Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 12037–12046

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]

Takuya Washio, Reika Yamaguchi, Takumi Abe, Hisanori Nambu, Masahiro Anada and Shunichi Hashimoto*

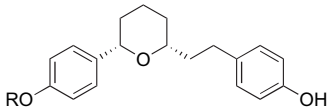
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

Received 17 August 2007; revised 3 September 2007; accepted 4 September 2007
Available online 7 September 2007

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], Rh_2(*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] calyxins[3] and diospongins,[4] exhibit a wide range of biological activities. 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**)

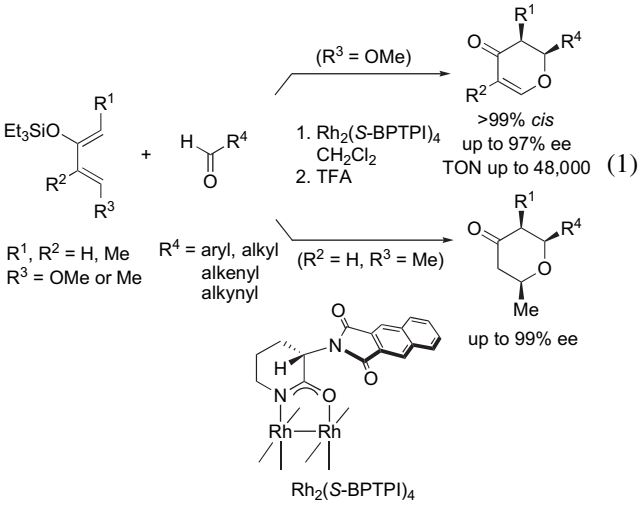
(−)-Centrolobine (**1**) is an antibiotic isolated from the heartwood of *Centrolobium robustum* and from the stem of *Brosinum potabile* in the Amazon rain forest.[1] (−)-De-*O*-methylcentrolobine (**2**), isolated from the same heartwood of *C. robustum*, displays a good antileishmanial activity.[1c,2] 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 racemic[9] 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 sequence,[10i] and $FeCl_3$-mediated cyclization of 1,5-diol.[10j]

The hetero-Diels–Alder (HDA) reaction[11] 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], Rh_2-(*S*-BPTPI)$_4$, is a highly efficient Lewis acid catalyst for *endo*- and enantioselective 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

Keywords: Diarylheptanoids; Hetero-Diels–Alder reaction; (−)-Centrolobine; (−)-De-*O*-methylcentrolobine; Chiral Rh(II) catalyst.
* Corresponding author. Tel.: +81 11 706 3236; fax: +81 11 706 4981; e-mail: hsmt@pharm.hokudai.ac.jp

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.09.003

to demonstrate the utility of this catalytic methodology, we now address asymmetric syntheses of (−)-centrolobine (**1**) and (−)-de-*O*-methylcentrolobine (**2**), focusing on the Rh_2(*R*-BPTPI)$_4$-catalyzed HDA reaction between 4-aryl-2-silyloxy-1,3-butadienes and phenylpropargyl aldehyde derivatives.



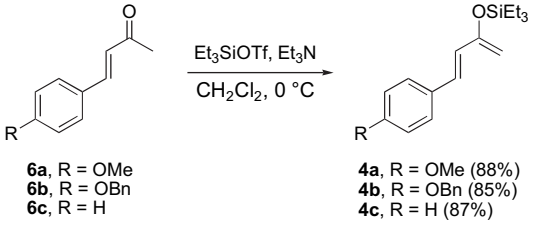
2. Results and discussion

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 Rh_2-(*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. For this type of HDA reaction, Baldoli and co-workers reported a $ZnCl_2$-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 $BF_3\cdot OEt_2$-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.

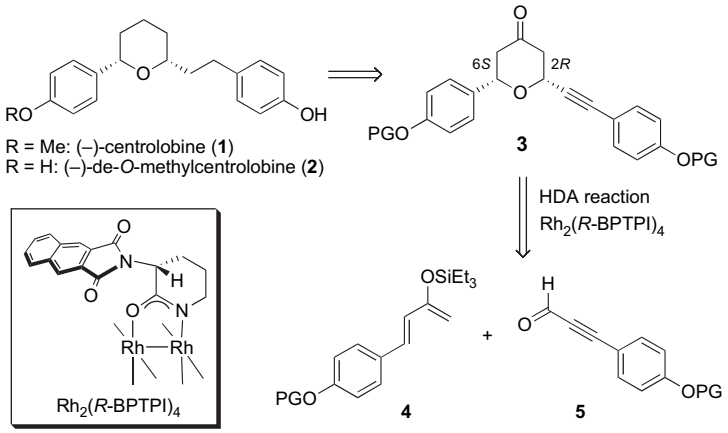
2.2. Preparation of dienes and aldehydes for the HDA reaction

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 Et_3SiOTf in the presence of Et_3N in CH_2Cl_2 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.

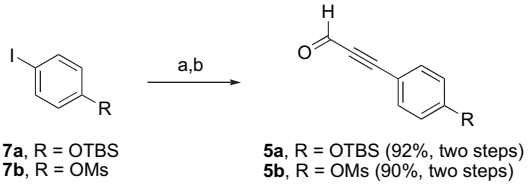


Scheme 2. Preparation of dienes **4a**–**4c**.

Phenylpropargyl aldehydes **5a** and **5b**, bearing *tert*-butyldimethylsilyloxy and methanesulfonyloxy groups at the *para*-position on the benzene ring, were prepared by the Sonogashira coupling[22] of propargyl alcohol with iodophenol derivatives **7a**[23] and **7b**,[24] and subsequent Dess–Martin oxidation (Scheme 3).



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



Scheme 3. Reagents and conditions: (a) propargyl alcohol, $PdCl_2(PPh_3)_2$ (0.5 mol %), CuI (1 mol %), Et_3N, 23 °C; (b) Dess–Martin periodinane, CH_2Cl_2, 0 °C.

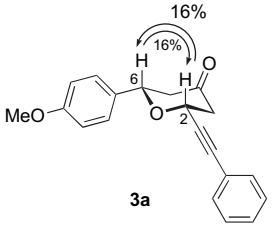
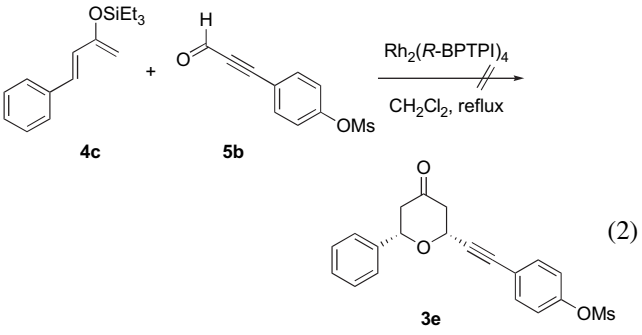


Figure 1. NOE experiments of **3a**.

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 Rh_2-(*R*-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 ^{1}H NOE between C2-H and C6-H (Fig. 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 (−)-de-*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).

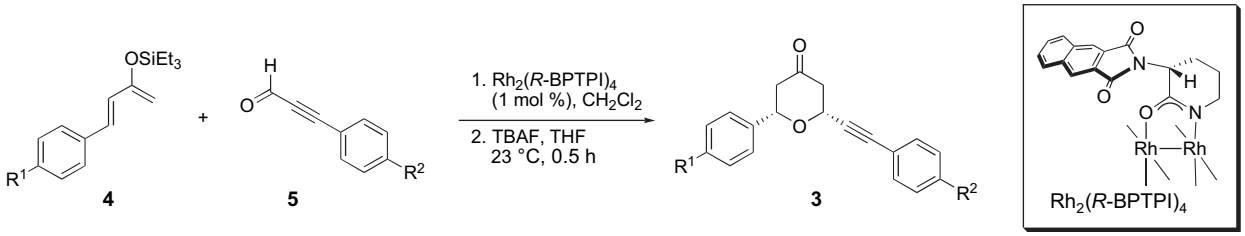
For comparison, the HDA reaction between 4-phenyl-2-triethylsilyloxy-1,3-butadiene (**4c**) and aldehyde **5b** in the presence of Rh_2(*R*-BPTPI)$_4$ was then attempted. However, the reaction did not proceed at all (Eq. 2). These results suggest that the combination of an increase in the HOMO energy of silyloxydienes **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.



(2)

As an alternative approach to *cis*-2,6-disubstituted tetrahydropyran-4-ones, we finally investigated the HDA reaction

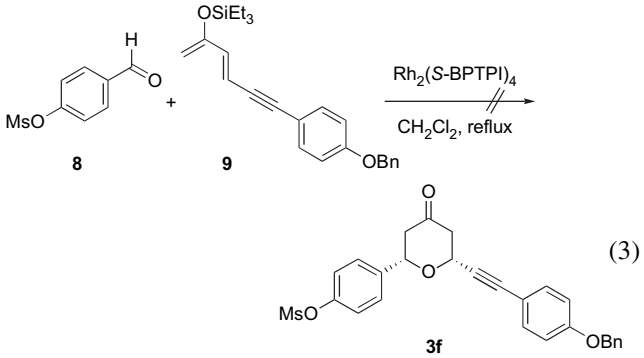
Table 1. Enantioselective hetero-Diels–Alder reactions catalyzed by Rh_2(*R*-BPTPI)$_4$



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] Rh_2(*R*-BPTPI)$_4$: 5 mol % was used.
[e] Only phenol product was obtained due to the concomitant desilylation.
[f] Determined by HPLC (Daicel Chiralpak AD-H).

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 Rh_2(*R*-BPTPI)$_4$-catalyzed HDA reaction with monooxygenated dienes.

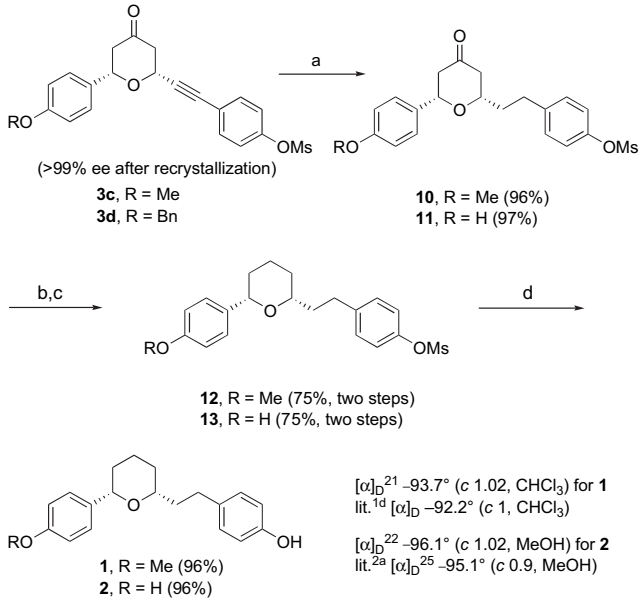


(3)

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. Tosylhydrazone 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, ^{1}H NMR, ^{13}C 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 atom[28] in rhodium catalyst–aldehyde complexes (Fig. 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.

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, $[\alpha]_D^{20}$ −4.76 (*c* 3.20, CH_3CN) in 73% yield. Sequential catalytic hydrogenation of the triple bond and hydrogenolysis of the benzyl ether in a single flask furnished tetrahydoropyran-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, ^{1}H NMR, ^{13}C NMR, HRMS) identical with natural (−)-de-*O*-methylcentrolobine,[2a] and also had an optical rotation, $[\alpha]_D^{22}$ −96.1 (*c* 1.02, MeOH), in good agreement with the literature value [lit.,[2a] $[\alpha]_D^{25}$ −95.1 (*c* 0.9, MeOH)]. Thus, the preferred absolute stereochemistry of cycloadduct **3d** was established as (2*R*,6*S*).



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.

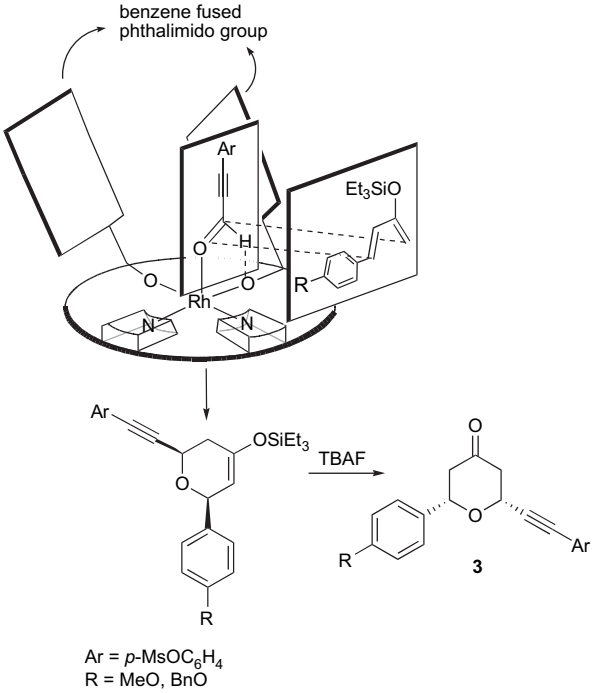


Figure 2. Plausible stereochemical pathway.

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 Rh_2(*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 seven steps and 41% overall yield from 4-iodophenyl methanesulfonate (**7b**), and the first asymmetric synthesis of (−)-de-*O*-methylcentrolobine in eight 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, $CDCl_3$: 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. ^{13}C NMR spectra were recorded on JEOL JNM-AL 400 (100 MHz) spectrometer. The following internal references were used ($CDCl_3$: 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). EIMS spectra were obtained on a JEOL JMS-FABmate spectrometer, operating with ionization energy of 70 eV. FABMS 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 F_{254} plates with visualization by UV light, 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×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 CH_2Cl_2 was purchased from Kanto Chemical Co., Inc. Rh_2(*R*-BPTPI)$_4\cdot 3H_2O$ was prepared from D-ornithine according to the literature procedure of Rh_2(*S*-BPTPI)$_4\cdot 3H_2O$.[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 Et_3N (2.4 mL, 17 mmol) in CH_2Cl_2 (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 $NaHCO_3$ solution (10 mL), and the whole was extracted with EtOAc (2×30 mL). The combined organic layers were washed with brine (2×10 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo followed by column chromatography (Wakogel® C-200, 100:1 hexane/EtOAc with 2% Et_3N) 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, $CDCl_3$) δ 0.77 (q, *J*=7.9 Hz, 6H, $SiCH_2CH_3$), 1.03 (t, *J*=7.9 Hz, 9H, $SiCH_2CH_3$), 3.81 (s, 3H, OCH_3), 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*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 5.0 (CH_2), 6.8 (CH_3), 55.2 (CH_3), 95.3 (CH_2), 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 $C_{17}H_{27}O_2Si$ $(M+H)^+$ 291.1775, found 291.1781. Anal. Calcd for $C_{17}H_{26}O_2Si$: 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), Et_3N (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 $C_{23}H_{31}O_2Si$ $(M+H)^+$ 367.2093, found 367.2090. Anal. Calcd for $C_{23}H_{30}O_2Si$: 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

$C_{16}H_{24}O_2Si$ $(M)^+$ 260.1596, found 260.1597. Anal. Calcd for $C_{16}H_{24}OSi$: 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 solution of 3-(4-benzyloxyphenyl)-2-propyn-1-ol[26] (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, C*H*O); ^{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 $C_{16}H_{12}O_2$ $(M)^+$ 236.0837, found 236.0837. Anal. Calcd for $C_{16}H_{12}O_2$: 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 $C_{19}H_{16}O_2$ $(M)^+$ 276.1150, found 276.1157. Anal. Calcd for $C_{19}H_{16}O_2$: 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$_2$CH_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 $C_{25}H_{30}O_2Si$ $(M)^+$ 390.2015, found 390.2006. Anal. Calcd for $C_{25}H_{30}O_2Si$: 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 %), $PdCl_2(PPh_3)_2$ (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, Si(CH_3)$_2$), 0.97 (s, 9H, SiC(CH_3)$_3$), 1.66 (t, 1H, *J*=6.2 Hz, O*H*), 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 $Na_2S_2O_3 \cdot H_2O$ (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, Si(CH_3)$_2$), 0.98 (s, 9H, SiC(CH_3)$_3$), 6.84–6.86 (m, 2H, *Ar*), 7.50–7.52 (m, 2H, *Ar*), 9.39 (s, 1H, C*H*O); ^{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 $C_{15}H_{20}O_2Si$ $(M)^+$ 260.1232, found 260.1232. Anal. Calcd for $C_{15}H_{20}O_2Si$: 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 %), $PdCl_2(PPh_3)_2$ (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, O*H*), 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, C*H*O); ^{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 $C_{10}H_8O_4S$ $(M)^+$ 224.0143, found 224.0144. Anal. Calcd for $C_{10}H_8O_4S$: 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 Rh_2(*R*-BPTPI)$_4\cdot 3H_2O$ (29 mg, 0.02 mmol, 1 mol %). Then the color of the 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 a deep green solution. The whole mixture was concentrated in vacuo furnishing 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 $C_{21}H_{20}O_6S$ $(M)^+$ 400.0980, found 400.0983. Anal. Calcd for $C_{21}H_{20}O_6S$: 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 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 Rh_2(*R*-BPTPI)$_4\cdot 3H_2O$ (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 $C_{20}H_{18}O_3$ $(M)^+$ 306.1256, found 306.1258. Anal. Calcd for $C_{20}H_{18}O_3$: 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 Rh_2(*R*-BPTPI)$_4\cdot 3H_2O$ (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, O*H*), 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 $C_{20}H_{18}O_4$ $(M)^+$ 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 $Rh_2(R\text{-BPTPI})_4\cdot 3H_2O$ (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 $C_{27}H_{24}O_6S$ $(M)^+$ 476.1294, found 476.1296. Anal. Calcd for $C_{27}H_{24}O_6S$: 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 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, CH_2CH_2CH), 3.13 (s, 3H, SO_2CH_3), 3.69–3.76 (m, 1H, C6–*H*), 3.83 (s, 3H, OCH_3), 4.58 (dd, *J*=4.1, 10.0 Hz, 1H, C2–*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 $C_{21}H_{24}O_6S$ $(M)^+$ 404.1293, found 404.1292. Anal. Calcd for $C_{21}H_{24}O_6S$: 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 $TsNHNH_2$ (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), $TsOH\cdot H_2O$ (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 CH_2CH_2CH), 2.70–2.85 (m, 2H, CH_2CH_2CH), 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 $C_{21}H_{26}O_5S$ $(M)^+$ 390.1501, found 390.1497. Anal. Calcd for $C_{21}H_{26}O_5S$: 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_2CH*H*CH), 2.61–2.76 (m, 2H, CH_2CH_2CH), 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, O*H*), 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 $C_{20}H_{24}O_3$ $(M)^+$ 312.1725, found 312.1733. The synthetic material **1** was identical in all respects with the reported spectral data for the natural substance (IR, ^{1}H NMR, ^{13}C NMR, HRMS), including optical rotation.

4.6. Synthesis of (−)-de-*O*-methylcentrolobine

4.6.1. (2*S*,6*S*)-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}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83–1.92 (m, 1H, CH_2CH*H*CH), 2.01–2.10 (m, 1H, CH_2C*H*HCH), 2.37–2.47 (m, 2H, COCH_2), 2.53–2.63 (m, 2H, COCH_2), 2.74–2.91 (m, 2H, CH_2CH_2CH), 3.13 (s, 3H, SO_2CH_3), 3.69–3.75 (m, 1H, C6–*H*), 4.56 (dd, *J*=3.2, 10.4 Hz, 1H, C2–*H*), 5.06 (br, 1H, O*H*), 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 $C_{20}H_{22}O_6S$ $(M)^+$ 390.1137, found 390.1131. Anal. Calcd for $C_{20}H_{22}O_6S$: C, 61.52; H, 5.68; S, 8.21. Found: C, 61.54; H, 5.70; S, 8.48.

4.6.2. (2*S*,6*R*)-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), $TsOH\cdot H_2O$ (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}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25–1.95 (m, 8H, C3–*H*, C4–*H*, C5–*H*, and CH_2C*H*$_2$CH), 2.69–2.85 (m, 2H, CH_2CH_2CH), 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, O*H*), 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 $C_{20}H_{24}O_5S$ $(M)^+$ 376.1344, found 376.1336. Anal. Calcd for $C_{20}H_{24}O_5S$: 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}; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.20–1.90 (m, 8H, C3–*H*, C4–*H*, C5–*H*, and CH_2C*H*$_2$CH), 2.55–2.70 (m, 2H, CH_2CH_2CH), 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, O*H*), 8.17 (br, 1H, O*H*); ^{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 $C_{19}H_{22}O_3$ $(M)^+$ 298.1569, found 298.1576. The synthetic material **2** was identical in all respects with the reported spectral data for the natural substance (IR, ^{1}H NMR, ^{13}C NMR, HRMS), including optical rotation.

Acknowledgements

This research was supported, in part, by a Grant-in-Aid for Scientific Research on Priority Areas 'Advanced Molecular Transformations of Carbon Resources' from the Ministry of Education, Culture, Sports, Science and Technology, Japan. T.W. is grateful to JSPS for a graduate fellowship. We thank Ms. S. Oka, M. Kiuchi, A. Maeda, and H. Matsumoto of the Center for Instrumental Analysis at Hokkaido University for mass measurements and elemental analysis.

References and notes

1. (a) De Albuquerque, I. L.; Galeffi, C.; Casinovi, C. G.; Marini-Bettòlo, G. B. *Gazz. Chim. Ital.* **1964**, 287–295; (b) Galeffi, C.; Casinovi, C. G.; Marini-Bettòlo, G. B. *Gazz. Chim. Ital.* **1965**, 95–100; (c) Aragão Craveiro, A.; da Costa Prado, A.; Gottlieb, O. R.; Welerson de Albuquerque, P. C. *Phytochemistry* **1970**, *9*, 1869–1875; (d) Alcântara, A. F.; de, C.; Souza, M. R.; Piló-Veloso, D. *Fitoterapia* **2000**, *71*, 613–615.
2. (a) Jurd, L.; Wong, R. Y. *Aust. J. Chem.* **1984**, *37*, 1127–1133; (b) Araujo, C. A. C.; Alegrio, L. V.; Leon, L. L. *Phytochemistry* **1998**, *49*, 751–754.
3. (a) Prasain, J. K.; Li, J.-X.; Tezuka, Y.; Tanaka, K.; Basnet, P.; Dong, H.; Namba, T.; Kadota, S. *J. Nat. Prod.* **1998**, *61*, 212–216; (b) Gewali, M. B.; Tezuka, Y.; Banskota, A. H.; Ali, M. S.; Saiki, I.; Dong, H.; Kadota, S. *Org. Lett.* **1999**, *1*, 1733–1736; (c) Tezuka, Y.; Ali, M. S.; Banskota, A. H.; Kadota, S. *Tetrahedron Lett.* **2000**, *41*, 5903–5907; (d) Tezuka, Y.; Gewali, M. B.; Ali, M. S.; Banskota, A. H.; Kadota, S. *J. Nat. Prod.* **2001**, *64*, 208–213; (e) Ali, M. S.; Tezuka, Y.; Banskota, A. H.; Kadota, S. *J. Nat. Prod.* **2001**, *64*, 491–496; (f) Ali, M. S.; Banskota, A. H.; Tezuka, Y.; Saiki, I.; Kadota, S. *Biol. Pharm. Bull.* **2001**, *24*, 525–528.
4. Yin, J.; Kouda, K.; Tezuka, Y.; Tran, Q. L.; Miyahara, T.; Chen, Y.; Kadota, S. *Planta Med.* **2004**, *70*, 54–58.
5. For total syntheses and structure revisions of calyxins F, G, L, and M and epicalyxins G and M, see: (a) Tian, X.; Jaber, J. J.; Rychnovsky, S. D. *J. Org. Chem.* **2006**, *71*, 3176–3183; For total syntheses of blepharocalyxin D, see: (b) Ko, H. M.; Lee, D. G.; Kim, M. A.; Kim, H. J.; Park, J.; Lah, M. S.; Lee, E. *Org. Lett.* **2007**, *9*, 141–144; (c) Ko, H. M.; Lee, D. G.; Kim,

M. A.; Kim, H. J.; Park, J.; Lah, M. S.; Lee, E. *Tetrahedron* **2007**, *63*, 5797–5805; For synthetic studies of calyxins, see: (d) Li, W.; Mead, K. T.; Smith, L. T. *Tetrahedron Lett.* **2003**, *44*, 6351–6353; (e) Cakir, S. P.; Mead, K. T. *J. Org. Chem.* **2004**, *69*, 2203–2205; (f) Yang, X.-F.; Wang, M.; Zhang, Y.; Li, C.-J. *Synlett* **2005**, 1912–1916; (g) Cakir, S. P.; Mead, K. T. *Tetrahedron Lett.* **2006**, *47*, 2451–2454.

6. For total syntheses of diospongins, see: (a) Chandrasekhar, S.; Shyamsunder, T.; Prakash, S. J.; Prabhakar, A.; Jagadeesh, B. *Tetrahedron Lett.* **2006**, *47*, 47–49; (b) Sawant, K. B.; Jennings, M. P. *J. Org. Chem.* **2006**, *71*, 7911–7914; (c) Bressy, C.; Allais, F.; Cossy, J. *Synlett* **2006**, 3455–3456; (d) Bates, R. W.; Song, P. *Tetrahedron* **2007**, *63*, 4497–4499; (e) Hiebel, M.-A.; Pelotier, B.; Piva, O. *Tetrahedron* **2007**, *63*, 7874–7878; (f) Kawai, N.; Hande, S. M.; Uenishi, J. *Tetrahedron* **2007**, *63*, 9049–9056.
7. For reviews on the construction of the tetrahydropyran ring system, see: (a) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309–3362; (b) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045–2053.
8. (a) Colobert, F.; Mazery, R. D.; Solladie, G.; Carreño, M. C. *Org. Lett.* **2002**, *4*, 1723–1725; (b) Carreño, M. C.; Mazery, R. D.; Urbano, A.; Colobert, F.; Solladie, G. *J. Org. Chem.* **2003**, *68*, 7779–7787.
9. (a) Clarke, P. A.; Martin, W. H. C. *Tetrahedron Lett.* **2004**, *45*, 9061–9063; (b) Clarke, P. A.; Martin, W. H. C. *Tetrahedron* **2005**, *61*, 5433–5438; (c) Sabitha, G.; Reddy, K. B.; Reddy, G. S. K. K.; Fatima, N.; Yadav, J. S. *Synlett* **2005**, 2347–2351.
10. (a) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919–3922; (b) Evans, P. A.; Cui, J.; Gharpure, S. J. *Org. Lett.* **2003**, *5*, 3883–3885; (c) Boulard, L.; BouzBouz, S.; Cossy, J.; Franck, X.; Figadère, B. *Tetrahedron Lett.* **2004**, *45*, 6603–6605; (d) Lee, E.; Kim, H. J.; Jang, W. S. *Bull. Korean Chem. Soc.* **2004**, *25*, 1609–1610; (e) Jennings, M. P.; Clemens, R. T. *Tetrahedron Lett.* **2005**, *46*, 2021–2024; (f) Chandrasekhar, S.; Prakash, S. J.; Shyamsunder, T. *Tetrahedron Lett.* **2005**, *46*, 6651–6653; (g) Chan, K.-P.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 4491–4494; (h) Lee, C.-H. A.; Loh, T.-P. *Tetrahedron Lett.* **2006**, *47*, 1641–1644; (i) Böhrsch, V.; Blechert, S. *Chem. Commun.* **2006**, 1968–1970; (j) Prasad, K. R.; Anbarasan, P. *Tetrahedron* **2007**, *63*, 1089–1092.
11. For reviews on the HDA reaction, see: (a) Danishefsky, S. J. *Aldrichimica Acta* **1986**, *19*, 59–69; (b) Danishefsky, S. *Chemtracts: Org. Chem.* **1989**, *2*, 273–297; (c) Boger, D. L.; Weinreb, S. M. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic: New York, NY, 1987; Vol. 47; (d) Weinreb, S. M. *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon: Oxford, 1991; Vol. 5, p 401; (e) Boger, D. L. *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon: Oxford, 1991; Vol. 5, p 451; (f) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558–3588; (g) Kobayashi, S.; Jørgensen, K. A. *Cycloaddition Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2002.
12. (a) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398–2400; (b) Chavez, D. E.; Jacobsen, E. N. *Org. Synth.* **2005**, *82*, 34–42.
13. (a) Bhattacharjee, A.; De Brabander, J. K. *Tetrahedron Lett.* **2000**, *41*, 8069–8073; (b) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2000**, *122*, 10482–10483; (c) Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3667–3670; (d) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9974–9983; (e) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772–10773; (f) Paterson, I.; Tudge, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 343–347; (g) Lucas, B. S.; Luther, L. M.; Burke, S. D. *J. Org. Chem.* **2005**, *70*, 3757–3760; (h) Smith, A. B., III; Fox, R. J.; Vanecko, J. A. *Org. Lett.* **2005**, *7*, 3099–3102; (i) Majumder, U.; Cox, J. M.; Johnson, H. W. B.; Rainier, J. D. *Chem.—Eur. J.* **2006**, *12*, 1736–1746; (j) Louis, I.; Hungerford, N. L.; Humphries, E. J.; McLeod, M. D. *Org. Lett.* **2006**, *8*, 1117–1120; (k) Wender, P. A.; Hilinski, M. K.; Soldermann, N.; Mooberry, S. L. *Org. Lett.* **2006**, *8*, 1507–1510; (l) Ghosh, A. K.; Gong, G. *Org. Lett.* **2007**, *9*, 1437–1440.
14. Waldmann and co-workers reported the asymmetric synthesis of the diarylheptanoid tetrahydropyran system employing the HDA reaction of Danishefsky's diene with polymer-bound aldehydes and subsequent conjugate addition of aryl cuprates: Sanz, M. A.; Voigt, T.; Waldmann, H. *Adv. Synth. Catal.* **2006**, *348*, 1511–1515.
15. Anada, M.; Washio, T.; Shimada, N.; Kitagaki, S.; Nakajima, M.; Shiro, M.; Hashimoto, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 2665–2668.
16. Doyle and co-workers were the first to demonstrate that chiral dirhodium(II) carboxamidates are highly efficient Lewis acid catalysts for enantioselective HDA reactions between Danishefsky's diene and aldehydes: (a) Doyle, M. P.; Phillips, I. M.; Hu, W. *J. Am. Chem. Soc.* **2001**, *123*, 5366–5367; (b) Doyle, M. P.; Valenzuela, M.; Huang, P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5391–5395; (c) Valenzuela, M.; Doyle, M. P.; Hedberg, C.; Hu, W.; Holmstrom, A. *Synlett* **2004**, 2425–2428.
17. Baldoli, C.; Maiorana, S.; Licandro, E.; Zinzalla, G.; Lanfranchi, M.; Tiripicchio, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2159–2167.
18. Yamamoto and co-workers have recently reported the enantioselective HDA reaction between 4-aryl-2-silyloxy-1,3-butadienes and 2-nitroso- or 2-azopyridine derivatives: (a) Yamamoto, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 7082–7085; (b) Kawasaki, M.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 16482–16483.
19. Ruijter, E.; Schültingkemper, H.; Wessjohann, L. A. *J. Org. Chem.* **2005**, *70*, 2820–2823.
20. Knölker, H.-J.; Ahrens, B.; Gonser, P.; Heininger, M.; Jones, P. G. *Tetrahedron* **2000**, *56*, 2259–2271.
21. Takeuchi, N.; Nakano, T.; Goto, K.; Tobinaga, S. *Heterocycles* **1993**, *35*, 289–297.
22. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470.
23. Figadère, B.; Norman, A. W.; Henry, H. L.; Koeffler, H. P.; Zhou, J.-Y.; Okamura, W. H. *J. Med. Chem.* **1991**, *34*, 2452–2463.
24. Lee, T.-S.; Kim, J.; Bae, J.-Y. *Polymer* **2004**, *45*, 5065–5076.
25. Diene **9** was prepared in three steps and 83% overall yield from 3-(4-benzyloxyphenyl)-2-propyn-1-ol.[26] This procedure is in Section 4.2.4.
26. Fürst, M.; Rück-Braun, K. *Synlett* **2002**, 1991–1994.
27. Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662–3668.
28. Corey, E. J.; Lee, T. W. *Chem. Commun.* **2001**, 1321–1329.