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Total Synthesis of Neomarchantin A: Key Bond Constructions Performed Using Continuous Flow Methods

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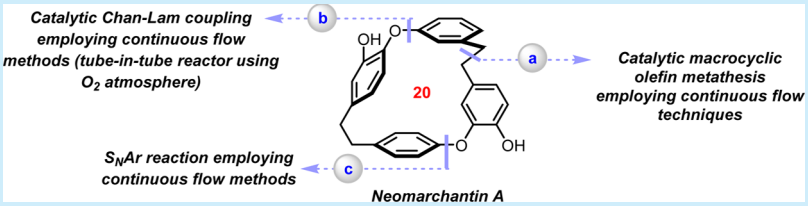
Supporting Information



ABSTRACT: A synthesis of neomarchantin A has been achieved wherein key bond constructions involving C−O or C−C bond formations were augmented via continuous flow techniques. Of note, the synthesis of neomarchantin A represents the first demonstration of catalytic macrocyclic olefin metathesis as a key step for the synthesis of a macrocyclic bisbibenzyl natural product.

Macrocyclic bisbibenzyl natural products have been isolated from liverworts, other bryophytes,[1] and higher flowering plants.[2] Their biosynthetic origin stems from the dimerization of two molecules of lunularin,[3] which results in macrocycles having ethano and biaryl ether linkages (Figure 1).

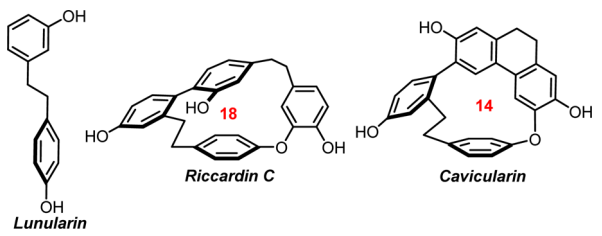


Figure 1. Representative structural features of the macrocyclic bisbibenzyl family of natural products: lunularin (the monomeric unit) and examples of macrocycles having ethano, biaryl ether, and biaryl linkages. Ring sizes are indicated in red.

Members of the bisbibenzyl family can exhibit varying connectivity patterns and substitution by hydroxy and/or alkoxy groups. Some macrocyclic bisbibenzyls possess aromatics that are halogenated or further oxidized.[4] An additional structural feature of the macrocyclic bisbibenzyl natural products is that a number of the compounds exhibit atropisomerism.[5] Neomarchantin A (Figure 2) is a member of the marchantin subclass of macrocyclic bisbibenzyls.[6] Although the macrocycle is achiral, the presence of two biaryl ether subunits in conjunction with their respective connectivities (two para- and two meta-substituted benzene rings) results in a rigidified structure.[7] Aside from their interesting structural features, the marchantins have displayed antibacterial and antimycotic effects as well as inhibition of 5-lipoxygenase and

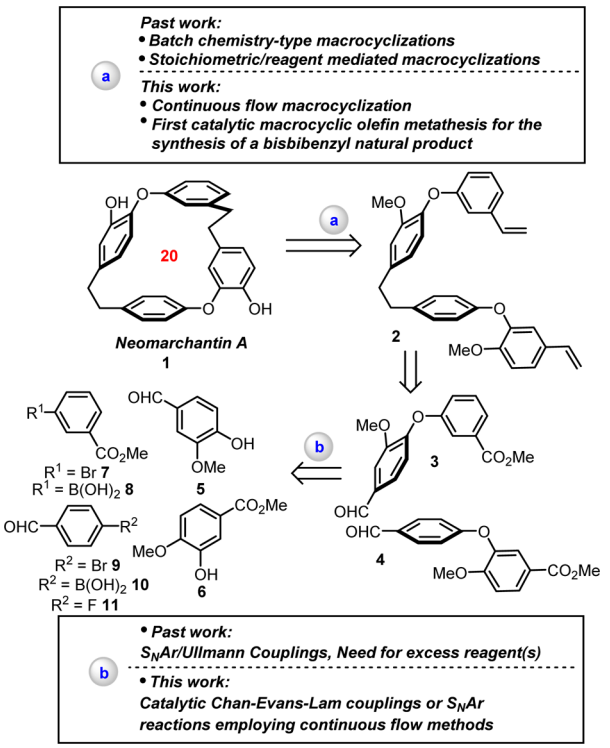


Figure 2. Retrosynthetic analysis of neomarchantin A. Ring size is indicated in red.

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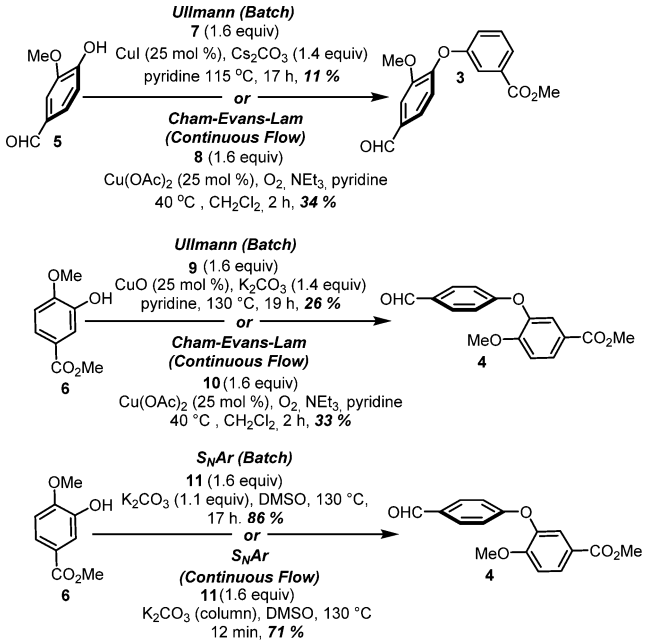
activity as antioxidants.[8] Marchantins have shown cytotoxicity in P-388 mouse leukemia cells and KB cell lines and inhibition of the growth and migrating ability of human glioma A 172 cells.[9] Recently, the marchantins have been revealed to possess activity against influenza A (both H3N2 and H1N1) and influenza B viruses.[10] The combination of impressive diversity in biological activity and intriguing macrocyclic structures has bolstered interest in bisbibenzyl natural products.[4] The key synthetic challenges of macrocyclic bisbibenzyls are generally regarded as formation of the biaryl ethers and formation of the eventual macrocycle. The former is generally addressed via S_NAr reactions or Ullmann couplings, which typically employ harsh conditions (excess reagents, high temperatures). The macrocyclization processes are often olefinations (Wittig, McMurry), which can afford excellent yields but require lengthy syntheses and stoichiometric reagents. Some other macrocyclization strategies have included Pd-catalyzed cross-coupling for the construction of biaryl linkages and de novo synthesis of an arene via a Diels–Alder reaction.[11] Herein, a total synthesis of neomarchantin A is presented that employs catalysis and continuous flow methods to address the key synthetic challenges of biaryl ether formation and macrocyclic ring closure (Figure 2).

The synthesis of neomarchantin A commenced with the synthesis of two key biaryl ether intermediates following established Ullmann coupling protocols, which proved to be challenging (Scheme 1). The preparation of the first biaryl ether **3** from phenol **5** was catalyzed by CuI (25 mol %) using Cs_2CO_3 as a base in refluxing pyridine, affording a low yield of ether **3** (11%). An extensive optimization was performed, and higher temperatures, alternative ligands, palladium-based catalysis, or the use of an iodo coupling partner did not improve the yield.[12]

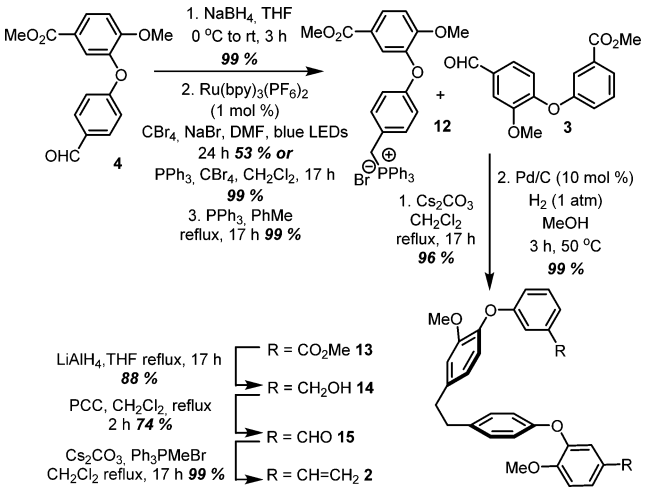
As an alternative route to biaryl ethers, the use of Cu-catalyzed Chan–Evans–Lam couplings was envisioned. The synthesis of C–N bonds via the coupling of amines and arylboronic acids has recently been reported in continuous flow employing tube-in-tube reactors for efficient delivery of molecular oxygen.[13] However, similar cross-couplings for the formation of C–O bonds have not been reported. When the conditions reported by Baxendale and co-workers for C–N bond formation were employed (25 mol % $Cu(OAc)_2$, CH_2Cl_2, O_2) in continuous flow using the tube-in-tube reactor for C–O bond formation, the yield of biaryl ether **3** was increased 3-fold (34% vs 11% using the Ullmann conditions; Scheme 1).[14] For comparison, the Chan–Evans–Lam cross-coupling of boronic acid **8** and phenol **5** was performed with the same catalyst system in a batch reactor, but the oxygen pressure was only 1 atm or ~14 psi (vs 100 psi in flow), and only an 8% yield of the desired product was isolated. Consequently, the flow reactor afforded higher efficiency than the batch reactor. The synthesis of the second biaryl ether unit **4** was also first investigated using the Ullmann coupling (Scheme 1). Again the yield was disappointing, as the reaction afforded 26% biaryl ether **4** (25 mol % CuO, pyridine).[15] With the continuous flow/Chan–Evans–Lam conditions, a similar yield of 33% was obtained.

As an alternative approach to prepare biaryl ether intermediate **4**, an S_NAr route arising from aryl fluoride **11** was investigated. The coupling of phenol **6** and aryl fluoride **11** occurred in 86% yield when performed under K_2CO_3/DMSO/130 °C reaction conditions. Various S_NAr reactions have been reported to provide high yields and short reaction times under continuous flow conditions,[16] while the synthesis of biaryl ethers specifically has been shown to proceed when performed in supercritical CO_2.[17] Given the possibility to augment the process via continuous flow, the S_NAr synthesis of biaryl ether **4** was repeated using a heated column of K_2CO_3 at 130 °C, affording the desired ether **4** in 71% yield but with a significantly shorter reaction time of 12 min.[18] The synthesis of the ethano bridge between the two biaryl ethers was performed using Wittig chemistry (Scheme 2). Functional group manipulation was necessary to prepare a phosphonium salt from ester **12**. A series of reduction ($NaBH_4$), halogenation (CBr_4),[19] and phosphonium salt generation (PPh_3) steps were then performed in a linear sequence to afford the salt **12**. Biaryl ether aldehyde **3** and phosphonium salt **14** could then undergo Wittig olefination (Cs_2CO_3 in refluxing CH_2Cl_2) to afford a 96% yield of the desired stilbene. Subsequent reduction (H_2,

Scheme 1. Comparison of Ullmann, Chan–Evans–Lam Coupling, and S_NAr Routes to Key Biaryl Ether Intermediates



Scheme 2. Synthesis of Macrocyclization Precursor 2



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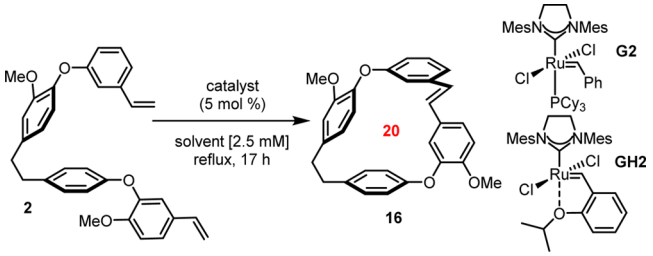
Pd/C) completed one of the ethano bridges of neomarchantin A. A sequence involving reduction ($LiAlH_4$), oxidation (PCC), and olefination ($MePPh_3Br$, Cs_2CO_3) was used to prepare the bis-styrenyl intermediate **2**.

In view of its widespread use in macrocyclization of natural products, it is surprising that macrocyclic olefin metathesis has yet to be successfully described as a viable tactic for the synthesis of macrocyclic bisbibenzyls. A single report by Harrowven and co-workers describes attempts to prepare the macrocyclic core of riccardin C using macrocyclic ring-closing metathesis,[20] but only a cyclic dimer product was isolated in 32% yield. The macrocyclization of diene **2** to form the macrocyclic core **16** of neomarchantin A was first investigated in batch, and both the catalyst and diene **2** were added in one portion without the aid of any slow addition techniques (Table 1). When catalyst **G2** was investigated for macrocyclization in

Table 1. Synthesis of the Macrocyclic Core of Neomarchantin A in Batch via Olefin Metathesis



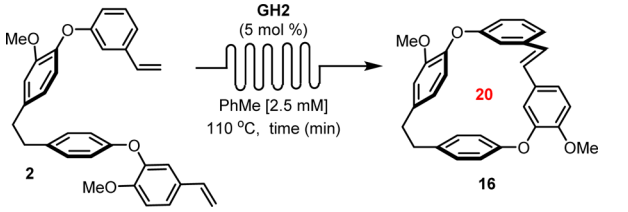
entry	catalyst	solvent	yield of **16** (%)[a]
1	**G2**	PhMe	35 (65)
2	**G2**	CH_2Cl_2	30 (25)
3	**GH2**	PhMe	43 (0)
4	**GH2**	CH_2Cl_2	30 (60)

[a]Yields following chromatography. Recovered starting material **2** in parentheses. Ring size in red.

either PhMe or CH_2Cl_2 at reflux, macrocycle **16** was isolated as the *E* isomer in 30−35% yield with varying quantities of recovered starting material **2** (25−65%). The more active **GH2** catalyst resulted in a slightly improved 43% yield of the 20-membered ring **16**. Changing the solvent to CH_2Cl_2 afforded a slight drop in the yield of macrocycle **16** to 30%. Next, attempts to improve the macrocyclization via continuous flow were investigated, where the efficient energy transfer could help to promote the difficult ring-closing event in macrocyclization. Macrocyclization via olefin metathesis in continuous flow has been reported for the synthesis of musc-like macrolactones. Both Fogg[21] and Skowerski[22] had previously described macrocyclic olefin metathesis reactions in continuous flow that were problematic if the corresponding reaction setups were not designed to efficiently remove ethylene from the reaction mixture.

The cyclization of diene **2** in continuous flow was carried out using a tube-in-tube reactor[23] connected to a vacuum pump to help remove ethylene. Following elution from the reactor coil, the solution was collected in a round-bottom flask containing ethyl vinyl ether to quench any residual catalyst. In view of the propensity of flow processes to improve reaction times, our initial attempt was performed with a 10 min residence time and afforded the desired macrocycle **16** in 49% yield with 51% residual unreacted **2** (Table 2). Increasing the concentration did not improve conversion and attempts at ring-closing using

Table 2. Synthesis of the Macrocyclic Core of Neomarchantin A in Continuous Flow via Olefin Metathesis

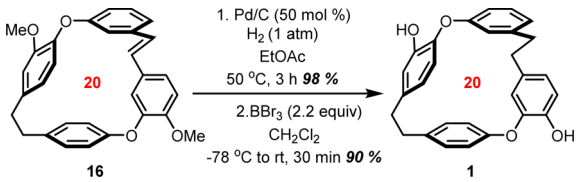


entry	time (min)	yield of **16** (%)[a]
1	10	49 (51)
2[b]	10	37 (45)
3[c]	10	15 (85)
4	30	42 (45)
5	60	33 (55)

[a]Yields following chromatography. Recovered **2** in parentheses. Ring size in red. [b]At 5 mM. [c]with **G2** (5 mol %).

G2 resulted in lower yields. Changes in the residence time (30 or 60 min) also did not improve the yield. Interestingly, when the macrocyclization was repeated with a 10 min residence time but without the applied vacuum, the yield of **16** neither improved nor decreased. Attempts to perform the reaction at higher temperatures or with higher catalyst loadings did not promote conversion, suggesting that the catalyst degrades fully in the 10 min reaction window. The completion of the synthesis was achieved via hydrogenolysis of the olefin of macrocycle **16** and subsequent deprotection of the methyl ethers to afford neomarchantin A (**1**), whose spectral analyses matched those in the literature (Scheme 3).[6]

Scheme 3. Completing the Synthesis of Neomarchantin A



In summary, a synthesis of neomarchantin A has been described that involves the first report of a catalytic macrocyclic olefin metathesis reaction as a key step for the synthesis of a macrocyclic bisbibenzyl natural product. In addition, the chemistries used for the key bond constructions were augmented through continuous flow techniques. The biaryl ether formation via C−O bond formation was conducted at lower temperatures with shorter reaction times and afforded either comparable or higher yields. An S_NAr approach was also shown to be applicable to prepare a biaryl ether intermediate in short reaction times versus batch processes. The macrocyclization event via C−C bond formation proceeded in similar yields in batch and in continuous flow, while the latter provided a dramatic improvement in reaction time (10 min vs 17 h) and should improve the scalability of the olefin metathesis process. The continuous flow strategies used for the aforementioned bond constructions should find additional application in the synthesis of other members of the bisbibenzyl family of natural products as well as in the synthesis of other biologically active compounds containing biaryl ether and macrocycle structural features.

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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(12) Optimization included exploring the effects of temperature (80 → 130 °C), electrophile (Br vs I), solvent (pyridine, DMF, PhMe, dioxane, DMSO), base (K_2CO_3, Cs_2CO_3), copper source (CuO, Cu_2O, CuCl, $CuBr_2$, CuI, $Cu(acac)_2$), and ligand (tetramethylphenanthroline, tetramethylheptadione, glycine, proline, 8-hydroxyquinoline). At best, a 29% yield of **3** could be achieved when 1.4 equiv of CuI and 6 equiv of the coupling partner **7** were used. Ullmann couplings of **3** and **7** were not attempted in flow because of their heterogeneous nature.

(13) For examples of Chan−Lam couplings in flow, see: (a) Mallia, C. J.; Burton, P. M.; Smith, Al. M. R.; Walter, G. C.; Baxendale, I. R. *Beilstein J. Org. Chem.* **2016**, *12*, 1598−1607. (b) Bao, J.; Tranmer, G. K. *Tetrahedron Lett.* **2016**, *57*, 654−657. For other examples of C−N coupling in flow, see: (c) Yang, J. C.; Niu, D.; Karsten, B. P.; Lima, F.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2016**, *55*, 2531−2535. (d) Naber, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 9469−9474.

(14) Optimization of the Cham−Evans−Lam in continuous flow included changing the ligand (TMEDA, pyridine), varying the quantity of Et_3N, using myristic acid as a solubilizing agent for the copper catalyst, and changing the residence time (1 → 4 h).

(15) A 91% yield of **4** could be achieved but required excess CuO (1.4 equiv) and coupling partner **9** (6 equiv).

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