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Asymmetric Synthesis of Neolignans (−)-*epi*-Conocarpan and (+)-Conocarpan via Rh(II)-Catalyzed C−H Insertion Process and Revision of the Absolute Configuration of (−)-*epi*-Conocarpan

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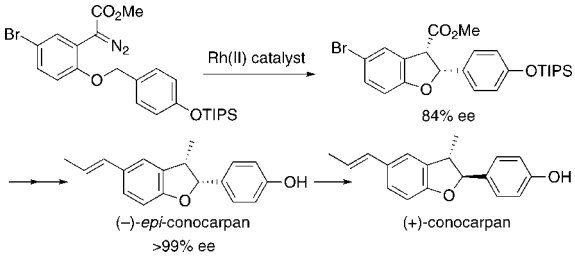
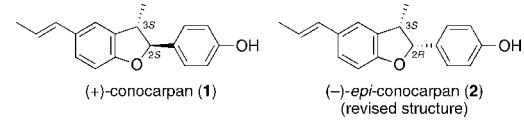


Catalytic asymmetric synthesis of neolignan natural products (−)-*epi*-conocarpan and (+)-conocarpan has been achieved by exploiting an enantio- and diastereoselective intramolecular C−H insertion reaction to construct a *cis*-2-aryl-2,3-dihydrobenzofuran ring system as a key step. The C−H insertion reaction of 5-bromoaryldiazoacetate catalyzed by Rh_2(*S*-PTTEA)$_4$, a new dirhodium(II) carboxylate complex that incorporates *N*-phthaloyl-(*S*)-triethylalaninate as chiral bridging ligands, provided 2-aryl-5-bromo-3-methoxycarbonyl-2,3-dihydrobenzofuran with exceptionally high diastereoselectivity (*cis*/*trans* = 97:3) and high enantioselectivity for the *cis* isomer (84% ee).

Neolignan natural products containing a 2-aryl-2,3-dihydrobenzofuran ring, such as conocarpan,[1] *epi*-conocarpan,[2] 3′,4-di-*O*-methylcedrusin,[3] and brugnanin,[4] display a wide range of biological activities.[5] Consequently, much effort has been devoted to the stereocontrolled synthesis of 2-aryl-2,3-dihydrobenzofuran derivatives.[6]



(+)-Conocarpan (**1**), first isolated from the wood of *Conocarpus erectus* by Hayashi and Thomson in 1975,[1] exhibits a diverse array of biological activities, including insecticidal,[7] antifungal,[8] and antitrypanosomal properties.[9] (−)-*epi*-Conocarpan (**2**) was isolated from the roots of *Piper regnellii* by Kato and co-workers in 1999.[2] The absolute configuration of (+)-conocarpan was assigned as (2*R*,3*R*) by comparing the CD curve of conocarpan acetate with those of reference compounds possessing different substitution patterns in the aromatic rings.[1,10] However, a later chiroptical study of 2,3-dihydrobenzofurans fused to the steroid nucleus[11] indicated that its absolute configuration should be reversed. Recently, Clive and Stoffman established the absolute configuration of (+)-conocarpan as (2*S*,3*S*) through their asymmetric synthesis of (−)-conocarpan (vide infra).[12] Since the absolute configuration of (−)-*epi*-conocarpan was determined to be (2*S*,3*R*) by CD spectra,[2] this assignment should also be reversed.

Racemic conocarpan can be easily synthesized either by an oxidative dimerization of *p*-propenylphenol with $FeCl_3$[1,13] or by a $Mn(OAc)_3$-based oxidative cycloaddition of 4-(3-chloropropyl)-2-cyclohexenone with anethole.[14] Kato and co-workers reported an enantioselective conversion of *p*-propenylphenol to (+)-conocarpan by an enzyme fraction obtained from *Piper regnellii* leaves.[13] Clive and Stoffman have accomplished an asymmetric synthesis of (−)-conocarpan by means of a Sharpless asymmetric epoxidation and a radical cyclization of optically active benzylic ethers.[12] The Zheng and Che groups achieved the synthesis of (±)-*epi*-conocarpan by employing a ruthenium(II) porphyrin-catalyzed intramolecular C−H insertion of aryl tosylhydrazone salt as a key step.[15] However, to the best of our knowledge, an asymmetric synthesis of (−)-*epi*-conocarpan has not been reported. In this respect, we have provided a protocol for asymmetric synthesis of *cis*-2-aryl-3-methoxy-

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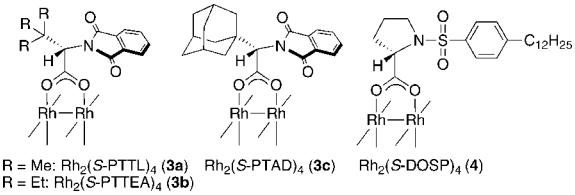
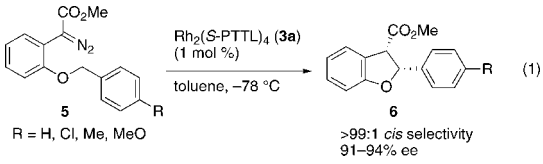


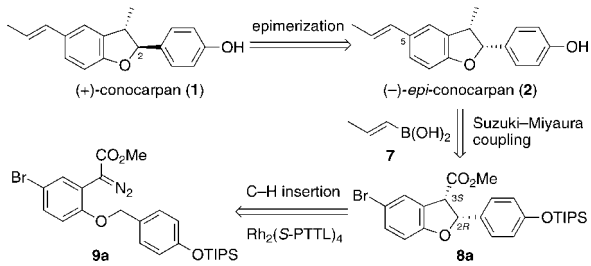
FIGURE 1. Structure of chiral dirhodium(II) complexes.

carbonyl-2,3-dihydrobenzofurans **6** via enantio- and diastereoselective C−H insertions of phenyldiazoacetates **5** catalyzed by dirhodium tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-PTTL)$_4$ (**3a**) (Figure 1), wherein perfect *cis* selectivity and high enantioselectivity (up to 94% ee) are achieved (eq 1).[16,17] In

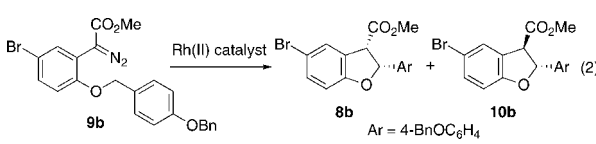


order to demonstrate the synthetic potential of this catalytic methodology, we herein report asymmetric synthesis of (−)-*epi*-conocarpan and (+)-conocarpan and a revision of the absolute configuration of natural (−)-*epi*-conocarpan.

SCHEME 1. Retrosynthetic Analysis of 1 and 2

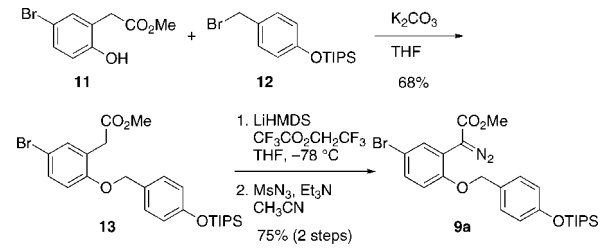


Our retrosynthetic analysis of **1** and **2** is outlined in Scheme 1. It has been documented that thermodynamically less-stable *cis*-2-(4-hydroxyphenyl)-2,3-dihydrobezofurans are epimerized to *trans* isomers by treatment with an acid (TFA in CH_2Cl_2)[18] or a base (Na_2CO_3 in MeOH).[19] Thus, synthesis of **1** would be achieved by epimerization at the C2 stereocenter of **2**. We carefully selected the TIPS ether as the protecting group for the phenolic moiety, reasoning that a TIPS-protected *p*-cresol is stable under basic conditions.[20] It was anticipated that a propenyl group at C5 would be introduced by a Suzuki−Miyaura coupling of 5-bromo-2,3-dihydrobenzofuran **8a** with propenylboronic acid (**7**).[21] As mentioned above,[16] we envisioned that Rh_2(*S*-PTTL)$_4$-catalyzed C−H insertion of methyl [5-bromo-2-(4-triisopropylsilyloxybenzyloxy)phenyl]diazoacetate (**9a**) would provide *cis*-(2*R*,3*S*)-5-bromo-2,3-dihydrobenzofuran **8a**. C−H insertion reactions of 5-bromoaryldiazoacetates catalyzed by chiral dirhodium(II) complexes have already been reported by two research groups (eq 2). Fukuyama and co-workers dem-



onstrated that the reaction of 5-bromoaryldiazoacetate **9b** catalyzed by Rh_2(*S*-DOSP)$_4$ (**4**) afforded the corresponding 5-bromo-2,3-dihydrobenzofurans **8b/10b** in 72% yield as 3:2−5:1

SCHEME 2. Preparation of 5-Bromoaryldiazoacetate 9a



mixtures of *cis* and *trans* isomers with 32% ee for **10b**.[18,22] Davies and co-workers reported that Rh_2(*S*-PTAD)$_4$ (**3c**),[23] derived from adamantylglycine, is an effective catalyst for the reaction of **9b**, providing stereoisomers **8b/10b** in 72% yield with a 14:1 preference for the *cis* isomer **8b** and 79% ee for **8b**.[23a,24]

5-Bromoaryldiazoacetate **9a** was prepared as shown in Scheme 2. *O*-Alkylation of methyl (5-bromo-2-hydroxyphenyl)-acetate (**11**)[25] with 4-(triisopropylsilyloxy)benzyl bromide (**12**)[26] provided 5-bromoarylacetate **13** in 68% yield. Since attempted direct diazo transfer to **13** with *p*-acetamidebenzenesulfonyl azide and DBU in CH_3CN gave decomposition products, we used the Danheiser modification of Regitz's diazo transfer reaction.[27] Deprotonation of **13** with LiHMDS in THF at −78 °C followed by treatment of the resulting enolate with trifluoroethyl trifluoroacetate afforded a trifluoroacetylated product, which upon diazo transfer with methanesulfonyl azide and triethylamine in CH_3CN gave 5-bromoaryldiazoacetate **9a** in 75% yield.

On the basis of our previous work,[16] we initially explored the intramolecular C−H insertion of **9a** in toluene using 1 mol

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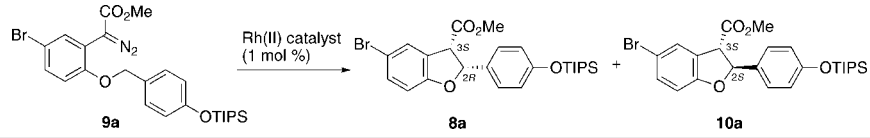
TABLE 1. Enantioselective C−H Insertion of Aryldiazoacetate 9a Catalyzed by Chiral Dirhodium(II) Complexes 3a,b[a]



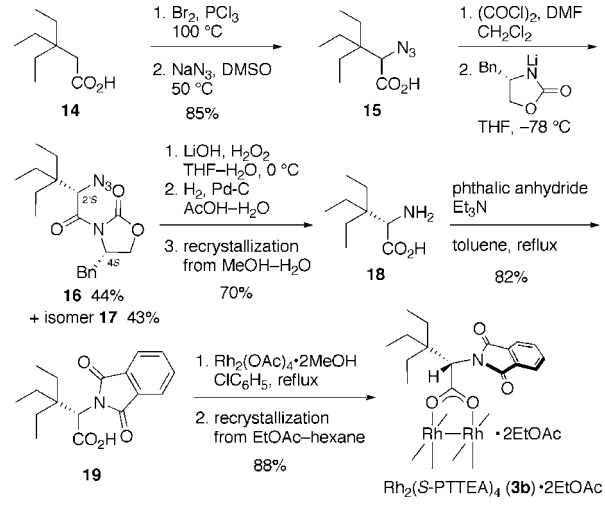
entry	Rh(II) catalyst	solvent	additive	temp (°C)	time (h)	yield (%)[b]	**8a**:**10a**[c]	ee (%) **8a**[d]	ee (%) **10a**[e]
1	Rh_2(*S*-PTTL)$_4$ (**3a**)	toluene		−23	2.5	62	98:2	53	
2	Rh_2(*S*-PTTL)$_4$ (**3a**)	CH_2Cl_2		−23	0.5	72	89:11	75	32
3	Rh_2(*S*-PTTL)$_4$ (**3a**)	CH_2Cl_2		−40	1	88	84:16	76	28
4	Rh_2(*S*-PTTL)$_4$ (**3a**)	CH_2Cl_2		−60	12	68	71:29	85	22
5	Rh_2(*S*-PTTL)$_4$ (**3a**)	CH_2Cl_2	4 Å MS	−60	14	78	74:26	82	22
6	Rh_2(*S*-PTTEA)$_4$ (**3b**)	CH_2Cl_2		−40	3	87	98:2	82	
7	Rh_2(*S*-PTTEA)$_4$ (**3b**)	CH_2Cl_2		−60	22	34[f]	97:3	89	
8	Rh_2(*S*-PTTEA)$_4$ (**3b**)	CH_2Cl_2	4 Å MS	−60	24	80[f]	97:3	84	

[a] All reactions were carried out as follows: Rh(II) catalyst (1 mol %) was added to a solution of **9a** (0.10 mmol) in the indicated solvent (1 mL) at the indicated temperature. [b] Combined yield of *cis* and *trans* isomers. [c] Determined by ^{1}H NMR analysis of the crude product. [d] Determined by HPLC (Chiralcel OD-H). [e] Determined by HPLC (Chiralpak IA). [f] Isolated yield of *cis* isomer.

% of Rh_2(*S*-PTTL)$_4$ (**3a**) at −23 °C (Table 1, entry 1). The reaction proceeded to completion in less than 2.5 h, giving a 98:2 *cis*/*trans* mixture of 2-aryl-5-bromo-2,3-dihydrobenzofurans **8a/10a** in 62% combined yield. The enantiomeric excess of the *cis* isomer **8a** was determined to be 53% by HPLC analysis (Chiralcel OD-H). The preferred absolute configuration of **8a** was assigned as (2*R*,3*S*) by single-crystal X-ray analysis (see Supporting Information).[28,29] Switching the solvent from toluene to CH_2Cl_2 improved the reaction rate, product yield and enantioselectivity, although a considerable drop in diastereoselectivity was observed (*cis*/*trans* = 89:11, entry 2). While lowering the reaction temperature to −40 °C had little impact on selectivities (*cis*/*trans* = 84:16, 76% ee, entry 3), the reaction at −60 °C increased enantioselectivity but significantly reduced diastereoselectivity (85% ee, *cis*/*trans* = 71:29, entry 4). The addition of 4 Å molecular sieves (MS) at −60 °C led to minor improvements in product yield and diastereoselectivity with a slight erosion in enantioselectivity (78% yield, *cis*/*trans* = 74:26, 82% ee, entry 5).

To further enhance the diastereoselectivity, we directed our efforts to the development of new dirhodium(II) carboxylate catalysts. Eventually, we found that the reaction with dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-triethylalaninate], Rh_2(*S*-PTTEA)$_4$ (**3b**) (vide infra), characterized by an exceptionally large triethylmethyl group, proceeded at −40 °C to afford 2,3-dihydrobenzofurans **8a/10a** in 87% yield as a 98:2 mixture of stereoisomers with 82% ee for **8a** (entry 6). Although the reason for the decreased diastereoselectivity in the reaction using Rh_2(*S*-PTTL)$_4$ (**3a**) at a lower temperature is unclear at present, Rh_2(*S*-PTTEA)$_4$ (**3b**) proved to be more effective than **3a** in terms of diastereoselectivity. Aside from high *cis* selectivity, the highest enantioselectivity (89% ee) was observed at −60 °C, although the product yield was only 34% (entry 7). Gratifyingly, this problem could be overcome with the addition of 4 Å MS as a desiccant. The reaction in the presence of 4 Å MS afforded *cis* isomer **8a** in 80% yield with a similar level of enantioselectivity (84% ee, entry 8).

SCHEME 3. Preparation of Rh_2(*S*-PTTEA)$_4$ (3b)



The new dirhodium(II) carboxylate catalyst **3b** was prepared from the known carboxylic acid **14**[30] (Scheme 3). Bromination of **14** with bromine and PCl_3[31] followed by azidation with NaN_3 provided α-azidocarboxylic acid **15**. Optical resolution of **15** was accomplished through formation of diastereomeric carboximides with (*S*)-4-benzyl-2-oxazolidinone[32] as a resolving reagent. The absolute configuration of more polar isomer **16** was established as (4*S*,2′*S*) by single-crystal X-ray analysis.[28] Hydrolytic removal of the chiral auxiliary[33] and azide reduction followed by recrystallization from MeOH−H_2O furnished amino acid **18**. Rh_2(*S*-PTTEA)$_4$ (**3b**) was prepared from amino acid **18** in 72% yield according to the reported procedure for the preparation of Rh_2(*S*-PTTL)$_4$ (**3a**).[34]

With the efficient construction of (2*R*,3*S*)-*cis*-2-aryl-5-bromo-2,3-dihydrobenzofuran **8a** realized, the stage was now set for the completion of the asymmetric synthesis of (−)-*epi*-cono-

(28) CCDC 703985 (**8a**) and CCDC 695667 (**16**) contain the crystallographic data for this paper. These can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(29) The preferred absolute configuration of *trans* isomer **10a** was determined to be (2*S*,3*S*) by comparison of the sign of optical rotation with that of the compound obtained by epimerization of **8a** at the C3 stereocenter. See Supporting Information.

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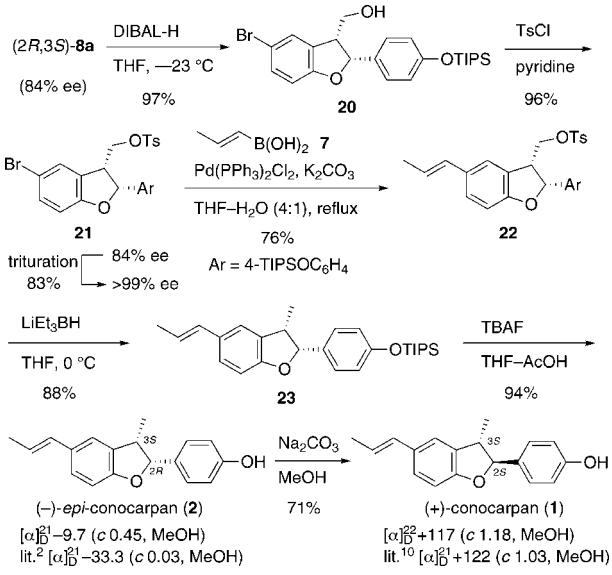
SCHEME 4. Synthesis of 1 and 2



carpan (**2**) and (+)-conocarpan (**1**) as illustrated in Scheme 4. Reduction of (2*R*,3*S*)-**8a** (84% ee) with DIBAL-H was followed by tosylation of the resultant hydroxy group to afford tosylate **21** in 93% yield. Trituration of **21** [84% ee, mp 69.0−71.0 °C, $[\alpha]^{21}_D$ +4.9 (*c* 1.18, $CHCl_3$)] in hexane−EtOAc produced optically pure material [mp 54.0−55.0 °C, $[\alpha]^{22}_D$ +6.2 (*c* 1.15, $CHCl_3$)] from the mother liquor in 83% yield. Suzuki−Miyaura coupling of **21** (>99% ee) with propenylboronic acid **7** in the presence of $Pd(PPh_3)_2Cl_2$ and K_2CO_3 provided the coupling product **22** in 76% yield. Reduction of **22** with $LiEt_3BH$ followed by removal of the TIPS protecting group with TBAF in THF−AcOH furnished (−)-*epi*-conocarpan (**2**) in 83% yield without epimerization of the C2 stereocenter. The spectroscopic data (^1H and ^{13}C NMR, IR, and CD) of this product were consistent with those reported for natural (−)-**2**.[2] Although an optical rotation of synthetic product (2*R*,3*S*)-**2**, $[\alpha]^{21}_D$ −9.7 (*c* 0.45, MeOH), was lower than that of natural (−)-**2** [lit.[2] $[\alpha]^{21}_D$ −33.3 (*c* 0.03, MeOH)], the enantiomeric purity of synthetic (−)-**2** was confirmed to be >99% by HPLC analysis (Chiralcel OD-H). Based on the identical CD spectrum and sign of optical rotation of synthetic (2*R*,3*S*)-**2** compared to those reported for natural (−)-*epi*-conocarpan,[2] the absolute configuration of (−)-*epi*-conocarpan should be revised to be (2*R*,3*S*). Epimerization of (−)-**2** with Na_2CO_3 in MeOH[19,35] followed by recrystallization from hexane−EtOAc provided (+)-conocarpan (**1**) in 71% yield. Synthetic material **1** was spectroscopically (^1H and ^{13}C NMR, and IR) identical to natural (+)-**1**[1] and also had an optical rotation, $[\alpha]^{22}_D$ +117 (*c* 1.18, MeOH), in good agreement with the literature value [lit.[10] $[\alpha]^{21}_D$ +122 (*c* 1.03, MeOH)].

In summary, the Rh_2(*S*-PTTEA)$_4$-catalyzed intramolecular C−H insertion reaction of 5-bromoaryldiazoacetate showed considerable promise for asymmetric synthesis of *cis*-2-aryl-5-bromo-2,3-dihydrobenzofurans. While Rh_2(*S*-PTTL)$_4$ has proven to be optimal in a wide range of enantioselective C−H insertion reactions,[16,36] newly developed Rh_2(*S*-PTTEA)$_4$ has been found to exhibit even higher diastereoselectivity (*cis*/*trans* = 97:3) and slightly higher enantioselectivity (84% ee) compared to those of Rh_2(*S*-PTTL)$_4$ in this system. Using this catalytic methodology, we have achieved the first asymmetric synthesis of (−)-*epi*-conocarpan (**2**) in nine steps and 20% overall yield from methyl arylacetate **11** and an asymmetric synthesis of (+)-conocarpan (**1**) via epimerization of (−)-**2**. We also described a revision of the originally reported absolute configuration of (−)-*epi*-conocarpan. Further application of this methodology to asymmetric synthesis of biologically active neolignans containing a 2,3-dihydrobenzofuran skeleton is currently in progress.

(35) The epimerization afforded a 12:1 mixture of (+)-conocarpan (**1**)/(−)-*epi*-conocarpan (**2**) in 98% yield. These isomers could not be separated by column chromatography on silica gel.

Experimental Section

Representative Procedure for the C−H Insertion of 9a (Table 1, entry 8). Rh_2(*S*-PTTEA)$_4$ (**3b**)·2EtOAc (47.7 mg, 0.03 mmol, 1 mol %) was added to a mixture of **9a** (1.60 g, 3.0 mmol) and 4 Å MS (1.60 g) in CH_2Cl_2 (30 mL) at −60 °C under Ar atmosphere. After stirring at this temperature for 24 h, the 4 Å MS was filtrated through a Celite pad, and the filtrate was concentrated in vacuo. The ratio of **8a**/**10a** was determined to be 97:3 by ^1H NMR of the crude product. The residue (1.7 g) was purified by column chromatography (silica gel 90 g, 25:1 hexane/Et_2O) to give **8a** (1.21 g, 80%) as a white solid: R_f = 0.50 (6:1 hexane/Et_2O); mp 62.0−63.0 °C for 84% ee; $[\alpha]^{21}_D$ −31.4 (*c* 1.15, $CHCl_3$) for 84% ee; IR ($CHCl_3$) ν 1738 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.08 (d, *J* = 7.2 Hz, 18H), 1.20−1.29 (m, 3H), 3.27 (s, 3H), 4.56 (d, *J* = 9.9 Hz, 1H), 5.94 (d, *J* = 9.9 Hz, 1H), 6.80−6.85 (m, 3H), 7.17 (d, *J* = 8.6 Hz, 2H), 7.33−7.36 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6, 17.9, 51.8, 53.6, 86.1, 111.4, 112.8, 119.7, 127.0, 127.5, 128.9, 129.0, 132.3, 156.3, 159.6, 169.7; HRMS (EI) calcd for $C_{25}H_{33}O_4SiBr$ (M^+) 504.1331, found 504.1332. Anal. Calcd for $C_{25}H_{33}O_4SiBr$: C, 59.40; H, 6.58; Br, 15.81. Found: C, 59.11; H, 6.36; Br, 16.11. The enantiomeric excess of **8a** was determined to be 84% by HPLC with a Chiralcel OD-H column (100:1 hexane/*i*-PrOH, 0.5 mL/min): t_R (major) = 20.6 min for (2*R*,3*S*)-**8a**; t_R (minor) = 25.6 min for (2*S*,3*R*)-**8a**.

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Supporting Information Available: Full experimental, characterization data, and copies of ^1H and ^{13}C NMR spectra for all new compounds, as well as X-ray crystallographic data in CIF format for **8a** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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