The Free Internet Journal for Organic Chemistry

Paper

Archive for Organic Chemistry

Arkivoc **2018**, part iv, 50-69

Investigating the stereochemical outcome of a tandem cyclization - coupling reaction leading to a 3-arylmethylideneisobenzofuran-1-one

Christian A. Moore, Brian F. Ohman, Matthew J. Garman, Michael E. Liquori, David M. Degan, Kailey B. Voellinger, Michael J. DePersis, and Erin T. Pelkey*

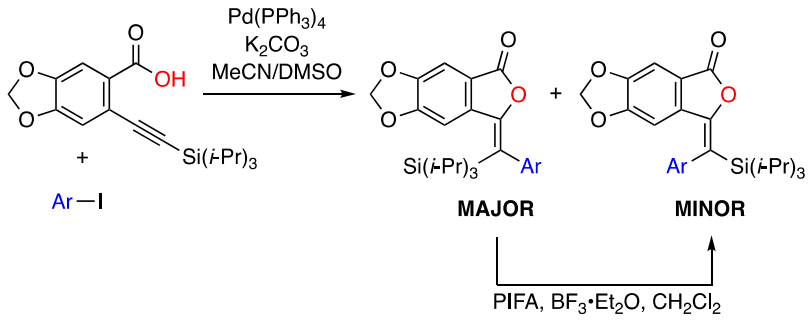
Department of Chemistry, Hobart and William Smith Colleges, 300 Pulteney St., Geneva, NY 14456, USA
Email: pelkey@hws.edu

Dedicated to Professor Gordon W. Gribble on the occasion of his retirement

Received 01-10-2018 **Accepted** 02-04-2018 **Published on line** 02-08-2018

Abstract

A palladium-catalyzed tandem cyclization-coupling reaction of *o*-ethynylbenzoic acids with *p*-iodoanisole led to a stereochemical mixture of 3-arylmethylideneisobenzofuran-1-ones. The major product resulted from an unexpected *syn* addition of the aryl group and carboxylic acid across the alkyne. Treatment of the major product with the hypervalent iodine reagent (bis(trifluoroacetoxy)iodo)benzene (phenyliodine bis(trifluoacetate)) (PIFA) led to an alkene isomerization that produced the minor tandem product. The structure and stereochemistry of the major and minor tandem reaction products were confirmed by independent syntheses. This work provides access to both the (*E*) and (*Z*) stereoisomers of arylmethylideneisobenzofuran-1-ones (phthalides).

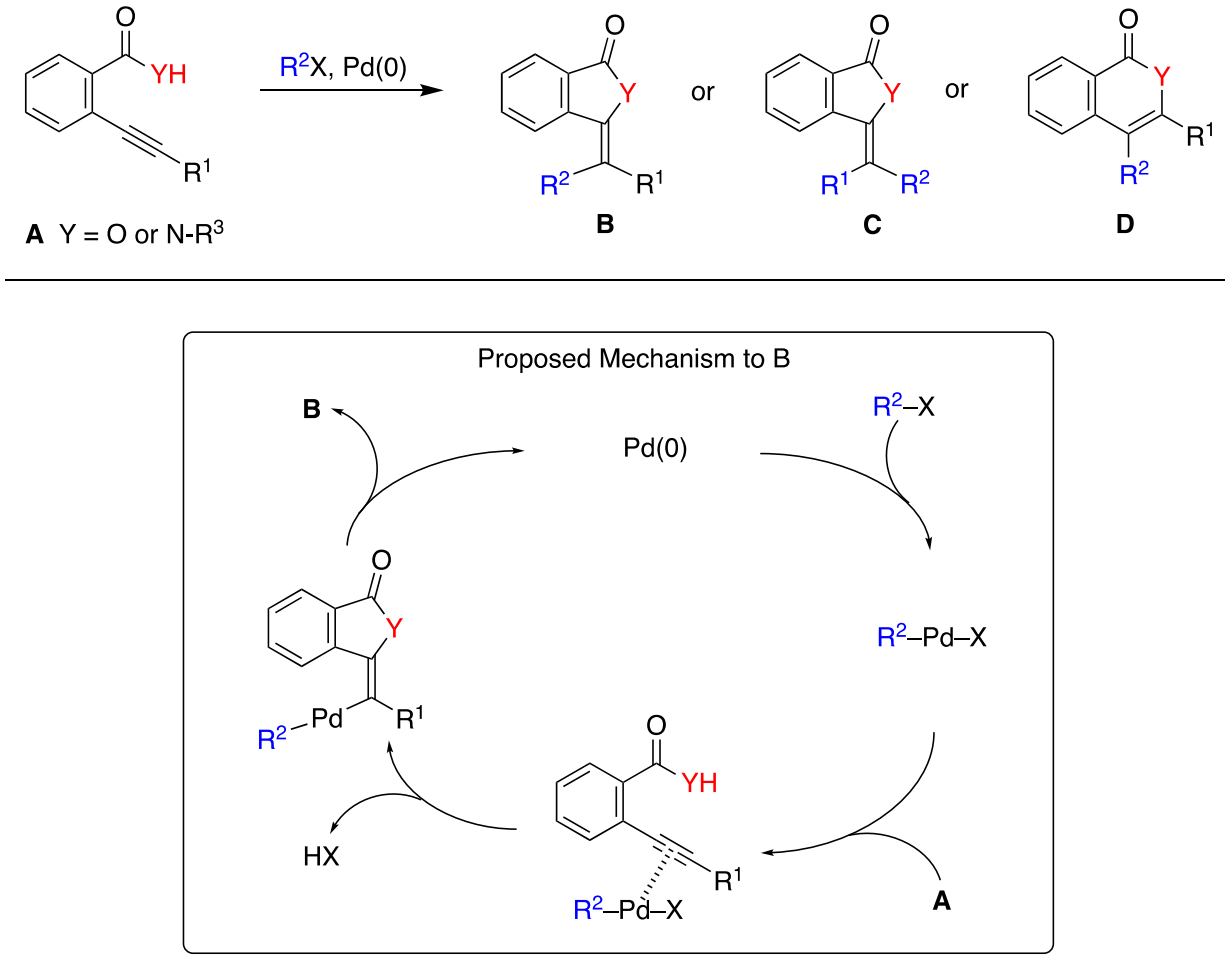


Keywords: phthalides, heterocycles, alkynes, tandem, isomerization

Introduction

Tandem reactions provide an excellent strategy for constructing complex molecules as multiple bonds are formed in one operation often with high levels of regioselectivity and stereoselectivity.[1-3] In addition, tandem reactions offer a number of ancillary environmental benefits over the corresponding stepwise processes including fewer synthetic transformations, work-ups, purification steps, and less waste.[2]

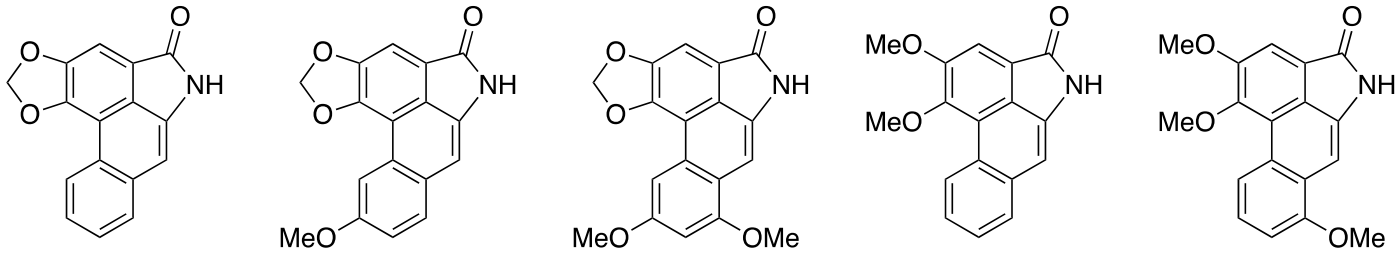
The cyclization of heteroatom nucleophiles onto pendant alkynes mediated by Pd(II)-arene species represents an important type of tandem reaction that has been utilized to prepare a wide variety of heterocycles.[4,5] For the tandem cyclization-coupling reaction of 2-ethynylbenzoic acid derivatives **A**, there are three possible regiochemical and stereochemical outcomes (Scheme 1): (1) product type **B** via a 5-*exo*-cyclization with *anti* arrangement of the nucleophilic and Pd(II) moieties; (2) product type **C** via a 5-*exo*-cyclization with *syn* arrangement of the nucleophilic and Pd(II) moieties; and (3) product type **D** via a 6-*endo*-cyclization. A possible mechanism for the transformations leading to the type **B** products is as follows:[4,5] (i) oxidative addition of haloarenes generating a Pd(II)-arene species; (ii) coordination of the Pd(II)-arene species with the alkyne; (iii) cyclization onto the Pd(II)-coordinated alkyne by a proximate heteroatom nucleophile; and (iv) reductive elimination giving **C**.



Scheme 1. Stereochemical and regiochemical outcomes of tandem cyclization-coupling reaction of **A**.

This transformation has been studied in a few systems previously, by others with differing results. Rossi and co-workers reported that the cyclization-coupling of 2-ethynylbenzoic acid **A** (Y = O; R^1 = propyl) with iodoarenes led to a mixture of isobenzofuran-1-ones **B** and isochromen-1-ones **D** where structures **B** were the major products.[6] Balme and co-workers reported an intramolecular cyclization-coupling variation which also led primarily to 5-*exo* products **B**.[7-9] Also of note are tandem cyclization-coupling reactions involving *anti*-additions of acyclic substrates (β-alkynylcarboxylic acids) that have been reported to give monocyclic 5-*exo* products structurally related to **B**.[10-17] On the other hand, there are fewer reports of this type of tandem cyclization-coupling reaction involving *syn*-additions of acyclic substrates. In a palladium-catalyzed cyclization-coupling reaction involving β-alkynylcarboxamides, Hiemstra and co-workers obtained 5-*exo* products structurally related to **C** (Y = *N*-alkyl; R^1 = $SiMe_3$) that resulted from *syn*-additions across the alkynes.[18]

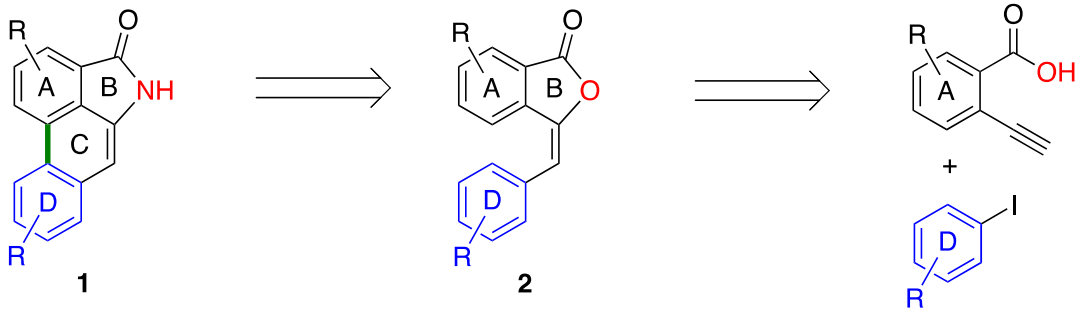
We set out to explore a palladium-mediated tandem cyclization-coupling strategy that could contribute to a novel strategy aimed at the total syntheses of the aristolactam alkaloids **1**. Aristolactam alkaloids are highly oxygenated phenanthrene lactam natural products[19,20] that display modest biological activity including anti-cancer activity (Figure 1).[21] Some previously reported synthetic approaches to the aristolactam alkaloids include: (1) photocyclization of isoindolinones;[22] (2) iodocyclization of alkynylbenzamide;[23] (3) Horner olefination-radical cyclization;[24,25] (4) intramolecular aryne cycloaddition;[26,27] (5) carbonylation of amino-phenanthrenes;[28] and (6) tandem Suzuki coupling-aldol condensation.[29]



1a cepharanone A | **1b** aristolactam III | **1c** aristolactam IV | **1d** cepharanone B | **1e** taliscanine

Figure 1. Structures of selected aristolactam alkaloids.

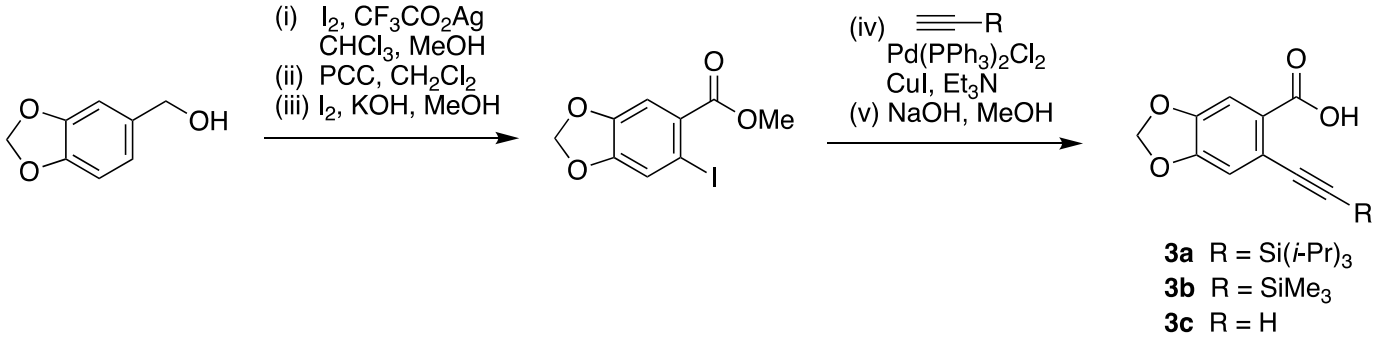
In our retrosynthetic analysis aimed at the construction of the aristolactam alkaloids (Scheme 2), the fused lactam ring can be derived from an amidation of the corresponding fused lactone ring.[30] Next, by taking advantage of the electron-donating groups present in all of the aristolactam congeners, formation of the C-ring might be possible via an oxidative cyclization[31-33] of (*E*)-arylmethylideneisobenzofuran-1-ones **2** (phthalides). Kita[34,35]and others[36.38] have demonstrated the use of the hypervalent iodine reagent phenyliodine(III) bis(trifluoroacetate) (PIFA) in oxidative cyclizations leading to electron-rich phenanthrenes. Inspired by the precedent discussed at the outset, phthalides **2** would arise from the tandem cyclization-coupling reaction between 2-ethynylbenzoic acids and iodoarenes.



Scheme 2. Proposed approach to aristolactam alkaloids.

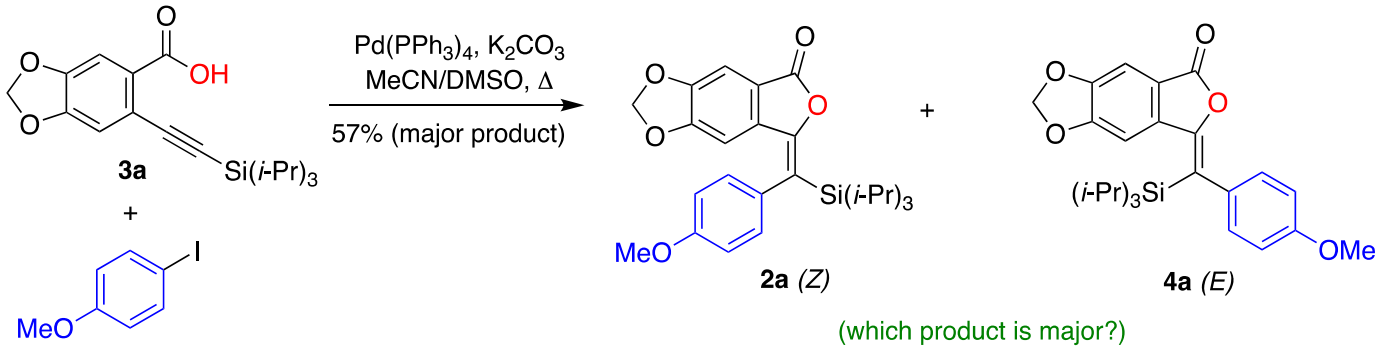
Results and Discussion

We commenced our study with the synthesis of *o*-ethynylbenzoic acid substrates **3**. After some experimentation, we settled on 2-ethynylbenzoic acid **3a**, which was prepared following a five-step sequence (Scheme 3): (i) iodination[39] of piperonyl alcohol giving the known 6-iodopiperonyl alcohol;[40] (ii) PCC oxidation giving the known 6-iodopiperonal;[41] (iii) oxidative conversion[42,43] to the corresponding ester with iodine in the presence of methanol to give the known methyl 6-iodopiperonylate;[44] (iv) Sonogashira cross-coupling[45] to the triisopropyl-substituted alkyne; and (v) hydrolysis of the methyl ester with hydroxide giving **3a**. We found it necessary to cap the alkyne moiety with a triisopropylsilyl group; structurally related substrates **3b** or **3c** were not stable and readily produced the corresponding 3-methylidenephthalide[46] or keto hydrolysis product[47] under mildly acidic or basic conditions (see Experimental Section); this same problem was also observed by Boger and Wolkenberg.[47]



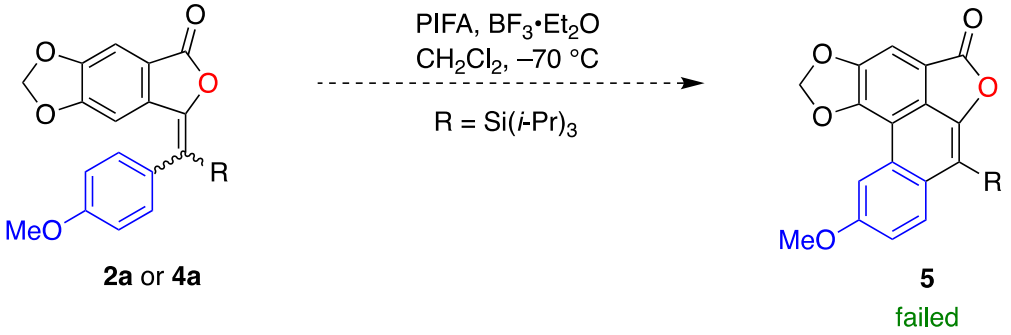
Scheme 3. Synthesis of *o*-ethynylbenzoic acid substrate **3a**.

With **3a** in hand, we next explored tandem cyclization-coupling reactions (Scheme 4). Using a modification of the conditions previously reported by Rossi and co-workers for the tandem cyclization of 2-(1'-butynyl)benzoic acid, treatment of **3a** and *p*-iodoanisole with $Pd(PPh_3)_4$ in the presence of potassium carbonate in MeCN/DMSO gave a ~5:1 mixture of two isolable products (note: omission of DMSO significantly diminished the yield). We presumed the major product to be the expected *anti*-addition product **2a** by analogy and the minor product to be the *syn*-addition product **4a**. Purification by column chromatography gave the major product in 57% yield (average yield of six runs). Spectroscopic (^{1}H and ^{13}C NMR) and analytical data (CHN and HRMS) for the major product were consistent with the presumed structure **2a**.



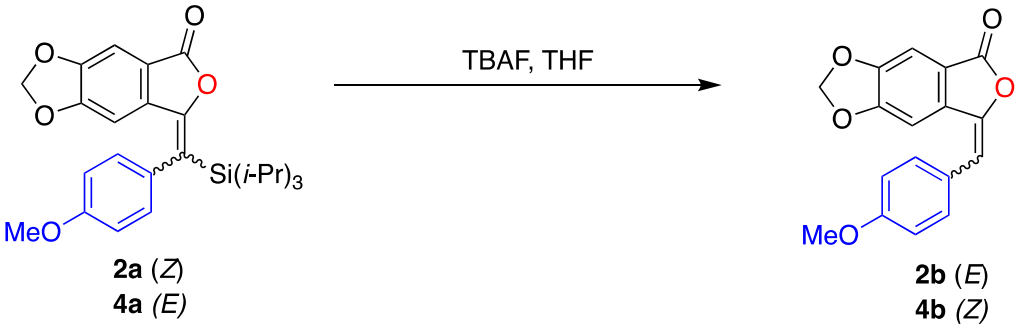
Scheme 4. Tandem cyclization-coupling reaction of **3a**.

We next attempted an oxidative ring closure of the C-ring. In the event, treatment of the major product (**2a** or **4a**) of the tandem cyclization-coupling reaction with PIFA and boron trifluoride-etherate at –70 °C did not give the expected oxidative cyclization product, phenanthrene **5** (Scheme 5). Instead, the reaction led to an isomerization of the major tandem product (at this point, presumably **2a**) to the minor tandem product (at this point, presumably **4a**). Harsher reaction conditions (rt) led to decomposition of the starting material and no identifiable products.



Scheme 5. Attempted oxidative cyclization.

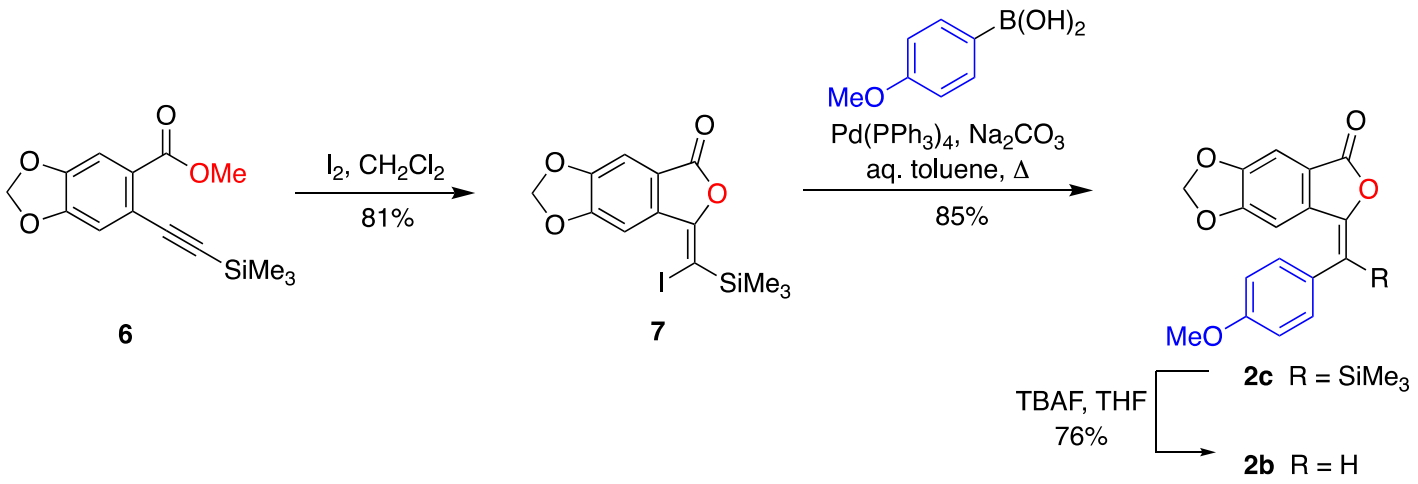
In order to understand better what was going on, we decided to synthesize the parent (desilylated) arylmethylideneisobenzofuran-1-ones **2b** and **4b** independently. The desilylated products **2b** and **4b** were obtained by treatment of **2a** and **4a**, respectively, with tetrabutylammonium fluoride (TBAF) (Scheme 6).



Scheme 6. Desilylation of **2a**/**4a**.

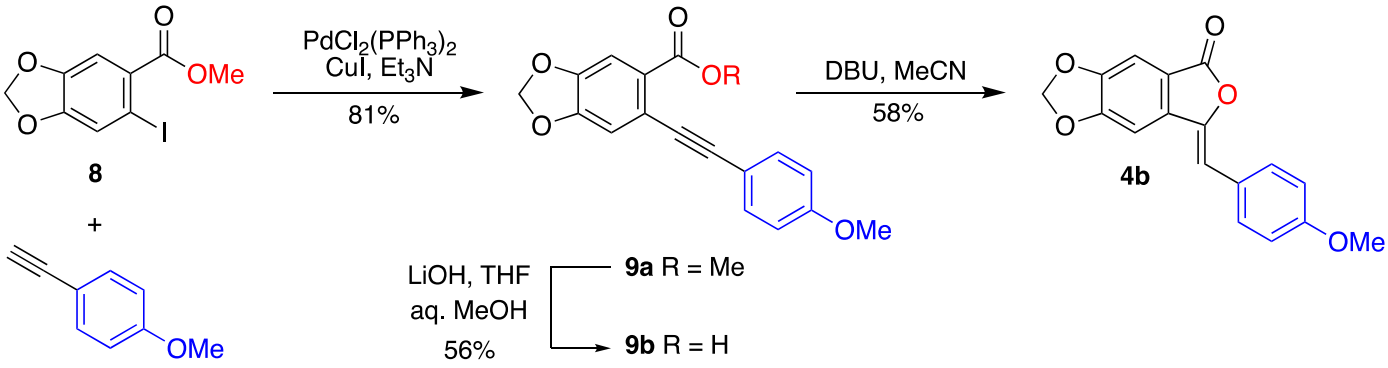
The independent synthesis of **2b** utilized the iodocyclization method developed by Larock and co-workers (Scheme 7).[45] Substrate **6** was prepared by Sonogashira alkynylation of methyl 6-iodopiperonylate (available

from our synthesis of **3**). Treatment of **6** with iodine led to 3-methylideneisobenzofuran-1-one **7** via an iodocyclization. Suzuki-Miyaura cross-coupling of **7** with *p*-methoxyphenylboronic acid gave the expected isobenzofuran-1-one **2c**. Desilylation of **2c** then gave **2b**. Unexpectedly, **2b** was not identical to the material derived from the desilylation of the major product of the tandem cyclization-coupling reaction. Thus, our tandem reaction did not give the *anti*-addition product observed in the closely related system by Rossi and co-workers.[6]



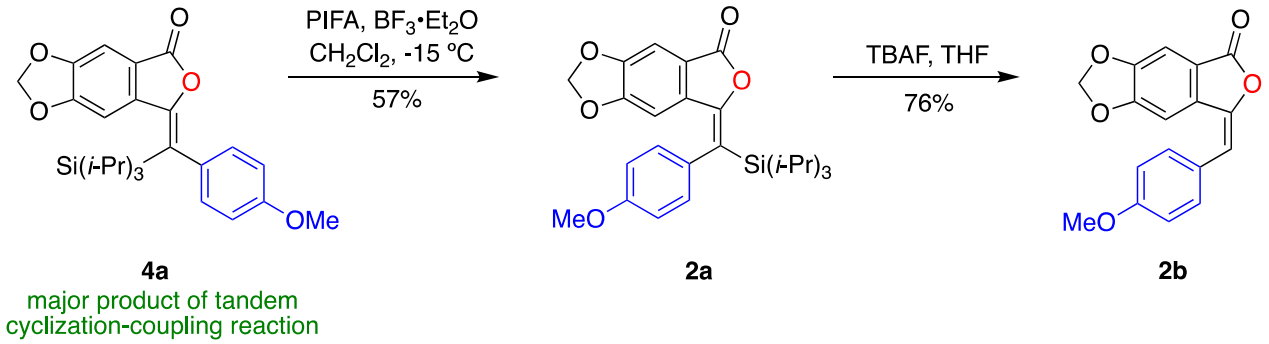
Scheme 7. Independent synthesis of (*E*) product **2b**.

We next turned our attention to the independent synthesis of stereoisomer **4b**. The synthesis of **4b** utilized the method developed by Terada and Kanazawa (Scheme 8) for the synthesis of (*E*)-arylmethylidene-isobenzofuran-1-ones by 5-*exo*-cyclization of the corresponding *o*-alkynylbenzoates.[48,49] Sonogashira cross-coupling of methyl 6-iodopiperonylate (**8**) with 4-ethynylanisole produced alkyne **9a**. Mild hydrolysis of **9a** with lithium hydroxide gave benzoic acid **9b**. Treatment of **9b** with DBU led to the formation of known isobenzofuran-1-one **4b**.[50] Compound **4b** turned out to be identical to the desilylated material derived from the major tandem cyclization-coupling product. Overall, these independent syntheses provide excellent support that our original tandem cyclization-coupling reaction of **3** led to a mixture of **4a** and **2a** where the *syn*-addition product **4a** was the major product.

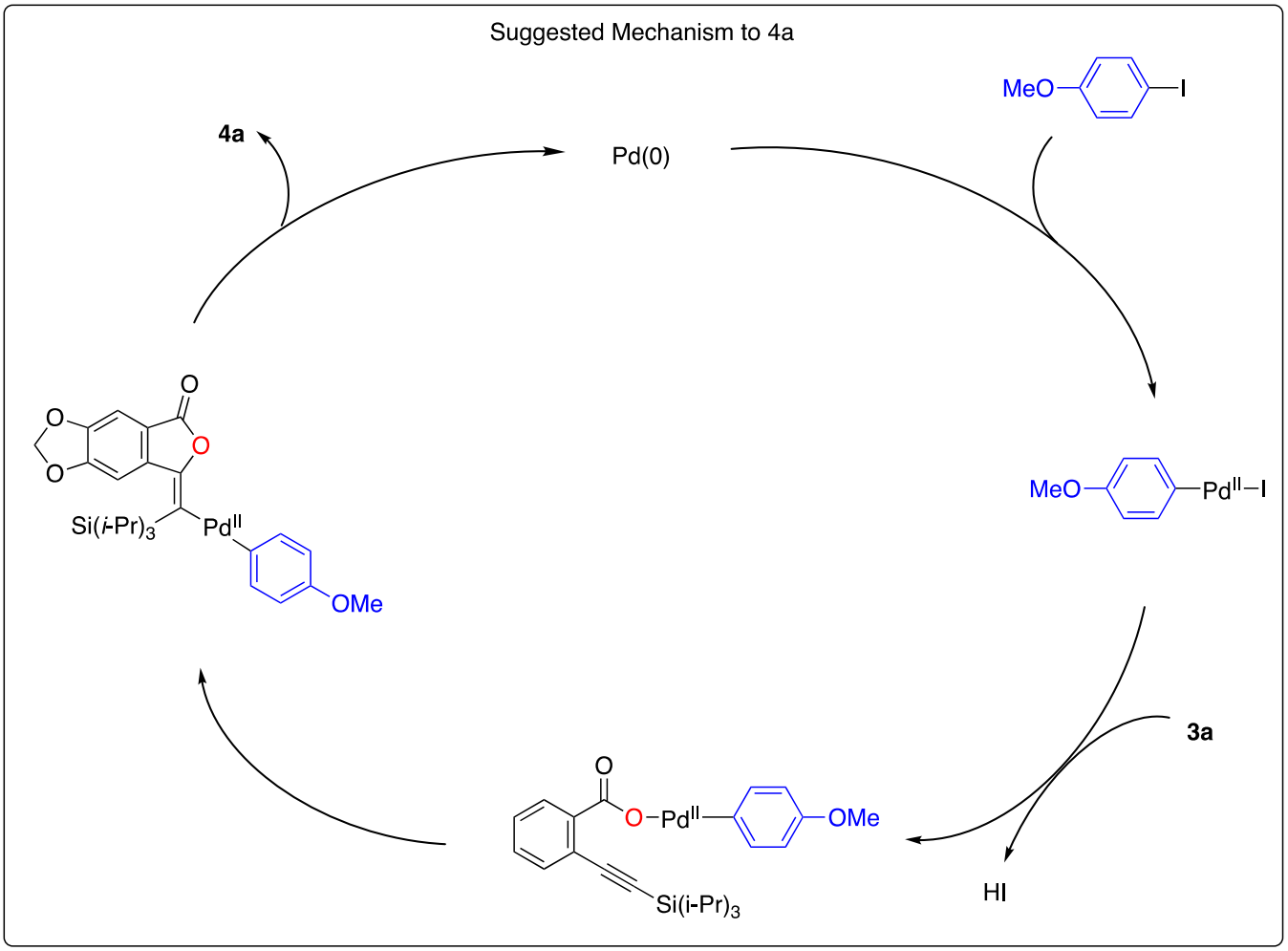


Scheme 8. Independent synthesis of (*Z*) product **4b**.

Although we observed the *syn*-addition product **4a** as the major product from our palladium-mediated tandem reaction, we were still able to achieve a synthesis of the desired (*E*)-arylmethylideneisobenzofuran-1-one **2b** (Scheme 9). Treatment of **4a** with PIFA led to the formation of **2a** via an alkene isomerization (presumably via a radical intermediate). The spectral data obtained for isomerization product **2a** matched spectral data obtained for the minor product of the original tandem cyclization-coupling reaction involving **3a**. Finally, desilylation of **2a** by treatment with TBAF gave **2b**. As discussed above, **2b** matched the material prepared utilizing the Larock iodocyclization methodology (Scheme 7).



Scheme 9. Overall results.



Scheme 10. Mechanism to major product **4a**.

Given the stereochemical outcome that we observed with the tandem cyclization-coupling reaction of **3a**, we propose the following mechanism for the formation of **4a** (Scheme 10). This type of mechanism was suggested by Hiemstra and co-workers in a similar system.[18] The mechanism consists of four steps: (i) oxidative addition of haloarenes generating a Pd(II)-arene species; (ii) nucleophilic substitution of the Pd(II)-arene species with the carboxylic acid; (iii) *syn*-oxypalladation across the alkyne; and (iv) reductive elimination giving **4a**.

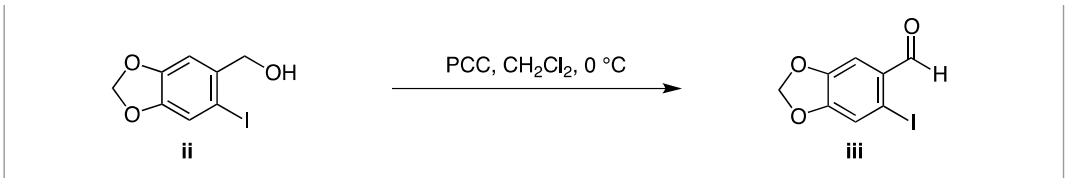
Conclusions

In summary, we have developed new methodology that can be utilized to prepare both (*Z*)- and (*E*)-arylmethylideneisobenzofuran-1-ones. The tandem cyclization-coupling reaction of **3a** with *p*-iodoanisole gave a ~5:1 mixture of the syn-addition product **4a** and the anti-addition product **2a**, respectively. A novel PIFA-mediated *E*/*Z* isomerization was discovered that converted **4a** into **2a**. We plan to further investigate the use of the isobenzofuran-1-ones prepared for the synthesis of complex heterocycles including the aristolactam alkaloids.

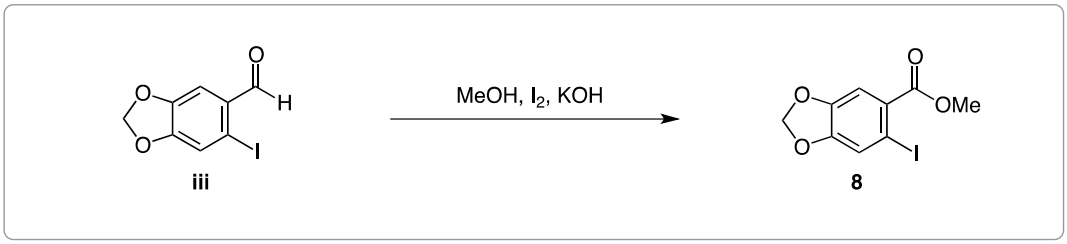
Experimental Section

General.[38] All reactions were performed under a positive atmosphere of argon with magnetic stirring unless otherwise noted. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were purified by passage through a column of alumina utilizing a PureSolv 400 solvent purification system. Unless otherwise indicated, all other reagents and solvents were purchased from commercial sources and were used without further purification. ^{1}H NMR and ^{13}C NMR chemical shifts are reported in parts per million (ppm δ) using the residual proton or carbon signal of the solvent ($CDCl_3$: δ 7.26 ppm, C δ 77.3 ppm; d_6-DMSO: H δ 2.50 ppm, C δ 39.5 ppm) as an internal reference. Flash chromatography was performed with silica gel (230-400 mesh), and thin-layer chromatography (TLC) was performed with glass-backed silica gel plates and visualized with UV (254 nm). IR spectra were measured utilizing an infrared spectrometer fitted with an ATR (attenuated total reflectance) sampler. High resolution mass spectra (HRMS) were obtained using a Fourier transfer ion cyclotron resonance (FTICR) mass spectrometer and electrospray ionization (ESI).

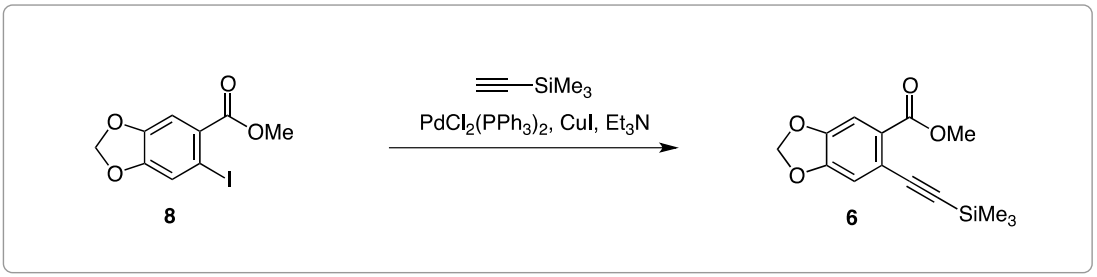
6-Iodo-1,3-benzodioxole-5-methanol (ii).[40] A modification of a literature procedure was followed.[39] To a 0 °C stirred solution of piperonyl alcohol (5.00 g, 32.9 mmol) and silver trifluoroacetate (8.71 g, 39.4 mmol) in $CHCl_3$ (80 mL) in the dark (aluminum foil wrapped flask) was added a solution of I_2 (10.01 g, 39.44 mmol) in MeOH (90 mL) dropwise via an addition funnel. The reaction mixture was stirred at 0 °C for 2 h and then at rt for an additional 22 h. The reaction mixture was filtered through Celite and the Celite layer was washed with $CHCl_3$ (2 x 50 mL). The solvent was removed in vacuo and the crude material obtained was taken up in CH_2Cl_2 (100 mL). The organic layer was washed with a saturated aqueous solution of $Na_2S_2O_3$ (3 x 100 mL) and then dried over Na_2SO_4. Removal of the solvent *in vacuo* gave the title compound **ii** (8.27 g, 29.7 mmol, 91% yield), which was used without further purification. Off-white amorphous solid. mp 110-111 °C (lit.[39] 110-111 mp °C). R_f 0.30 (1:5 EtOAc/petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1H), 7.00 (s, 1H), 5.98 (s, 2H), 4.60 (d, *J* 6.4 Hz, 2H), 1.89 (t, *J* 6.4 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 148.2, 136.5, 118.8, 109.4 102.0, 85.7, 69.6 ppm. [CAS # 69048-76-6]



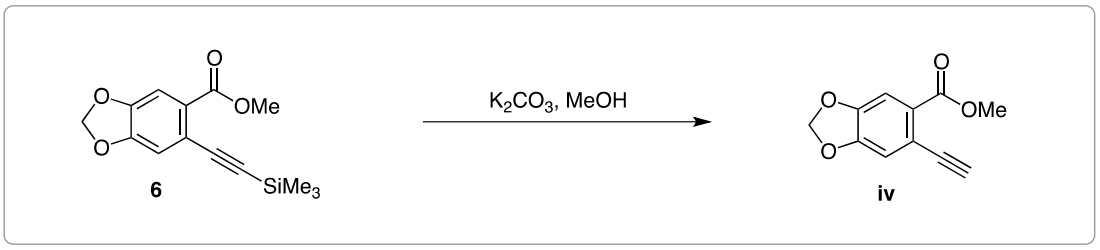
6-Iodo-1,3-benzodioxole-5-carboxaldehyde (iii).[41] A modification of a literature procedure was followed.[41] To a stirred solution of 6-iodo-1,3-benzodioxole-5-methanol (**ii**) (3.10 g, 11.2 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added pyridinium chlorochromate (PCC) (4.81 g, 22.3 mmol). The reaction mixture was stirred at 0 °C for 2 h and then for an additional 16 h at rt by which time TLC showed complete conversion. The reaction mixture was filtered through a short plug of silica gel. The silica gel was washed with additional CH_2Cl_2 (100 mL). The combined organic layers were dried over Na_2SO_4 and removal of the solvent in vacuo gave the title compound **iii** (2.67 g, 9.67 mmol, 87% yield), which was used without further purification. Off-white amorphous solid. mp 108-109 °C (lit.[41] mp 112-113 °C). R_f 0.31 (1:10 EtOAc/petroleum ether). IR (ATR, neat) 2890, 1755, 1668, 1609, 1593, 1502, 1475, 1398, 1381, 1340, 1246, 1109, 1032, 962, 929, 871, 846, 783 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.38 (s, 1H), 7.34 (s, 1H), 6.08 (s, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 153.8, 149.5, 129.9, 119.7, 109.2, 103.0, 93.6 ppm. [CAS # 58343-53-6]



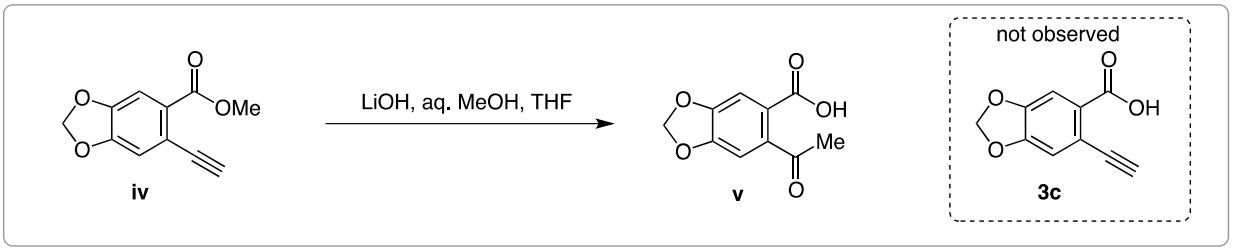
Methyl 6-iodo-1,3-benzodioxole-5-carboxylate (8).[41,44] A modification of a literature procedure was followed.[42] To a 0 °C stirred solution of KOH (0.800 g, 14.5 mmol) in MeOH (50 mL) was added a solution of 6-iodo-1,3-benzodioxole-5-carboxaldehyde (**iii**) (0.500 g, 1.81 mmol) in MeOH (80 mL) followed by solid I_2 (1.84 g, 7.24 mmol). The reaction was mixture was stirred at 0 °C for 2 h and then at rt for an additional 14 h. The reaction mixture was treated with solid $Na_2S_2O_3$until the brown color dissipated. The bulk of the solvent was removed in vacuo and the residue was taken up in CH_2Cl_2 (100 mL). The organic layer was washed with a saturated solution of $Na_2S_2O_3$ (2 x 100 mL), brine (100 mL), and dried over Na_2SO_4. Removal of the solvent in vacuo gave a crude yellow solid (0.59 g). Purification by flash chromatography (1:20 EtOAc/petroleum ether to 1:10 EtOAc/petroleum ether) gave the title compound **8** (0.510 g, 1.67 mmol, 92% yield). Off-white amorphous solid. mp 83-85 °C (lit.[41] mp 84.6-86.1 °C). R_f 0.31 (1:10 EtOAc/petroleum ether). IR (ATR, neat) 3008, 2959, 2915, 1716, 1611, 1501, 1487, 1437, 1405, 1374, 1347, 1240, 1223, 1183, 1135, 1121, 1084, 1026, 984, 929, 911, 867, 840, 798, 771 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.37 (s, 1H), 6.04 (s, 2H), 3.89 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 151.4, 148.4, 127.7, 121.2, 111.3, 102.7, 85.2, 52.7 ppm. [CAS # 61599-80-2]



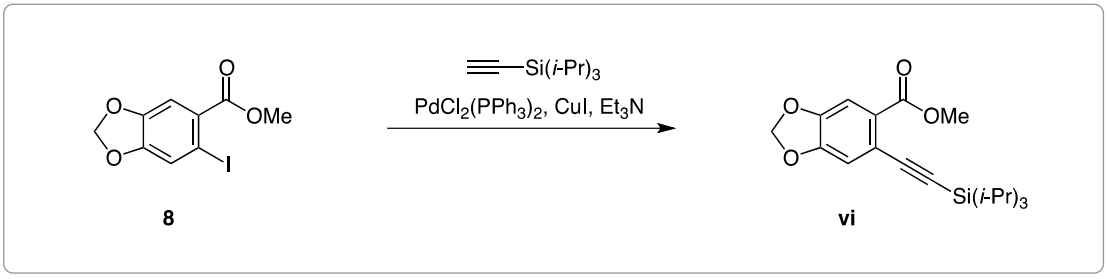
Methyl 6-(trimethylsilylethynyl)-1,3-benzodioxole-5-carboxylate (6). A modification of a literature procedure was followed.[42] To a stirred solution of methyl ester (**8**) (0.500 g, 1.63 mmol) and TMS-acetylene (0.460 mL, 3.26 mmol) in Et_3N (15 mL) at rt was added $Pd(PPh_3)_2Cl_2$ (0.110 g, 0.163 mmol) and CuI (6 mg, 0.03 mmol) with stirring. The reaction mixture was heated to 55 °C for 23 h. The resulting solution was filtered through a plug of Celite (washing with excess CH_2Cl_2) and the filtrate was washed with 1.0 M HCl (2 x 75 mL) and brine (150 mL). Solvent was removed in vacuo giving a crude brown solid (0.57 g). Purification by flash chromatography (1:40 EtOAc/petroleum ether to 1:20 EtOAc/petroleum ether) gave the title compound **6** (0.350 g, 0.127 mmol, 78% yield). White amorphous solid. mp 67-70 °C. R_f 0.43 (1:10 EtOAc/petroleum ether). IR (ATR, neat) 3064, 2956, 2911, 2152, 1706, 1610, 1508, 1489, 1433, 1368, 1241, 1218, 1180, 1128, 1035, 956, 933, 884, 840, 803, 779, 758 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 6.98 (s, 1H), 6.04 (s, 2H), 3.88 (s, 3H), 0.26 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 150.5, 148.1, 127.4, 118.9, 114.0, 110.4, 103.6, 102.5, 98.7, 52.2, 0.2 ppm. HRMS (ESI-FTICR) calcd for spray dimer $(C_{14}H_{16}O_4Si)_2{\cdot}Na^+$ ($M_2{\cdot}Na^+$) 575.1528, found 575.1518.



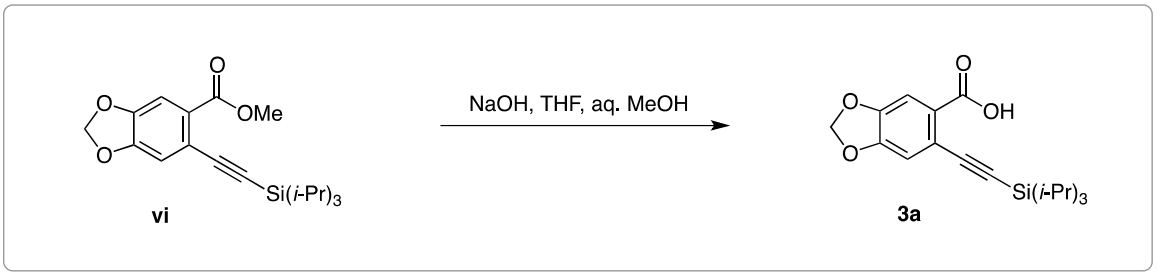
Methyl 6-ethynyl-1,3-benzodioxole-5-carboxylate (iv).[47] To a stirred solution of methyl ester (**6**) (0.500 g, 1.81 mmol) in MeOH (10 mL) at rt was added K_2CO_3 (0.500 g, 3.62 mmol) and the reaction was monitored by TLC (1:8 EtOAc/petroleum ether). After 0.5 h, TLC showed complete conversion. The solvent was removed in vacuo giving a crude solid (0.97 g). Purification by flash chromatography (1:15 EtOAc/petroleum ether to 1:5 EtOAc/petroleum ether) gave the title compound **iv** (0.240 g, 1.18 mmol, 65% yield). White crystalline solid. mp 105-107 °C. R_f 0.26 (1:8 EtOAc/petroleum ether). IR (ATR, neat) 3300, 3063, 3009, 2965, 2928, 1724, 1607, 1502, 1488, 1438, 1397, 1377, 1250, 1223, 1183, 1166, 1105, 1027, 953, 922, 872, 861, 804, 779, 742, 715 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.02 (s, 1H), 6.06 (s, 2H), 3.89 (s, 3H), 3.33 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 150.7, 148.3, 127.4, 118.3, 114.4, 110.4, 102.6, 82.3, 81.5, 52.4 ppm. HRMS (ESI-FTICR) calcd for $C_{11}H_8O_4{\cdot}Na^+$ ($M{\cdot}Na^+$) 227.0315, found 227.0312.



6-Acetyl-1,3-benzodioxole-5-carboxylic acid (v).[47] To a rt stirred solution of ester **iv** (0.050 g, 0.24 mmol) in THF (5 mL) was added a mixture of $LiOH·H_2O$ (0.050 g, 1.2 mmol) in MeOH (5 mL) and H_2O (5 mL). The reaction mixture was heated to 40 °C for 19 h and then the solvent was removed in vacuo. The crude orange residue was taken up in H_2O (50 mL) and the resulting aqueous solution was washed with Et_2O (50 mL). The aqueous layer was then acidified by the addition of an aqueous HCl (1.0 M, 2 mL) and then was extracted with EtOAc (2 x 50 mL). The combined organic layers were ashed with brine (100 mL) and dried over Na_2SO_4. Removal of the solvent in vacuo gave the title compound **v** (42 mg, 0.20 mmol, 83% yield). White film. mp 167-169 °C. R_f 0.64 (EtOAc). IR (ATR, neat) 3228, 3069, 2990, 2934, 1706, 1609, 1523, 1497, 1483, 1445, 1376, 1309, 1240, 1212, 1193, 1175, 1153, 1124, 1101, 1050, 1033, 995, 960, 928, 882, 869, 851, 825, 809, 790, 725 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO) δ 7.78 (br s, 1H), 7.21 (s, 1H), 7.19 (s, 1H), 1.75 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 153.0, 149.4, 146.7, 119.8, 103.5, 102.84, 102.79, 26.4 (*missing carbon*) ppm. HRMS (ESI-FTICR) calcd for $C_{10}H_8O_5·Na^+$ ($M·Na^+$) 231.0264, found 231.0262. [CAS # 1027081-13-5]

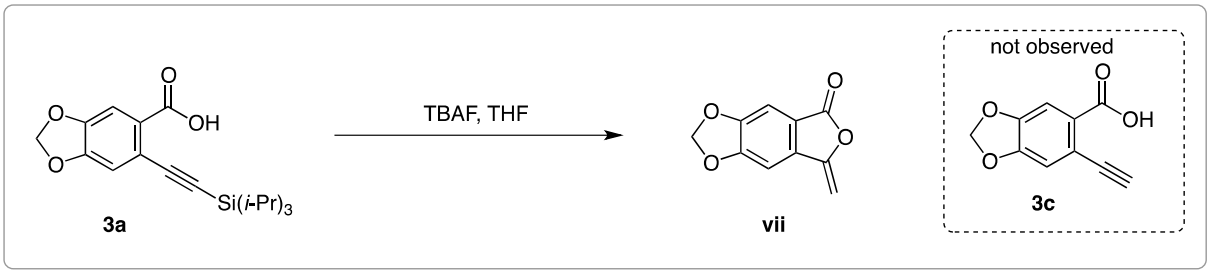


Methyl 6-((triisopropylsilyl)ethynyl)-1,3-benzodioxole-5-carboxylate (vi). A modification of a literature procedure was followed.[45] To a stirred solution of ester **8** (2.00 g, 6.54 mmol) and triisopropylsilylacetylene (2.2 mL, 10 mmol) in Et_3N (20 mL) at rt was added $PdCl_2(PPh_3)_2$ (0.23 g, 0.33 mmol) and CuI (0.020 g, 0.13 mmol). The reaction was stirred at 55 °C for 24 h and then allowed to cool to rt. The reaction mixture was filtered through Celite; the Celite plug was rinsed with CH_2Cl_2 (100 mL). The organic layer was washed with aqueous HCl (1.0 M, 2 x 100 mL), brine (100 mL), and dried over Na_2SO_4. Removal of the solvent in vacuo gave a crude orange solid (2.64 g). Purification by flash chromatography (1:50 EtOAc/petroleum ether to 1:25 EtOAc/petroleum ether) gave the title compound **vi** (2.02 g, 5.60 mmol, 86% yield). White amorphous solid. mp 50-52 °C. R_f 0.50 (1:8 EtOAc/petroleum ether). IR (ATR, neat) 2942, 2891, 2864, 2148, 1701, 1614, 1511, 1488, 1461, 1437, 1371, 1262, 1218, 1181, 1127, 1072, 1034, 1015, 992, 957, 928, 877, 849, 781, 721 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (s, 1H), 6.98 (s, 1H), 6.03 (s, 2H), 3.87 (s, 3H), 1.14 (s, 21H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 150.4, 148.0, 127.4, 119.1, 114.4, 110.4, 105.4, 102.4, 95.4, 52.4, 19.0, 11.7 ppm. HRMS (ESI-FTICR) calcd for $C_{20}H_{28}O_4Si·Na^+$ ($M·Na^+$) 383.1649, found 383.1647.



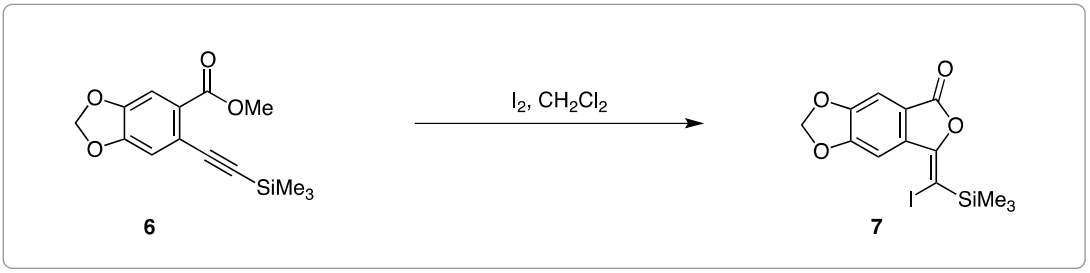
vi 3a

6-((Triisopropylsilyl)ethynyl)-1,3-benzodioxole-5-carboxylic acid (3a). To a rt stirred solution of ester **vi** (1.22 g, 3.39 mmol) in THF (60 mL) was added a solution of NaOH (0.270 g, 6.77 mmol) in H_2O (30 mL) and MeOH (30 mL). The reaction mixture was heated to reflux for 24 h. The bulk of the organic solvent was removed in vacuo and the residue was treated with H_2O (100 mL). The aqueous solution was extracted with Et_2O (100 mL) and the organic layer was set aside. The aqueous layer was cooled to 0 °C and acidified by the addition of aqueous HCl (1.0 M) until pH 2. The acidic layer was extracted with Et_2O (3 x 100 mL) and the combined organic layers were dried over Na_2SO_4. Removal of the solvent in vacuo gave the title compound **3a** (1.05 g, 3.03 mmol, 89% yield), which was used without further purification. An analytical sample was obtained by recrystallization from 1:1 CH_2Cl_2/petroleum ether. White amorphous solid. mp 206-209 °C. R_f 0.11 (1:8 EtOAc/petroleum ether). IR (ATR, neat) 2940, 2864, 2148, 1688, 1602, 1508, 1487, 1464, 1422, 1408, 1392, 1365, 1316, 1278, 1247, 1177, 1132, 1073, 1035, 1017, 994, 930, 879, 855, 785, 773, 721 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ7.52 (s, 1H), 7.01 (s, 1H), 6.07 (s, 2H), 1.14 (s, 21H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 151.3, 148.3, 126.2, 119.5, 114.2, 111.1, 104.8, 102.7, 98.4, 18.9, 11.6 ppm. Anal calcd for $C_{19}H_{36}O_4Si$: C 65.86, H 7.56; found: C 65.59, H 7.45. HRMS (ESI-FTICR) calcd for $C_{19}H_{26}O_4Si{\cdot}Na^+$ (M·Na$^+$) 369.1493, found 369.1491.



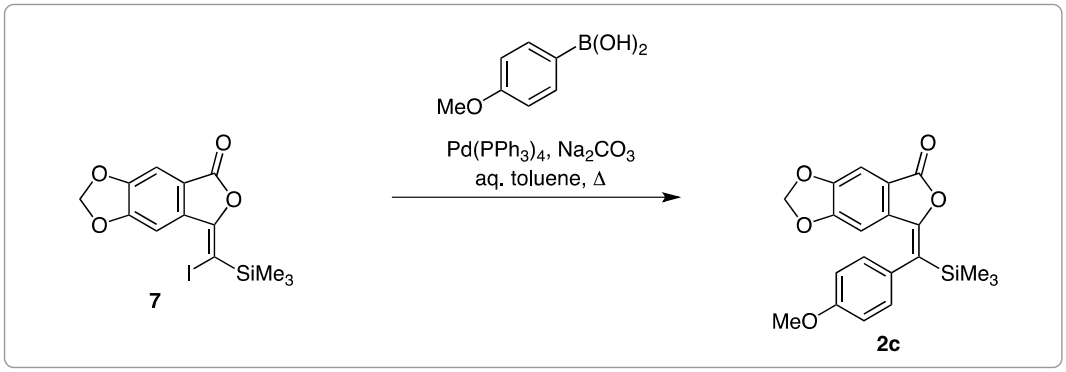
3a vii 3c

7-Methylenefuro[3,4-*f*]-1,3-benzodioxol-5(7*H*)-one (vii).[46] To a 0 °C stirred mixture of carboxylic acid **3a** (0.100 g, 0.289 mmol) in THF (5 mL) was added solid tetrabutylammonium fluoride trihydrate (TBAF) (91 mg, 0.289 mmol). The reaction mixture was stirred at 0 °C for 4 h. The pink reaction mixture was diluted with Et_2O (20 mL) and the organic solution was washed with aqueous NaOH (20 mL, 1.0 M), H_2O (20 mL), brine (20 mL), and dried over Na_2SO_4. Removal of the solvent gave the title compound **vii** (41 mg, 0.22 mmol, 76% yield). Yellow amorphous solid. mp 143-145 (dec) °C (lit.[46] mp 263-265 °C). R_f 0.44 (1:1 CH_2Cl_2/petroleum ether). IR (ATR, neat) 3135, 3070, 3046, 3016, 2923, 2855, 1752, 1659, 1609, 1503, 1470, 1391, 1375, 1315, 1236, 1175, 1120, 1105, 1077, 1031, 970, 952, 930, 865, 854, 826, 807, 780, 742 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18 (d, *J* 0.8 Hz, 1H), 7.02 (d, *J* 0.8 Hz, 1H), 6.15 (s, 2H), 5.13 (d, *J* 3.0 Hz, 1H), 5.04 (d, *J* 3.0 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 154.3, 151.8, 150.8, 136.0, 120.0, 104.0, 103.1, 100.3, 90.6 ppm. NMR data matches literature values.[46] [CAS # 1642342-95-7]



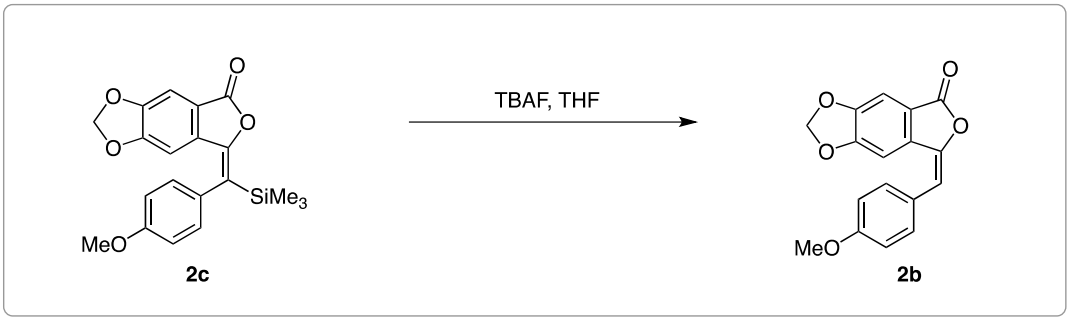
6 7

(*E*)-7-(Iodotrimethylsilylmethylene)furo[3,4-*f*]-1,3-benzodioxol-5(7*H*)-one (7). A modification of a literature procedure was followed.[45] To a stirred solution of ester **6** (0.75 g, 2.7 mmol) in CH_2Cl_2 (30 mL) was added solid I_2 (0.83 g, 3.3 mmol). The mixture was stirred at rt for 60 min and then diluted with Et_2O (100 mL). The organic solution was washed with aqueous $Na_2S_2O_3$ (3 x 50 mL, saturated) and dried over Na_2SO_4. Removal of the solvent in vacuo gave a crude brown solid (1.13 g). Purification by flash chromatography (1:40 ethyl acetate/petroleum ether to 1:30 ethyl acetate/petroleum ether) gave the title compound **7** (0.85 g, 2.2 mmol, 81% yield). Orange amorphous solid. mp 94-96 °C. R_f 0.37 (1:8 EtOAc/petroleum ether). IR (ATR, neat) 2954, 2915, 1759, 1590, 1496, 1468, 1403, 1303, 1246, 1166, 1117, 1080, 1031, 980, 927, 864, 842, 819, 776, 756, 718 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* 0.4 Hz, 1H), 7.22 (d, *J* 0.4 Hz, 1H), 6.17 (s, 2H), 0.39 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 153.4, 152.1, 150.7, 135.5, 122.1, 105.5, 104.4, 103.3, 86.2, 1.0 ppm. HRMS (ESI-FTICR) calcd for $C_{13}H_{13}IO_4Si{\cdot}Na^+$ ($M{\cdot}Na^+$) 410.9520, found 410.9518.

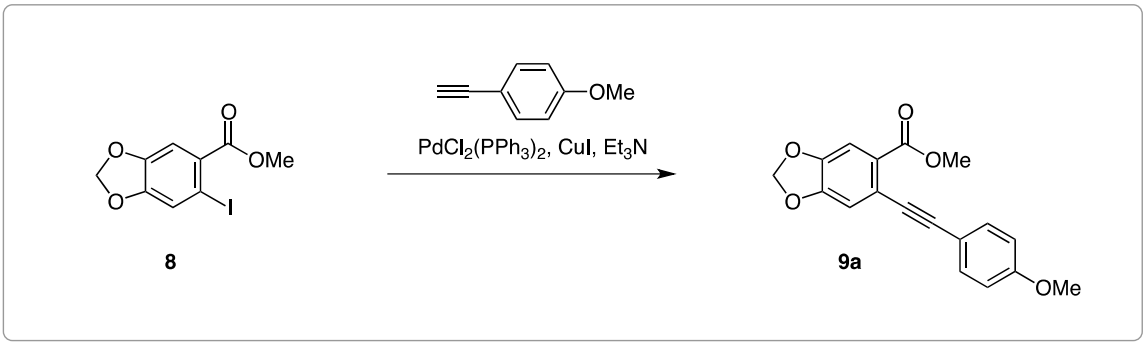


7 2c

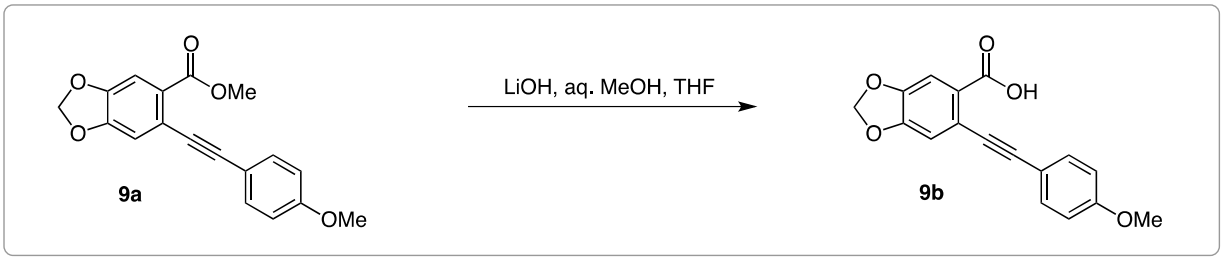
(*Z*)-7-((4'-Methoxyphenyl)trimethylsilylmethylene)furo[3,4-*f*]-1,3-benzodioxol-5(7*H*)-one (2c). A modification of a literature procedure was followed.[45] To a rt stirred solution of iodoalkene 7 (1.00 g, 2.58 mmol) and 4-methoxyphenylboronic acid (0.75 g, 4.8 mmol) in toluene (25 mL) was added $Pd(PPh_3)_4$ (0.28 g, 0.24 mmol) and a solution of Na_2CO_3 (0.94 g, 8.9 mmol) in H_2O (2.5 mL). The reaction mixture was heated to 80 °C for 20 h. The reaction mixture was allowed to cool to rt and then was poured into a saturated solution of NH_4Cl (50 mL) and extracted with EtOAc (4 x 50 mL). The combined organic layers were dried over Na_2SO_4. Removal of the solvent in vacuo gave a dark solid (1.76 g). Purification by flash chromatography (1:20 EtOAc/petroleum ether to 1:10 EtOAc/petroleum ether) gave the title compound **2c** (0.81 g, 2.2 mmol, 85% yield). Yellow amorphous solid. mp 179-181 °C. R_f 0.22 (1:8 EtOAc/petroleum ether). IR (ATR, neat) 2963, 2841, 1749, 1625, 1604, 1507, 1462, 1443, 1409, 1305, 1281, 1241, 1184, 1170, 1108, 1088, 1070, 1031, 992, 933, 912, 895, 836, 785, 758, 736, 723 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* 0.4 Hz, 1H), 6.98 ("AB" quartet, *J* 8.8 Hz, 4H), 6.00 (s, 2H), 5.70 (d, *J* 0.4 Hz, 1H), 3.87 (s, 3H), 0.20 (s, 9H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 158.8, 153.2, 151.2, 149.9, 135.1, 131.0, 129.2, 126.5, 120.9, 114.8, 103.85, 103.78, 102.7, 55.6, -0.4 ppm. HRMS (ESI-FTICR) calcd for $C_{20}H_{20}O_5Si{\cdot}Na^+$ ($M{\cdot}Na^+$) 391.0972, found 391.0969.



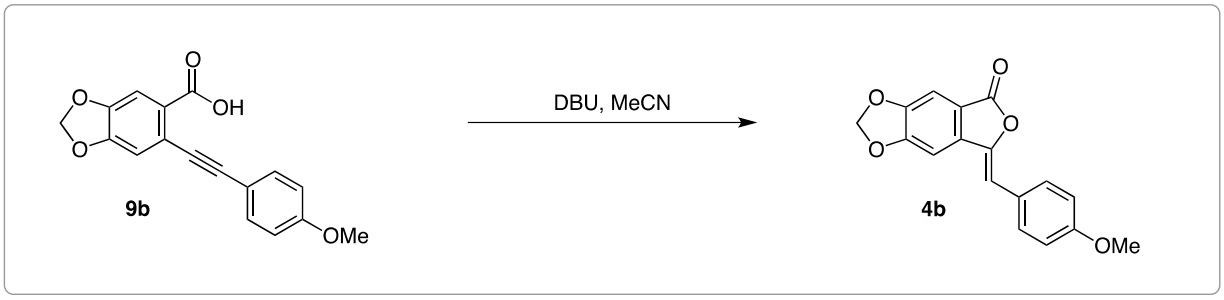
(*E*)-7-((4'-Methoxyphenyl)methylene)furo[3,4-*f*]-1,3-benzodioxol-5(7*H*)-one (2b). To a 0 °C stirred solution of isobenzofuranone **2c** (0.100 g, 0.272 mmol) in THF (5 mL) was added tetrabutylammonium fluoride trihydrate (TBAF) (0.086 g, 0.27 mmol). The reaction was allowed to warm to rt and stirred for 1 h by which time TLC showed complete conversion of the starting material. The reaction mixture was diluted with Et_2O (20 mL) and the organic layer was washed with brine (25 mL) and dried over Na_2SO_4. Removal of the solvent in vacuo gave a crude solid (0.100 g). Purification by flash chromatography (1:40 EtOAc/petroleum ether to 1:10 EtOAc/petroleum ether) gave the title compound **2b** (0.061 g, 0.21 mmol, 76% yield), which gave spectral data that matched the material obtained by desilylation of **2a** (*vide supra*).



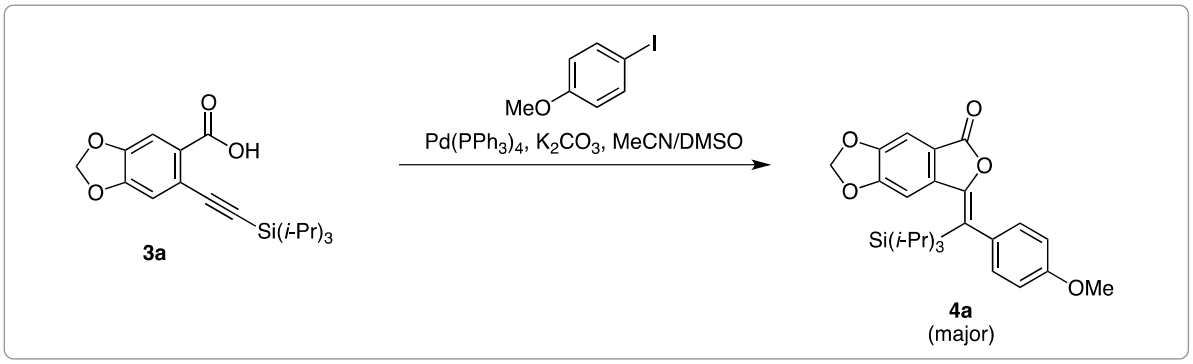
Methyl 6-((4-methoxyphenyl)ethynyl)-1,3-benzodioxole-5-carboxylate (9a). A modification of a literature procedure was followed.[45] To a rt stirred mixture of ester **8** (1.50 g, 4.90 mmol) and 4-ethynylanisole (0.95 mL, 7.3 mmol) in Et_3N (20 mL) was added $PdCl_2(PPh_3)_2$ (0.34 g, 0.49 mmol) followed by CuI (0.019 g, 0.10 mmol). The reaction was heated to 55 °C for 24 h and then allowed to cool to rt. The reaction mixture was poured through a plug of celite, which was washed with CH_2Cl_2 (50 mL). The organic layer was washed with an aqueous solution of HCl (1.0 M, 2 x 100 mL) and brine (100 mL). The solvent was removed in vacuo giving a crude black solid (1.72 g). Purification by flash chromatography (1:40 EtOAc/petroleum ether to 1:30 EtOAc/petroleum ether) gave the title compound **9a** (1.27 g, 4.09 mmol, 81% yield). White amorphous solid. mp 89-93 °C. R_f 0.22 (1:8 EtOAc/petroleum ether). IR (ATR, neat) 2945, 2840, 2204, 1719, 1602, 1567, 1512, 1483, 1456, 1442, 1432, 1404, 1377, 1298, 1247, 1173, 1145, 1106, 1026, 956, 926, 888, 851, 835, 801, 779, 765, 714 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* 8.4 Hz, 2H), 7.43 (d, *J* 0.4 Hz, 1H), 7.02 (d, *J* 0.4 Hz, 1H), 6.88 (d, *J* 8.4 Hz, 2H), 6.05 (s, 2H), 3.92 (s, 3H), 3.83 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 160.0, 150.7, 147.6, 133.4, 126.3, 119.9, 115.8, 114.3, 113.3, 110.5, 102.5, 93.7, 87.5, 55.6, 52.4 ppm. HRMS (ESI-FTICR) calcd for spray dimer $(C_{18}H_{14}O_5)_2 \cdot Na^+$ ($M_2 \cdot Na^+$) 643.1575, found 643.1563.



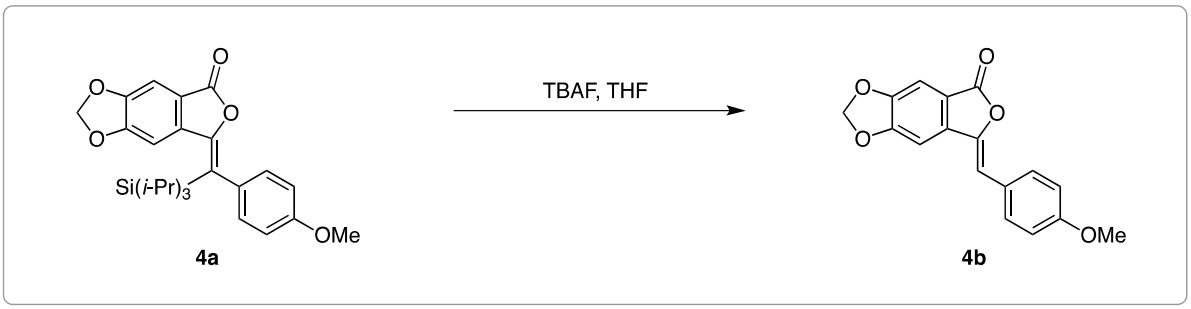
6-((4-Methoxyphenyl)ethynyl)-1,3-benzodioxole-5-carboxylic acid (9b). To a rt stirred solution of ester **9a** (0.224 g, 0.722 mmol) in THF (10 mL) was added a solution of LiOH monohydrate (0.151 g, 3.61 mmol) in MeOH (5 mL) and H_2O (5 mL). The reaction mixture was heated to 50 °C for 40 min by which time TLC showed incomplete conversion to product along with the formation of two UV-active by-products. At this point, the solvent was removed in vacuo giving a brown residue which was taken up in H_2O (30 mL). The aqueous layer was washed with Et_2O (2 x 30 mL) and then acidified by the addition of an aqueous solution of HCl (1.0 M, 3 mL). The acidified aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine (60 mL) and dried over Na_2SO_4. Removal of the solvent in vacuo gave a yellow film (0.201 g). Trituration (CH_2Cl_2/petroleum ether) of the yellow film gave title compound **9b** (note: flash chromatography of a different batch led to decomposition of this material). Light green amorphous solid. mp 170-174 °C. R_f 0.30 (1:1 EtOAc/petroleum ether). IR (ATR, neat) 2912, 2841, 2611, 2205, 1680, 1597, 1568, 1509, 1478, 1414, 1367, 1302, 1268, 1236, 1174, 1152, 1106, 1031, 931, 877, 856, 827, 803, 784, 766, 724 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 12.91 (br s, 1H), 7.43 (d, *J* 8.8 Hz, 2H), 7.36 (s, 1H), 7.14 (s, 1H), 6.99 (d, *J* 8.8 Hz, 2H), 6.16 (s, 2H), 3.79 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 150.0, 147.3, 132.7, 127.4, 117.9, 114.8, 114.4, 112.3, 109.7, 102.5, 92.6, 87.6, 55.3 ppm. HRMS (ESI-FTICR) calcd for spray dimer $(C_{17}H_{12}O_5)_2 \cdot Na^+$ ($M_2 \cdot Na^+$) 615.1262, found 615.1259.



(*Z*)-7-((4'-Methoxyphenyl)methylene)furo[3,4-*f*]-1,3-benzodioxol-5(7*H*)-one (4b).[50] A modification of a literature procedure was followed.[48] To a rt stirred solution of carboxylic acid **9b** (0.050 g, 0.17 mmol) in MeCN (2 mL) was added DBU (1 drop, catalytic). The reaction mixture was stirred at 80 °C for 2.5 h and then allowed to cool to rt. Removal of the solvent in vacuo gave a crude solid product (0.10 g). Purification by flash chromatography (1:4 EtOAc/petroleum ether) gave the title compound **4b** (0.029 g, 0.10 mmol, 58% yield), which gave spectral data that matched the material obtained by desilylation of **4a** (*vide supra*).

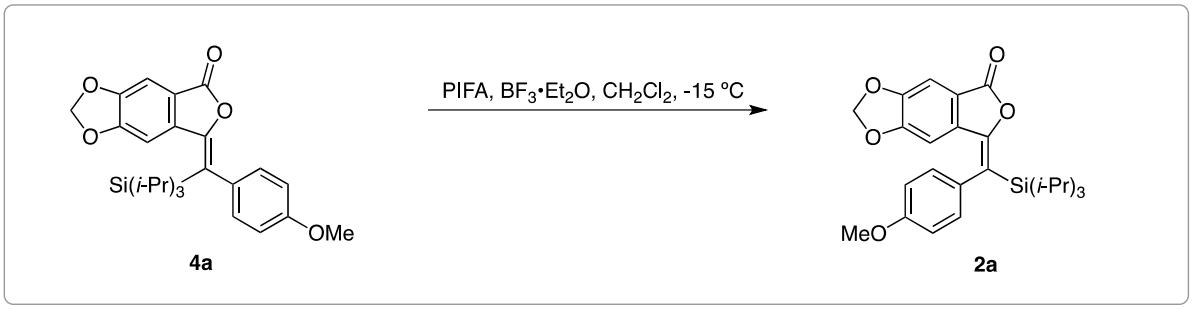


(*E*)-7-((4'-Methoxyphenyl)triisopropylsilylmethylene)furo[3,4-*f*]-1,3-benzodioxolo-5(7*H*)-one (4a). A modification of a literature procedure was followed.[50] A stirred solution of carboxylic acid **3a** (0.150 g, 0.433 mmol) in MeCN (14 mL) and DMSO (2 mL) was purged with Ar gas for 30 min. To this solution was added 4-iodoanisole (0.122 g, 0.520 mmol) and $Pd(PPh_3)_4$ (0.050 g, 0.043 mmol) and purging with Ar was resumed for another 20 min. Finally, K_2CO_3 (0.239 g, 1.73 mmol) was added to the solution, which was purged for another 5 min then heated to 80 ˚C for 24 h. The reaction mixture was cooled to rt then partitioned between water (15 mL) and Et_2O (15 mL). Removal of solvent in vacuo gave a crude brown solid (0.22 g). Purification by flash chromatography (1:25 EtOAc/petroleum ether to 1:15 EtOAc/petroleum ether) gave the title compound **4a** (0.110 g, 0.243 mmol, 57% yield). Average yield for six runs 57%. White amorphous solid. mp 212-215 °C. R_f 0.20 (1:8 EtOAc/petroleum ether). IR (ATR, neat) 2948, 2866, 1759, 1607, 1586, 1503, 1474, 1384, 1364, 1304, 1245, 1169, 1106, 1080, 1028, 987, 931, 908, 881, 839, 781, 766, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (s, 1H), 7.19 (s, 1H), 7.01 (d, *J* 8.7 Hz, 2H), 6.85 (d, *J* 8.7 Hz, 2H), 6.16 (s, 2H), 3.81 (s, 3H), 1.45 (sept, *J* 7.5 Hz, 3H), 1.11 (d, *J* 7.5 Hz, 18H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.1, 158.1, 153.4, 151.4, 150.0, 134.7, 132.9, 129.6, 124.6, 122.5, 113.5, 104.3, 103.3, 103.2, 55.5, 19.5, 14.2 ppm. HRMS (ESI-FTICR) calcd for $C_{26}H_{32}O_5Si{\cdot}Na^+$ ($M{\cdot}Na^+$) 475.1911, found 475.1908.

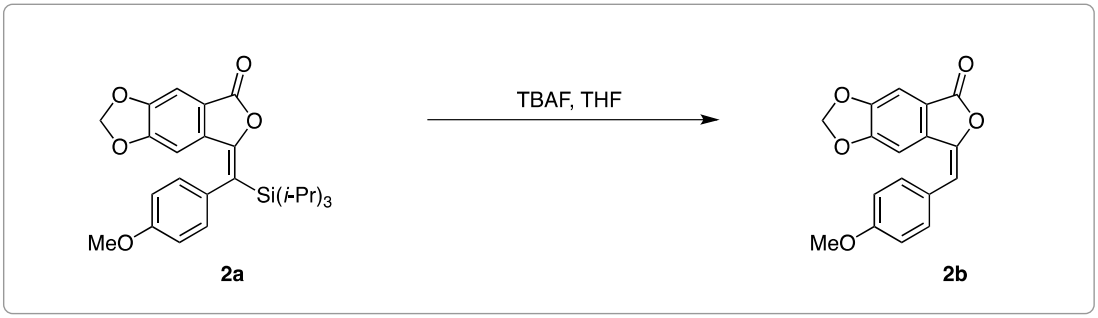


(*Z*)-7-((4'-Methoxyphenyl)methylene)furo[3,4-*f*]-1,3-benzodioxol-5(7*H*)-one (4b).[50] To a 0 °C stirred solution of isobenzofuranone **4a** (0.150 g, 0.330 mmol) in THF (5 mL) was added tetrabutylammonium fluoride trihydrate (TBAF) (0.104 g, 0.330 mmol). The reaction mixture was stirred at 0 °C for 3 h and then allowed to warm to rt. The reaction mixture was treated with H_2O (30 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (80 mL) and dried over Na_2SO_4. Removal of the solvent in vacuo gave a crude white solid (0.17 g). Purification by flash chromatography (1:10 EtOAc/petroleum ether to 1:4 EtOAc/petroleum ether) gave the title compound **4b** (0.077 g, 0.26 mmol, 79% yield). White amorphous solid. mp 209-213 °C (lit.[50] mp 210-215 °C). R_f 0.23 (1:4 EtOAc/petroleum ether). IR (ATR, neat) 3048, 2926, 1749, 1656, 1602, 1508, 1496, 1474, 1397, 1325, 1307, 1292, 1257, 1225, 1169, 1115, 1070, 1019, 964, 935, 895, 854, 818, 778, 714 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* 8.6 Hz, 2H), 7.21 (d, *J* 0.4 Hz, 1H), 7.06 (d, *J*

0.4 Hz, 1H), 6.93 (d, *J* 8.6 Hz, 2H), 6.20 (s, 1H), 6.15 (s, 2H), 3.85 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 159.9, 154.3, 150.0, 143.3, 138.0, 131.8, 126.2, 117.8, 114.5, 106.4, 104.1, 103.0, 99.1, 55.6 ppm. HRMS (ESI-FTICR) calcd for spray dimer $(C_{17}H_{12}O_5)_2{\cdot}Na^+$ ($M_2{\cdot}Na^+$) 615.1262, found 615.1259. [CAS # 55159-68-7]



(*Z*)-7-((4'-Methoxyphenyl)triisopropylsilylmethylene)furo[3,4-*f*]-1,3-benzodioxolo-5(7*H*)-one (2a). To a -15 °C (external ice/salt/acetone bath) stirred solution of isobenzofuranone **4a** (0.214 g, 0.473 mmol) in CH_2Cl_2 (15 mL) was phenyliodine(III) bis(trifluoroacetate) (PIFA) (0.244 g, 0.568 mmol) followed by a solution of $BF_3{\cdot}Et_2O$ in dissolved in CH_2Cl_2 (15 mL). The reaction mixture was stirred at -15 °C for 25 min and the solvent was removed in vacuo giving a crude brown oil (0.33 g). Purification by flash chromatography (1:30 EtOAc/petroleum ether to 1:20 EtOAc/petroleum ether) gave the title compound **2a** (0.123 g, 0.272 mmol, 57% yield). Off-white amorphous solid. mp 155-160 (dec) °C. R_f 0.26 (1:8 EtOAc/petroleum ether). IR (ATR, neat) 2942, 2864, 1763, 1604, 1508, 1461, 1378, 1311, 1286, 1242, 1167, 1103, 1087, 1066, 1027, 988, 936, 912, 882, 862, 835, 812, 795, 779, 740, 718 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* 0.4 Hz), 7.09 (d, *J* 8.4 Hz, 2H), 6.95 (d, *J* 8.4 Hz, 2H), 6.00 (s, 2H), 5.49 (d, *J* 0.4 Hz, 1H), 3.87 (s, 3H), 1.37 (sept, *J* 7.6 Hz, 3H), 1.07 (d, *J* 7.6 Hz, 18H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 158.8, 153.3, 151.9, 149.8, 135.0, 131.5, 129.9, 124.9, 120.9, 114.6, 104.2, 103.7, 102.7, 55.6, 19.3, 12.6 ppm. HRMS (ESI-FTICR) calcd for $C_{26}H_{32}O_5Si{\cdot}Na^+$ ($M{\cdot}Na^+$) 475.1911, found 475.1909.



(*E*)-7-((4'-Methoxyphenyl)methylene)furo[3,4-*f*]-1,3-benzodioxol-5(7*H*)-one (2b). To a 0 °C stirred solution of isobenzofuranone **2a** (0.050 g, 0.11 mmol) in THF (5 mL) was added tetrabutylammonium fluoride trihydrate (TBAF) (0.040 g, 0.12 mmol). The reaction mixture was stirred at 0 °C for 1 h and then diluted with H_2O (30 mL). The aqueous solution was extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4. Removal of the solvent in vacuo gave a cream-colored amorphous solid (0.042 g). Purification by flash chromatography (1:25 EtOAc/petroleum ether to 1:10 EtOAc/petroleum ether) gave the title compound **2b** (0.022 g, 0.074, 68% yield). White amorphous solid. mp 154-157 °C. R_f 0.27 (1:4 EtOAc/petroleum ether). IR (ATR, neat) 2928, 1759, 1661, 1605, 1510, 1501, 1474, 1439, 1396, 1359, 1277, 1247, 1172, 1157, 1108, 1025, 979, 927, 868, 845, 822, 780, 732, 720 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.35 (dd, *J* 0.8, 9.2 Hz, 2H), 7.20 (d, *J* 0.8 Hz, 1H), 6.97 (d, *J* 8.4 Hz, 2H), 6.87 (s, 1H), 6.75 (s, 1H), 6.08 (s, 2H), 3.87 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 159.9, 153.6, 150.3, 146.1, 134.5, 130.8, 125.4, 121.2, 114.6, 112.0, 104.1, 103.0, 102.5, 55.6 ppm. HRMS (ESI-FTICR) calcd for spray dimer $(C_{17}H_{12}O_5)_2 \cdot Na^+$ ($M_2 \cdot Na^+$) 615.1262, found 615.1258.

Supplemental Data

Copies of ^{1}H and ^{13}C NMR spectra are available as part of the supplemental data.

Acknowledgements

We gratefully acknowledge the Donors of the American Chemical Society Petroleum Research Fund for support of this research. We also acknowledge the Patchett Foundation (MEL, BFO, DMD, and CAM), Perkin Foundation (KBV), Dr. Todd Patterson (MJG), and Hobart and William Smith Colleges for support of this research in the form of summer student stipends. We were greatly aided in identifying the PIFA-mediated isomerization after a conversation with Professor Yasayuki Kita.

References

1. Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115-136. https://doi.org/10.1021/cr950027e
2. Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134-7186. https://doi.org/10.1002/anie.200601872
3. Pellissier, H. *Chem. Rev.* **2013**, *113*, 442-524. https://doi.org/10.1021/cr300271k
4. Cacchi, S. *J. Organomet. Chem.* **1999**, *576*, 42-64. https://doi.org/10.1016/S0022-328X(98)01051-1
5. Balme, G.; Bouyssi, D.; Lomberget, T.; Monteiro, N. *Synthesis* **2003**, 2115-2134. https://doi.org/10.1055/s-2003-42082
6. Rossi, R.; Bellina, F.; Biagetti, M.; Catanese, A.; Mannina, L. *Tetrahedron Lett.* **2000**, *41*, 5281-5286. https://doi.org/10.1016/S0040-4039(00)00806-6
7. Cavicchiolo, M.; Bouyssi, D.; Goré, J.; Balme, G. *Tetrahedron Lett.* **1996**, *37*, 1429-1432. https://doi.org/10.1016/0040-4039(96)00063-9
8. Cavicchioli, M.; Decortiat, S.; Bouyssi, D.; Goré, J.; Balme, G. *Tetrahedron* **1996**, *52*, 11463-11478. https://doi.org/10.1016/0040-4020(96)00637-0
9. Bouyssi, D.; Balme, G. *Synlett* **2001**, 1191-1193. https://doi.org/10.1055/s-2001-15147
10. Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B.R. *J. Org. Chem.* **1992**, *57*, 976-982. https://doi.org/10.1021/jo00029a035

11. Bouyssi, D.; Gore, J.; Balme, G. *Tetrahedron Lett.* **1992**, *33*, 2811-2814. https://doi.org/10.1016/S0040-4039(00)78865-4
12. Wang, Z.; Lu, X. *J. Org. Chem.* **1996**, *61*, 2254-2255. https://doi.org/10.1021/jo9522466
13. Wolf, L. B.; Tjen, K. C. M. F.; Rutjes, F. P. J. T. Hiemstra, H.; Schoemaker, H. E. *Tetrahedron Lett.* **1998**, *30*, 5081-5084. https://doi.org/10.1016/S0040-4039(98)00910-1
14. Wolf, L. B.; Tjen, K. C. M. F.; ten Brink, H. T.; Blaauw, R. H.; Hiemstra, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2002**, *344*, 70-83. https://doi.org/10.1002/1615-4169(200201)344:1<70::AID-ADSC70>3.0.CO;2-1
15. O'Neal, W. G.; Roberts, W. P.; Ghosh, I.; Jacobi, P. A. *J. Org. Chem.* **2005**, *70*, 7243-7251. https://doi.org/10.1021/jo050907l
16. Arcadi, A. *Synlett* **1997**, 941-943. https://doi.org/10.1055/s-1997-927
17. Bouyssi, D.; Cavicchioli, M.; Balme, G. *Synlett* **1997**, 944-946. https://doi.org/10.1055/s-1997-935
18. Karstens, W. F. J.; Stol, M.; Rutjes, F. P. J. T.; Kooijman, H.; Spek, A. L.; Hiemstra, H. *J. Organomet. Chem.* **2001**, *624*, 244-258. https://doi.org/10.1016/S0022-328X(00)00935-9
19. Kumar, V.; Prasad, A. K.; Parmar, V. S. *Nat. Prod. Rep.* **2003**, *20*, 565-583. https://doi.org/10.1039/b303648k
20. Michl, J.; Ingrouille, M. J.; Simmonds, M. S. J.; Heinrich, M. *Nat Prod. Rep.* **2014**, *31*, 676-685. https://doi.org/10.1039/c3np70114j
21. Couture, A.; Deniau, E.; Grandclaudon, P.; Rybalko-Rosen, H.; Léonce, S.; Pfeiffer, B.; Renard, P. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3557-3559. https://doi.org/10.1016/S0960-894X(02)00794-1
22. Castedo, L.; Guitián, E.; Saá, J. M.; Suau, R. *Heterocycles* **1982**, *19*, 279-280. https://doi.org/10.3987/R-1982-02-0279
23. Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 1432-1437. https://doi.org/10.1021/jo048007c
24. Couture, A.; Deniau, E.; Grandclaudon, P.; Lebrun, S. *Synlett* **1997**, 1475-1477.
25. Rys, V.; Couture, A.; Deniau, E.; Grandclaudon, P. *Eur. J. Org. Chem.* **2003**, 1231-1237. https://doi.org/10.1002/ejoc.200390177
26. Castedo, L.; Guitián, E.; Saá, J. M.; Suau, R. *Tetrahedron Lett.* **1982**, *23*, 457-458. https://doi.org/10.1016/S0040-4039(00)86859-8
27. Estévez, J. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **1995**, *51*, 10801-10810. https://doi.org/10.1016/0040-4020(95)00644-N
28. Benesch, L.; Bury, P.; Guillaneux, D.; Houldsworth, S.; Wang, X.; Snieckus, V. *Tetrahedron Lett.* **1998**, *39*, 961-964. https://doi.org/10.1016/S0040-4039(97)10670-0
29. Kim, J. K.; Kim, Y. H.; Nam, H. T.; Kim, B. T.; Heo, J.-N. *Org. Lett.* **2008**, *10*, 3543-3546. https://doi.org/10.1021/ol801291k
30. Estévez, J. C.; Villaverde, M. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **1995**, *51*, 4075-4082. https://doi.org/10.1016/0040-4020(95)00124-Q

31. King, B. T.; Kroulík, J.; Robertson, C. R.; Rempala, P.; Hilton, C. L.; Korinek, J. D.; Gortari, L. M. *J. Org. Chem.* **2007**, *72*, 2279-2288. https://doi.org/10.1021/jo061515x
32. Zhai, L.; Shukla, R.; Wadumethrige, S.H.; Rathore, R. *J. Org. Chem.* **2010**, *75*, 4748-4760. https://doi.org/10.1021/jo100611k
33. Grzybowski, M.; Skonieczny, K.; Butenschön, H.; Gryko, D. T. *Angew. Chem. Int. Ed.* **2013**, *52*, 9900-9930. https://doi.org/10.1002/anie.201210238
34. Kita, Y.; Gyoten, M.; Ohtsubo, M.; Tohma, H.; Takada, T. *Chem. Commun.* **1996**, 1481-1482. https://doi.org/10.1039/cc9960001481
35. Tohma, H.; Kita, Y. *Top. Curr. Chem.* **2003**, *224*, 209-248. https://doi.org/10.1007/3-540-46114-0_8
36. Olivera, R.; SanMartín, R.; Pascual, S.; Herrero, M.; Domínguez, E. *Tetrahedron Lett.* **1999**, *40*, 3479-3480. https://doi.org/10.1016/S0040-4039(99)00428-1
37. Niphakis, M. J.; Georg, G. I. *J. Org. Chem.* **2010**, *75*, 6019-6022. https://doi.org/10.1021/jo101051w
38. van Loon, A. A.; Holton, M. K.; Downey, C. R.; White, T. M.; Rolph, C. E.; Bruening, S. R.; Li, G.; Delaney, K. M.; Pelkey, S. J.; Pelkey, E. T. *J. Org. Chem.* **2014**, *79*, 8049-8058. https://doi.org/10.1021/jo501185f
39. Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959-6964. https://doi.org/10.1021/ja00175a033
40. Takeda, S.; Abe, H.; Takeuchi, Y.; Harayama, T. *Tetrahedron* **2007**, *63*, 396-408. https://doi.org/10.1016/j.tet.2006.10.059
41. Matveenko, M.; Kokas, O. J.; Banwell, M. G.; Willis, A. C. *Org. Lett.* **2007**, *9*, 3683-3685. https://doi.org/10.1021/ol701552r
42. Yamada, S.; Morizono, D.; Yamamoto, K. *Tetrahedron Lett.* **1992**, *33*, 4329-4332. https://doi.org/10.1016/S0040-4039(00)74252-3
43. Lima, P. C.; Lima, L. M.; da Silva, K. C. M.; Léda, P. H. O.; de Miranda, A. L. P.; Fraga, C. A. M.; Barreiro, E.J. *Eur. J. Med. Chem.* **2000**, *35*, 187-203. https://doi.org/10.1016/S0223-5234(00)00120-3
44. Keck, G. W.; Wager, T. T.; Rodriguez, J. F. D. *J. Am. Chem. Soc.* **1999**, *121*, 5176-5190. https://doi.org/10.1021/ja9826688
45. Yao, T.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 5936-5942. https://doi.org/10.1021/jo034308v
46. Gadakh, S. K.; Sudalai, A. *RSC Adv.* **2014**, *4*, 57658-57661. https://doi.org/10.1039/C4RA10372F
47. Boger, D. L.; Wolkenberg, S. E. *J. Org. Chem.* **2000**, *65*, 9120-9124. https://doi.org/10.1021/jo0012546
48. Kanazawa, C.; Terada, M. *Tetrahedron Lett.* **2007**, *48*, 933-935. https://doi.org/10.1016/j.tetlet.2006.12.015
49. Terada, M.; Kanazawa, C.; Yamanaka, M. *Heterocycles* **2007**, *74*, 819-825. https://doi.org/10.3987/COM-07-S(W)73
50. Lee, N. S.; Lim, C. K.; Cho, T. S.; Won, C. H.; Moon, D. W.; Park, I. S.; Kim, M. G.; Min, Y. S.; Chung, J. S.; Cho, Y. B.; No, Y. S. *Yakhak Hoeji* **1974**, *18*, 59-73; *Chem. Abstr.* **1975**, *82*, 139878.

