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Total Synthesis of Pyrolaside B: Phenol Trimerization via Sequenced Oxidative C-C and C-O Coupling

William C. Neuhaus and Marisa C. Kozlowski*

Abstract: A facile method to oxidatively trimerize phenols using a low loading catalytic aerobic copper system is described. The mechanism of this transformation is probed, an understanding of which enabled cross coupling trimerizations. With this method, the natural product pyrolaside B has been synthesized for the first time. The key strategy used for this novel synthesis is the facile one-step construction of a spiroketal trimer intermediate which can be selectively reduced to give the natural product framework without recourse to stepwise Ullmann- and Suzuki-type couplings. As a result, pyrolaside B can be obtained expeditiously in five steps and 16% overall yield. Two other analogues were synthesized highlighting the utility of the method and new accessibility to this range of chemical space. A novel xanthene was also synthesized through controlled Lewis acid promoted rearrangement of a spiroketal trimer.

Phenol trimers (Figure 1) encompass a diverse range of compounds found in nature which have been shown to have unique biological activities. Pyrolaside B (**1**) was isolated from Pyrola rotundifoliai in 2005 and from *Pyrola calliantha* in 2010, and was found to inhibit *Micrococcus luteus* and *Staphylococcus aureus*.[1] Fucophlorethol C (**2**)[2] from brown alga *Colpomenia bullosa* acts as a lipoxygenase inhibitor. Pyrocallianthaside B (**3**)[3] and isotrityrosin (**4**)[4] have been isolated from *Pyrola calliantha* and *haemonchus contortus* infective larvae, respectively.

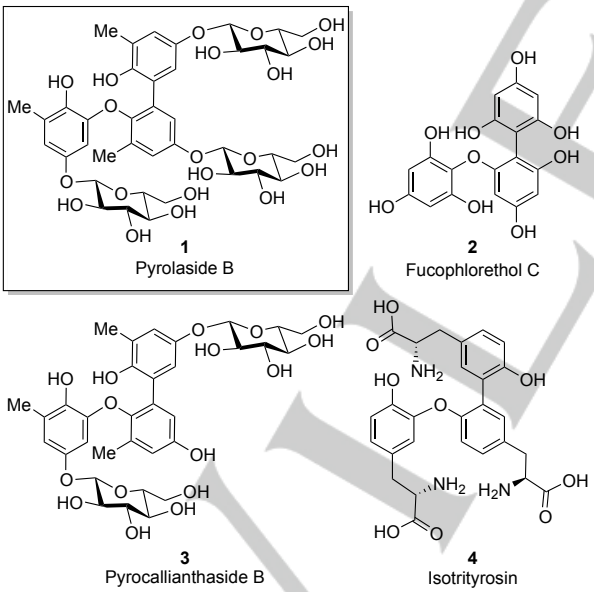
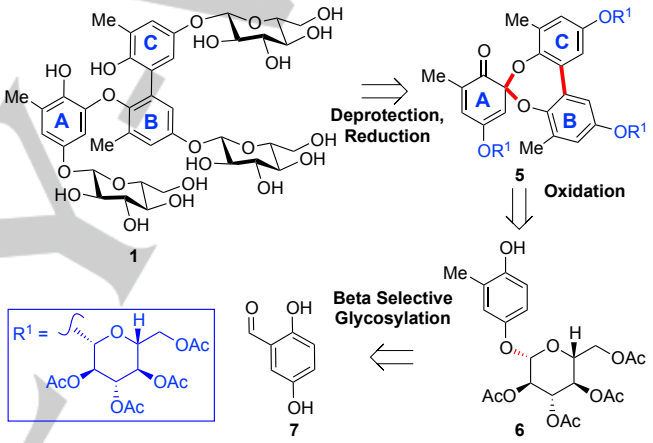


Figure 1: Phenol trimer natural products.

We envisaged that pyrolaside B could be constructed by reduction of the corresponding *ortho*-quinone/bisphenol dimer spiroketal (**5**) illustrated in Scheme 1. In particular, utilization of a version of **5** with each of the phenols already appended a glucose equivalent would circumvent the considerable challenges entailed in selectively glucosylating three of the five phenols of the pyrasolide B aglycone. In turn, **5** can be dissected to monomer **6**. However, oxidative trimerization to **6** would involve the challenging selective formation of one C-C bond as well as two C-O bonds. Finally, stereoselective glycosylation of phenol precursor **7** would be needed to set the stage for the oxidative trimerization.



Scheme 1: Retrosynthetic analysis of pyrolaside B.

Beginning in 1965, limited reports of stoichiometric oxidative trimerizations of phenols to form spiroketals of structure **9** have appeared (Scheme 2).[5,6] In 2012, the Lei Group gave one example of cyclic trimer formation via stoichiometric silver oxidation (Scheme 2a).[7] In the same year, the Beifuss group generated a similar cyclic trimer from sesamol via laccase oxidation in 3% yields (Scheme 2b).[8] Likewise, in 2018, it was found that methylcarbazoles were able to form spiroketal trimers, albeit in low yield (Scheme 2c).[9] The low yields in such processes likely arise from the selectivity challenges associated with phenol C-C dimerization in addition to two C-O bond forming reactions.

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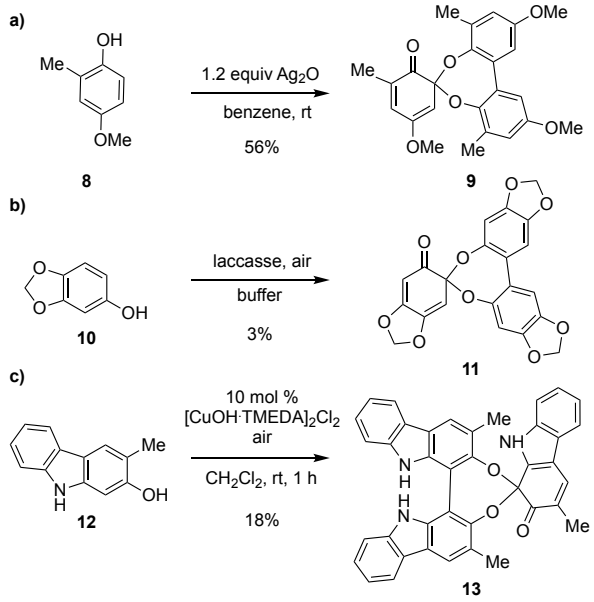
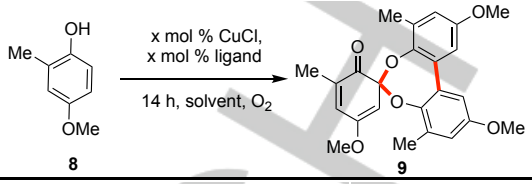


Scheme 2: Precedents for oxidative trimer cyclization.

In the course of examining catalytic C-C[10,11,12,13,14,15,16,17] vs C-O[18] phenol dimerization using our oxidative catalyst library,[14] copper complexes were identified as potential candidates for C-O coupling. However, mixed selectivity was observed including spiroketal trimer **9**, which had not been observed previously. Generally speaking there is wide precedent for C-C oxidative dimerizations of phenols with copper systems.[19,20] There are, however few examples of oxidative couplings which give controlled selectivity for both C-C and C-O coupled products.[19,20,21,22,23] In polymerization of 1-naphthol, the relative amount of C-O vs C-C coupling with a Cu (I) pyridine system heavily depends on the number of pyridine ligand equivalents.[24] In 2014 and 2016, the Lumb group elegantly showed that the formation of *ortho*-quinones from *para*-substituted phenols proceeds well with an aerobic copper (I) system with nitrogen ligands.[18, 25] In 2015, the Lumb and Ottenwaelder group elaborated on this finding by describing the mechanism of Cu (I) promoted selective oxygenation of 4-*tert*-butylphenol.[26] In 2014, this group also presented that copper salt choice, as well as ligand can alter the ratios of C-C oxidative coupling versus *ortho*-quinone oxygenation products.[19a]

Reasoning that an *ortho*-quinone might be an intermediate en route to *ortho*-quinone/bisphenol dimer spiroketal **9**, further copper catalyst conditions were screened with the goal of identifying conditions that would allow catalytic oxidative C-C coupling as well as oxygenation to the *ortho*-quinone. It was further postulated that the copper(II) species formed under oxygen could also act as a Lewis acid catalyst to permit the spiroketalization. A brief screen (Table 1, entires 1-11) showed that toluene was the optimum solvent with high pyridine concentrations relative to copper being necessary (entry 6). A series of control experiments (entries 12-14) verified that the copper ligand system was indeed acting catalytically, and both the ligand and the copper were necessary for any conversion to occur.

Table 1. Optimization of reaction conditions and control reactions



#	Solvent (M)	Ligand (mol%)	CuCl (mol%)	Yield[a]
1	toluene (0.05M)	*t*-BuNH$_2$ (20)	2	0%
2	toluene (0.05M)	pyridine (200)	20	(57%)
3	THF (0.05 M)	pyridine (20)	2	0%
4	EtOAc (0.05 M)	pyridine (20)	2	(40%)
5	CH_2Cl_2 (0.05 M)	pyridine (20)	2	(26%)
6	toluene (0.5M)	pyridine (20)	2	(63%)
7	toluene (0.05 M)	pyridine (20)	2	(39%)[b]
8	toluene (0.05M)	pyridine (4)	2	(42%)
9	toluene (0.05M)	pyridine (20)	2	(26%)[c]
10	toluene (0.05M)	pyridine (20)	2	(57%)[d]
11	toluene (0.05M)	pyridine (20)	2	64%
12	toluene (0.05M)	None	2	0
13	toluene (0.05M)	pyridine (20)	0	0
14	toluene (0.05M)	None	0	0

[a] Yields in parantheses determined by NMR spectroscopy using CH_2Br_2 as internal standard. [b] Air used as oxidant. [c] Reaction conducted at 0 °C. [d] Reaction conducted at 60 °C.

A variety of analogous phenols also afford the cyclic trimer under these conditions (Figure 2). Substrates **16-19** with the same *ortho*-alkyl, *para*-alkoxy motif all proceeded well. Even, allyl groups are tolerated under these oxidizing conditions in the case of **19** with a yield of 76%. A *para tert*-butyl group likewise appears sufficient to promote the desired reactivity with **20** giving 22% yield. A sterically unencumbered *ortho*-alkyl group was proposed as necessary for the selectivity, but **21** shows that even a phenyl group is well-tolerated. Having a *para*-aryl substituent is also well-tolerated as in the case of **22** which forms in 84% yield at slightly elevated temperatures (40 °C). Other bulky *para*-alkyl groups are tolerated but give low yields (c.f. **20**, **22-25**). On the other hand, 2,4-dimethylphenol, 2-methyl-4-isopropylphenol, 2-methyl-4-chlorophenol, and 2-methyl-4-dimethylaminophenol resulted in decomposition.

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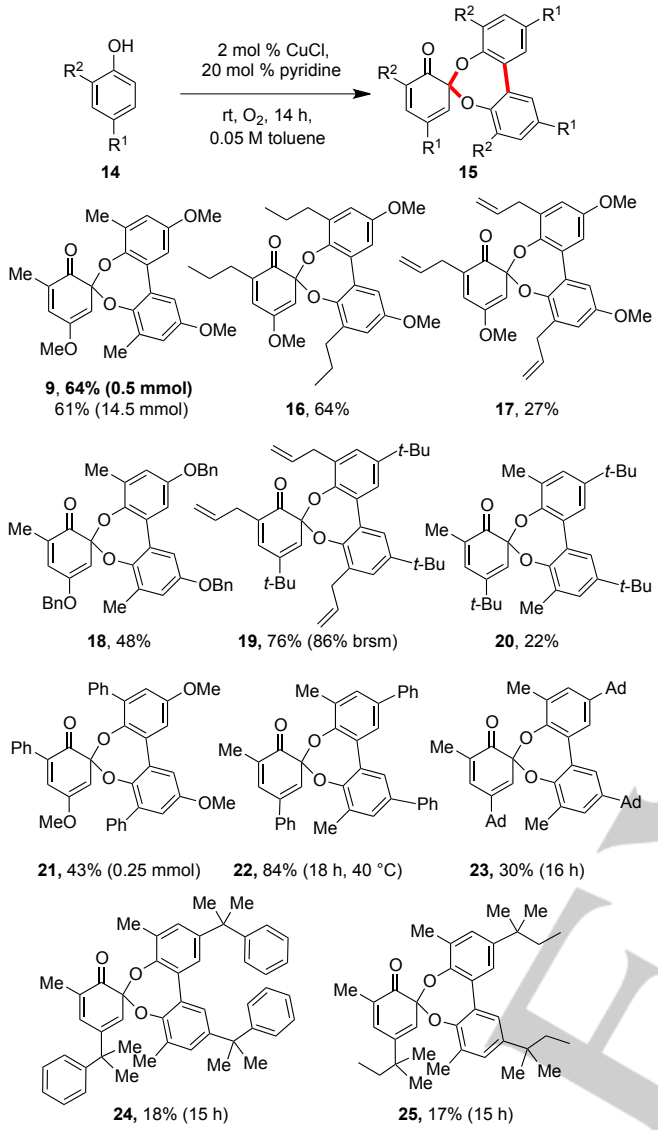
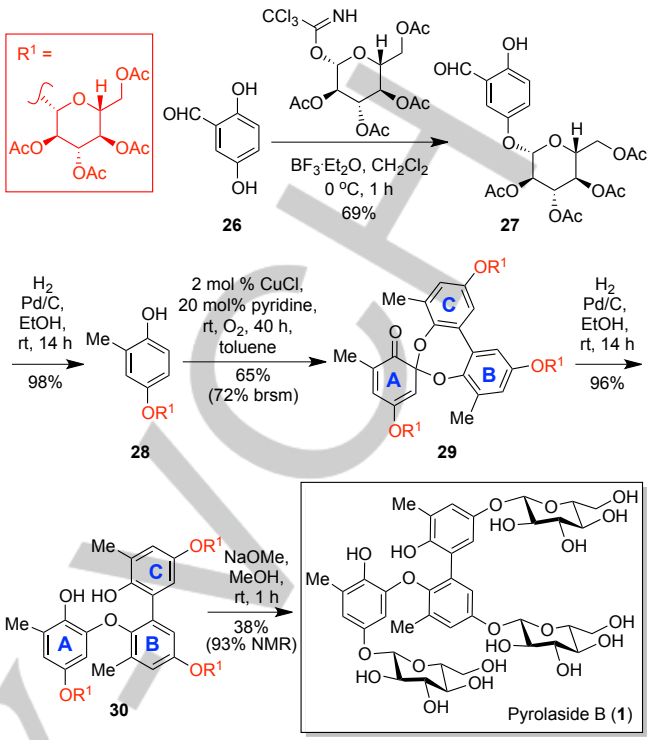


Figure 2: Scope of phenol trimerization (Ad = adamantyl).

To implement this method in a synthesis of pyraloside B, commercially available phenol **26** was glycosylated in good yield (Scheme 3). The glycosylated monomer was then hydrogenated to **28** using Pd/C in 98% yield without the need for purification. With monomeric phenol **28** in hand, an oxidation using our aerobic copper (I) pyridine system was explored. To our delight, cyclic trimer **29** was generated in 65% with some starting material remaining.



Scheme 3: Route to synthetic pyrolaside B.

Deconvolution of quinone-like intermediate **29** to the acyclic trimer precursor to pyrolaside B **30** occurred in near quantitative yield via hydrogenation with Pd/C. Notably, the spiroketal underwent scission under these conditions while the anomeric ketal linkage remained intact. Removal of the acetate protecting groups was performed with NaOMe resulting in an efficient reaction (93% yield, ~95% purity; see ^{1}H NMR in SI). Preparatory HPLC was needed to remove trace aromatic impurities, but led to poor mass recovery (38% isolated yield). All spectra matched the spectra for the reported natural product (see SI). Thus, pyrolaside B was synthesized in 16% yield over 5 steps.

In order to afford the α-anomer of a pyrolaside B analogue monomer, longer glycosylation conditions, a greater amount of Lewis acid, and a less electrophilic glucose donor were used to drive the reaction to the thermodynamic product (Scheme 4). Reduction of the *ortho*-aldehyde **31** via hydrogenation using Pd/C gave the alkane in 98% yield without purification. The oxidative trimerization of the *cis*-glycosylated substrate **32** similarly formed **33**.

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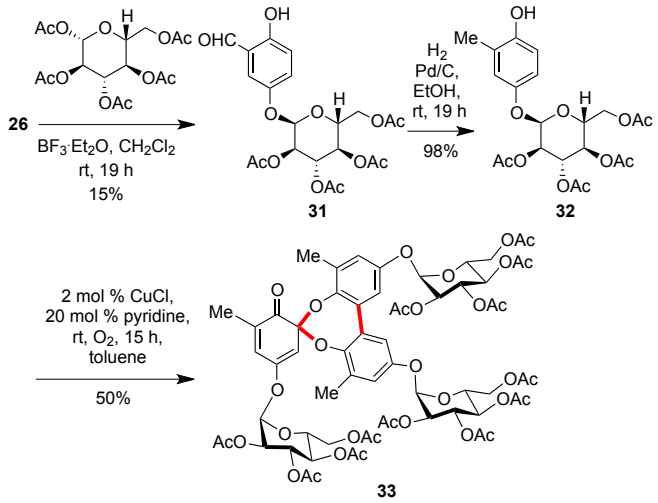
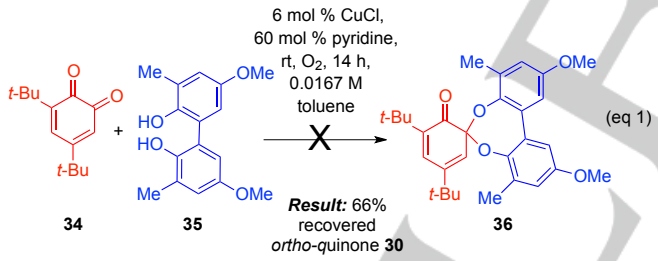
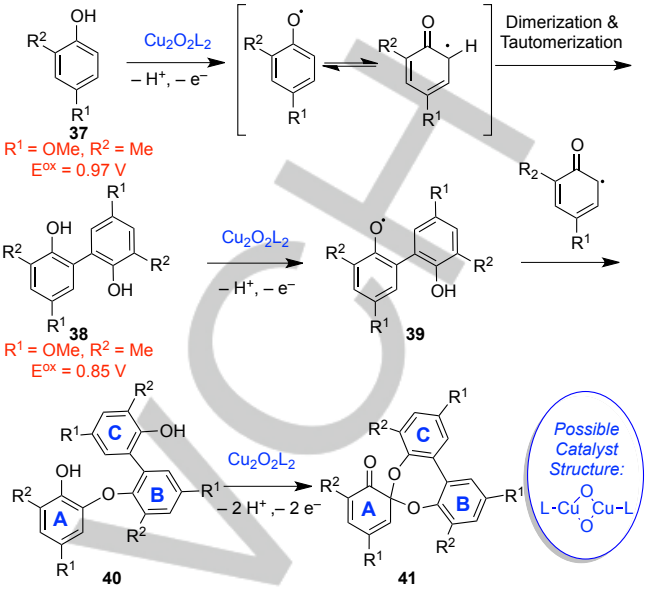


Scheme 4: Synthesis of tris-α-glucosyl epimer of pyrolaside B.

With this success, we interrogated the initially proposed mechanism involving formation of *ortho*-quinone and C-C coupled dimer intermediates that subsequently spiroketalize. Monitoring of reactions revealed that the C-C dimer did form initially and was then converted to product. To probe the mechanism, the reaction in eq 1 was attempted. However, no condensation product was observed and the majority of the *ortho*-quinone was recovered, while the C-C homodimer decomposed. Previous work on *ortho*-quinones also shows that typically the 4-position is more reactive to nucleophiles.[18] Altogether, these results point away from an *ortho*-quinone intermediate.

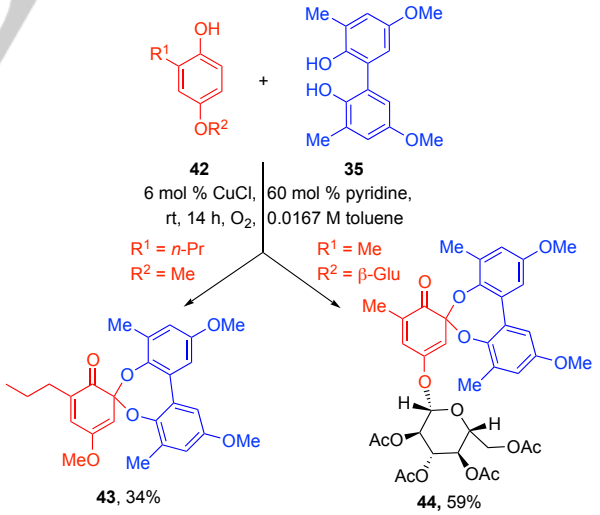


It was then hypothesized that cross C-O coupling of the phenol and C-C coupled dimer lead to product (Scheme 5). The monomeric phenol is first oxidized to C-C dimer **38** via a copper (II) pyridine complex formed in situ.[19a] Previous work in phenol oxidation would suggest that this homodimerization most likely goes through a one electron pathway in which two identical radicals recombine to allow for maximum SOMO orbital overlap.[16d] Once the dimer is formed it is more oxidizable giving rise to **39** which has no open positions for C-C coupling; instead, coupling occurs from the oxygen of the bisphenol with a carbon of the phenol monomer. The measured oxidation potentials (vs ferrocene in MeCN) of the monomer (0.97 V) and dimer (0.85 V) (see SI for details) support this sequence. A final oxidation then could occur at the more electron rich A-ring of **40** to form the cyclic trimer. Support for this last step comes from precedent with the acyclic trimer of 2,4-diphenylphenol being converted to the corresponding cyclized trimer with MnO_2 in 92% yield.[6]



Scheme 5: Proposed mechanism for trimerization.

From this mechanism, cross-couplings of dimer intermediate **38** with different phenols should be possible. Reaction pairs were selected where the corresponding phenol constituents had similar oxidation potentials such that dimer **35** would remain more oxidizable than monomer **42** (Scheme 6). In doing so, products **43** and **44** were afforded with similar efficiency as homotrimerization. In line with the reasoning above, no homotrimers were observed in the reaction mixture.



Scheme 6: Formation of mixed trimers.

With these new products in hand, formation of the linear trimers was examined (Figure 3). With the same reductive conditions, linear trimers **47, 48** and **49** were obtained in good yields. Importantly, selective installation of a glucose group is

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feasible providing an entry to a large number of selectively substituted trisphenol C-O/C-C linked compounds.

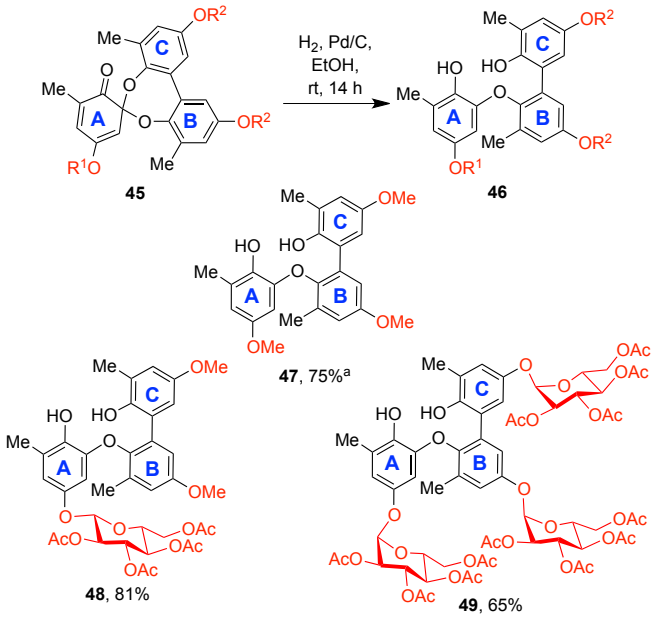
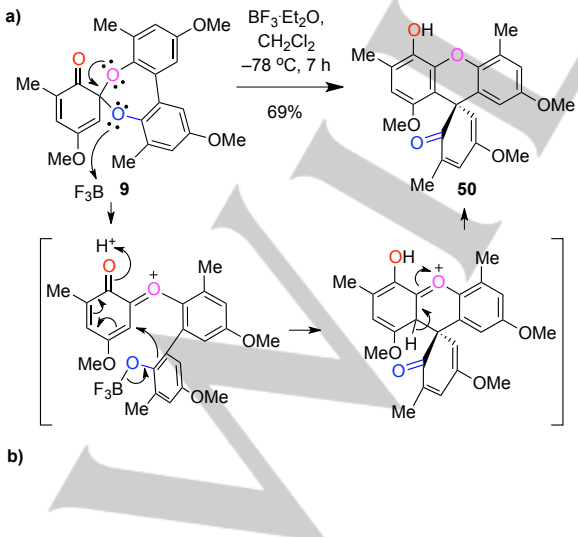


Figure 3: Scope of phenol trimer reduction. [a]Reaction time was 16 h.

It was postulated that the inherit instability of a 7-membered ring containing four sp^2 carbons facilitated the reductive openings in Figure 3. In a similar vein, these same driving forces were harnessed in a redox neutral rearrangement. With a mild Lewis acid ($BF_3{\cdot}Et_2O$) under mild conditions (–78 °C), a bright yellow compound, tetracyclic xanthene **50**,[27] was formed in 69% yield (Figure 4a). With the limited number of hydrogens to probe structure by ^1H NMR spectroscopy, the structure of **50** was secured by single crystal X-ray analysis (Figure 4b). At higher temperatures, this process was not nearly as selective leading to the possibility of a variety of other rearrangements that could be performed using cyclic phenol trimers.



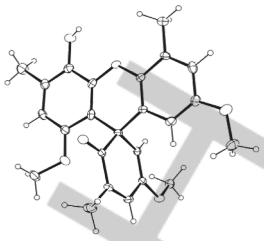


Figure 4: a) Rearrangement to xanthene. b) X-ray structure of **50**.

In summary, a process for a catalytic coupling of phenols to afford trimeric spiroketal adducts has been described using a base metal catalyst and environmentally benign oxygen as the terminal oxidant. Mechanism studies reveal that the dioxepine adducts arise from a controlled sequence of three two electron oxidations involving C-C, C-O, and C-O coupling. The relative reactivity of dimerization vs trimerization is controlled by the slightly higher susceptibility of the intermediate dimer toward oxidation. Undoubtedly, such oxidation events occur in a number of other reported dimerizations. [10-17] In most cases, the oxidation would be readily reversible allowing the dimer to accumulated. In other cases, such oxidation gives rise to decomposition. A hallmark of this case is the ability of the oxidized dimer to engage in selective C-O bond formation with an additional monomer. This method allowed the expeditious assembly of the natural product pyrolaside B over 5 steps. This first total synthesis of pyrolaside B overcomes the challenges associated with conventional approaches that involve multiple functionalizations to allow Ullmann- and Suzuki-type couplings and selective O-glycosylation of some phenols in the presence of others.[28] The oxidative coupling protocol tolerates incorporation of the glucose linkage into the monomer allowing construction of the overall architecture in a single assembly step that unites three monomers. The resultant spiroketal trimers can be reduced to the linear C-C/C-O linked timers or rearranged to a xanthene scaffold.

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Conflicts of interest

The authors declare no conflicts of interest

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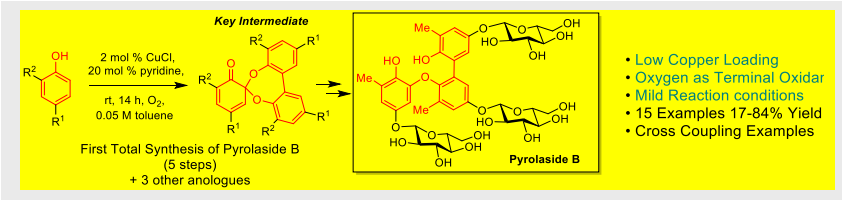

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Title

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A facile method to oxidatively trimerize phenols using a low loading catalytic aerobic copper system is described. The natural product pyrolaside B has been synthesized for the first time using this method, which allows an expeditious entry in five steps and 16% overall yield. Two analogues were also synthesized.