Concise Asymmetric Synthesis of (+)-Conocarpan and Obtusafuran

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Abstract: The asymmetric synthesis of three natural products: (+)-conocarpan, both (+)- and (–)- obtusafuran is disclosed. The highlights of the synthesis are the enantioselective hydrogenation of prochiral ketones via dynamic kinetic resolution to afford chiral alcohols. Intramolecular ring closure via either S_NAr reaction or metal-catalyzed C–O bond formation led to the construction of the *trans*-dihydrobenzofuran core.

Key words: (+)-conocarpan, (+)- and (–)-obtusafuran, dynamic kinetic resolution, S_NAr reaction, metal-catalyzed C–O bond formation, *trans*-dihydrobenzofuran, 8,5′-neolignans, 8-aryl-2,3-dihydrobenzofuran

8,5′-Neolignans containing an 8-aryl-2,3-dihydrobenzofuran skeleton are the most abundant natural products found in several families of plants (Figure 1).[1] These dihydrobenzofuran neolignans displayed a wide array of biological activities including cytotoxic, antiviral, and antifungal peroperties.[1] (+)-Conocarpan (**1**), for example, was first isolated from the wood of *Conocarpus erectus*[2] by Hayashi and Thomson in 1975 and exhibits a diverse array of biological activities, including insecticidal, antifungal, anti-inflammatory, and antitrypanosomal properties.[3] Another structurally similar neolignan, (+)-obtusafuran (**3**), isolated from *Dalbergia obtusa*,[4] also exhibits an array of interesting biological activities ranging from anticarcenogenic to insect antifeedant.[5] These molecules vary in substitution but all share a *trans*-dihydrobenzofuran heterocycle as a key structural element. The diverse biological activities coupled with unique structural features make this class of compounds an attractive synthetic target. Consequently, a few stereocontrolled syntheses of 2-aryl-2,3-dihydrobenzofuran derivatives have been reported.[6] Asymmetric syntheses, however, are less common as only three asymmetric routes have been described for (+)-conocarpan (**1**).[7] Recently, Clive and Stoffman correctly established the absolute configuration of (+)-conocarpan (**1**) as 2*S*,3*S* through their asymmetric synthesis of the enantiomer, (–)-(2*R*,3*R*)-conocarpan. Importantly, this synthetic work led to the correction of the absolute configuration of a number of other 8,5′-neolignan natural products. Hashimoto et al. reported another asymmetric synthesis of (+)-conocarpan (**1**) which was generated from its epimer (–)-*epi*-conocarpan (**2**).[8] This catalytic asymmetric synthesis relied on an enantio- and diastereoselective intramolecular C–H insertion reaction to construct a *cis*-2-aryl-2,3-dihydrobenzofuran ring system as a key step with decent enantioselectivity (84% ee). The intermediate was further elaborated to afford the (–)-*epi*-conocarpan (**2**) which was converted to (+)-conocarpan (**1**) upon treatment with base. Given the biological importance and structural uniqueness of these natural products, we herein wish to report a concise and efficient asymmetric synthesis of both (+)-conocarpan (**1**) and (+)-obtusafuran (**3**).

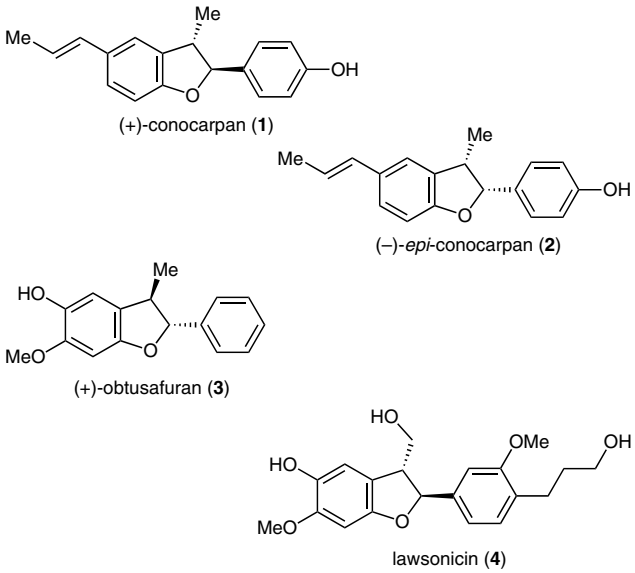

Figure 1 Selected examples of 8,5′-neolignans

We wish to devise a common strategy for the efficient construction of the *trans*-configured dihydrobenzofuran core in an enantioselective manner such that it can be applied to the synthesis of (+)-conocarpan (**1**), (+)-obtusafuran (**3**), and their structural analogues. As shown in Scheme 1, we envisioned that the *trans*-dihydrobenzofuran core **5** could be prepared via an intramolecular C–O bond formation from the corresponding *ortho*-halo carbinol **6** either via a metal-catalyzed intramolecular C–O bond formation (X = Br) or a simple S_NAr reaction (X = F). The two stereocenters in carbinol **6** could in turn be established from the enantioselective reduction of ketone via hydrogenation under dynamic kinetic resolution (DKR)[9] conditions. We have previously applied the concept of using dynamic kinetic resolution to the efficient synthesis of a potent CB-1 inverse agonist, taranabant, where an acyclic ketone bearing an α-substituent group was reduced in an enantioselective manner using $RuCl_2$[(*R*)-xylbinap][(*R*)-diapen] catalyst in the presence

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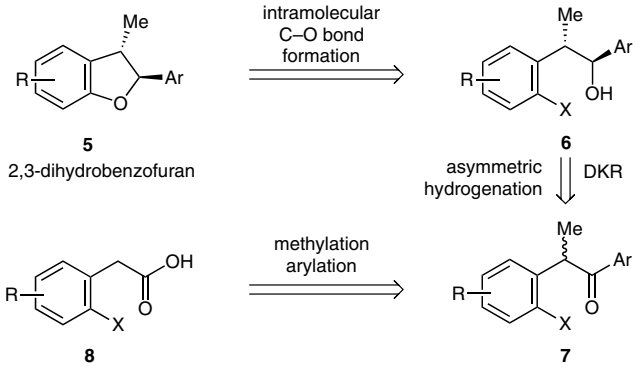
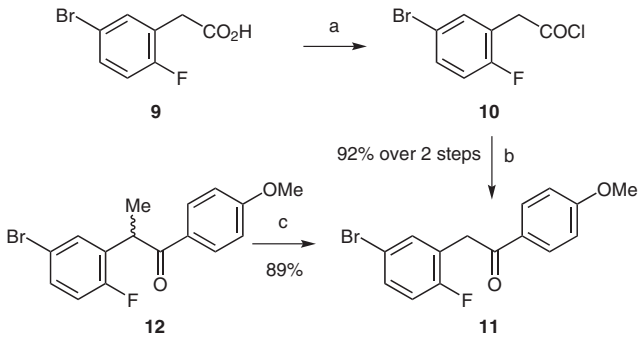
of KO*t*-Bu.[10] A similar reaction was previously reported by us as a useful methodology for the establishment of two consecutive chiral carbinol centers from prochiral ketones.[11] The application of reactions based on dynamic kinetic resolution to the synthesis of natural products, however, has not been widely described.[12] Herein, we wish to demonstrate that this powerful synthetic method could be applied in the synthesis of two chosen targets, (+)-conocarpan and (+)-obtusafuran. Moreover, it is our hope that the methodology we developed for the synthesis of these two natural products can be readily extended to the other 8,5′-neolignans with similar structural motifs.



Scheme 1 Synthetic strategy for *trans*-dihydrobenzofuran cores

We chose (+)-conocarpan as our first synthetic target to validate our strategy and planned to install the propenyl group at a later stage of the synthesis via Suzuki coupling with an aryl bromide species. The synthesis for (+)-conocarpan (**1**) began with a commercially available starting material, 2′-fluoro-5′-bromophenyl acetic acid (**9**, Scheme 2). The acid was converted into acid chloride **10** followed by Friedel–Crafts reaction with a slight excess of anisole to afford ketone **11** in 92% yield over two steps. Methylation of ketone **11** using methyl iodide in the presence of sodium hydride gave prochiral ketone **12** in 89% yield after crystallization.

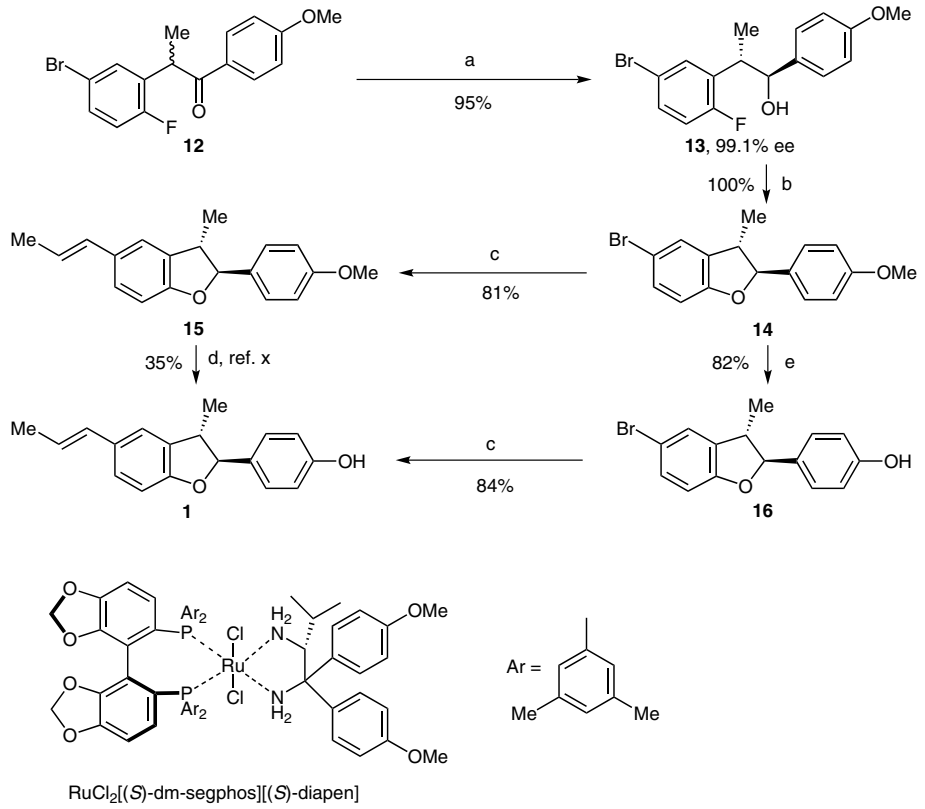


Scheme 2 Preparation of ketone **12**. *Reagents and conditions*: a) cat. DMF, $(COCl)_2$ (1.2 equiv), CH_2Cl_2; b) anisole (2 equiv), $AlCl_3$ (1.5 equiv), –5 °C to 23 °C; c) 65% NaH (1.3 equiv), MeI (1.2 equiv), DMF.

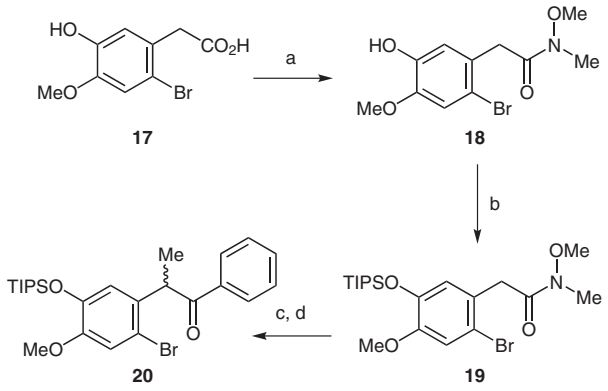
As shown in Scheme 3, ketone **12** was next subjected to asymmetric hydrogenation under DKR conditions. The asymmetric hydrogenation was initially carried out in isopropanol at 3.1 bar of hydrogen employing 1 mol% of $RuCl_2$[(*S*)-dm-segphos][(*S*)-diapen][13] as the chiral catalyst and KO*t*-Bu as a base to facilitate epimerization of the α-carbon center. The reaction, however, afforded a 1:1 mixture of two diastereomers (98.4% ee assayed for the desired diastereoisomer **13**). Apparently, the catalyst was so effective for the asymmetric hydrogenation such that at high catalyst loading (1 mol%) no dynamic kinetic resolution was occurring. Lowering the catalyst to 0.1 mol% restored the dynamic kinetic resolution, giving the desired diastereomer carbinol **13** in a nearly perfect selectivity (99.1% ee, >50:1 dr) and excellent yield (95%). The intramolecular ring closure of **13** to form the *trans*-dihydrobenzofuran ring via a S_NAr reaction using KO*t*-Bu as base in dioxane also went smoothly to afford *trans*-dihydrobenzofuran **14** quantitatively. The propenyl moiety was next installed in the 5-position of the phenyl ring using a Suzuki coupling protocol to afford conocarpan methyl ether **15** in 81% yield. Demethylation of the racemic methyl ether to carocarpan was reported to proceed in 92% yield using excess Ph_2PLi.[14] We, however, were unable to achieve this efficiency as the protocol afforded (+)-conocarpan (**1**) in only 35% yield. Attempts to facilitate demethylation of **15** using BBr_3 completely decomposed the substrate. An alternative aiming for higher efficiency was thus devised to carry out demethylation and subsequent Suzuki coupling. We found that demethylation of methyl ether **14** using BBr_3 in dichloromethane afforded bromophenol **16** in 82% yield. Finally, the Suzuki coupling reaction of bromophenol **16** with (*E*)-propenyl boronic acid led to the natural product, (+)-conocarpan (**1**) in 84% yield. The synthetic (+)-conocarpan (**1**) matches with all reported characterization data of the isolated natural product.[8]

Having successfully synthesized (+)-conocarpan (**1**), we decided to extend the strategy of combining asymmetric hydrogenation via DKR and intramolecular C–O bond formation for the effective construction of *trans*-configured dihydrobenzofurans to the enantioselective total synthesis of another 8,5′-neolignan, (+)-obtusafuran (**3**). To the best of our knowledge, no asymmetric synthesis of this natural product has been reported. As shown in Scheme 4, the prochiral ketone **20** was prepared in a straightforward manner. Hence, 2-bromo-4-methoxy-5-hydroxylphenyl acetic acid[15] was converted to the corresponding Weinreb amide **18** with sequential Weinreb amide formation and protection of the hydroxyl group using tris(isopropyl)silyl chloride (TIPSCl). The Weinreb amide was converted into the ketone in a one-pot procedure via methylation and phenylation to afford ketone **20** in 85% overall yield.

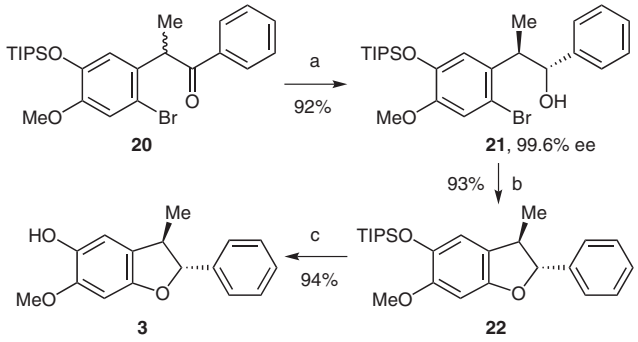
As shown in Scheme 5, asymmetric hydrogenation of ketone **20** under identical conditions for **12** but using $RuCl_2$[(*S*)-dm-segphos][(*S*)-diapen] as catalyst afforded the desired stereoisomer (**21**, 99.6% ee) exclusively in 92% yield. CuI-catalyzed intramolecular C–O bond formation to construct the dihydrobenzofuran ring employing 8-hydroxyquinoline as ligand in the presence of



Scheme 3 Asymmetric synthesis of (+)-conocarpan (**1**). *Reagents and conditions*: a) $RuCl_2$[(*S*)-dm-segphos][(*S*)-diapen] (0.15 mol%), KO*t*-Bu (20 mol%), H_2 (100 psi), 2-PrOH (5 mL/g substrate); b) KO*t*-Bu (2 equiv), dioxane, 100 °C; c) $PdCl_2$(dppf) (5 mol%), (*E*)-propenyl boronic acid (2.0 equiv), toluene–K_2CO_3 (aq), 80 °C; d) excess Ph_2PLi, THF; e) BBr_3 (2 equiv), CH_2Cl_2, –20 °C to 23 °C.



Scheme 4 Preparation of ketone **20**. *Reagents and conditions*: a) MeONHMe, EDC, pyridine, MeCN; b) TIPSCl, imidazole, MeCN; c) Li-HMDS, MeI; d) PhMgCl.



Scheme 5 Synthesis of (+)-obtusafuran (**3**). *Reagents and conditions*: a) $RuCl_2$[(*S*)-dm-segphos][(*S*)-diapen] (0.15 mol%), KO*t*-Bu (20 mol%), H_2 (6.9 bar), 2-PrOH (5 mL/g substrate); b) CuI (5 mol%), 8-hydroxyquinoline (10 mol%), Cs_2CO_3, toluene, 110 °C; c) *n*-Bu_4NF (1.5 equiv), THF.

Cs_2CO_3 afforded *trans*-dihydrobenzofuran **22** in 93% yield. TBAF-mediated desilylation of the TIPS ether **22** at ambient temperature proceeded smoothly to afford (+)-obtusafuran (**3**, 99.1% ee, 94% yield). The chemistry was repeated using the *S*-catalyst unequivocally to deliver the other enantiomer, (–)-obtusafuran (**3**, >99% ee).

In conclusion, we have demonstrated that the combination of asymmetric hydrogenation via dynamic kinetic resolution (DKR) and intramolecular C–O bond formation serves as an effective protocol for the construction of *trans*-dihydrobenzofuran and ultimately leads to the total synthesis of two natural products: (+)-conocarpan (**1**), (+)- and (–)-obtusafuran (**3**). The efficiency of the two key transformations in the syntheses is remarkable and we envision that it could be readily applied to the synthesis of other 8,5′-neolignans bearing *trans*-dihydrobenzofuran cores.

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(8) (a) Yoshihiro, N.; Hideyuki, T.; Sato, N.; Nakamura, S.; Nambu, H.; Shiro, M.; Hashimoto, S. *J. Org. Chem.* **2009**, *74*, 4418. (b) **Procedure for the preparation of (+)-conocarpan from bromophenol 16:** To bromophenol **16** (0.60 g, 1.966 mmol) in toluene (7.20 mL) was added potassium carbonate (0.815 g, 5.90 mmol), water (3.00 mL), trans-1-propen-1-ylboronic acid (0.338 g, 3.93 mmol) and [1,1′-bis(diphenylphospino)ferrocene]dichloropalladium(II) (0.072 g, 0.098 mmol). The mixture was degassed via nitrogen/vacuum followed by heating to 95 °C and kept at this temperature for 3 h to complete the coupling reaction. The reaction mixture was cooled to ambient temperature and the aqueous layer was removed. The organic layer was dried over $MgSO_4$, concentrated and the residue was subjected to biotage separation to afford (+)-conocarpan (0.482 g, 1.809 mmol, 92% yield) as a white solid: mp 136–138 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.41 (d, *J* = 6.8 Hz, 3 H), 1.89 (d, *J* = 1.6, 6.7 Hz, 3 H), 3.42 (m, 1 H), 5.0 (br s, 1 H), 5.10 (d, *J* = 8.6 Hz, 1 H), 6.10 (dq, *J* = 6.7, 15.5 Hz, 1 H), 6.40 (dd, *J* = 1.6, 15.5 Hz, 1 H), 6.78 (d, *J* = 8.1 Hz, 1 H), 6.83 (m, 2 H), 7.16 (m, 2 H), 7.31 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 17.8, 18.4, 45.2, 92.6, 109.3, 115.5, 120.7, 123.0, 126.3, 127.9, 130.8, 131.3, 132.4, 132.9, 155.7, 158.3. The enantiopurity of (+)-conocarpan was determined to be 99.6% using the reported method cited in reference 7a.

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(16) **Procedure for the preparation of (+)-obtusafuran:** Obtusafuran OTIP ether (**22**, 0.40 g, 0.969 mmol) and tetrabutylammonium fluoride trihydrate (0.459 g, 1.454 mmol) in THF (4.00 ml) were stirred at ambient temperature for 12 h to complete the desilylation reaction. Methyl *tert*-butylether (5 mL) was added. The organic layer was washed with water (2 × 5 mL), dried (Na_2SO_4) and concentrated in vacuum to an oil. The oil was chromatographed over silica gel, eluted with methyl *tert*-butylether–hexanes (1:3), to afford (+)-obtusafuran (0.234 g, 0.931 mmol, 94% yield) as a solid. mp 111–113 °C. $[\alpha]_D^{25}$ +50 (*c* 0.33, MeOH) [lit. 4 $[\alpha]_D^{25}$+47 (*c* 0.86, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ = 1.41 (d, *J* = 6.7 Hz, 3 H), 3.40 (m, 1 H), 3.90 (s, 3 H), 5.14 (d, *J* = 8.5 Hz, 1 H), 5.29 (s, 1 H), 6.54 (s, 1 H), 6.76 (s, 1 H), 7.40 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ = 18.5, 45.7, 56.3, 92.8, 94.2, 109.5, 122.9, 126.0, 128.2, 128.6, 140.0, 141.0, 146.3, 152.4. The enantiopurity of (+)-conocarpan was determined to be 99.1% using Chiralcel OZ column (250 × 4.6 mm), gradient method: 4% MeOH/25 mM IBA/CO_2 for 4 min, then ramp at 6%/min to 40% MeOH, hold 5 min, 15 min runtime, 200 bar, 35 °C, 3 mL/min, 215 nm, retention time: 9.56 min.

