Multigram Scale Total Synthesis of Piperarborenines C-E

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Abstract: We report the development of a multigram scale total synthesis of heterodimeric β-truxinic imides piperarborenines C-E using a catechol-mediated diastereoselective intramolecular [2+2] photocycloaddition. Key innovations lie in the use of (1) catechol as a highly selective auxiliary for the robust and scalable synthesis of homo- and heterodimeric β-truxinates, (2) UV LEDs for direct excitation in the [2+2] cycloaddition step, and (3) a bis pentafluorophenyl ester and LDA for the challenging installation of the *syn* dihydropyridinone imides. This approach is exceptionally scalable – requiring minimal chromatography, no photocatalysts, and no cryogenic conditions - and will enable thorough evaluation of the biological properties and anticancer profiles of piperaborenines C-E and derivatives thereof.

Piperarborenines A-E are cinnamic imide photo-dimers isolated from *Piper arborescens*,[1] and are among the most active anticancer constituents known from the genus, with *in vitro* activities of C-E (**1**-**3**) ranging from 0.02-0.35 μM (IC_{50}) against several cell lines.[1,2] Piperlongumine (piplartine) – the [2+2] precursor of piplartine dimer A[3] – and related derivatives have been the subject of extensive study in selective inhibition of cancer cells and suppression of tumor growth,[4] re-sensitization of drug-resistant cancer strains,[5] and other desirable effects.[6] The collective body of literature has demonstrated piperlongumine as a strong candidate for cancer treatment,[7] and the potential link between the activity of piperlongumine and its β-truxinic dimer point to the β piperarborenines (**1**-**3**) as possible anticancer leads with improved potency.[8]

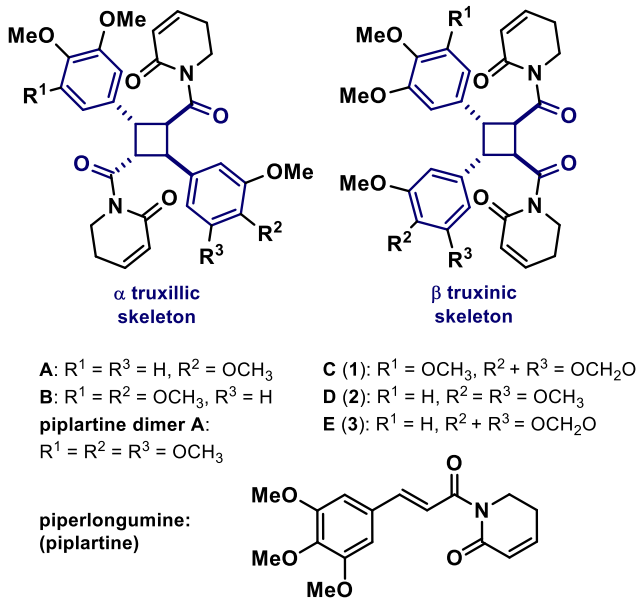


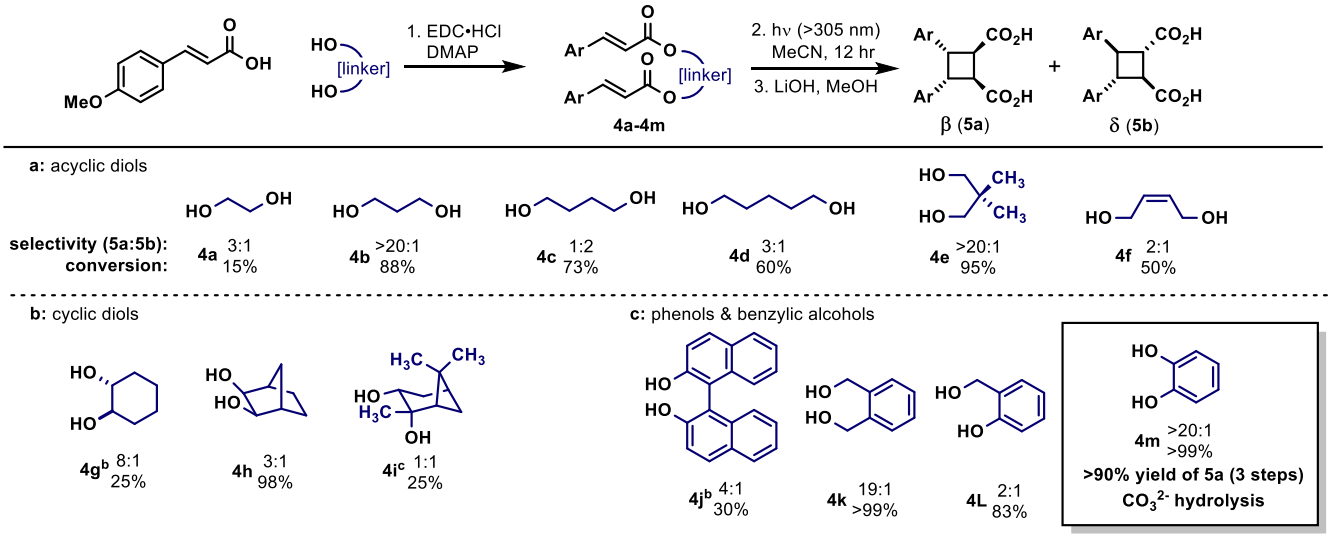
Figure 1. Piperarborenines A-E, piplartine dimer A, and piperlongumine.

This work describes our development of a robust and highly scalable strategy for accessing these most potent β-truxinic congeners of the piperarborenine family. In addition to the piperarborenines, the dense structures and promising biological activities of other cyclobutane natural products have prompted considerable development in the construction of such scaffolds.[9] In 2011, the C-H functionalization driven total synthesis of piperarborenines B and D by Baran & Gutekunst[10] led to the structural reassignment of **1**-**3** as the β-truxinic[11] imides, and in 2016 the groups of Tang & Xie[12] and Fox[13] each reported total syntheses of piperarborenine B; these efforts led to notable innovations in asymmetric cyclobutane synthesis. Recently, a landmark work from Hu & Su reported a caged ruthenium(II) photocatalyst capable of highly-selective photodimerization of cinnamates and chalcones at low (<1 mol%) catalyst loadings.[14] In the interest of scalability and utility in the synthesis of **1**-**3**, we focused our efforts on developing a diastereoselective [2+2] photocycloaddition which required no photocatalysts, could be carried out in continuous flow, and relied minimally on chromatographic purifications.

In previous studies, our lab and others have demonstrated that intermolecular photodimerization of cinnamic esters strongly favors the δ-diastereomer.[15] Conversely, geometric confinement of cinnamates generally disfavors the δ-diastereomer, thus favoring the β-diastereomer.[16] Covalent,[16a-f] non-covalent,[16g-h] and solid-state[17] strategies for selective [2+2] photocycloaddition of cinnamates and other alkenes have been covered in depth,[18] and a wealth of auxiliaries or “templates” have been used to synthesize cyclobutanes with varied performance. In pursuit of a more practical method amenable to efficient synthesis of homo- and heterodimeric

β-truxinate natural products, we sought an improved carboxylate linker which was (1) highly selective, (2) inexpensive, (3) operable in solution-phase, and (4) easily installed and removed in high yields. To this end, we screened commercially available alcohols and phenols in the following manner (Scheme 1): *p*-methoxycinnamic acid was coupled to the diol using EDC•HCl and DMAP. The diester was then irradiated for 12 hours using a metal halide UV lamp, the percent conversion was determined by consumption of diester **4**, and the β:δ ratio (**5a**:**5b**) was determined by ^{1}H-NMR after hydrolysis with LiOH•H_2O in MeOH. Among a set of acyclic diols (Scheme 1a), three-carbon glycols 1,3-propanediol and neopentane glycol showed optimal conversion (88-95%) and selectivity (>20:1 d.r.).[19] Next, a small group of cyclic diols were tested, all of which showed poor to modest selectivity and/or conversion (Scheme 1b). Lastly, from a handful of phenols and benzylic alcohols, both catechol[20] and phthalol[21] provided high conversion and β-selectivity (Scheme 1c). Of the promising auxiliaries, catechol was chosen due to its low cost, high selectivity (>20:1 d.r.) and reaction rate, mild hydrolysis with carbonate bases, and good overall yield of **5a** across three steps (>90%).

Scheme 1. Evaluation of Diol Auxiliaries.[a]



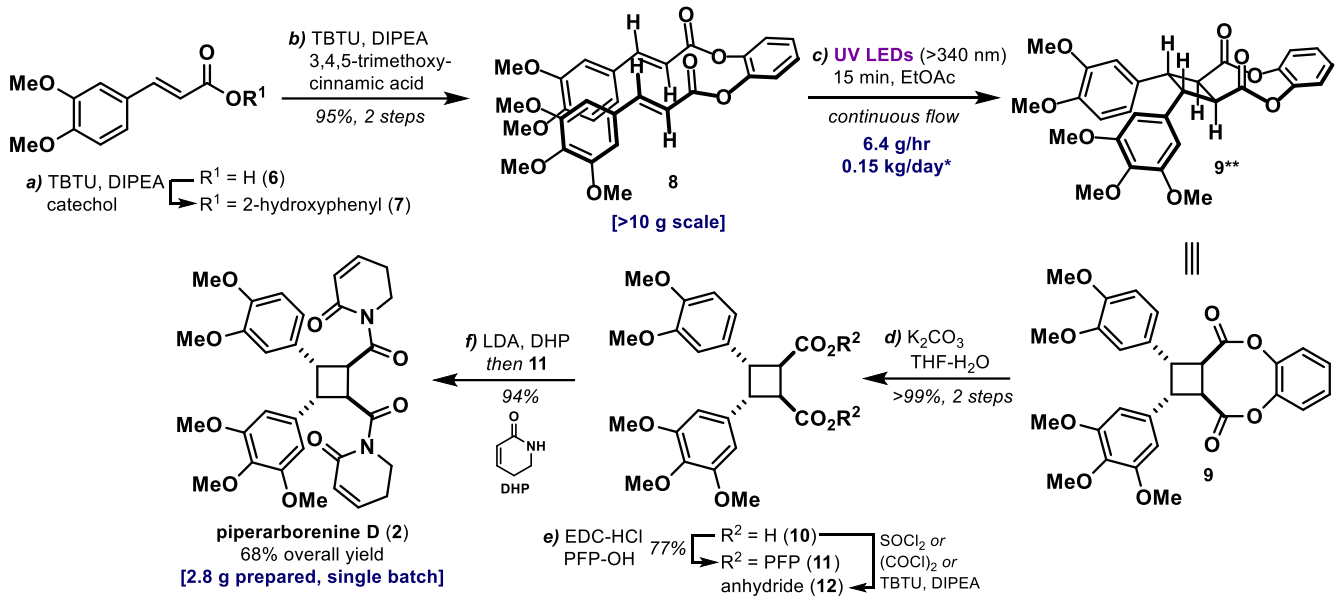
[a] Experimental details for auxiliary trials are in the Supporting Information. Compound numbers (**4a**-**4m**) denote the corresponding bis-*p*-methoxycinnamate esters for each auxiliary. Ar = *p*-methoxyphenyl [b] racemic [c] (+)-α-pinanediol.

Given its prior synthesis and the availability of cinnamic acid precursors, we first assessed the utility of the catechol auxiliary in the synthesis of piperarborenine D (**2**) (Scheme 2). The forward synthesis began with two-step sequential esterification using 3,4-dimethoxy- and 3,4,5-trimethoxycinnamic acids, and coupling reagent 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate (TBTU). Formation of monoester **7** from **6** was promoted

by use of excess (5 eq.) of catechol, which was readily removed in extractive workup. Use of close stoichiometric control of 3,4,5-trimethoxycinnamic acid and TBTU (1.00 eq. each) cleanly formed **8** in high yield (95%, 2 steps), which was quickly stockpiled in decagram quantities. The UV-Vis spectrum of **8** showed a red-shifted λ_{max}, greater extinction coefficient, and peak broadening compared to **4m**, which introduced the possibility of using UV LEDs in the photocycloaddition, rather than traditional metal halide lamps whose excessive heat can be difficult to manage. Based on this observation, we built a 140W 365 nm LED array which was used in a homemade large-capacity (53 ml) flow photoreactor. Under optimized conditions in the [2+2] photocycloaddition (0.05 M EtOAc, 15 min), we achieved 6.4 g per hr rates of production of **9** in steady-state continuous flow, with projected productivity of 0.15 kg per day. From a small screen of conditions, we found that hydrolysis of **9** was efficiently carried out using K_2CO_3 under biphasic conditions (THF-H_2O). By this method, we obtained 3 g of β-truxinic acid **10** in a single pass, with >99% mass recovery over two steps from **8**.

The final steps towards **2** involved installation of the dihydropyridinone imides. On review of the literature, we found the synthesis of mixed acyclic imides of the type in **1**-**3** to be somewhat sparse; the most common route is amide addition to an acyl chloride,[22] although other methods have seen recent development.[23] The most straightforward approach to **2** proved problematic, as attempts to form a bis acyl chloride from **10** resulted in formation of cyclic anhydride (**12**) using thionyl chloride, and oxalyl chloride with catalytic DMF.[24] Similarly, attempts to synthesize a bis-HOBt (1-hyroxybenzotriazole) ester using TBTU and DIPEA resulted in anhydride (**12**) formation exclusively. The unique challenge of synthesizing activated esters on *syn* dicarboxylic acid **10** prompted further review of the mixed imide literature, where we found that 2,3,4,5,6-pentafluorophenyl (PFP) esters react cleanly with *N*-metallated amides to provide mixed imides.[25] Fortunately, synthesis of bis-PFP ester **11** proceeded without issue under standard conditions using EDC•HCl. At this stage, a single chromatographic purification removed polar impurities which were carried through from the [2+2] and hydrolysis, giving 4 g of **11** (77%). With **11** in hand, we tested conditions to achieve double imidation and complete the synthesis of **2**. Trials at 0-5 °C revealed that direct deprotonation of 5,6-dihydropyridin-2(1*H*)-one (DHP) with *n*BuLi leads to uncontrolled reactivity. Alternatively, using lithium diisopropylamide (LDA) generated *in situ* as the base, double addition of Li-DHP to bis-PFP ester **11** was achieved in high yield (94%), providing 2.8 g of piperarborenine D (**2**) in 68% overall yield in a single batch.

Scheme 2. Synthesis of Piperarborenine D.[a]

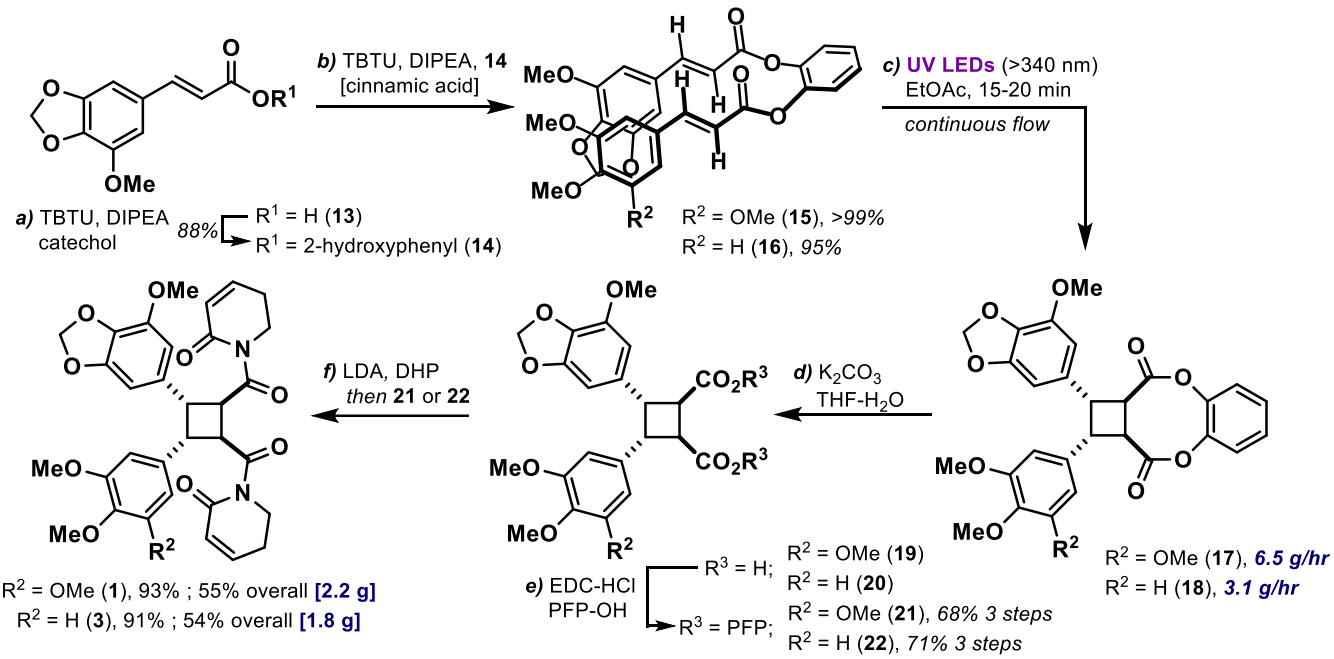


[a] Reagents and conditions: (a) TBTU (1.0 eq.), DIPEA (5 eq.), 1:1 DCM:MeCN (0.1 M), 20 °C, 30 min, then catechol (5 eq.), 15 min, 96%; (b) 3,4,5-trimethoxycinnamic acid (1.00 eq.), DIPEA (5 eq.), TBTU (1.00 eq.), 1:1 DCM:MeCN (0.1 M), 20 °C, 30 min then **7**, 3 hour, >99%; (c-d) 365 nm LEDs, EtOAc (0.05 M), 20-25 °C, 15 min in flow, then; K_2CO_3 (10 eq.), 60 °C, 2 hr, THF:H_2O (0.1M THF), >99% 2 steps (e) EDC•HCl (3 eq.), PFP-OH (3 eq.), DCM (0.1 M), 20 °C, 3-6 hr, 77%; (f) LDA (2.05 eq.), DHP (2.05 eq.), 0-5 °C (0.05 M THF), then **11**, 94%. * Projected rate ** Single enantiomer of **9** shown for clarity. Abbreviations: TBTU = 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium tetrafluoroborate, PFP = 2,3,4,5,6-pentafluorophenyl, DHP = 5,6-dihydropyridin-2(1*H*)-one.

The synthesis of piperarborenines C and E (**1** and **3**) differed from **2** only in the preparation of the intermediate catechol monoester **14**, which was made from myristicin-derived (7-methoxy-1,3-benzodioxol-5-)yl cinnamic acid **13** using the prior TBTU coupling conditions in 88% yield (Scheme 3). While **13** is commercially available, its high cost and limited availability required its preparation in-house from myristicin aldehyde by Doebner-Knoevenagel condensation. Divergence in the second TBTU coupling using 3,4,5-trimethoxycinnamic acid and 3,4-dimethoxycinnamic acid led to diesters **15** and **16**, respectively, in high yields (95-99%). While full conversion in the subsequent [2+2] photocycloaddition was achieved in 15 minutes at 0.05 M for **15** and **8**, diester **16** required a 20 min residence time at 0.025 M due to lower reactivity and solubility of the 3,4-dimethoxycinnamate. Under these conditions, **17** and **18** were produced in gram quantities in continuous flow at high g per hr rates. Hydrolysis and PFP esterification provided **21** and **22** with similar efficiency (68-71%, 3 steps) to **11**. As with conversion of **11** to **2**, a single chromatographic purification of **21** and **22** was sufficient to ensure high purity of the piperarborenine products. Double imidation of **21** and **22** using LDA and DHP provided

piperarborenines C (**1**) and E (**3**) in 93% and 91% yield, with overall yields of 55% and 54% from **13**, respectively.

Scheme 3. Synthesis of Piperarborenines C and E.[a]



[a] Reagents and conditions: (a) TBTU (1.0 eq.), DIPEA (5 eq.), 30 min, then catechol (5 eq.), 15 min, 1:1 DCM:MeCN (0.2 M), 20 °C, 88%; (b) TBTU (1.00 eq.), DIPEA (5 eq.), 30 min, then [cinnamic acid] (1.00 eq.), 3 hour, 95-99%; (c-d) 365 nm LEDs, EtOAc (0.025-0.050 M), 20-25 °C, 15-20 min in flow, then; K_2CO_3 (10 eq.), 60 °C, THF:H_2O, 2-3 hr, >99% 2 steps (**19** and **20**); (e) EDC•HCl (3 eq.), PFP-OH (3 eq.), DCM (0.1M), 20 °C 18 hour, 78% (**21**), 85% (**22**); (f) LDA (2.05 eq.), DHP (2.05 eq.), 0-5 °C (0.05 M THF), then **21** or **22**, 93% (**1**), 91% (**3**).

In summary, we have developed a highly practical and diastereoselective intramolecular [2+2] photocycloaddition for the synthesis of homo- and heterodimeric β-truxinates using catechol as an auxiliary. This approach was applied expediently to the 6-step total synthesis of anticancer leads piperarborenines C, D, and E on multigram scale; access to such quantities will enable thorough evaluation of their biological activity. Should larger amounts of **1**-**3** or a related derivative be required, we imagine this route could be scaled quite readily. An investigation of the anticancer properties of **1**-**3** is underway in our group, and a thorough analysis of the scope, limitations, and applications of the catechol-mediated cyclobutane synthesis is forthcoming.

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