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Liebeskind–Srogl cross coupling mediated synthesis of verbenachalcone ☆

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ABSTRACT

A flexible and scalable total synthesis of verbenachalcone is achieved in eight linear steps from cheap commercially available starting material, 3-(4-hydroxyphenyl)propanoic acid.

The biaryl ether subunits are prevalent in a variety of medicinally important natural products such as verbenachalcone (**1**),[2] littorachalcone (**2**),[3] combretastatin (**3**, antifungal),[4] and ricccardin C (**4**, cytotoxin),[5] as well as in purely synthetic bioactive compounds, such as triclosan (**5**, antibacterial and antifungal),[6] RH6201 (**6**, herbicidal)[7], and LY293111 (**7**, LTB_4 receptor antagonist).[8] The 2-hydroxydiphenyl ether functionality is the core unit in the majority of these bioactive compounds.

The two novel dimeric dihydrochalcones, **1** and **2** were isolated from the aerial parts of *Verbena littoralis* (Verbenaceae) by Li et al., and are known to act as enhancers of nerve growth factor (NGF)-mediated neurite outgrowth and axonal branching in PC12D cells.[2,3] Recently, both natural products and a few verbenachalcone analogs have been synthesized.[9,10] The first total synthesis of **1** was reported by Cuny and co-workers[9a] using an Ullmann ether coupling reaction as a key step for constructing the biaryl ether core. Subsequently, Tanabe et al. have achieved the syntheses of **1** by employing anodic oxidation of the mixed-halogenated phenol derivative.[9c] Kraus et al. have reported a synthetic route to **2** by the desymmetrization of the commercially available *para*-tolyl ether.[10]

As part of our research interests in developing novel therapies for treating neurological diseases, we have actively been involved in identifying and preparing small molecules, such as verbenachalcone that can enhance the activity of NGF, assist in elucidating the patho-physiological role of neurotrophins, and provide lead compounds for therapeutic development.[11] Currently, we have focused on developing a more flexible and scalable synthetic strategy for **1**, which could easily be amenable for making numerous derivatives for expanding the SAR studies of verbenachalcone NGF-potentiating efficacies. For this endeavor, we have chosen the classical Ullmann ether synthesis[12] and Liebeskind–Srogl cross coupling reactions[13] as two key transformations. Herein, we describe a facile and scalable total synthesis of verbenachalcone (**1**).

Our retrosynthetic strategy of **1** depicted in Scheme 1 relied on a copper-mediated palladium-catalyzed Liebeskind–Srogl cross coupling reaction of dithioester derivative **8** and 2,4-bis(methoxymethoxy)phenylboronic acid (**9**) under neutral conditions. In our attempts to synthesize a series of verbenachalcone derivatives,[1,11] initial use of Cuny and co-workers' approach toward removing the benzyl-protecting group in the final step proved to be problematic due to inconsistent yields that were caused by the complete reduction of the vital ketone functionality. In order to overcome this hurdle, we chose an acid labile MOM group for protecting the phenol.

Accordingly, our synthesis commenced from commercially available 3-(4-hydroxyphenyl)propanoic acid (**10**) by first converting to the corresponding ethyl ester after esterification with EtOH in the presence of a catalytic amount of H_2SO_4 and *ortho*-bromination of the phenol with bromine in acetic acid to give **11**.[9a,b,14] Treatment of **11** with MOMCl and DIPEA produced MOM-protected compound **12**. The other coupling partner, ethyl 3-(4-hydroxy-3-methoxyphenyl)propanoate (**14**) was prepared from ferulic acid (**13**) in two steps. Palladium-catalyzed hydrogenation of **13**,[15] and the subsequent transformation of carboxylic acid to ethyl ester furnished **14** in excellent yield (Scheme 2).

With the appropriate precursors in hand, we next carried out the Ullmann ether coupling reaction of **12** and **14** with different copper catalysts, such as $(CuOTf)_2PhMe$, CuOAc, and CuI using a mild base Cs_2CO_3 in boiling pyridine. Anticipating better yields,

☆ See Ref. 1.

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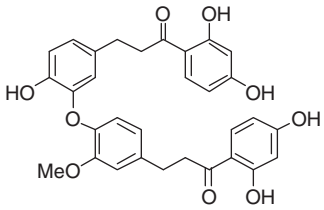
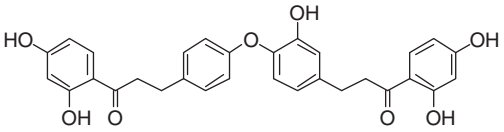
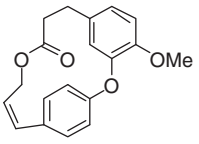


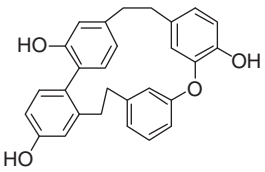
Verbenachalcone (1)



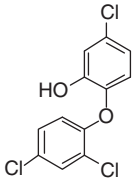
Littorachalcone (2)



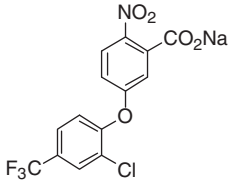
Combretastatin D-2 (3)



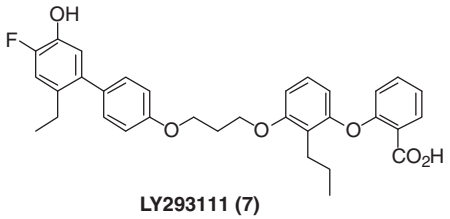
Riccardin (4)



Triclosan (5)



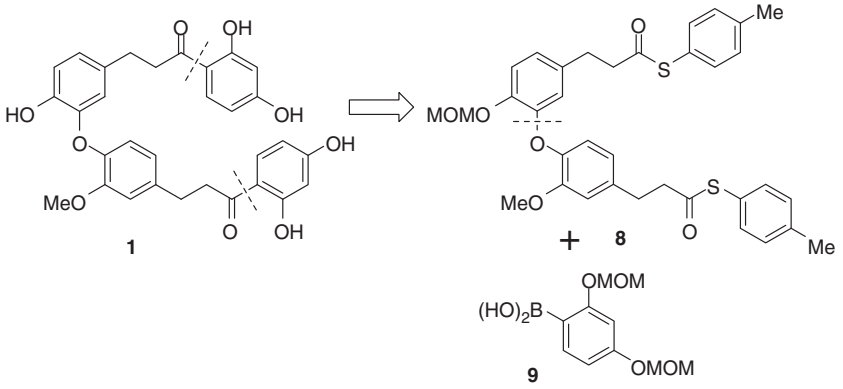
RH6201 (6)



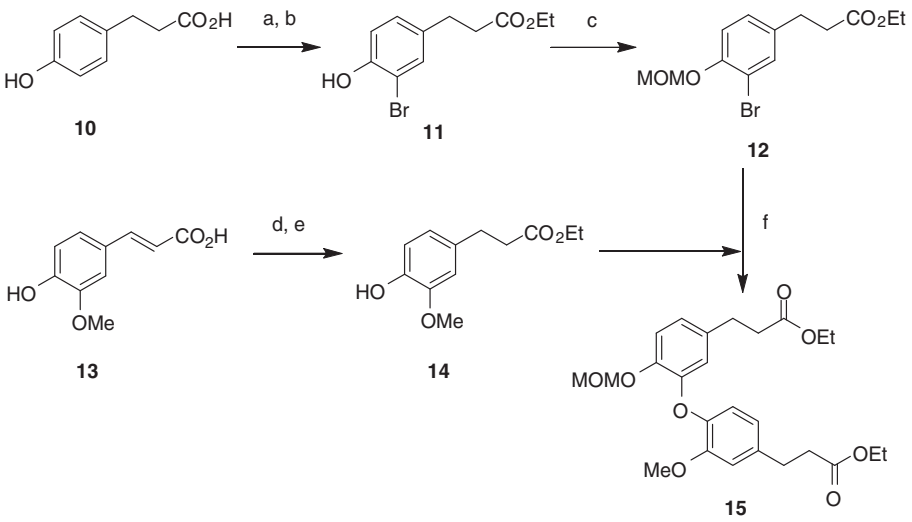
LY293111 (7)

we also used 2-picolinic acid as an additive with the above-mentioned copper catalysts.[16] 2-Picolinic acid assisted in reducing the reaction times but failed to improve the yields of biaryl ether **15**. Eventually, we found that the $(CuOTf)_2PhMe$ was the better catalyst system for the synthesis of biaryl ether **15**.[9a]

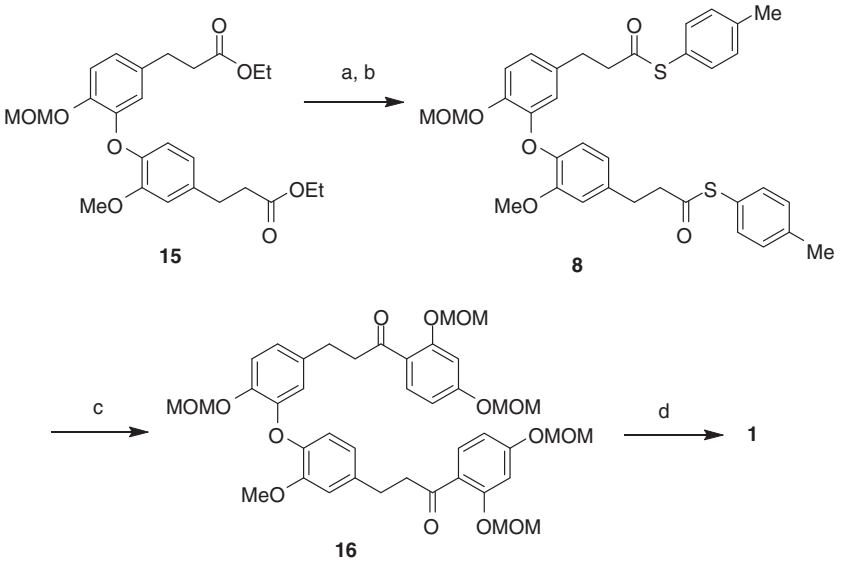
Having synthesized biaryl ether **15**, we next focused our attention on exploring the Liebeskind–Srogl cross coupling reaction for the introduction of the terminal resorcinol units. Thus, **15** was subjected to saponification using 2 M aqueous NaOH solution in a solvent mixture of THF and MeOH to obtain the diacid derivative,[17] which was further reacted with *p*-toluenethiol in the presence of a coupling reagent, *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluroniumhexafluorophosphate (HBTU) and DIPEA in CH_2Cl_2 to furnish dithioester derivative **8**.[18]



Scheme 1. Retrosynthetic strategy.



Scheme 2. Reagents and conditions: (a) EtOH, H_2SO_4 (cat.), rt, 4 h, 99%; (b) Br_2, AcOH, rt, 1 h, 86%; (c) MOMCl, DIPEA, CH_2Cl_2, 0 °C–rt, 4 h, 99%; (d) 10% Pd/C, H_2, MeOH, rt, 24 h, 99%; (e) EtOH, H_2SO_4 (cat.), 0 °C–rt, 12 h, 96%; (f) $(CuOTf)_2PhMe$ (10 mol %), Cs_2CO_3, py, 110 °C, 48 h, 62% (BRSM).



Scheme 3. Reagents and conditions: (a) 2 N NaOH, THF/MeOH (2:1), 6 h, rt; (b) *p*-toluenethiol, HBTU, DIPEA, CH_2Cl_2, rt, 48 h, 77% (2 steps); (c) **9** (3 equiv), CuTC (3 equiv), $Pd(PPh_3)_4$ (2 mol %), THF, 60 °C, 1 h, 73%; (d) *p*-TSA, MeOH, 50 °C, 3 h, 96%.

Then, **8** was subjected to Liebeskind–Srogl cross coupling reaction using boronic acid **9**,[19] copper(I)thiophene-2-carboxylate (CuTC),[20] and $Pd(PPh_3)_4$ in anhydrous THF to obtain **16**,[9c] in 73% yield. Other attempted catalyst/ligand systems, $Pd_2dba_3{\cdot}CHCl_3$/PPh_3 and $Pd(OAc)_2$/dppf gave **16** in 67% and 61% yields, respectively. Finally, the acidic hydrolysis of **16** with *p*-TSA in MeOH at 50 °C afforded the natural product **1** in excellent yield (Scheme 3). The spectral data of the synthetic product was identical in all respects to the reported data of natural product.

In conclusion, a flexible and scalable synthetic route to verbenachalcone has been developed in eight linear steps from 3-(4-hydroxyphenyl)propanoic acid in 28% overall yield.[21] The copper-mediated palladium-catalyzed Liebeskind–Srogl cross coupling reaction was successfully applied for introducing the aryl ketone moieties. Our method is practically more suitable for incorporating diverse terminal aryl groups with numerous readily available boronic acids and can be carried on a gram scale. Its application for generating various verbenachalcone derivatives together with their biological activities will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data (copies of ^1H and ^{13}C NMR spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.073.

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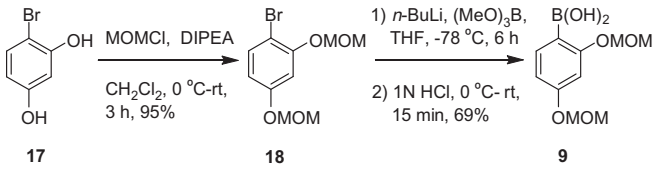

21. *Spectroscopic data of the selected compounds*: *ethyl 3-(4-(5-(3-ethoxy-3-oxopropyl)-2-(methoxymethoxy)phenoxy)-3-methoxyphenyl) propanoate* (**15**): Colorless syrup. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 1.21 (t, 3H, J = 7.5 Hz), 1.25 (t, 3H, J = 7.5 Hz), 2.51 (t, 2H, J = 7.5 Hz), 2.63 (t, 2H, J = 7.5 Hz), 2.81 (t, 2H, J = 7.5 Hz), 2.93 (t, 2H, J = 7.5 Hz), 3.45 (s, 3H), 3.83 (s, 3H), 4.08 (q, 2H, J = 7.5 Hz), 4.14 (q, 2H, J = 7.5 Hz), 5.17 (s, 2H), 6.65 (d, 1H, J = 2.0 Hz), 6.69 (dd, 1H, J = 2.0, 8.0 Hz), 6.74 (d, 1H, J = 8.0 Hz), 6.82 (d, 1H, J = 2.0 Hz), 6.85 (dd, 1H, J = 2.0, 8.5 Hz), 7.11 (d, 1H, J = 8.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 14.1, 14.2, 30.3, 30.7, 36.0 (2C), 55.9, 56.1, 60.3, 60.4, 95.6, 112.8, 117.8, 118.8, 119.0, 120.3, 123.3, 135.2, 136.5, 144.2, 146.2, 147.1, 150.4, 172.7, 172.8. HRMS (ESI) m/z calcd for $C_{25}H_{32}NaO_8$ $[M+Na]^+$ 483.1995, obsd: 483.1970. *S-p-Tolyl 3-(3-methoxy-4-(2-(methoxymethoxy)-5-(3-oxo-3-(p-tolylthio)propyl)phenoxy)phenyl) propanethioate* (**8**): Colorless syrup. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 2.36 (2s, 6H), 2.82–2.88 (m, 4H), 2.93–3.01 (m, 4H), 3.45 (s, 3H), 3.83 (s, 3H), 5.18 (s, 2H), 6.66 (d, 1H, J = 2.0 Hz), 6.69 (dd, 1H, J = 2.0, 8.0 Hz), 6.76 (d, 1H, J = 8.0 Hz), 6.81 (d, 1H, J = 1.5 Hz), 6.85 (dd, 1H, J = 2.0, 8.5 Hz), 7.12 (d, 1H, J = 8.5 Hz), 7.18–7.27 (m, 8H). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 21.3, 30.6, 31.2, 44.9, 45.1, 55.9, 56.1, 95.5, 112.9, 117.7, 118.8, 119.0, 120.5, 123.4, 124.1, 129.9, 130.0, 134.3, 134.4, 134.5, 135.9, 139.6, 139.7, 144.3, 146.3, 147.1, 150.4, 196.9, 197.1. HRMS (ESI) m/z calcd for $C_{35}H_{36}NaO_6S_2$ $[M+Na]^+$ 639.1851, obsd: 639.1841. *1-(2,4-Bis(methoxymethoxy)phenyl)-3-(4-(5-(3-(2,4-bis(methoxyme-thoxy)phenyl)-3-oxopropyl)-2-(methoxymethoxy) phenoxy)-3-methoxyphenyl)propan-1-one* (**16**): ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 2.88 (t, 2H, J = 7.5 Hz), 3.00 (t, 2H, J = 7.5 Hz), 3.18 (t, 2H, J = 7.5 Hz), 3.30 (t, 2H, J = 7.5 Hz), 3.43 (s, 3H), 3.46 (s, 3H), 3.47 (s, 3H), 3.48 (s, 6H), 3.82 (s, 3H), 5.17 (s, 2H), 5.18 (s, 2H), 5.19 (s, 2H), 5.20 (s, 2H), 5.24 (s, 2H), 6.69–6.75 (m, 6H), 6.80 (d, 1H, J = 2.0 Hz), 6.82 (d, 1H, J = 2.0 Hz), 6.85 (d, 1H, J = 2.0 Hz), 6.88 (dd, 1H, J = 1.5, 3.0 Hz), 7.10 (d, 1H, J = 3.0 Hz), 7.69 (d, 1H, J = 3.5 Hz), 7.74 (d, 1H, J = 3.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 29.9, 30.3, 45.2 (2C), 55.9, 56.1, 56.3, 56.4, 56.5, 94.2, 94.4, 94.6, 95.7, 102.8, 102.9, 108.9, 109.0, 113.0, 117.8, 118.9, 119.0, 120.3, 122.5, 122.6, 123.4, 132.2 (2C), 136.5, 137.7, 144.0, 145.9, 147.1, 150.3, 158.0, 161.6 (2C), 199.6, 199.7. HRMS (ESI) m/z calcd for $C_{41}H_{48}NaO_{14}$ $[M+Na]^+$ 787.2936, obsd: 787.2922. *Verbenachalcone* (**1**): White pluffy solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 2.89 (t, 2H, J = 7.5 Hz), 3.06 (t, 2H, J = 7.5 Hz), 3.12 (t, 2H, J = 7.5 Hz), 3.22 (t, 2H, J = 7.5 Hz), 3.80 (s, 3H), 5.39 (s, 1H, OH), 5.84 (s, 1H, OH), 5.94 (s, 1H, OH), 6.34 (dd, 1H, J = 3.5, 8.5 Hz), 6.35 (dd, 1H, J = 3.0, 8.5 Hz), 6.37 (d, 1H, J = 2.5 Hz), 6.38 (d, 1H, J = 2.5 Hz), 6.57 (d, 1H, J = 2.0 Hz), 6.75 (dd, 1H, J = 2.0, 8.0 Hz), 6.81 (d, 1H, J = 1.5 Hz), 6.83 (dd, 1H, J = 2.0, 8.5 Hz), 6.91 (t, 2H, J = 8.0 Hz), 7.56 (d, 1H, J = 9.0 Hz), 7.59 (d, 1H, J = 9.0 Hz), 12.60 (s, 1H, OH), 12.76 (s, 1H, OH). ^{13}C NMR (125 MHz, $CDCl_3$ + CD_3OD) δ (ppm) 29.7, 30.1, 39.3, 39.4, 55.7, 102.8 (2C), 108.2, 108.3, 112.5, 112.9, 116.4, 118.0, 119.1, 120.7, 123.6, 132.0, 132.6, 137.1, 143.7, 144.2, 145.5, 149.9, 164.7, 203.3, 203.5. HRMS (ESI) m/z calcd for $C_{31}H_{28}O_9$ $[M+H]^+$ 545.1806, obsd: 545.1807.