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First synthesis of naturally occurring (±)-*epi*-conocarpan

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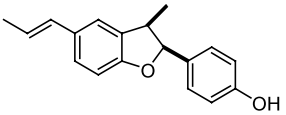
Abstract—(±)-*epi*-Conocarpan **1** was synthesized via the key intermediate 5-bromo-*cis*-2-(4-methoxyphenyl)-3-methyl-2,3-dihydrobenzofuran **6** which was synthesized by a ruthenium(II) porphyrin-catalyzed intramolecular C–H insertion reaction using aryl tosylhydrazone salt **5** as the carbene source, starting from the commercially available 5-bromo-2-hydroxyacetophenone.

Piperaceae species are pioneer shrubs with economic and medicinal importance. (−)-*epi*-Conocarpan was isolated from the roots of *Piper regnellii* (Piperaceae).[1] *epi*-Conocarpan **1** is the epimer of conocarpan **2**,[2] *epi*-conocarpan and *epi*-conocarpan have the 3-methyl-2,3-dihydrobenzofuran skeleton, the basic structure of a sub-class of neolignan natural products which possess a wide variety of antibacterial, cytotoxic, antiproliferative, immunosuppressive, antioxidant, antiangiogenic and insecticidal activities.[3] Conocarpan is toxic to the larvae of the European corn borer at 10 μg/mL.[4] However, due to the limited amounts of (−)-*epi*-conocarpan, its biological activity has not yet been established. Here we report the first synthesis of (±)-*epi*-conocarpan **1**.



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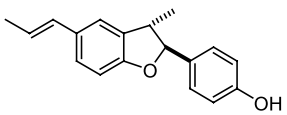

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Although there are several approaches available for the formation of the 3-methyl-2,3-dihydrobenzofuran skeleton,[5] all methods yield only the *trans*-3-methyl-2,3-dihydrobenzofurans as the major product. So, the synthesis of the intermediate *cis*-2,3-dihydrobenzofuran derivative **6** is the key step (see Scheme 1). Intra- and intermolecular metal carbene C–H insertion has emerged as a general strategy for the formation of carbocycles and heterocycles.[6] High-valent oxo- and imidoruthenium porphyrins are known to effect alkane hydroxylations and amidations via C–H bond activation.[7] However, our earlier studies revealed that the reaction of [Ru^{II}(TTP)(CO)] (H_2TTP = *meso*-tetrakis(*p*-tolyl) porphyrin) with γ-alkoxy-α-diazo-β-ketoesters afforded ruthenium–carbene porphyrin complexes, which then underwent subsequent intramolecular cyclization to furnish 1,3-dioxolanes exclusively.[8] Fortunately, we recently found the first ruthenium porphyrin-catalyzed intramolecular carbenoid C–H insertion to afford selectively *cis*-2,3-disubstituted-2,3-dihydrobenzofurans using aryl tosylhydrazone salts as the carbene sources.

The reaction conditions of the ruthenium(II) porphyrin-catalyzed intramolecular C–H insertion reactions using aryl tosylhydrazone salt **5** as carbene source to provide 5-bromo-*cis*-2-(4-methoxyphenyl)-3-methyl-2,3-dihydrobenzofuran **6** was investigated. As shown in Table 1, when the [Ru^{II}(TTP)(CO)]-catalyzed C–H insertion reaction of **5** was performed in refluxing toluene, the reaction was finished in only 2 h affording **6** in 82% yield, albeit with slightly compromised *cis*-selectivity (entry 3). Phase transfer catalysts (PTC) n-$Bu_4N^+Br^-$ and $BnEt_3N^+Cl^-$ gave similar ratios under identical conditions (entries 1 and 2). Contrary to expectation, $Rh_2(OAc)_4$ was a less effective catalyst giving low yields and stereoselectivity (entry 5). In the absence of a catalyst, no product was found according to ^{1}H NMR analysis of the reaction mixture (entry 4).

The benzylation of 5-bromo-2-hydroxyacetophenone with *p*-methoxybenzyl chloride afforded 5-bromo-2-(4-methoxy benzyloxy)acetophenone **3**[9] under microwave irradiation in only a few minutes, which was then

Keywords: (±)-*epi*-conocarpan; *cis*-2,3-dihydrobenzofuran; intramolecular C–H insertion; ruthenium(II) porphyrin.

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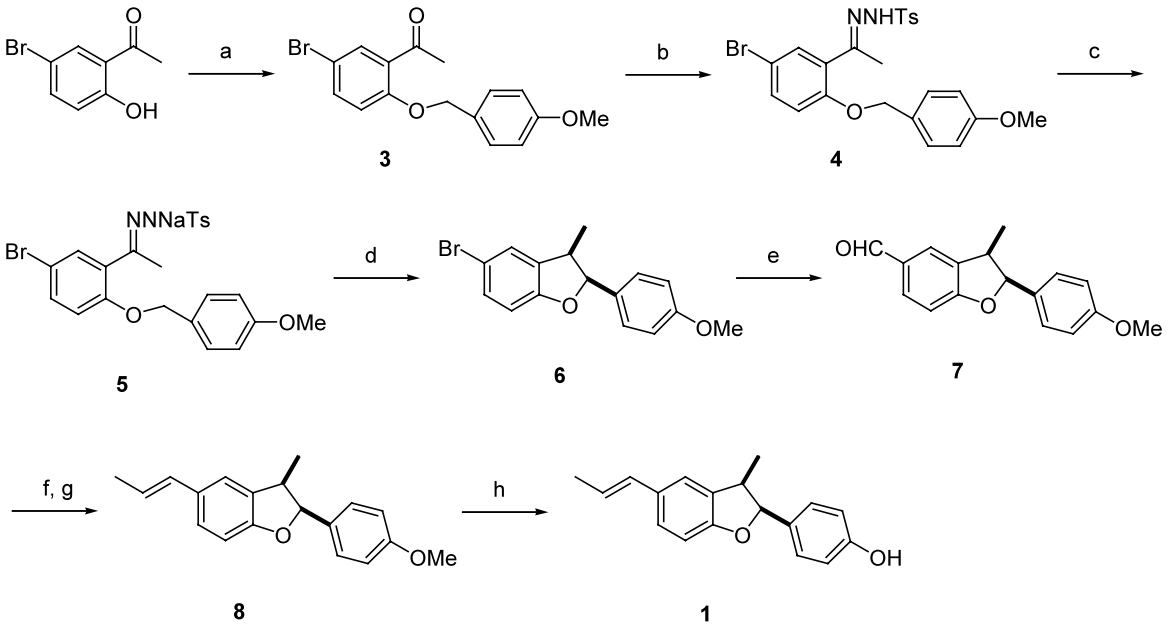

Scheme 1. *Reagents and conditions*: (a) *p*-methoxybenzyl chloride, K_2CO_3, microwave irradiation, 99%; (b) $TsNHNH_2$, ethanol, reflux, 86%; (c) sodium, methanol; (d) $Bn(Et)_3N^+Cl^-$, [Ru^{II}(TTP)(CO)], toluene, 60–70°C, 48 h, 77% (two steps including c and d); (e) *n*-BuLi, THF, 0.5 h; then DMF, −78–25°C, 1.5 h, 48%; (f) *n*-BuLi, THF, $(Ph)_3P^+EtBr^-$, 79%; (g) $PdCl_2{\cdot}2CH_3CN$, CH_2Cl_2, 93%; (h) *n*-BuLi, $(Ph)_2PH$, THF, 85%.

Table 1. Ru- or Rh-catalyzed intramolecular C–H insertion reaction to form **6** using aryl tosylhydrazone salt **5** as carbene source

Entry	Catalyst	PTC	Temp. (°C)	Time (h)	Yield (%)	*cis*:*trans*[a]
1	[Ru^{II}(TTP)(CO)]	*n*-$Bu_4N^+Br^-$	60–70	48	77	>98
2	[Ru^{II}(TTP)(CO)]	$BnEt_3N^+Cl^-$	60–70	48	75	>98
3	[Ru^{II}(TTP)(CO)]	*n*-$Bu_4N^+Br^-$	110[b]	2	82	84:16
4	None	*n*-$Bu_4N^+Br^-$	60–70	48	0	–
5	[$Rh_2(OAc)_4$]	*n*-$Bu_4N^+Br^-$	60–70	48	29	76:24

[a] The ratio of *cis* to *trans* was determined by ^1H NMR.
[b] The reaction was performed in refluxing toluene.

treated with *p*-toluenesulfonohydrazide to afford 2-(4-methoxybenzyloxy)-5-bromo-acetophenone tosylhydrazone **4**[9] in 86% yield. The compound **4** was transformed to the salt **5** with sodium methoxide, which was formed in situ by the reaction of sodium with methanol. 5-Bromo-*cis*-2-(4-methoxyphenyl)-3-methyl-2,3-dihydrobenzofuran **6**[9] was formed by [Ru^{II}(TTP)(CO)]-catalyzed intramolecular C–H insertion using the salt **5** as carbene source with high stereoselectivity (>98%, *cis*). The replacement[10] of the bromine substituent in **6** with an aldehyde group using *n*-butyllithium as the metallation reagent and DMF as the formyl source afforded 2-(4-methoxyphenyl)-3-methyl-*cis*-2,3-dihydrobenzofuran-5-carbaldehyde **7**.[9] The Wittig reaction[11] of compound **7** with ethyltriphenylphosphonium bromide using potassium carbonate in moist dioxane led to the formation of an oily mixture of stereoisomers of 2-(4-methoxyphenyl)-3-methyl-5-(1-propenyl)-*cis*-2,3-dihydrobenzofuran. The isomerization reaction[11b] of the stereoisomers using bis-(acetonitrile)dichloropalladium(II) in dichloromethane produced the (*E*)-isomer **8**.[9] Demethylation[5b] of **8** with $LiPPh_2$ in anhydrous tetrahydrofuran gave an 85% yield of (±)-*epi*-conocarpan **1** as a crystalline solid with identical spectral data to those of the natural product.[1]

In conclusion, a total synthesis of (±)-*epi*-conocarpan was achieved in eight steps with a 20% overall yield from 5-bromo-2-hydroxyacetophenone. Ruthenium(II) porphyrin-catalyzed intramolecular C–H insertion using aryl tosylhydrazone salt **5** as the carbene source provided a general route to the key intermediate 5-bromo-*cis*-2-(4-methoxyphenyl)-3-methyl-2,3-dihydrobenzofuran **6** with high stereoselectivity (>98% *cis*) for the synthesis of **1**. It is our belief that this strategy will be versatile and practical for the synthesis of a variety of other natural products with *cis*-2,3-dihydrobenzofuran skeleton.

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9. Selected spectroscopic and physicochemical properties: compound **3**, colorless crystal, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, $J=2.6$ Hz, 1H); 7.52 (dd, $J=2.6$ Hz and 8.8 Hz, 1H); 7.35 (d, $J=8.7$ Hz, 2H); 6.92 (m, 3H); 5.07 (s, 2H); 3.83 (s, 3H); 2.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 159.7, 157.1, 136.0, 133.0, 130.1, 129.4, 127.7, 114.8, 114.1, 113.3, 70.8, 55.3, 32.0. IR (KBr, cm^{-1}): 2928, 1666, 1616, 1586, 1515, 1483, 1459, 1280, 1239, 1034, 643, 523. MS (EI): 334 (M^+, 2), 258 (22), 228 (25), 197 (20), 150 (15), 135 (17), 121 (100), 107 (15). HRMS (EI): Found M^+ 334.0211, $C_{16}H_{15}BrO_3$ requires 334.0205. Anal. calcd for $C_{16}H_{15}BrO_3$: C, 57.33; H, 4.51. Found: C, 57.44; H, 4.50%. Compound **4**, colorless crystal, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, $J=8.3$ Hz, 2H); 7.53 (bs, 1H); 7.38–7.22 (m, 6H); 6.90–6.78 (m, 3H); 4.93 (s, 2H); 3.82 (s, 3H); 2.44 (s, 3H); 2.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 155.7, 144.2, 135.3, 132.9, 132.6, 130.2, 129.6, 129.1, 128.2, 128.0, 114.2, 114.0, 113.1, 70.6, 55.5, 21.7, 16.7. IR (KBr, cm^{-1}): 3203, 2934, 1612, 1587, 1514, 1486, 1463, 1397, 1375, 1337, 1299, 1235, 1046, 990, 915, 817, 660, 592. MS (EI): 502 (M^+, 0.6), 318 (9), 224 (3), 139 (3), 121 (100), 108 (4). HRMS (EI): Found M^+ 502.0562, $C_{23}H_{23}BrN_2O_4S$ requires 502.0562. Compound **6**, colorless oil, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.17 (m, 4H); 6.90–6.86 (m, 2H); 6.76 (d, $J=8.1$ Hz, 1H), 5.77 (d, $J=8.8$ Hz, 1H); 3.81 (s, 3H); 3.64 (m, 1H); 0.81 (d, $J=7.2$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 158.3, 135.3, 130.9, 129.5, 127.5, 127.4, 113.6, 112.4, 111.0, 88.2, 55.2, 40.9, 16.7. IR (neat, cm^{-1}): 2964, 2929, 1613, 1586, 1513, 1470, 1304, 1250, 1172, 1034, 957, 809, 657. MS (EI): 320 (89), 318 (M^+, 100), 224 (19), 134 (12), 121 (36), 108 (5). HRMS (EI): Found M^+ 318.0256, $C_{16}H_{15}BrO_2$ requires 318.0255. Anal. calcd for $C_{16}H_{15}BrO_2$: C, 60.21; H, 4.74. Found: C, 59.98; H, 4.67%. Compound **7**, colorless liquid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 7.74–7.72 (m, 2H), 7.20–7.16 (m, 2H), 6.99 (m, 1H), 6.91–6.89 (m, 2H), 5.90 (d, $J=9.0$ Hz, 1H), 3.81 (s, 3H), 3.75 (m, 1H), 0.88 (d, $J=8.3$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.6 (d), 164.8 (s), 159.4 (s), 134.3 (s), 133.3 (d), 130.9 (s), 129.0 (s), 127.5 (d), 125.4 (d), 113.8 (d), 109.7 (d), 89.2 (d), 55.3 (q), 40.0 (d), 16.7 (q). IR (neat, cm^{-1}): 3354, 2969, 2928, 2836, 1744, 2252, 1684, 1604, 1514, 1332, 1243, 1175, 1090, 1033, 949, 823, 728, 627. MS (EI): 269 (M^++1, 21), 268 (M^+, 100), 266 (19), 253 (11), 121 (13). HRMS (EI): Found M^+ 268.1101, $C_{17}H_{16}O_3$ requires 268.1099. Compound **8**, colorless liquid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22–7.11 (m, 4H); 6.91–6.86 (m, 2H); 6.80 (d, $J=8.2$ Hz, 1H); 6.36 (dd, $J=15.7$ Hz and 1.5 Hz, 1H); 6.07 (m, 1H); 5.75 (d, $J=8.7$ Hz, 1H); 3.80 (s, 3H); 3.62 (m, 1H); 1.86 (dd, $J=6.6$ Hz and 1.6 Hz, 3H); 0.82 (d, $J=7.2$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.1, 158.3, 133.1, 131.3, 130.8, 130.1, 127.6, 126.2, 122.9, 121.5, 113.6, 109.2, 87.9, 55.3, 40.8, 18.4, 16.8. IR (neat, cm^{-1}): 3020, 2963, 2929, 1614, 1515, 1488, 1243, 961, 823. MS (EI): 281 (M^++1, 18), 280 (M^+, 100), 279 (7), 278 (31), 265 (11), 263 (5), 121 (5). HRMS (EI): Found M^+ 280.1467, $C_{19}H_{20}O_2$ requires 280.1463. Anal. calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.23; H, 7.18%.
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