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Total synthesis of polemannones B and C

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ABSTRACT

The first total synthesis of polemannones B and C, higly oxygenated benzoxanthenones derivatives from *Polemannia montana*, is reported employing our new catalytic Cu(II)/sparteine system for β,β-phenolic couplings and tandem inverse-electron demand Diels–Alder reaction cascade in 75–90% yield.

Benzoxanthenones are a class of ligan natural products, exemplified by a highly oxygenated tetracyclic ring system with four to five contiguous stereocenters, isolated as single diastereomers, but racemic. Notable members include (Fig. 1) carpanone (**1**),[1] sauchinone (**2**),[2] and unnatural benzoxanthenones such as (**3**).[3,4] In 1987, Jakupovic and Eid described three new, more highly oxygenated congeners, 4,5-dimethoxy-4′,5′-methylenedioxypolemannone or polemannone A (**4**), 4,5, 4′,5′-bismethylenedioxypolemannone or polemannone B (**5**), and 4,5,4′,5′-tetramethoxypolemannone or polemannone C (**6**), isolated from root of *Polemannia montana*.[5] To date, there have been no synthetic efforts directed toward the polemannones, nor have the polemannones been subjected to biological evaluation.

Benzoxanthenones have garnered a great deal of attention since the classic biomimetic synthesis of carpananone (**1**) by Chapman in 1971 (Scheme 1), which utilized $PdCl_2$ and NaOAc to promote the β,β-phenolic coupling and subsequent endo-selective, inverse-electron demand Diels–Alder reaction.[6] Chapman's approach afforded carpanone (**1**) in 46% yield as a single diastereomer, which was confirmed by single X-ray crystallography. After this initial report, several labs disclosed additional oxidative systems, both stoichiometric and catalytic, to produce carpanone including metal (II) salen/O_2 (metal = Co, Mn, Fe),[7] O_2 (*hv*, rose bengal),[7] AIBN, dibenzoyl peroxide,[7] and AgO[8] in yields ranging from 14 to 94%. In 2001, Ley reported on the total synthesis of carpanone employing only solid-supported reagents and scavengers.[9] At the same time, a hetero-β,β-phenolic coupling reaction, facilitated by $IPh(OAc)_2$, to deliver hetero-tetracyclic analogs of carpanone was described by Lindsley and Shair; however, this oxidant system was unable to produce carpanone itself, but it was able to produce less electron-rich homodimers.[3] In all of these cases, single diastereomers were produced, due to the anti-β,β-phenolic coupling and endo-selective inverse-electron demand Diels–Alder reaction, but enantioselective syntheses/asymmetric syntheses have never been reported.

Jakupovic and Eid proposed a similar biosynthetic route for polemannones A–C (**4**–**6**), but classical oxidant systems failed with such electron-rich styrenyl phenols.[3,5] We recently developed a novel, catalytic $CuCl_2$/(−)-sparteine oxidative β,β-phenolic coupling reaction of styrenyl phenols which, after a rapid inverse-electron demand Diels–Alder reaction, affords the benzoxanthanone natural product carpanone **1** and related unnatural congeners, such as **3**, in yields exceeding 85% (Scheme 2) as single diastereomers, but racemic.[4] This new methodology has proven to be general with regard to substrate scope, but was found to afford no enantioselectivity. In this Letter, we describe the application of this new catalytic oxidant system for the first total synthesis of polemannones B and C.

The polemannones are unique in that there is an extra electron-donating ether moiety.[5] In all previous synthetic works, only 1 or 2 electron-donating ether moieties were present, and one of these was always positioned *para* to the phenol to stabilize the *ortho*-quinone methide intermediate and provide the 'push' in the inverse-electron demand Diels–Alder reaction (Scheme 1).[1–9] In cases where two electron-donating ether moieties were present, the second was always positioned *meta* to the phenol.

While unprecendented, we wondered if a lone *ortho*-methoxy group, as in **8**, could equally stabilize the *ortho*-quinone methide intermediate and provide the 'push' in the inverse-electron demand Diels–Alder reaction to provide unnatural benzoxanthenone **9** (Scheme 3). Starting from 2-hydroxy-3-methoxybenzaldehyde **7**, an *E*-selective Wittig reaction[10] produced styrenyl phenol **8** in 71% yield.

Employing our catalytic oxidant system,[4] unnatural benzoxanthenone **9** was obtained as a single diastereomer in 70% yield and NOE measurements confirmed the relative stereochemistry. This is the first example of a β,β-phenolic coupling and tandem inverse-electron demand Diels–Alder reaction cascade without a

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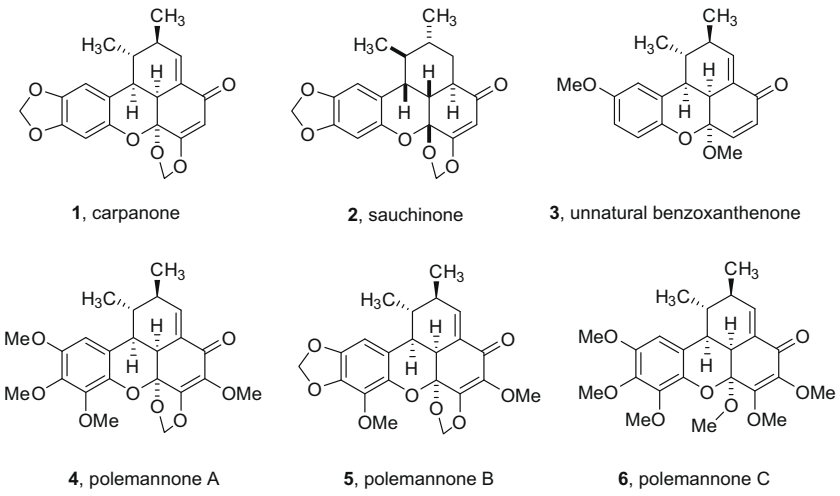
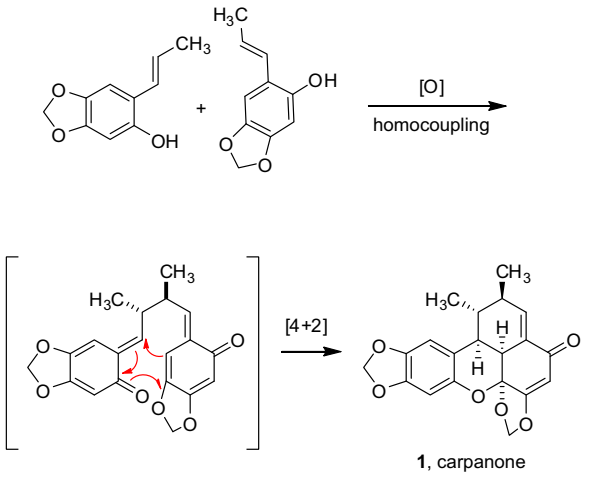
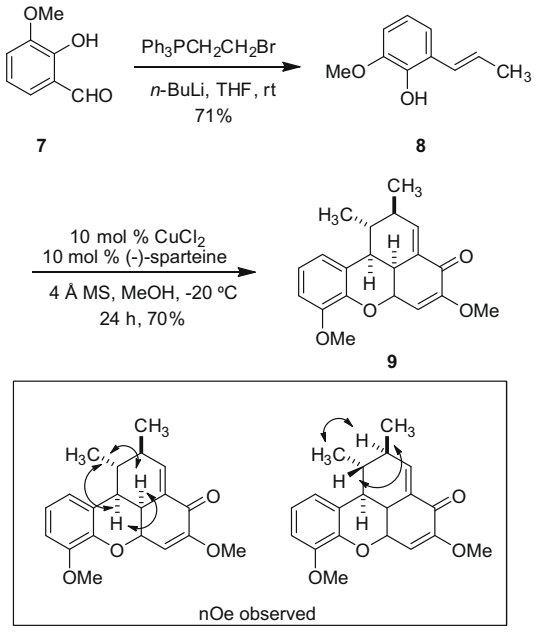


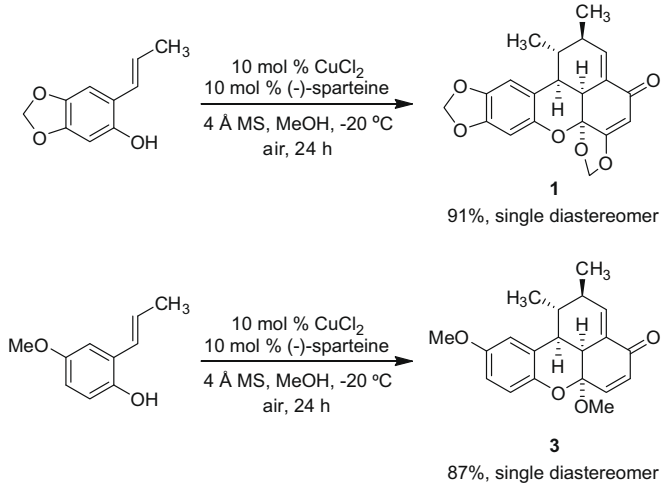
Figure 1. Structures of benzoxanthenone natural and unnatural products.



Scheme 1. Biomimetic synthesis of carpanone.



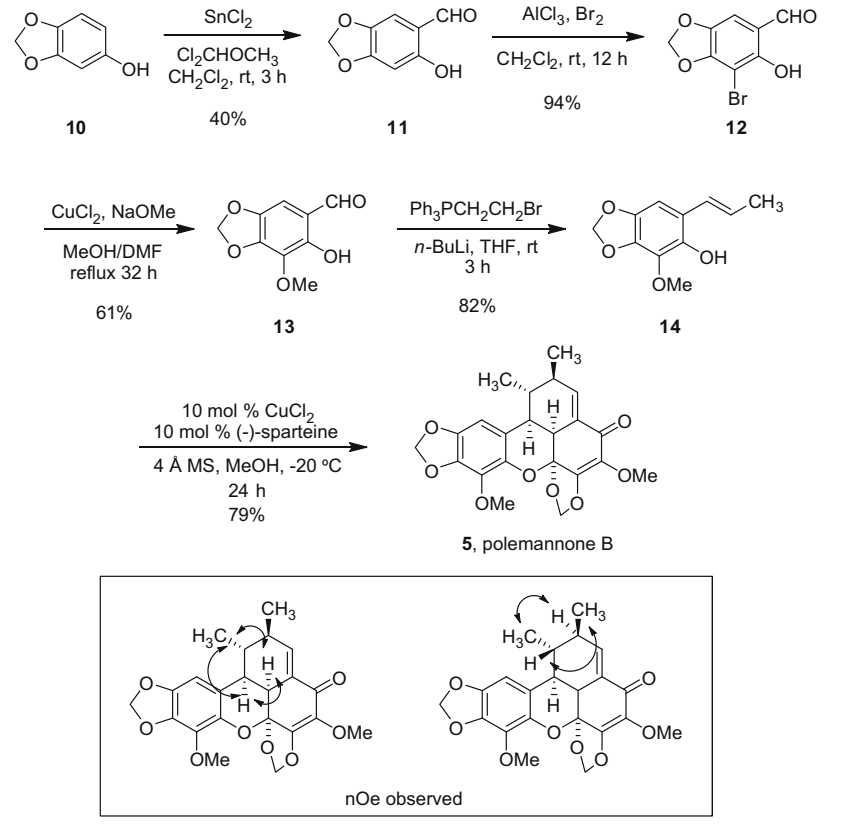
Scheme 3. Synthesis of unnatural benzoxanthenone **9** and observed NOEs.



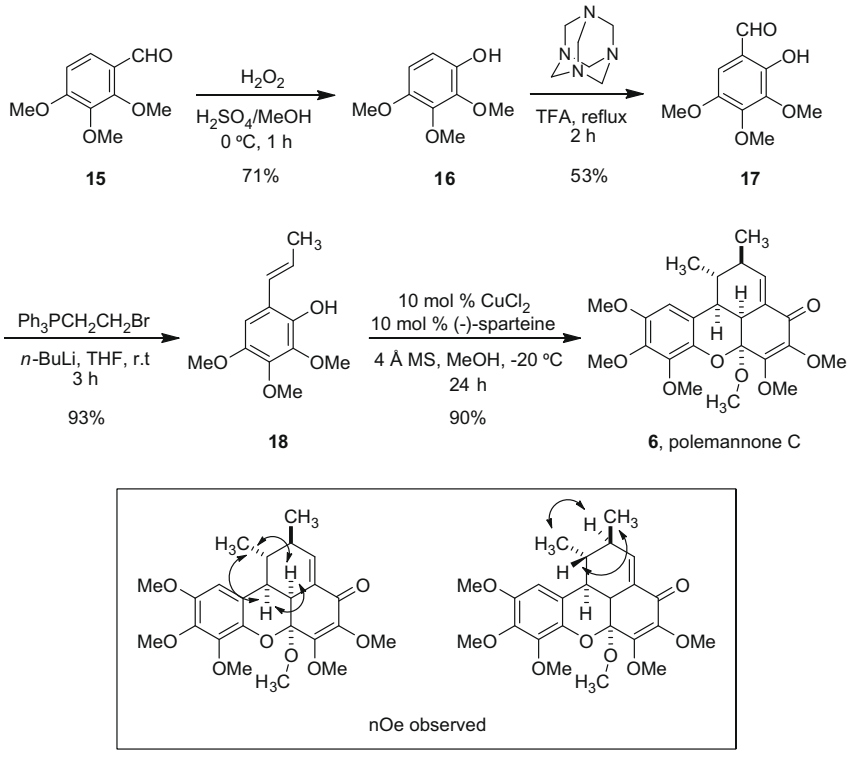
Scheme 2. Catalytic Cu(II)/(−)-sparteine oxidant system to promote β,β-phenolic couplings/tandem inverse-electron demand Diels–Alder reaction cascade to provide carpaonone (**1**) and unnatural benzoxantheone (**3**).

para-OMe group, and **9** represents a fundamentally new chemotype within the benzoxanthenone family. Importantly, this result was encouraging and suggested that our methodology may successfully allow for the first total synthesis of members of the polemannone family of benzoxanthenones, as they all possess an electron-donating ether moiety in the *ortho*-position.

Thus, we initiated a synthetic campaign to deliver polemannones B and C—both homodimers of electron-rich styrenyl phenols **14** and **18**, respectively. The requisite styrenyl phenol for polemannone B, **14**, was prepared in four steps from commercial sesamol **10** (Scheme 4). Formylation provided **11** in 40% yield, followed by an $AlCl_3$-mediated bromination to produce **12** in 94% yield. The key methoxy group was installed via a Cu(II) etherification reaction to afford a 61% yield of **13**. Finally, an *E*-selective Wittig reaction[10] produced styrenyl phenol **14** in 82% yield, or 19% for the four steps. Employing our catalytic Cu(II)/(−)-sparteine oxidant system,[4] polemannone B (**5**) was delivered as a single diastereomer in 79% yield and once again, NOE measurements confirmed the



Scheme 4. Synthesis of polemannone B **5** and observed NOEs.



Scheme 5. Synthesis of polemannone C **6** and observed NOEs.

relative stereochemistry. As with the natural product, our synthetic material was racemic. Moreover, spectral data for our synthetic polemannone B were in complete accord with those reported for the natural product.[5,11]

The requisite styrenyl phenol for polemannone C, **18**, was prepared in four steps from commercial 2,3,4-trimethoxybenzaldehyde **15** (Scheme 5). **15** was smoothly converted into the corresponding phenol **16** by treatment with acidic hydrogen per-

oxide. The *ortho*-formylation step for **16** proved to be problematic. The *ortho*-formylation protocol employed for the synthesis of **11**, utilizing $SnCl_2$ and dichloro(methoxy)methane, surprisingly afforded *meta*-formylation exclusively. Ultimately, hexamethylenetetramine in refluxing TFA provided the desired *ortho*-formylation product **17** in 53% yield. Then, an *E*-selective Wittig reaction[10] produced styrenyl phenol **18** in 93% yield, or 35% for the three steps. Employing our catalytic Cu(II)/(−)-sparteine oxidant system[4] polemannone C (**6**) was delivered as a single diastereomer in 90% yield and once again, NOE measurements confirmed the relative stereochemistry. As with the natural product, our synthetic material was racemic. Moreover, spectral data for our synthetic polemannone C were in complete accord with those reported for the natural product.[5,12]

In summary, we have extended the substrate scope of β,β-phenolic coupling/tandem inverse-electron demand Diels-Alder reaction cascade of styrenyl phenols to include *ortho*-substituted ethers to afford novel, unnatural benzoxanthenones such as **9** by application of our novel, catalytic $CuCl_2$/(−)-sparteine oxidation system. More importantly, this new catalytic system enabled the first total synthesis of the highly oxygenated benzoxanthenone ligans polemannones B and C from commercial starting materials in overall yields of 15% and 31.5%, respectively. Extensive NOE work confirmed the relative stereochemistry of **9** and polemannones B and C. Biological evaluation of these compounds against large panels of discrete receptors (GPCRs, ion channels, transporters, and kinases) is underway, and results will be reported in due course.

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11. *General experimental for β,β-phenolic coupling:* A solution of copper catalyst (0.1 equiv), 4 Å molecular sieves and sparteine (0.1 equiv) in MeOH (0.15 M) was stirred for 15–20 min until no solid copper salt was visible and then cooled to −20 °C followed by the addition of phenol (1.0 equiv). The reaction mixture was stirred at −20 °C for 24 h with exposure to air. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2 (3×). The combined organic extracts were washed with 0.5 N HCl, water, and the dried over $MgSO_4$. Filtration and concentration afforded the crude product, which was purified by flash chromatography (4:1 to 1:1 Hex/EtOAc). *Polemannone B:* Yellow solid, R_f = 0.61 (1:1 Hex/EtOAc); ^{1}H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 7.05 (dd, J = 4.9, 1.5 Hz, 1H), 6.51 (s, 1H), 5.89 (d, J = 1.3 Hz, 1H), 5.85 (d, J = 1.3 Hz, 1H), 5.66 (s, 1H), 5.64 (s,1H), 3.96 (s, 1H), 3.93 (s, 1H), 3.26 (dd, J = 7.5, 2.3 Hz, 1H), 3.17 (dt, J = 7.5, 2.3 Hz, 1H), 2.48 (q, J = 7.2 Hz, 1H), 2.21 (m, 1H), 1.12 (d, J = 7.2 Hz, 3H), 0.70 (d, J = 7.6 Hz, 3H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ (ppm): 183.2, 151.4, 143.7, 143.0, 137.9, 135.7, 133.6, 131.5, 126.4, 126.4, 116.8, 101.3, 101.1, 100.6, 98.7, 60.2, 59.7, 36.3, 35.6, 35.1, 34.0, 21.4, 21.1; HRMS (TOF, ES+) $C_{22}H_{22}O_8$ $[M+H]^+$ calcd 415.1393, found 415.1383.
12. *Experimental data for poelmanonne C:* Yellow solid, R_f = 0.58 (1:1 Hex/EtOAc); ^{1}H NMR (600.1 MHz, $CDCl_3$) δ (ppm): 6.95 (m, 1H), 6.57 (s, 1H), 4.18 (s, 3H), 3.81 (s, 6H), 3.77 (s, 3H), 3.74 (s, 3H), 3.39 (s, 3H), 3.20 (dd, J = 7.0, 1.8 Hz, 1H), 3.07 (m, 1H), 2.53 (q, J = 7.0 Hz, 1H), 2.15 (m, 1H), 1.09 (d, J = 7.2 Hz, 3H), 0.62 (d, J = 7.8 Hz, 3H); ^{13}C NMR (150.9 MHz, $CDCl_3$) δ (ppm): 183.2, 161.2, 147.3, 141.9, 141.2, 139.0, 138.5, 127.0, 119.1, 106.1, 97.0, 61.2, 60.9, 60.4, 56.2, 53.1, 36.3, 35.6, 35.1, 33.7, 21.3, 21.0; HRMS (TOF, ES+) $C_{24}H_{30}O_8$ $[M+H]^+$ calcd 447.2019, found 447.2019.