-4-one (10). A solution of **3c** (200 mg, 0.50 mmol, >99% ee) in EtOAc (10 mL) was stirred with 10% Pd/C (20 mg) under 1 atm of H_2 at 23 °C for 2 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 3:2 hexane/EtOAc) to afford **10** (194 mg, 96%) as a white solid: mp 105–106 °C; TLC R_f = 0.29 (1:1 hexane/EtOAc); $[\alpha]_D^{20}$ -72.6° (*c* 1.01, CHCl_3); IR (KBr) 1717, 1368, 1198, 1177, 1150 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.83–1.92 (m, 1H, CH_2CHHCH), 2.02–2.11 (m, 1H, CH_2CHHCH), 2.37–2.47 (m, 2H, COCH_2), 2.54–2.65 (m, 2H, COCH_2), 2.74–2.91 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}$), 3.13 (s, 3H, SO_2CH_3), 3.69–3.76 (m, 1H, C2-*H*), 3.83 (s, 3H, OCH_3), 4.58 (dd, J = 4.1, 10.0 Hz, 1H, C6-*H*), 6.91–6.95 (m, 2H, *Ar*), 7.18–7.33 (m, 6H, *Ar*); ^{13}C NMR (100 MHz, CDCl_3) δ 30.9 (CH_2), 37.2 (CH_3), 37.7 (CH_2), 47.6 (CH_2), 49.3 (CH_2), 55.3 (CH_3), 75.9 (CH), 78.2 (CH), 113.9 (CH), 121.9 (CH), 126.9 (CH), 129.8 (CH), 132.7 (C), 140.7 (C), 147.3 (C), 159.2 (C), 206.5 (C=O); EI-HRMS m/z calcd for $\text{C}_{21}\text{H}_{24}\text{O}_6\text{S}$ (M^+) 404.1293, found 404.1292. Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{O}_6\text{S}$: C, 62.36; H, 5.98; S, 7.93. Found: C, 62.07; H, 5.87; S, 8.01.

4.5.2. (2*S*,6*R*)-6-[2-(4-Methanesulfonyloxyphenyl)ethyl]-2-(4-methoxyphenyl)tetrahydropyran (12). To a solution of **10** (170 mg, 0.43 mmol) in MeOH (3 mL) was added TsNHNH₂ (80 mg, 0.43 mmol). The mixture was stirred at reflux for 2 h. After cooling, the solvent was removed *in vacuo* to give the crude product (260 mg) as a pale yellow solid, which was used without further purification. To a solution of the crude tosylhydrazone (260 mg), TsOH·H₂O (25 mg, 0.13 mmol) in DMF (3 mL) and sulfolane (3 mL)

was added NaBH_3CN (110 mg, 1.7 mmol) at 23 °C. After stirring at 110 °C for 1 h, the mixture was cooled to room temperature and poured into water (3 mL). The whole was extracted with EtOAc (2×10 mL). The combined organic layers were washed with water (2×5 mL) and brine (2×5 mL), and dried over anhydrous Na_2SO_4 . Filtration and evaporation *in vacuo* followed by column chromatography (silica gel, 3:1 hexane/EtOAc) provided **12** (128 mg, 75%) as a white solid: mp 56.5–57.0 °C; TLC R_f = 0.25 (3:1 hexane/EtOAc); $[\alpha]_D^{21}$ –67.3° (*c* 1.00, CHCl_3); IR (KBr) 1368, 1198, 1177, 1150 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.25–1.95 (m, 8H, C3-*H*, C4-*H*, C5-*H* and $\text{CH}_2\text{CH}_2\text{CH}$), 2.70–2.85 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}$), 3.12 (s, 3H, SO_2CH_3), 3.41–3.47 (m, 1H, C6-*H*), 3.81 (s, 3H, OCH_3), 4.30 (dd, J = 2.1, 11.1 Hz, 1H, C2-*H*), 6.86–6.90 (m, 2H, *Ar*), 7.15–7.19 (m, 2H, *Ar*), 7.21–7.24 (m, 2H, *Ar*), 7.29–7.32 (m, 2H, *Ar*); ^{13}C NMR (100 MHz, CDCl_3) δ 24.0 (CH_2), 31.1 (CH_2), 31.3 (CH_2), 33.3 (CH_2), 37.2 (CH_3), 37.9 (CH_2), 55.3 (CH_3), 76.9 (CH), 79.1 (CH), 113.5 (CH), 121.6 (CH), 126.9 (CH), 129.9 (CH), 135.6 (C), 141.9 (C), 147.1 (C), 158.6 (C); EI-HRMS m/z calcd for $\text{C}_{21}\text{H}_{26}\text{O}_5\text{S}$ (M^+) 390.1501, found 390.1497. Anal. Calcd for $\text{C}_{21}\text{H}_{26}\text{O}_5\text{S}$: C, 64.59; H, 6.71; S, 8.21. Found: C, 64.34; H, 6.53; S, 8.41.

4.5.3. (–)-Centrolobine (1). To a solution of **12** (110 mg, 0.28 mmol) in MeOH (5 mL) was added K_2CO_3 (390 mg, 2.8 mmol). The mixture was stirred at reflux for 3 h. After cooling, the reaction mixture was partitioned between EtOAc (10 mL) and water (5 mL). The whole was extracted with EtOAc (2×10 mL). The combined organic layers were washed with water (2×5 mL) and brine (2×5 mL), and dried over anhydrous Na_2SO_4 . Filtration and evaporation *in vacuo* followed by column chromatography (silica gel, 4:1 hexane/EtOAc) provided **1** (82.0 mg, 96%) as a white solid. mp 85.0–85.5 °C [lit.^{1c} mp 84–86 °C]; TLC R_f = 0.25 (3:1 hexane/EtOAc); $[\alpha]_D^{21}$ –93.7° (*c* 1.02, CHCl_3) [lit.^{1d} $[\alpha]_D$ –92.2° (*c* 1, CHCl_3)]; IR (KBr) 3385, 3013, 2936, 2857, 1613, 1514, 1454, 1366, 1304, 1246, 1177, 1078, 1036 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.25–1.37 (m, 1H, C5-*H*), 1.45–1.55 (m, 1H, C3-*H*), 1.61–1.66 (m, 2H, C4-*H* and C5-*H*), 1.67–1.76 (m, 1H, CH_2CHHCH), 1.80–1.95 (m, 3H, C3-*H*, C4-*H* and CH_2CHHCH), 2.61–2.76 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}$), 3.41–3.46 (m, 1H, C6-*H*), 3.80 (s, 3H, OCH_3), 4.29 (dd, J = 2.1, 9.0 Hz, 1H, C2-*H*), 4.66 (br, 1H, *OH*), 6.71–6.75 (m, 2H, *Ar*), 6.86–6.90 (m, 2H, *Ar*), 7.03–7.07 (m, 2H, *Ar*), 7.29–7.33 (m, 2H, *Ar*); ^{13}C NMR (100 MHz, CDCl_3) δ 23.9 (CH_2), 30.6 (CH_2), 31.1 (CH_2), 33.1 (CH_2), 38.1 (CH_2), 55.1 (CH_3), 76.9 (CH), 78.9 (CH), 113.4 (CH), 114.8 (CH), 126.9 (CH), 129.3 (CH), 134.4 (C), 135.5 (C), 153.2 (C), 158.4 (C). EI-HRMS m/z calcd for $\text{C}_{20}\text{H}_{24}\text{O}_3$ (M^+) 312.1725, found 312.1733. The synthetic material **1** was identical in all respects with the reported spectral data for the natural substance (IR, ^1H NMR, ^{13}C NMR, HRMS), including optical rotation.

4.6. Synthesis of (–)-de-O-methylcentrolobine

4.6.1. (2S,6S)-2-(4-Hydroxyphenyl)-6-[2-(4-methanesulfonyloxyphenyl)ethyl]tetrahydropyran-4-one (11). Following the procedure for the preparation of **10**,

starting from **3d** (240 mg, 0.50 mmol, >99% ee) and 10% Pd/C (25 mg), **11** (190 mg, 97%) was obtained as a white solid: mp 45.0–46.0 °C; TLC R_f = 0.20 (1:1 hexane/EtOAc); $[\alpha]_D^{23}$ –69.9° (*c* 1.09, CHCl_3); IR (KBr) 3421 (br), 1713, 1364, 1173, 1147 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.83–1.92 (m, 1H, CH_2CHHCH), 2.01–2.10 (m, 1H, CH_2CHHCH), 2.37–2.47 (m, 2H, COCH_2), 2.53–2.63 (m, 2H, COCH_2), 2.74–2.91 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}$), 3.13 (s, 3H, SO_2CH_3), 3.69–3.75 (m, 1H, C2-*H*), 4.56 (dd, J = 3.2, 10.4 Hz, 1H, C6-*H*), 5.06 (br, 1H, *OH*), 6.84–6.87 (m, 2H, *Ar*), 7.18–7.28 (m, 6H, *Ar*); ^{13}C NMR (100 MHz, CDCl_3) δ 30.9 (CH_2), 37.2 (CH_3), 37.6 (CH_2), 47.5 (CH_2), 49.2 (CH_2), 75.9 (CH), 78.2 (CH), 115.4 (CH), 121.8 (CH), 127.1 (CH), 129.8 (CH), 132.3 (C), 140.7 (C), 147.2 (C), 155.6 (C), 207.7 (C=O); EI-HRMS m/z calcd for $\text{C}_{20}\text{H}_{22}\text{O}_6\text{S}$ (M^+) 390.1137, found 390.1131. Anal. Calcd for $\text{C}_{20}\text{H}_{22}\text{O}_6\text{S}$: C, 61.52; H, 5.68; S, 8.21. Found: C, 61.54; H, 5.70; S, 8.48.

4.6.2. (2S,6R)-2-(4-Hydroxyphenyl)-6-[2-(4-methanesulfonyloxyphenyl)ethyl]tetrahydropyran (13).

Following the procedure for the preparation of **12**, starting from **11** (160 mg, 0.40 mmol) and TsNHNH_2 (74 mg, 0.40 mmol), $\text{TsOH}\cdot\text{H}_2\text{O}$ (23 mg, 0.12 mmol) and NaBH_3CN (100 mg, 1.6 mmol), **13** (112 mg, 75%) was obtained as a white solid: mp 126–127 °C; TLC R_f = 0.28 (3:2 hexane/EtOAc); $[\alpha]_D^{22}$ –57.5° (*c* 1.00, CHCl_3); IR (KBr) 3356 (br), 1352, 1175, 1151 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.25–1.95 (m, 8H, C3-*H*, C4-*H*, C5-*H* and $\text{CH}_2\text{CH}_2\text{CH}$), 2.69–2.85 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}$), 3.12 (s, 3H, SO_2CH_3), 3.41–3.48 (m, 1H, C6-*H*), 4.28 (dd, J = 2.3, 10.8 Hz, 1H, C2-*H*), 4.78 (br, 1H, *OH*), 6.78–6.82 (m, 2H, *Ar*), 7.16–7.26 (m, 6H, *Ar*); ^{13}C NMR (100 MHz, acetone- d_6) δ 25.1 (CH_2), 32.1 (CH_2), 32.4 (CH_2), 34.9 (CH_2), 37.7 (CH_3), 39.3 (CH_2), 77.9 (CH), 80.2 (CH), 115.9 (CH), 123.1 (CH), 128.1 (CH), 131.0 (CH), 136.1 (C), 143.0 (C), 148.8 (C), 157.4 (C); EI-HRMS m/z calcd for $\text{C}_{20}\text{H}_{24}\text{O}_5\text{S}$ (M^+) 376.1344, found 376.1336. Anal. Calcd for $\text{C}_{20}\text{H}_{24}\text{O}_5\text{S}$: C, 63.81; H, 6.43; S, 8.52. Found: C, 63.41; H, 6.41; S, 8.65.

4.6.3. (–)-De-O-methylcentrolobine (2). Following the procedure for the preparation of **1**, starting from **13** (110 mg, 0.29 mmol) and K_2CO_3 (400 mg, 2.9 mmol), **2** (83.7 mg, 96%) was obtained as a white solid: mp 181–182 °C [lit.^{2a} mp 183 °C]; TLC R_f = 0.21 (2:1 hexane/EtOAc); $[\alpha]_D^{22}$ –96.1° (*c* 1.02, MeOH) [lit.^{2a} $[\alpha]_D^{25}$ –95.1° (*c* 0.9, MeOH)]; IR (KBr) 3362, 1614 cm^{-1} ; ^1H NMR (400 MHz, acetone- d_6) δ 1.20–1.90 (m, 8H, C3-*H*, C4-*H*, C5-*H* and $\text{CH}_2\text{CH}_2\text{CH}$), 2.55–2.70 (m, 2H, $\text{CH}_2\text{CH}_2\text{CH}$), 3.37–3.44 (m, 1H, C6-*H*), 4.25 (dd, J = 2.3, 11.3 Hz, 1H, C2-*H*), 6.71–6.80 (m, 4H, *Ar*), 6.99–7.03 (m, 2H, *Ar*), 7.19–7.22 (m, 2H, *Ar*), 8.03 (br, 1H, *OH*), 8.17 (br, 1H, *OH*); ^{13}C NMR (100 MHz, acetone- d_6) δ 24.7 (CH_2), 31.4 (CH_2), 32.0 (CH_2), 34.6 (CH_2), 39.4 (CH_2), 77.6 (CH), 79.8 (CH), 115.5 (CH), 115.8 (CH), 127.8 (CH), 130.1 (CH), 133.9 (C), 135.9 (C), 156.1 (C), 157.1 (C). EI-HRMS m/z calcd for $\text{C}_{19}\text{H}_{22}\text{O}_3$ (M^+) 298.1569, found 298.1576. The synthetic material **2** was identical in all respects with the reported spectral data for the natural substance (IR, ^1H NMR, ^{13}C NMR, HRMS), including optical rotation.

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