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Synthesis of 8-Aryl-Substituted Coumarins Based on Ring-Closing Metathesis and Suzuki−Miyaura Coupling: Synthesis of a Furyl Coumarin Natural Product from *Galipea panamensis*

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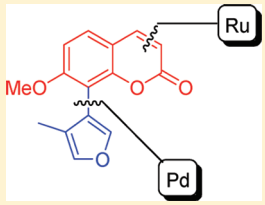
Supporting Information

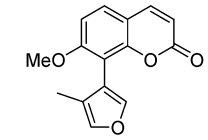
ABSTRACT: The synthesis of 7-methoxy-8-(4-methyl-3-furyl)-2*H*-chromen-2-one, a natural product with antileishmanial activity recently isolated from the plant *Galipea panamensis*, is described. The key step is a Suzuki−Miyaura coupling of a furan-3-boronic acid and an 8-halocoumarin, which is advantageously synthesized using a ring-closing metathesis reaction. Several non-natural analogues are also available along these lines.



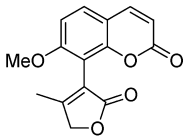
INTRODUCTION

The various forms of leishmaniasis are among the most serious tropical diseases with more than two million new infections per year. Like malaria and trypanosomiasis, it is caused by protozoan parasites which are transferred to humans by the bites of vector insects.[1−3] It is estimated that 350 million people, mostly living in the poorest countries, are threatened by infection with any form of leishmaniasis. This situation might become even more problematic by a worryingly increasing occurrence of leishmaniases and HIV coinfection which has been observed over the past few years.[4] Undesirable side effects of the established antimony-based drugs and the development of drug resistance have been driving forces for a more systematic phytochemical investigation of numerous medicinal plants which have traditionally been used for the treatment of leishmaniases.[1,3,5,6] Among these, various plants of the family Rutaceae, genus *Galipea*, have been investigated and were found to produce some structurally diverse metabolites such as quinolines or chromones with promising antiprotozoal activity.[7,8] Very recently, this observation prompted Sáez, Otálvaro et al. to investigate the plant *Galipea panamensis*, a small tree found in central America.[9] Although first described in 1970 by Elias,[10] no phytochemical investigations on *Galipea panamensis* had been reported previously. In their study, the authors report the isolation and structural elucidation of five coumarins, inter alia the novel 8-(3′-furyl)coumarin **1**, which was found to be active against the amastigote form of *Leishmania panamensis* with an effective concentration of 10.5 μg/mL.[9] Structurally related coumarins had earlier been isolated from other plants of the family Rutaceae. For instance, microminutin (**2**) with a butenolide substituent at the 8-position occurs in *Micromelum minutum*[11−13] and *Murraya paniculata*.[14] This compound was tested for its suppressive effect on nitric oxide generation.[15] A similar C-6-substituted coumarin is micromelin,[16] which has been isolated from *Micromelum integerrimum*[17] and *Micromelum minutum*[18] and is moderately cytotoxic against different tumor cell lines. Deoxymicromelin is a semisynthetic non-natural derivative, which was found to be completely inactive against the same tumor cell lines (Chart 1).[17]

Chart 1. Structures of Naturally Occurring 8-Furylcoumarins



7-Methoxy-8-(4-methyl-3-furyl)-2*H*-chromen-2-one (**1**)



Microminutin (**2**)

We are aware of only two reports describing synthetic studies directed at these compounds. Both describe syntheses of microminutin (**2**), starting from allyl ethers of umbelliferone which undergo a regioselective Claisen rearrangement to C-8-allylated coumarins. The allyl substituents are subsequently elaborated to the butenolide.[19,20] Intrigued by the interesting biological activities reported for coumarins in general[21−23] and for the novel natural product **1** in particular, we investigated synthetic routes to 7-methoxy-8-(4-methyl-3-furyl)-2*H*-chromen-2-one (**1**) using a Suzuki−Miyaura-coupling[24−26] reaction of an 8-halo-7-methoxycoumarin and a 4-methylfuran-3-boronic acid.

RESULTS AND DISCUSSION

Umbelliferone (**3**) undergoes a highly regioselective iodination at C-8 using KI_3 in aqueous ammonia, as previously reported in the literature.[27−29] Unfortunately, all attempts to improve the unsatisfactory yield of 8-iodoumbelliferone and to separate the product from unreacted starting material failed. Therefore, the

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Scheme 1. Syntheses of 8-Halocoumarins

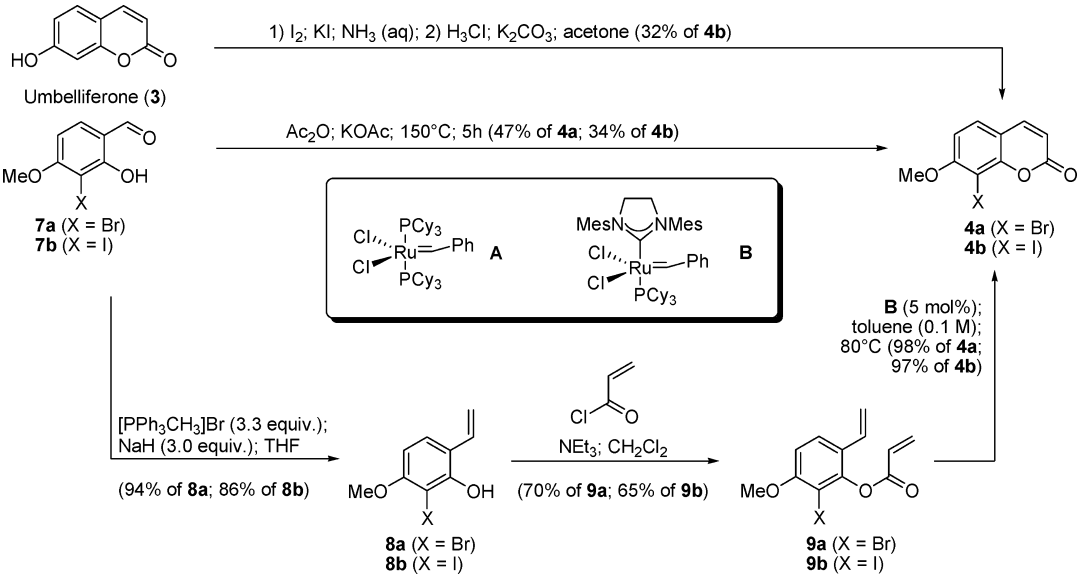
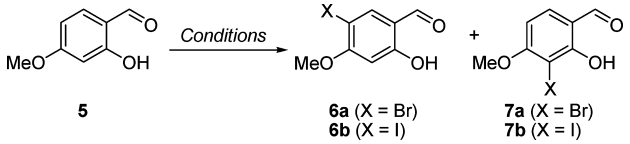


Table 1. Regioselective Halogenation of Aldehyde 5



entry	solvent	additive (equiv)	reagent[a]	conversion[b] (%)	ratio 6:7[b]	products (yield, %)
1	CH_2Cl_2		Br_2	>98	>19:1	**6a** (98)
2	CH_2Cl_2	$AlCl_3$ (1.0)	Br_2	90	<1:19	**7a** (83)
3	H_3CCN		NIS	94	2:3	nd
4	H_3CCN	*p*-TosOH (0.5)	NIS	80	5:1	**6b** (67)
						7b (13)
5	H_3CCN	$AlCl_3$ (1.0)	NIS	55	1:10	nd
6	CH_2Cl_2	NEt_3 (2.0)	NIS	83	2:1	nd
7	CH_2Cl_2	$AlCl_3$ (1.0)	NIS	90	<1:19	**7b** (90)

[a]NIS: *N*-iodosuccinimide. [b]Conversion and ratio of products were determined from ^{1}H NMR spectra of the crude reaction mixture.

crude reaction mixture obtained after iodination was treated with methyl iodide in the presence of a base. At this stage, the isolation of pure 8-iodo-7-methoxycoumarin (**4b**) was possible, albeit in only 32% yield based on **3**, along with 7-methoxycoumarin (Scheme 1). Unfortunately, this compound could not be halogenated regioselectively and had to be discarded. For these reasons, we thought that a synthesis involving the construction of the heterocycle after halogenation of the aromatic core might be overall more efficient. The commercially available aldehyde **5** was identified as a suitable starting material, and its regioselective halogenation was investigated using a variety of different conditions (Table 1).

Upon treatment of **5** with bromine in CH_2Cl_2, the undesired regioisomer **6a** was obtained in nearly quantitative yield,[30,31] which might be attributed to steric reasons (entry 1). In contrast, addition of one equivalent of $AlCl_3$ lead to a reversal of the regioselectivity.[32] Under these conditions, **7a** was observed exclusively and could be isolated in 83% yield (entry 2). Presumably, the phenol forms a chelate complex with the Lewis acid, which then directs the electrophile to the ortho position. A previous synthesis of this regioisomer proceeded via an organomercury compound which was subsequently cleaved with bromine.[33] For the synthesis of the iodo-analogue **7b**, NIS was used as a reagent. Initially, we tested acetonitrile as a solvent, however, either conversion or regioselectivity were unsatisfactory (entries 3−5). Synthetically useful results were eventually obtained in CH_2Cl_2 with $AlCl_3$ as a Lewis acid (entry 7).

For the conversion of **7a** and **7b** to the corresponding coumarins **4a** and **4b**, respectively, a Perkin condensation involving treatment with acetic anhydride and KOAc was first investigated.[34] Unfortunately, high reaction temperatures of 150 °C were necessary, resulting in modest yields of 47% in the case of bromo derivative **4a** and 34% in the case of iodo derivative **4b**. For these reasons, an olefin metathesis based route was investigated. Wittig olefination of **7a,b**, followed by treatment with acryloyl chloride gives acrylates **9a,b**, which undergo ring-closing metathesis in the presence of second-generation Grubbs' catalyst **B**. Excellent yields of **4a,b** were obtained with this catalyst if the initial substrate concentrations did not exceed 0.1 M.[35] Higher substrate concentrations, or the use of the less active first generation catalyst **A**, results in incomplete conversion, very low yields and occasionally in the formation of Rauhut−Currier products.[36] Therefore, the synthesis proceeding via RCM of acrylates **9** appears to be

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advantageous overall, with yields of 64% of **4a** and 54% of **4b**, starting from aldehydes **7a** or **7b**, respectively (Scheme 1).

The synthesis of the hitherto unknown 4-methylfuran-3-boronic acid (**12a**) was accomplished from 3-iodo-4-methylfuran (**11**), which is available from alkyne **10** in few steps following a literature procedure.[37] Iodofuran **11** was first treated with 2 equiv of *t*-BuLi and then with trimethyl borate. Acidic hydrolysis of the intermediate boronate yields the required boronic acid **12a** in nearly quantitative yield, based on iodofuran **11**. In the next step, the Suzuki–Miyaura coupling of **12a** and coumarins **4a**,**b** was optimized by testing different precatalysts (Scheme 2 and Table 2).

Scheme 2. Synthesis of 4-Methylfuran-3-boronic Acid (12a) and Suzuki–Miyaura Coupling with 8-Halocoumarins 4a and 4b

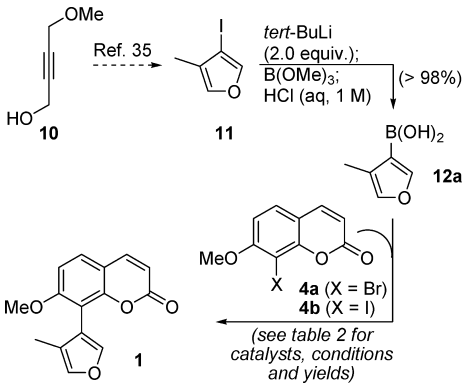

Table 2. Optimization of Conditions for the Suzuki–miyaura Coupling Reactions[a]

entry	coumarin **4**	X	precatalyst	yield (%)
1	**4a**	Br	$Pd(PPh_3)_4$	39
2	**4a**	Br	$Pd(PPh_3)_2Cl_2$	51
3	**4b**	I	$Pd(PPh_3)_4$	32
4	**4b**	I	Pd/C	29
5	**4b**	I	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	57
6	**4b**	I	$Pd(PPh_3)_2Cl_2$	77

[a]Experimental conditions: 8-halocoumarin **4** (1.0 equiv), boronic acid **12a** (1.5 equiv), precatalyst (5 mol %), Cs_2CO_3 (2.0 equiv), toluene, 110 °C.

A successful Suzuki–Miyaura coupling reaction[24,38] of an electron-rich, sterically congested aryl bromide and an electron-rich aryl boronic acid has recently been achieved using $Pd(PPh_3)_4$ as a precatalyst and cesium carbonate as a base.[39] Application of these conditions to the coupling of **4a** and **12a**, however, resulted in only moderate yields of **1** below 40% (Table 2, entry 1). Unfortunately, the presumably more reactive iodide **4b** gave an even lower yield of 32% with this precatalyst (Table 2, entry 3), and a comparable result was obtained with commercial Pd/C[40] (Table 2, entry 4). Significantly improved yields were eventually observed with Pd(II) precatalysts: starting from iodo coumarin **4b** and using $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ as a precatalyst, the desired coupling product **1** was isolated in 57% yield. The best precatalyst for this particular cross coupling reaction is $Pd(PPh_3)_2Cl_2$, with isolated yields of 51% from **4a** (Table 2, entry 2) and 77% from **4b** (Table 2, entry 6).

All spectroscopical data of synthetic 7-methoxy-8-(4-methyl-3-furyl)-2*H*-chromen-2-one (**1**) match those reported by Sáez, Otalvaro et al. for the natural product isolated from *Galipea panamensis* perfectly well.[9] While these authors obtained compound **1** from the extraction as an amorphous powder, we were able to obtain crystals suitable for single-crystal X-ray structure analysis by recrystallization from MTBE–hexane mixtures. Crystallographic analysis leads to the confirmation of the molecular structure assigned to compound **1**. The planes of the coumarin and the 3-methylfuran are not perpendicular but adopt an angle of approximately 60°, as can be seen from the C2–C3–C11–C12 torsion angle of 62.0(3)° and the C4–C3–C11–C14 torsion angle of 58.7(3)°. Nonclassical hydrogen bonds as well as π–π and C–H···π interactions contribute to the solid structure.

We then applied the optimized conditions for the Suzuki–Miyaura coupling of 8-halo-7-methoxycoumarins **4** to the synthesis of several analogues (Table 3). The 7-methoxy-8-phenylcoumarin **13a** was synthesized from phenylboronic acid **12b** and iodocoumarin **4b** in a yield similar to that for compound **1** under otherwise identical conditions (Table 3, entry 1). This compound had previously been synthesized from **4b** and iodobenzene in a mixed Ullmann-coupling mediated by copper bronze; unfortunately, no yield was reported. Over the past few years, potassium organotrifluoroborates have emerged as valuable, highly reactive reagents in Suzuki–Miyaura reactions.[41,42] In particular, application of these reagents often results in reduced amounts of byproducts originating from oxidation of the organoboron compound, such as phenols or homocoupling products. These beneficial properties have been attributed to a slow hydrolysis of the organotrifluoroborates under the reaction conditions, ensuring the presence of fluoride ions (which promote the reduction of phosphine containing Pd(II) precatalysts) and a low stationary concentration of boronic acid, which has been proposed as a rationale for the reduced amount of homocoupling products.[43,44] As a consequence, water is often used as a cosolvent, e.g., in combination with dioxane or alcohols, for cross-coupling reactions involving organotrifluoroborates.[45] However, dioxane–water mixtures have, in some cases, also been used advantageously for the coupling of aryl bromides and boronic acids.[46]

We found that the Suzuki–Miyaura reaction of **4b** and phenylboronic acid (**12b**) in aqueous dioxane results in a significantly decreased yield of 58% (Table 3, entry 2), whereas a quantitative conversion to **13a** was achieved in this solvent system with the analogous organotrifluoroborate **12c** (Table 3, entry 3). Very similar results were obtained for the synthesis of a benzodioxolane substituted coumarin **13b** (Table 3, entries 4–6), which becomes available in quantitative yield if **12e** is used. Three further examples (Table 3, entries 7–9) proceed with nearly quantitative yields of the corresponding 8-aryl oumarins **13c**,**d**,**e**.

CONCLUSIONS

In summary, we report the first synthesis and single-crystal X-ray structure analysis of a naturally occurring 8-furylcoumarin recently isolated from *Galipea panamensis* using a Suzuki–Miyaura cross-coupling reaction of an 8-halocoumarin and a furylboronic acid. Conventional syntheses of the required 8-halo coumarins turned out to be unsatisfactory due to low overall yields and harsh reaction conditions, and we therefore devised an olefin metathesis-based synthesis as a viable

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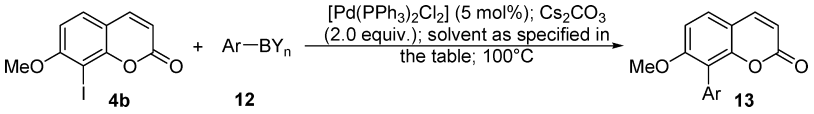
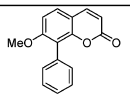
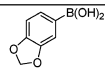
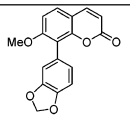
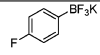
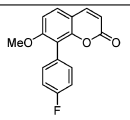
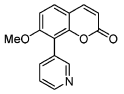
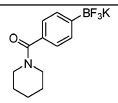
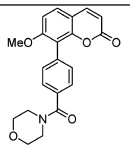
Table 3. Synthesis of 8-Arylcoumarin Analogues of Compound 1



entry	Ar-BY$_n$	12	Solvent	Product	13 (Yield)
1		12b	toluene		13a (75%)
2		12b	dioxane/water (4 : 1)		13a (58%)
3		12c	dioxane/water (4 : 1)		13a (> 98%)
4		12d	toluene		13b (78%)
5		12d	dioxane/water (4 : 1)		13b (67%)
6		12e	dioxane/water (4 : 1)		13b (> 98%)
7		12f	dioxane/water (4 : 1)		13c (98%)
8		12g	dioxane/water (4 : 1)		13d (95%)
9		12h	dioxane/water (4 : 1)		13e (94%)

alternative. Excellent yields of other 8-arylcoumarins were obtained using potassium organotrifluoroborates as coupling reagents.

EXPERIMENTAL SECTION

5-Bromo-2-hydroxy-4-methoxybenzaldehyde (6a). A solution of aldehyde **5** (912 mg, 6.0 mmol) in dichloromethane (24 mL) was cooled to −20 °C. Then a solution of bromine (957 mg, 309 μL, 6.0 mmol) in dichloromethane (10 mL) was added over 20 min. It was stirred overnight while warming to room temperature. Then a saturated solution of Na_2SO_3 (5 mL) was added. The aqueous layer was extracted three times with dichloromethane (in each case 25 mL). It was dried over magnesium sulfate, filtered, and concentrated in vacuo. After column chromatography, aldehyde **6a** was isolated as a colorless solid (1352 mg, 5.9 mmol, 98%): mp 118−120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.42 (s, 1H), 9.67 (s, 1H), 7.66 (s, 1H), 6.46 (s, 1H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.6, 163.7, 162.5, 137.2, 115.7, 102.1, 100.4, 56.7; IR (neat) ν 2923 (w), 1638 (s), 1619 (s), 1490 (m), 1442 (m), 1365 (s), 1273 (s), 1207 (s); HRMS (EI) calcd for $C_8H_7O_3$[79]Br $[M]^+$ 229.9579, found 229.9579; MS (EI) m/z 232 (M^+, 91), 231 (85), 230 (M^+, 100), 229 (85). Anal. Calcd for $C_8H_7O_3Br$ (231.04): C, 41.6; H, 3.1. Found: C, 41.3; H, 2.7.

3-Bromo-2-hydroxy-4-methoxybenzaldehyde (7a). A solution of aldehyde **5** (608 mg, 4.0 mmol) in dichloromethane (24 mL) was cooled to −20 °C. Then aluminum chloride (532 mg, 4.0 mmol) was added in three portions. The suspension was stirred for 15 min before a solution of bromine (638 mg, 206 μL, 4.0 mmol) in dichloromethane (10 mL) was added over 20 min. It was stirred overnight while warming to room temperature. Then a saturated solution of Na_2SO_3 (5 mL) and hydrochloric acid (4 M, 10 mL) was added in order. The aqueous layer was extracted two times with dichloromethane (15 mL each). It was dried over magnesium sulfate, filtered, and concentrated in vacuo. After column chromatography, aldehyde **7a** was isolated as a colorless solid (730 mg, 3.2 mmol, 79%): mp 118−120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.93 (s, 1H), 9.71 (s, 1H), 7.51 (d, 1H, J = 8.7), 6.63 (d, 1H, J = 8.7), 4.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.2, 162.7, 160.1, 134.5, 116.0, 103.7, 99.6, 56.8; IR (neat) ν 2955 (w), 2850 (w), 1633 (s), 1496 (s), 1289 (s), 1240 (s), 1144 (s), 1096 (s); HRMS (EI) calcd for $C_8H_7O_3$[79]Br $[M]^+$ 229.9579, found 229.9559; MS (EI) m/z 232 (M^+, 82), 231 (100), 230 (M^+, 86), 229 (100). Anal. Calcd for $C_8H_7O_3Br$ (231.04): C, 41.6; H, 3.1. Found: C, 41.9; H, 2.8.

5-Iodo-2-hydroxy-4-methoxybenzaldehyde (6b). To a solution of aldehyde **5** (152 mg, 1.0 mmol) in acetonitrile (3 mL) was added *p*-TosOH (95 mg, 0.5 mmol). The solution was stirred for 15 min before *N*-iodosuccinimide (225 mg, 1.0 mmol) was added. It was stirred overnight at room temperature. Then all volatiles were removed in vacuo. After column chromatography, aldehyde **6b** was isolated as a colorless solid (186 mg, 0.67 mmol, 67%). Additionally, aldehyde **7b** was isolated as a colorless solid (37 mg, 0.13 mmol, 13%): mp 110−112 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.44 (s, 1H), 9.68 (s, 1H), 7.88 (s, 1H), 6.42 (s, 1H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.5, 164.6, 164.5, 143.7, 117.0, 99.6, 73.9, 56.9; IR (neat) ν 1636 (s), 1614 (s), 1484 (m), 1441 (m), 1360 (m), 1270 (s); HRMS (EI) calcd for $C_8H_7O_3$[127]I $[M]^+$ 277.9440, found 277.9425; MS (EI) m/z 278 (M^+, 100), 277 (59). Anal. Calcd for $C_8H_7O_3I$ (278.04): C, 34.6; H, 2.5. Found: C, 34.4; H, 2.2.

2-Hydroxy-3-iodo-4-methoxybenzaldehyde (7b). A solution of aldehyde **5** (608 mg, 4.0 mmol) in dichloromethane (24 mL) was cooled to −20 °C. Then aluminum chloride (532 mg, 4.0 mmol) was added in three portions. The solution was stirred for 15 min before *N*-iodosuccinimide (990 mg, 4.4 mmol) was added in three portions. It was stirred overnight while warming to room temperature. Then hydrochloric acid (4 M, 10 mL) was added, and the aqueous layer was extracted two times with dichloromethane (15 mL each). It was dried with magnesium sulfate, filtered, and concentrated in vacuo. After column chromatography, aldehyde **7b** was isolated as a colorless solid (1000 mg, 3.6 mmol, 90%): mp 106−108 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.18 (s, 1H), 9.64 (s, 1H), 7.54 (d, 1H, J = 8.6), 6.57 (d,

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1H, J = 8.6), 3.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.9, 165.0, 162.7, 136.0, 115.8, 103.3, 76.2, 56.9; IR (neat) ν 2848 (w), 1635 (s), 1489 (m), 1285 (s), 1237 (s), 1141 (s), 1064 (s); HRMS (EI) calcd for $C_8H_7O_3$[127]I $[M]^+$ 277.9440, found 277.9437; MS (EI) m/z 278 (M^+, 100), 277 (59). Anal. Calcd for $C_8H_7O_3I$ (278.04): C, 34.6; H, 2.5. Found: C, 34.5 H, 2.2.

2-Bromo-3-methoxy-6-vinylphenol (8a). Sodium hydride (60% in mineral oil, 0.42 g, 10.5 mmol) was suspended in THF (30 mL). Then PPh_3MeBr (4.12 g, 11.6 mmol) was added to the suspension, which was heated to reflux for 1.5 h. After the suspension was cooled to 0 °C, a solution of aldehyde **7a** (767 mg, 3.3 mmol) in THF (10 mL) was added to the reaction mixture over 20 min. It was stirred overnight, diluted with ethyl acetate (100 mL), and washed with water (30 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. After column chromatography, styrene **8a** was isolated as a colorless solid (706 mg, 3.1 mmol, 94%): mp 70−72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (d, 1H, J = 8.7), 6.93 (dd, 1H, J = 17.7, 11.2), 6.48 (d, 1H, J = 8.6), 5.86 (s, 1H), 5.68 (dd, 1H, J = 17.7, 1.4), 5.22 (dd, 1H, J = 11.2, 1.4), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 150.6, 131.0, 126.1, 118.9, 113.7, 103.7, 100.5, 56.3; IR (neat) ν 3455 (m), 3017 (w), 2940 (w), 2838 (w), 1599 (s), 1494 (s), 1415 (s), 1288 (s); HRMS (EI) calcd for $C_9H_9O_2$[79]Br $[M]^+$ 227.9786, found 227.9792; MS (EI) m/z 230 (M^+, 50), 228 (M^+, 59), 134 (100), 83 (24), 57 (26). Anal. Calcd for $C_9H_9O_2Br$ (229.07): C, 47.2; H, 4.0. Found: C, 47.4; H, 3.8.

2-Iodo-3-methoxy-6-vinylphenol (8b). Sodium hydride (60% in mineral oil, 0.51 g, 12.7 mmol) was suspended in THF (40 mL). Then PPh_3MeBr (5.00 g, 14.0 mmol) was added to the suspension, and it was heated to reflux for 1.5 h. After the suspension was cooled to 0 °C, a solution of aldehyde **7b** (1.12 g, 4.0 mmol) in THF (10 mL) was added to the reaction mixture over 20 min. It was stirred overnight, diluted with ethyl acetate (100 mL), and washed with water (30 mL). The organic layer was dried with magnesium sulfate, filtered, and concentrated in vacuo. After column chromatography, styrene **8b** was isolated as a colorless solid (0.95 mg, 3.44 mmol, 86%): mp 70−72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, 1H, J = 8.5), 6.94 (dd, 1H, J = 17.7, 11.1), 6.39 (d, 1H, J = 8.6), 5.66 (s, 1H), 5.66 (dd, 1H, J = 17.7, 1.2), 5.20 (dd, 1H, J = 11.2, 1.2), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 150.6, 131.0, 126.1, 118.9, 113.7, 103.7, 100.5, 56.3; IR (neat) ν 3463 (m), 3006 (w), 2937 (m), 2838 (w), 1601 (s), 1484 (s), 1417 (m), 1285 (m); HRMS (EI) calcd for $C_9H_9O_2$[127]I $[M]^+$ 275.9647, found 275.9628; MS (EI) m/z 276 (M^+, 100), 134 (59).

2-Bromo-3-methoxy-6-vinylphenyl Acrylate (9a). A solution of styrene **8a** (606 mg, 2.7 mmol) and NEt_3 (803 mg, 1.1 mL, 7.9 mmol) in dichloromethane (20 mL) was cooled to 0 °C. Then acryloyl chloride (719 mg, 0.64 mL, 7.9 mmol) was added dropwise to the reaction mixture, which was stirred overnight while warming to room temperature. After the mixture was diluted with MTBE (100 mL), it was washed three times with diluted hydrochloric acid (0.5 M, in each case 15 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. After column chromatography, acrylate **9a** was isolated as a colorless oil (523 mg, 1.9 mmol, 70%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, 1H, J = 8.8), 6.81 (d, 1H, J = 8.8), 6.70 (dd, 1H, J = 17.4, 1.1), 6.62 (dd, 1H, J = 17.6, 11.1), 6.39 (dd, 1H, J = 17.3, 10.5), 6.09 (dd, 1H, J = 10.4, 1.0), 5.65 (dd, 1H, J = 17.6, 0.7), 5.24 (dd, 1H, J = 11.1, 0.7), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 156.6, 146.6, 133.5, 129.8, 127.0, 125.5, 125.1, 115.4, 109.6, 106.9, 56.5; IR (neat) ν 3088 (w), 2941 (w), 2841 (w), 1745 (s), 1599 (m), 1485 (s), 1397 (s); HRMS (EI) calcd for $C_{12}H_{11}O_3$[79]Br $[M]^+$ 281.9892, found 281.9899; MS (EI) m/z 284 (M^+, 19), 282 (M^+, 20), 230 (72), 228 (79), 203 (17), 148 (14), 134 (24), 133 (28), 77 (18), 55 (100). Anal. Calcd for $C_{12}H_{11}O_3Br$ (283.12): C, 50.9; H, 3.9. Found: C, 50.9; H, 3.9.

2-Iodo-3-methoxy-6-vinylphenyl Acrylate (9b). A solution of styrene **8b** (636 mg, 2.3 mmol) and NEt_3 (698 mg, 956 μL, 6.9 mmol) in dichloromethane (20 mL) was cooled to 0 °C. Then acryloyl chloride (719 mg, 642 μL, 6.9 mmol) was added dropwise to the reaction mixture. It was stirred overnight while warming to room temperature. After the mixture was diluted with MTBE (100 mL), it was washed three times with diluted hydrochloric acid (0.5 M, in each case 15 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo. After column chromatography, acrylate **9b** was isolated as a colorless oil (496 mg, 1.5 mmol, 65%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (d, 1H, J = 8.7), 6.73 (d, 1H, J = 8.5), 6.71 (dd, 1H, J = 17.3, 1.1), 6.61 (dd, 1H, J = 17.3, 11.1), 6.40 (dd, 1H, J = 17.3, 10.5), 6.10 (dd, 1H, J = 10.4, 1.2), 5.63 (dd, 1H, J = 17.5, 0.8), 5.21 (dd, 1H, J = 11.0, 0.8), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.0, 159.2, 149.7, 133.4, 130.3, 127.5, 127.1, 125.1, 115.4, 108.9, 84.3, 56.5; IR (neat) ν 2937 (w), 2840 (w), 1743 (s), 1626 (m), 1595 (m), 1478 (s), 1393 (s); HRMS (EI) calcd for $C_{12}H_{11}O_3$[127]I $[M]^+$ 329.9753, found 329.9767; MS (EI) m/z 330 (M^+, 10), 276 (32), 142 (100), 128 (30), 127 (62), 91 (15), 77 (22), 55 (30), 44 (14). Anal. Calcd for $C_{12}H_{11}O_3I$ (330.12): C, 43.7; H, 3.4. Found: C, 44.1; H, 3.3.

8-Bromo-7-methoxy-2*H*-chromen-2-one (4a). *Method A.* Acrylate **9a** (425 mg, 1.5 mmol) was dissolved in dry and degassed toluene (15 mL). After addition of catalyst **B** (64 mg, 0.075 mmol, 5 mol %), the solution was heated to 80 °C. After 2.5 h, all volatiles were removed in vacuo and the title compound was purified by column chromatography. Compound **4a** was isolated as a yellowish solid (374 mg, 1.47 mmol, 98%). *Method B.* Aldehyde **7a** (462 mg, 2.0 mmol) was dissolved in acetic anhydride (1.6 mL). Then potassium acetate (116 mg, 1.2 mmol) was added, and the mixture was heated to 160 °C for 5 h. After cooling, the mixture was diluted with ethyl acetate (100 mL). The organic layer was washed with brine (20 mL) and dried over $MgSO_4$. After filtration, all volatiles were removed in vacuo. The residue was purified by column chromatography, and the title compound was isolated as a yellowish solid (238 mg, 0.94 mmol, 47%): mp 166−168 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, 1H, J = 9.5), 7.41 (d, 1H, J = 8.7), 6.88 (d, 1H, J = 8.6), 6.28 (d, 1H, J = 9.5), 4.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.1, 159.1, 152.3, 143.1, 127.5, 113.7, 113.7, 107.9, 99.7, 56.8; IR (neat) ν 2946 (w), 1730 (s), 1600 (s), 1542 (m), 1296 (s); HRMS (EI) calcd for $C_{10}H_7O_3$[79]Br $[M]^+$ 253.9579, found 253.9569; MS (EI) m/z 256 (M^+, 94), 254 (M^+,100), 228 (59), 226 (61), 213 (77), 211 (82), 185 (10), 183 (11), 157 (15), 155 (18), 76 (20). Anal. Calcd for $C_{10}H_7O_3Br$ (255.06): C, 47.1; H, 2.8. Found: C, 46.8; H, 2.6.

8-Iodo-7-methoxy-2*H*-chromen-2-one (4b). *Method A.* Acrylate **9b** (495 mg, 1.5 mmol) was dissolved in dry and degassed toluene (15 mL). After addition of catalyst **B** (64 mg, 0.075 mmol, 5 mol %), the solution was heated to 80 °C. After 2.5 h, all volatiles were removed in vacuo and the title compound was purified by column chromatography. Compound **4b** was isolated as a yellowish solid (439 mg, 1.46 mmol, 97%). *Method B.* Aldehyde **7b** (278 mg, 1.0 mmol) was dissolved in acetic anhydride (0.8 mL). Then potassium acetate (58 mg, 0.6 mmol) was added, and the mixture was heated to 160 °C for 5 h. After cooling, the mixture was diluted with ethyl acetate (50 mL). The organic layer was washed with brine (10 mL) and dried with magnesium sulfate. After filtration all volatiles were removed in vacuo. The residue was purified by column chromatography, and the title compound was isolated as a yellowish solid (102 mg, 0.34 mmol, 34%). *Method C.* Umbelliferone (**3**) (8.00 g, 49.4 mmol) was dissolved in 20% ammonium hydroxide solution (200 mL). Then a solution of potassium iodide (20.00 g, 120 mmol) and iodine (12.50 g, 89.4 mmol) in water (400 mL) was added over 75 min. The mixture was stirred for 24 h at room temperature before 4 M sulfuric acid (200 mL) was added carefully. A precipitate was formed which was filtered. Then acetone (200 mL) was added to the solid, and the suspension was heated to reflux for 20 min. It was filtered, and the procedure was repeated once. The filtrates were combined, and the solvent was removed in vacuo. 8-Iodoumbelliferone was obtained together with umbelliferone (**3**) as a brown solid (6.80 g). The ratio of 8-iodoumbelliferone to **3** was determined to be approximately 1:1 via integration in the ^{1}H NMR spectrum of the crude product. The crude mixture of umbelliferone (**3**) and 8-iodoumbelliferone was dissolved in acetone (60 mL). Then potassium carbonate (7.76 g, 55.2 mmol) and MeI (3.46 mL, 7.84 g, 55.2 mmol) were added, and the reaction mixture was heated to 40 °C for 24 h. It was diluted with ethyl acetate (100 mL) and filtered. All volatiles were removed in vacuo, and the

residue was purified by column chromatography. Coumarin **4b** was obtained as a yellowish solid (4.77 g, 15.8 mmol, 32% over two steps): mp 160−162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63 (d, 1H, J = 9.5), 7.44 (d, 1H, J = 8.6), 6.81 (d, 1H, J = 8.6), 6.25 (d, 1H, J = 9.5) 3.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 160.4, 154.9, 143.0, 129.1, 113.8, 113.6, 107.4, 75.9, 56.9; IR (neat) ν 3438 (w), 2942 (w), 2843 (w), 2249 (w), 1721 (s), 1644 (m), 1594 (s), 1538 (m); HRMS (EI) calcd for $C_{10}H_7O_3$[127]I $[M]^+$ 301.9440, found 301.9424; MS (EI) m/z 302 (M^+, 100), 274 (34), 259 (49), 203 (9), 132 (20), 76 (30). Anal. Calcd for $C_{10}H_7O_3I$ (302.07): C, 39.8; H, 2.3. Found: C, 40.0; H: 2.3.

7-Methoxy-8-(4-methylfuran-3-yl)-2*H*-chromen-2-one (1). Coumarin **4b** (91 mg, 0.30 mmol) was dissolved in toluene (5 mL). Then Cs_2CO_3 (201 mg, 0.61 mmol), $Pd(PPh_3)_2Cl_2$ (11.0 mg, 0.015 mmol), and boronic acid **11a** (56 mg, 0.45 mmol) were added. This suspension was heated to 110 °C for 16 h. After the suspension was cooled to room temperature, water (5 mL) was added. After phase separation, the aqueous phase was extracted three times with dichloromethane (20 mL each). The combined organic extracts were dried over magnesium sulfate and filtered, and all volatiles were removed in vacuo. After column chromatography, coumarin **1** was isolated as a slightly yellow solid (59 mg, 0.23 mmol, 77%): mp 145−147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, 1H, J = 9.5), 7.48 (d, 1H, J = 1.5), 7.46 (d, 1H, J = 8.6), 7.34 (m, 1H), 6.95 (d, 1H, J = 8.7), 6.25 (d, 1H, J = 9.5), 3.88 (s, 3H), 1.90 (d, 3H, J = 1.0); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 160.3, 152.9, 143.5, 142.1, 139.6, 128.0, 121.0, 115.8, 113.2, 113.1, 109.9, 107.6, 56.1, 8.8; IR (neat) ν 3087 (w), 2926 (w), 2848 (w), 1723 (s), 1597 (s), 1541 (m), 1493 (m), 1460 (m), 1402 (m), 1283 (s), 1245 (s); HRMS (EI) calcd for $C_{15}H_{12}O_4$ $[M]^+$ 256.0736, found 256.0732; MS (EI) m/z 256 (M^+, 39), 213 (21), 128 (24), 127 (27), 111 (29), 98 (47), 97 (51), 95 (26), 85 (38), 84 (28), 83 (37), 71 (100), 70 (44), 69 (96), 57 (81), 56 (25), 55 (51), 43 (79), 41 (36).

4-Methoxybut-2-yn-1-ol (10). To a solution of methyl propargyl ether (4.9 g, 70 mmol) in THF was added *n*-butyllithium (1.7 M in pentane, 3.53 mL, 6.0 mmol) at −78 °C within 20 min. The solution was stirred for 1 h at this temperature before paraformaldehyde (3.46 g, 115 mmol) was added. The reaction was stirred overnight while warming to room temperature. Then saturated ammonium chloride solution (50 mL) was added. It was extracted three times with MTBE (50 mL in each case), dried with magnesium sulfate, and filtered. The solvent was removed in vacuo. The crude product was purified through distillation (80−82 °C, 20 mbar), and the title compound was obtained as a colorless liquid (5.5 g, 55 mmol, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.33 − 4.26 (2H), 4.15 − 4.11 (2H), 3.40 (s, 3H), 2.75 (s(br), 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 84.9, 81.1, 59.8, 57.5, 50.7; IR (neat) ν 3375 (m), 2933 (m), 1450 (m), 1356 (m), 1091 (s), 1011 (s); HRMS (ESI) calcd for $C_5H_8O_2Na$ $[M+Na]^+$ 123.0422, found 123.0409; MS (EI) m/z 98 (14), 97 (13), 85 (46), 83 (75), 71 (31), 69 (33), 57 (35), 55 (28), 43 (31), 41 (28), 38 (33), 36 (100).

4-Methylfuran-3-ylboronic Acid (12a). Furan **11** (3.0 mmol) was added dropwise to a solution of *tert*-butyllithium (1.7 M in pentane, 3.53 mL, 6.0 mmol) in THF (20 mL) at −78 °C. The mixture was stirred 30 min at this temperature before $B(OMe)_3$ (920 μL, 8.2 mmol) was added dropwise. After complete addition, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was cooled to 0 °C, and 1 M hydrochloric acid (10 mL) was added carefully. After complete addition, the reaction mixture was allowed to warm to room temperature and stirred for 45 min. Then the mixture was neutralized by addition of saturated sodium bicarbonate solution (approximately 6 mL). It was extracted three times with MTBE (20 mL in each case), dried with $MgSO_4$, and filtered. All volatiles were removed in vacuo. The title compound was isolated as a slight yellow solid (376 mg, quantitative) and used without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (d, 1H, J = 1.1), 7.28 (m), 2.27 (d, 1H, J = 0.6); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.6, 140.5, 123.9, 10.0 (signal for C3 not observed due to quadrupolar line broadening); IR (neat) ν 3210 (w), 2928 (w), 1589 (m), 1533 (s), 1383 (s), 1344 (s), 1294 (m); HRMS (EI) calcd for $C_5H_7O_3$[11]B $[M]^+$ 126.0483, found 126.0448.

7-Methoxy-8-phenyl-2*H*-chromen-2-one (13a). *Method A*: Coumarin **4b** (91 mg, 0.30 mmol) was dissolved in toluene (5 mL). Then Cs_2CO_3 (201 mg, 0.61 mmol), $Pd(PPh_3)_2Cl_2$ (11.0 mg, 0.015 mmol), and boronic acid **12b** (56 mg, 0.45 mmol) were added. This suspension was heated to 110 °C for 16 h. After the suspension was cooled to room temperature, water (5 mL) was added. After phase separation the aqueous phase was extracted three times with dichloromethane (20 mL each). The combined organic extracts were dried with magnesium sulfate and filtered, and all volatiles were removed in vacuo. After column chromatography, coumarin **13a** was isolated as a slightly yellow solid (57 mg, 0.23 mmol, 75%). *Method B*: Coumarin **4b** (91 mg, 0.30 mmol) was dissolved in a mixture of dioxane (4 mL) and water (1 mL). Then Cs_2CO_3 (201 mg, 0.61 mmol), $Pd(PPh_3)_2Cl_2$ (11.0 mg, 0.015 mmol), and boronic acid **12b** (56 mg, 0.45 mmol) were added. This solution was heated to 110 °C for 16 h. After the solution was cooled to room temperature, water (5 mL) was added. After phase separation, the aqueous phase was extracted three times with ethyl acetate (20 mL in each case). The combined organic extracts were dried with magnesium sulfate and filtered, and all volatiles were removed in vacuo. After column chromatography, coumarin **13a** was isolated as a slightly yellow solid (44 mg, 0.17 mmol, 58%). *Method C*: Coumarin **4b** (91 mg, 0.30 mmol) was dissolved in a mixture of dioxane (4 mL) and water (1 mL). Then Cs_2CO_3 (201 mg, 0.61 mmol), $Pd(PPh_3)_2Cl_2$ (11.0 mg, 0.015 mmol), and organotrifluoroborate **12c** (83 mg, 0.45 mmol) were added. This solution was heated to 110 °C for 16 h. After the solution was cooled to room temperature, water (5 mL) was added. After phase separation, the aqueous phase was extracted three times with ethyl acetate (20 mL each). The combined organic extracts were dried over magnesium sulfate and filtered, and all volatiles were removed in vacuo. After column chromatography, coumarin **13a** was isolated as a slightly yellow solid (76 mg, 0.30 mmol, quantitative): mp 124−126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, 1H, J = 9.5), 7.49 − 7.33 (6H), 6.96 (d, 1H, J = 8.6), 6.24 (d, 1H, J = 9.4), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 159.7, 152.3, 143.5, 131.1, 130.7, 128.0, 127.9, 127.7, 119.0, 113.3, 113.2, 107.8, 56.2; IR (neat) ν 3056 (w), 2943 (w), 2841 (w), 1720 (s), 1597 (s), 1535 (m), 1401 (m); HRMS (EI) calcd for $C_{16}H_{12}O_3$ $[M]^+$ 252.0786, found 252.0773; MS (EI) m/z 252 (M^+, 100), 224 (65), 209 (20), 181 (85), 152 (35).

8-(Benzo[*d*][1,3]dioxol-5-yl)-7-methoxy-2*H*-chromen-2-one (13b). *Method A*: Coumarin **4b** (91 mg, 0.30 mmol) was dissolved in toluene (5 mL). Then Cs_2CO_3 (201 mg, 0.61 mmol), $Pd(PPh_3)_2Cl_2$ (11.0 mg, 0.015 mmol), and boronic acid **12d** (74 mg, 0.45 mmol) were added. This suspension was heated to 110 °C for 16 h. After the suspension was cooled to room temperature, water (5 mL) was added. After phase separation, the aqueous phase was extracted three times with dichloromethane (20 mL in each case). The combined organic extracts were dried with magnesium sulfate and filtered, and all volatiles were removed in vacuo. After column chromatography, coumarin **13b** was isolated as a slightly yellow solid (70 mg, 0.23 mmol, 78%). *Method B*: Coumarin **4b** (91 mg, 0.30 mmol) was dissolved in a mixture of dioxane (4 mL) and water (1 mL). Then Cs_2CO_3 (201 mg, 0.61 mmol), $Pd(PPh_3)_2Cl_2$ (11.0 mg, 0.015 mmol), and boronic acid **12d** (74 mg, 0.45 mmol) were added. This solution was heated to 110 °C for 16 h. After the solution was cooled to room temperature, water (5 mL) was added. After phase separation, the aqueous phase was extracted three times with ethyl acetate (20 mL in each case). The combined organic extracts were dried with magnesium sulfate and filtered, and all volatiles were removed in vacuo. After column chromatography, coumarin **13b** was isolated as a slightly yellow solid (60 mg, 0.20 mmol, 67%). *Method C*: Coumarin **4b** (91 mg, 0.30 mmol) was dissolved in a mixture of dioxane (4 mL) and water (1 mL). Then Cs_2CO_3 (201 mg, 0.61 mmol), $Pd(PPh_3)_2Cl_2$ (11.0 mg, 0.015 mmol), and organo trifluoroborate **12e** (103 mg, 0.45 mmol) were added. This solution was heated to 110 °C for 16 h. After the solution was cooled to room temperature, water (5 mL) was added. After phase separation, the aqueous phase was extracted three times with ethyl acetate (20 mL each). The combined organic extracts were dried with magnesium sulfate and filtered, and all volatiles were removed in vacuo. After column chromatography, coumarin **13b** was

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isolated as a slightly yellow solid (90 mg, 0.30 mmol, quantitative): mp 154−156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, 1H, J = 9.5), 7.43 (d, 1H, J = 8.6), 6.95 (d, 1H, J = 8.7), 6.91 (d, 1H, J = 8.4), 6.85 (d, 1H, J = 1.6), 6.85 (dd, 1H, J = 8.4, 1.6), 6.25 (d, 1H, J = 9.4), 6.00 (s, 2H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 159.8, 152.5, 147.4, 147.2, 143.5, 127.7, 124.4, 124.3, 118.6, 113.3, 113.2, 111.2, 108.2, 107.8, 101.0, 56.3; IR (neat) ν 2957 (m), 2253 (w), 1719 (s), 1597 (s), 1488 (m), 1447 (s), 1276 (s); HRMS (EI) calcd for $C_{17}H_{12}O_5$ $[M]^+$ 296.0685, found 296.0675; MS (EI) m/z = 296 (M^+, 6), 267 (10), 134 (18), 98 (30), 85 (19), 84 (24), 71 (35), 69 (28), 57 (72), 55 (40), 43 (100). Anal. Calcd for $C_{17}H_{12}O_5$ (296.27): C, 68.9; H, 4.1. Found: C, 69.0; H, 4.2.

8-(4-Fluorophenyl)-7-methoxy-2*H*-chromen-2-one (13c). Coumarin **4b** (121 mg, 0.40 mmol) was dissolved in a mixture of dioxane (5.3 mL) and water (1.3 mL). Then Cs_2CO_3 (268 mg, 0.81 mmol), $Pd(PPh_3)_2Cl_2$ (15.0 mg, 0.020 mmol) and organo trifluoroborate **12f** (121 mg, 0.60 mmol) were added. This solution was heated to 110 °C for 16 h. After the solution was cooled to room temperature, water (10 mL) was added. After phase separation, the aqueous phase was extracted three times with ethyl acetate (20 mL in each case). The combined organic extracts were dried with magnesium sulfate and filtered, and all volatiles were removed in vacuo. After column chromatography, coumarin **13c** was isolated as a slightly yellow solid (106 mg, 0.39 mmol, 98%): mp 262−264 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (d, 1H, J = 9.5), 7.48 (d, 1H, J = 8.6), 7.37 (d, 2H, J = 8.9, 5.4), 7.48 (dd, 2H, J = 8.8, 8.8), 6.99 (d, 1H, J = 8.7), 6.27 (d, 1H, J = 9.5); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.4 (d, ^1J = 246.6), 160.9, 159.7, 152.3, 143.6, 132.5 (d, ^3J = 8.1), 128.1, 127.0 (d, ^4J = 3.5), 117.8, 115.1 (d, ^2J = 21.6), 113.3, 113.2, 107.8, 56.3; IR (neat) ν 2930 (w), 2849 (w), 1708 (s), 1598 (s), 1515 (m), 1489 (w), 1428 (w), 1400 (w), 1269 (s); HRMS (EI) calcd for $C_{16}H_{11}O_3F$ $[M]^+$ 270.0692, found 270.0681; MS (EI) m/z = 270 (M^+, 94), (242 (12), 227 (12), 199 (60), 170 (12), 134 (48), 112 (32), 98 (75), 97 (30), 85 (45), 84 (50), 74 (42), 71 (53), 69 (46), 57 (94), 55 (56), 43 (100).

7-Methoxy-8-(pyridin-3-yl)-2*H*-chromen-2-one (13d). Coumarin **4b** (121 mg, 0.40 mmol) was dissolved in a mixture of dioxane (5.3 mL) and water (1.3 mL). Then Cs_2CO_3 (268 mg, 0.81 mmol), $Pd(PPh_3)_2Cl_2$ (15.0 mg, 0.020 mmol), and organo trifluoroborate **12g** (111 mg, 0.60 mmol) were added. This solution was heated to 110 °C for 16 h. After the solution was cooled to room temperature, water (10 mL) was added. After phase separation, the aqueous phase was extracted three times with ethyl acetate (20 mL in each case). The combined organic extracts were dried with magnesium sulfate and filtered, and all volatiles were removed in vacuo. After column chromatography, coumarin **13d** was isolated as a slightly yellow solid (96 mg, 0.38 mmol, 95%): mp 165−167 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (dd, 1H, J = 2.1, 0.6), 8.60 (dd, 1H, J = 4.9, 1.6), 7.77 (ddd, 1H, J = 7.8, 2.0, 1.8), 7.70 (d, 1H, J = 9.5), 7.51 (d, 1H, J = 8.8), 7.40 (ddd, 1H, J = 7.9, 4.9, 0.7), 6.99 (d, 1H, J = 8.7), 6.27 (d, 1H, J = 9.5), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.5, 159.6, 152.4, 151.3, 148.5, 143.4, 138.2, 128.8, 127.4, 123.1, 115.2, 113.5, 113.2, 107.8, 56.2; IR (neat) ν 3373 (m), 2847 (w), 1731 (m), 1705 (m), 1603 (s), 1499 (m), 1406 (m); HRMS (EI) calcd for $C_{15}H_{11}O_3N$ $[M]^+$ 253.0739, found 253.0734; MS (EI) m/z = 253 (M^+, 100).

7-Methoxy-8-(4-(morpholine-4-carbonyl)phenyl)-2*H*-chromen-2-one (13e). Coumarin **4b** (121 mg, 0.40 mmol) was dissolved in a mixture of dioxane (5.3 mL) and water (1.3 mL). Then Cs_2CO_3 (268 mg, 0.81 mmol), $Pd(PPh_3)_2Cl_2$ (15.0 mg, 0.020 mmol), and organo trifluoroborate **12h** (134 mg, 0.60 mmol) were added. This solution was heated to 110 °C for 16 h. After the solution was cooled to room temperature, water (10 mL) was added. After phase separation, the aqueous phase was extracted three times with ethyl acetate (20 mL in each case). The combined organic extracts were dried with magnesium sulfate and filtered, and all volatiles were removed in vacuo. After column chromatography, coumarin **13e** was isolated as a slightly yellow solid (103 mg, 0.38 mmol, 94%): mp 198−200 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, 1H, J = 9.5), 7.52 − 7.42 (5H), 6.97 (d, 1H, J = 8.7), 6.26 (d, 1H, J = 9.5), 3.83 (s, 3H), 3.86 − 3.58 (broad due to hindered rotation around the amide bond, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 160.8, 159.7, 152.2, 143.6, 134.4, 133.2, 131.0, 128.4, 126.9, 117.9, 113.4, 113.2, 107.9, 67.0, 56.2, signal for CH_2N not observed due to hindered rotation and/or quadrupole broadening; IR (neat) ν 2921 (w), 2954 (w), 2247 (w), 1722 (s), 1600 (s), 1459 (m), 1430 (m), 1267 (s); HRMS (EI) calcd for $C_{21}H_{19}O_5N$ $[M]^+$ 365.1263, found 365.1270; MS (EI) m/z 365 (M^+, 15), 341 (10), 327 (12), 279 (46), 267 (36), 239 (25), 134 (46), 98 (52), 85 (75), 83 (100), 71 (35), 57 (44), 43 (48). Anal. Calcd for $C_{21}H_{19}O_5N$ (365.38): C, 69.0; H, 5.2; N, 3.8. Found: C, 69.0; H, 5.4; N, 3.8.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, analytical data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. Crystallographic details for compound **1** (CCDC-859533) (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Chan-Bacab, M. J.; Pena-Rodriguez, L. M. *Nat. Prod. Rep.* **2001**, *18*, 674−688.
(2) Croft, S. L.; Barrett, M. P.; Urbina, J. A. *Trends Parasitol.* **2005**, *21*, 508−512.
(3) Tiuman, T. S.; Santos, A. O.; Ueda-Nakamura, T.; Filho, B. P. D; Nakamura, C. V. *Int. J. Infect. Dis.* **2011**, *15*, e525−e532.
(4) World Health Organization. WHO Technical report series 949. Control of the Leishamniases - Meeting of the WHO Expert Committee on the Control of Leishmaniases. Geneva, 2010.
(5) Rocha, L. G.; Almeida, J. R. G. S.; Macêdo, R. O.; Barbosa-Filho, J. M. *Phytomedicine* **2005**, *12*, 514−535.
(6) Fournet, A.; Munoz, V. *Curr. Top. Med. Chem.* **2002**, *2*, 1215−1237.
(7) Fournet, A.; Barrios, A. A.; Munoz, V.; Hocquemiller, R.; Cave, A.; Bruneton, J. *Antimicrob. Agents Chemother.* **1993**, *37*, 859−863.
(8) López, J. A.; Barillas, W.; Gomez-Laurito, J.; Martin, G. E.; Al-Rehaily, A. J.; Zemaitis, M. A.; Schiff, P. L. *J. Nat. Prod.* **1997**, *60*, 24−26.
(9) Arango, V.; Robledo, S.; Séon-Méniel, B.; Figadère, B.; Cardona, W.; Sáez, J.; Otálvaro, F. *J. Nat. Prod.* **2010**, *73*, 1012−1014.
(10) Elias, T. S. *J. Arnold Arbor.* **1970**, *51*, 427−430.
(11) Tantivatana, P.; Ruangrungsi, N.; Vaisiriroj, V.; Lankin, D. C.; Bhacca, N. S.; Borris, R. P.; Cordell, G. A.; Johnson, L. F. *J. Org. Chem.* **1983**, *48*, 268−270.
(12) Ito, C.; Otsuka, T.; Ruangrungsi, N.; Furukawa, H. *Chem. Pharm. Bull.* **2000**, *48*, 334−338.
(13) Samuel, R.; Ehrendorfer, F.; Chase, M. W.; Greger, H. *Plant Biol.* **2001**, *3*, 77−87.
(14) Imai, F.; Kinoshita, T.; Sankawa, U. *Chem. Pham. Bull.* **1989**, *37*, 358−362.
(15) Murakami, A.; Gao, G.; Omura, M.; Yano, M.; Ito, C.; Furukawa, H.; Takahashi, D.; Koshimizu, K.; Ohigashi, H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 59−62.
(16) Fun, H.-K.; Siridechakorn, I.; Laphookhieo, S.; Chantrapromma, S. *Acta Crystallogr. E* **2011**, *67*, o1706−o1707.

(17) Cassady, J. M.; Ojima, N.; Chang, C.-j.; McLaughlin, J. L. *J. Nat. Prod.* **1979**, *42*, 274−278.
(18) Lekphrom, R.; Kanokmedhakul, S.; Kukongviriyapan, V.; Kanokmedhakul, K. *Arch. Pharm. Res.* **2011**, *34*, 527−531.
(19) Wakharkar, R. D.; Deshpande, V. H.; Landge, A. B.; Upadhye, B. K. *Org. Prep. Proc. Int.* **1988**, *20*, 527−532.
(20) Allison, S.; Burks, S. J.; Taylor, R. T. *Tetrahedron* **1991**, *47*, 9737−9742.
(21) Murray, R. D. H. *Nat. Prod. Rep.* **1995**, *12*, 477−505.
(22) Murray, R. D. H. *Fort. Chem. Org. Nat.* **2002**, *83*, 1−673.
(23) Estevez-Braun, A.; Gonzalez, A. G. *Nat. Prod. Rep.* **1997**, *14*, 465−475.
(24) Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866−867.
(25) Littke, A. In *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, 2009; pp 25−67.
(26) McGlacken, G. P.; Fairlamb, I. J. S. *Eur. J. Org. Chem.* **2009**, 4011−4029.
(27) Harayama, T.; Nishita, Y. *Chem. Pharm. Bull.* **1996**, *44*, 1986−1988.
(28) Gillmore, A.; Lauret, C.; Roberts, S. M. *Tetrahedron* **2003**, *59*, 4363−4375.
(29) Curini, M.; Epifano, F.; Maltese, F.; Marcotullio, M. C.; Tubaro, A.; Altinier, G.; Gonzales, S. P.; Rodriguez, J. C. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2241−2243.
(30) Meng, C. Q.; Ni, L.; Worsencroft, K. J.; Ye, Z.; Weingarten, M. D.; Simpson, J. E.; Skudlarek, J. W.; Marino, E. M.; Suen, K.-L.; Kunsch, C.; Souder, A.; Howard, R. B.; Sundell, C. L.; Wasserman, M. A.; Sikorski, J. A. *J. Med. Chem.* **2007**, *50*, 1304−1315.
(31) Radomkit, S.; Sarnpitak, P.; Tummatorn, J.; Batsomboon, P.; Ruchirawat, S.; Ploypradith, P. *Tetrahedron* **2011**, *67*, 3904−3914.
(32) Schmidt, B.; Berger, R.; Hölter, F. *Org. Biomol. Chem.* **2010**, *8*, 1406−1414.
(33) Narula, A. S.; Zalutsky, M. R. *Tetrahedron Lett.* **1988**, *29*, 4385−4388.
(34) Chen, L.; Hu, T.-S.; Yao, Z.-J. *Eur. J. Org. Chem.* **2008**, 6175−6182.
(35) Schmidt, B.; Geißler, D. *ChemCatChem* **2010**, *2*, 423−429.
(36) Schmidt, B.; Krehl, S. *Chem. Commun.* **2011**, *47*, 5879−5881.
(37) Reich, H. J.; Olson, R. E. *J. Org. Chem.* **1987**, *52*, 2315−2317.
(38) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.
(39) Ye, Y. Q.; Koshino, H.; Onose, J.-i.; Yoshikawa, K.; Abe, N.; Takahashi, S. *Org. Lett.* **2009**, *11*, 5074−5077.
(40) Felpin, F.-X.; Fouquet, E.; Zakri, C. *Adv. Synth. Catal.* **2009**, *351*, 649−655.
(41) Darses, S.; Genêt, J. P. *Chem. Rev.* **2008**, *108*, 288−325.
(42) Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240−9261.
(43) Butters, M.; Harvey, J. N.; Jover, J.; Lennox, A. J. J.; Lloyd-Jones, G. C.; Murray, P. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5156−5160.
(44) Lennox, A. J. J.; Lloyd-Jones, G. C. *Isr. J. Chem.* **2010**, *50*, 664−674.
(45) Bolliger, J. L.; Frech, C. M. *Adv. Synth. Catal.* **2010**, *352*, 1075−1080.
(46) Jang, M.; Jo, Y.; Oh, I.-K.; Jung, H. M.; Lee, S. *Synthesis* **2009**, *2073*, 2075.