# JOC<sub>Note</sub>

## 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<sub>2</sub>(S-PTTEA)<sub>4</sub>, a new dirhodium(II) carboxylate complex that incorporates *N*-phthaloyl-(*S*)-triethylalaninate as chiral bridging ligands, provided 2-aryl-5-bromo-3-methoxycarbo-nyl-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,<sup>1</sup> *epi*-conocarpan,<sup>2</sup> 3',4di-*O*-methylcedrusin,<sup>3</sup> and brugnanin,<sup>4</sup> display a wide range of biological activities.<sup>5</sup> Consequently, much effort has been devoted to the stereocontrolled synthesis of 2-aryl-2,3-dihydrobenzofuran derivatives.<sup>6</sup>



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

Racemic conocarpan can be easily synthesized either by an oxidative dimerization of *p*-propenylphenol with  $\text{FeCl}_3^{1,13}$  or by a Mn(OAc)<sub>3</sub>-based oxidative cycloaddition of 4-(3-chloropropyl)-2-cyclohexenone with anethole.<sup>14</sup> Kato and co-workers reported an enantioselective conversion of p-propenylphenol to (+)-conocarpan by an enzyme fraction obtained from Piper regnellii leaves.<sup>13</sup> 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.<sup>12</sup> The Zheng and Che groups achieved the synthesis of  $(\pm)$ -epi-conocarpan by employing a ruthenium(II) porphyrin-catalyzed intramolecular C-H insertion of aryl tosylhydrazone salt as a key step.<sup>15</sup> 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).<sup>16,17</sup> 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  $CH_2Cl_2$ )<sup>18</sup> or a base (Na<sub>2</sub>CO<sub>3</sub> in MeOH).<sup>19</sup> 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.<sup>20</sup> 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).<sup>21</sup> As mentioned above,<sup>16</sup> we envisioned that Rh<sub>2</sub>(S-PTTL)<sub>4</sub>-catalyzed C-H insertion of methyl [5-bromo-2-(4-triisopropylsilyloxybenzyloxy)phenyl]diazoacetate (9a) would provide cis-(2R,3S)-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**.<sup>18,22</sup> Davies and co-workers reported that  $Rh_2(S-PTAD)_4$  (**3c**),<sup>23</sup> 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**.<sup>23a,24</sup>

5-Bromoaryldiazoacetate **9a** was prepared as shown in Scheme 2. *O*-Alkylation of methyl (5-bromo-2-hydroxyphenyl)acetate (**11**)<sup>25</sup> with 4-(triisopropylsilyloxy)benzyl bromide (**12**)<sup>26</sup> provided 5-bromoarylacetate **13** in 68% yield. Since attempted direct diazo transfer to **13** with *p*-acetamidebenzenesulfonyl azide and DBU in CH<sub>3</sub>CN gave decomposition products, we used the Danheiser modification of Regitz's diazo transfer reaction.<sup>27</sup> 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<sub>3</sub>CN gave 5-bromoaryldiazoacetate **9a** in 75% yield.

On the basis of our previous work,<sup>16</sup> we initially explored the intramolecular C–H insertion of 9a in toluene using 1 mol

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<sup>&</sup>lt;sup>*a*</sup> 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. <sup>*b*</sup> Combined yield of *cis* and *trans* isomers. <sup>*c*</sup> Determined by <sup>1</sup>H NMR analysis of the crude product. <sup>*d*</sup> Determined by HPLC (Chiralcel OD-H). <sup>*e*</sup> Determined by HPLC (Chiralpak IA). <sup>*f*</sup> 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 (2R,3S) by single-crystal X-ray analysis (see Supporting Information).<sup>28,29</sup> Switching the solvent from toluene to CH<sub>2</sub>Cl<sub>2</sub> 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<sub>2</sub>(S-PT- $TEA_{4}$  (3b) (vide infra), characterized by an exceptionally large triethylmethyl group, proceeded at -40 °C to afford 2,3dihydrobenzofurans 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<sub>2</sub>(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).





The new dirhodium(II) carboxylate catalyst **3b** was prepared from the known carboxylic acid **14**<sup>30</sup> (Scheme 3). Bromination of **14** with bromine and PCl<sub>3</sub><sup>31</sup> followed by azidation with NaN<sub>3</sub> provided  $\alpha$ -azidocarboxylic acid **15**. Optical resolution of **15** was accomplished through formation of diastereomeric carboximides with (*S*)-4-benzyl-2-oxazolidinone<sup>32</sup> 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.<sup>28</sup> Hydrolytic removal of the chiral auxiliary<sup>33</sup> and azide reduction followed by recrystallization from MeOH $-H_2O$  furnished amino acid **18**. Rh<sub>2</sub>(*S*-PTTEA)<sub>4</sub> (**3b**) was prepared from amino acid **18** in 72% yield according to the reported procedure for the preparation of Rh<sub>2</sub>(*S*-PTTL)<sub>4</sub> (**3a**).<sup>34</sup>

With the efficient construction of (2R,3S)-*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-

<sup>(28)</sup> 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.

<sup>(29)</sup> The preferred absolute configuration of *trans* isomer **10a** was determined to be (2S,3S) 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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carpan (2) and (+)-conocarpan (1) as illustrated in Scheme 4. Reduction of (2R,3S)-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<sub>3</sub>)] in hexane–EtOAc produced optically pure material [mp 54.0-55.0 °C,  $[\alpha]^{22}_{D}$  +6.2 (c 1.15, CHCl<sub>3</sub>)] from the mother liquor in 83% yield. Suzuki-Miyaura coupling of 21 (>99% ee) with propenylboronic acid 7 in the presence of Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> and K<sub>2</sub>CO<sub>3</sub> provided the coupling product 22 in 76% yield. Reduction of 22 with LiEt<sub>3</sub>BH 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 (<sup>1</sup>H and <sup>13</sup>C NMR, IR, and CD) of this product were consistent with those reported for natural (-)-2.<sup>2</sup> 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.<sup>2</sup>  $[\alpha]^{21}$ <sub>D</sub> -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 (2R,3S)-2 compared to those reported for natural (-)-epi-conocarpan,<sup>2</sup> the absolute configuration of (-)epi-conocarpan should be revised to be (2R,3S). Epimerization of (-)-2 with Na<sub>2</sub>CO<sub>3</sub> in MeOH<sup>19,35</sup> followed by recrystallization from hexane-EtOAc provided (+)-conocarpan (1) in 71% yield. Synthetic material 1 was spectroscopically (<sup>1</sup>H and <sup>13</sup>C NMR, and IR) identical to natural (+)-1<sup>1</sup> and also had an optical rotation,  $[\alpha]^{22}_{D}$  +117 (c 1.18, MeOH), in good agreement with the literature value [lit.<sup>10</sup>  $[\alpha]^{21}_{D}$  +122 (*c* 1.03, MeOH)]. In summary, the Rh<sub>2</sub>(S-PTTEA)<sub>4</sub>-catalyzed intramolecular C-H insertion reaction of 5-bromoaryldiazoacetate showed considerable promise for asymmetric synthesis of cis-2-aryl-5bromo-2,3-dihydrobenzofurans. While Rh<sub>2</sub>(S-PTTL)<sub>4</sub> has proven to be optimal in a wide range of enantioselective C–H insertion reactions,<sup>16,36</sup> newly developed Rh<sub>2</sub>(*S*-PTTEA)<sub>4</sub> has been found to exhibit even higher diastereoselectivity (*cis/trans* = 97:3) and slightly higher enantioselectivity (84% ee) compared to those of Rh<sub>2</sub>(*S*-PTTL)<sub>4</sub> 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.

### **Experimental Section**

Representative Procedure for the C-H Insertion of 9a (Table 1, entry 8). Rh<sub>2</sub>(S-PTTEA)<sub>4</sub> (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<sub>2</sub>Cl<sub>2</sub> (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 <sup>1</sup>H NMR of the crude product. The residue (1.7 g) was purified by column chromatography (silica gel 90 g, 25:1 hexane/Et<sub>2</sub>O) to give **8a** (1.21 g, 80%) as a white solid:  $R_f = 0.50$  (6:1 hexane/Et<sub>2</sub>O); mp 62.0–63.0 °C for 84% ee;  $[\alpha]^{21}_{D}$  –31.4 (c 1.15, CHCl<sub>3</sub>) for 84% ee; IR (CHCl<sub>3</sub>)  $\nu$  1738 cm<sup>-1</sup>; <sup>1</sup>H NMR (270 MHz, CDCl<sub>3</sub>)  $\delta$ 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); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) & 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<sub>25</sub>H<sub>33</sub>O<sub>4</sub>SiBr (M<sup>+</sup>) 504.1331, found 504.1332. Anal. Calcd for C<sub>25</sub>H<sub>33</sub>O<sub>4</sub>SiBr: 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):  $t_{\rm R}$  (major) = 20.6 min for (2*R*,3*S*)-8*a*;  $t_{\rm R}$ (minor) = 25.6 min for (2S, 3R)-8a.

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**Supporting Information Available:** Full experimental, characterization data, and copies of <sup>1</sup>H and <sup>13</sup>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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<sup>(35)</sup> 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.

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