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Silver(I)-Catalyzed Route to Pyrroles: Synthesis of Halogenated Pseudilins as Allosteric Inhibitors for Myosin ATPase and X-ray Crystal Structures of the Protein–Inhibitor Complexes[‡]

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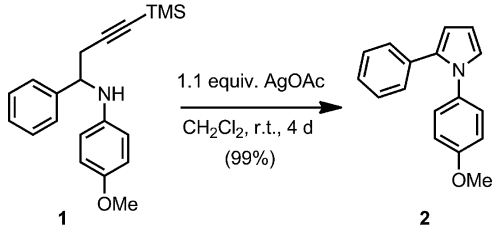
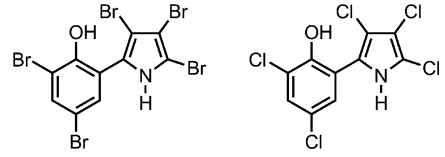
The pentahalogenated 2-arylpyrrole-type alkaloids pentabromopseudilin and pentachloropseudilin represent a new class of isoform-specific allosteric inhibitors of myosin ATPase. Herein, we describe an application of the silver(I)-catalyzed cycloisomerization of *N*-(homopropargyl)toluenesulfonamides to the total syntheses of these natural products and several non-natural analogues. Moreover, we examine the inhibitiory effect of pentahalogenated pseudilins on myosin ATPase activity.

Introduction

In 2004, we described a new approach to the pyrrole ring system that proceeds through a silver(I)-promoted oxidative cyclization of silyl-protected homopropargylamines **1** to 1,2-diarylpyrroles **2** (see Scheme 1).[1] This method was then applied to the total syntheses of (±)-crispine A and the antileishmanial active (±)-harmicine.[2] Subsequently, we reported the silver(I)-catalyzed cyclization of *N*-tosylhomopropargylamines to 2,3-dihydropyrroles, which led to the total syntheses of the pentahalogenated 2-arylpyrrole alkaloids pentabromopseudilin (**3**) and pentachloropseudilin (**4**, see Figure 1) as well as the hexahalogenated 2,2′-bipyrrole alkaloids.[3] Herein, we describe the synthesis of natural products **3** and **4** as well as their non-natural mixed halogenated derivatives.



Scheme 1. Silver(I)-promoted oxidative cyclization of homopropargylamines **1** to 1,2-diarylpyrroles **2** (TMS = trimethylsilyl).



Pentabromopseudilin (**3**) Pentachloropseudilin (**4**)

Figure 1. Naturally occurring pentahalogenated 2-(2-hydroxyphenyl)pyrroles.

A large variety of halogenated alkaloids have been obtained from natural sources, and the synthesis, biogenesis, and biological properties of these compounds have been under intense investigation.[4] Pentabromopseudilin (**3**) was first isolated in 1966 from the marine bacterium *Pseudomonas bromoutilis*.[5] The same compound was isolated in 1974 from the marine bacterium *Chromobacterium* I-L-33,[6] in 1989 from *Alteromonas luteo-violaceus*,[7] and in 2010 from the marine organism *Pseudoalteromonas* sp.[8] Pentachloropseudilin (**4**) was first described in 1978 as a synthetic analogue of **3**,[9] and later in the same year, compound **4** was isolated from the terrestrial actinomycete *Actinoplanes* ATCC 33002.[10] Both compounds have attracted the interests of various research groups because of their antibacterial properties[5a,6,10,11] and their puzzling biogenetic origins.[12] Therefore, a number of synthetic approaches have been developed.[3a,7,13] In the course of their studies,

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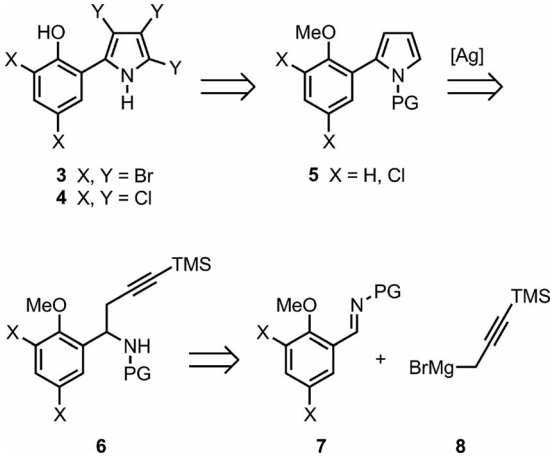
Toste and co-workers discovered the inhibitory activity of **3** on human lipoxygenase.[13f] In 2009, we described that pentabromopseudilin (**3**), pentachloropseudilin (**4**), and their analogues represent new isoform-specific allosteric inhibitors of myosin ATPases.[3a,3b,14]

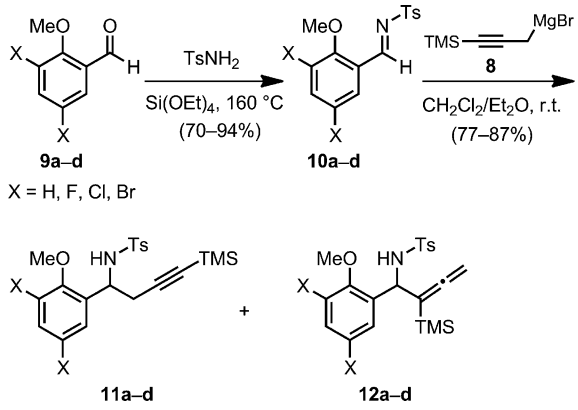
Results and Discussion

We envisaged an approach to the natural products **3** and **4** that involves a late stage halogenation of a 2-arylpyrrole **5** (see Scheme 2). By following our silver-promoted route to pyrroles,[1,2] compound **5** can be obtained by the cyclization of *N*-protected aryl-substituted homopropargylamine **6**. Compound **6** is easily available from the addition of trimethylsilylpropargylmagnesium bromide (**8**) to an aldimine **7**. For the synthesis of mixed halogenated compounds, the halogenated aldimines **7** (X = F, Cl, Br) can be used as starting materials. In our first report of the silver(I)-promoted synthesis of pyrroles,[1] we employed Schiff bases, which ultimately led to *N*-arylpyrroles. However, the cleavage of an aryl substituent from a pyrrole nitrogen requires harsh reaction conditions that may not be tolerated by an electron-rich pyrrole ring. Thus, we decided to replace the Schiff bases with *N*-tosylaldimines **10** (Ts = tosyl) to afford the *N*-tosylpyrroles (see Schemes 3 and 4). As a tosyl group can be easily removed from the pyrrole nitrogen, *N*-unsubstituted pyrroles should become available by this approach.



Scheme 2. Retrosynthetic analysis of the pentahalogenated pseudilins (PG = protecting group).

An adaptation of a literature procedure provided the aldimines **10** in high yields by reaction of the corresponding 2-methoxybenzaldehydes **9** with *p*-toluenesulfonamide in tetraethoxysilane (see Scheme 3).[15] Compound **9a** as well as the corresponding 3,5-difluoro- and 3,5-dibromo-substituted derivatives (i.e., **9b** and **9d**, respectively) are commercially available. 3,5-Dichloro-2-methoxybenzaldehyde (**9c**) was prepared by *O*-alkylation of 3,5-dichloro-2-hydroxybenzaldehyde (see Exp. Sect.). The addition of trimethylsilylpropargylmagnesium bromide (**8**), which was freshly prepared from trimethylsilylpropargyl bromide, afforded a mixture of the desired *N*-(homopropargyl)toluenesulfonamides **11** and *N*-(allenylmethyl)toluenesulfonamides **12** (see Scheme 3 and Table 1), which could be separated by column chromatography. The allenes **12** may be formed either by a γ-attack of the propargylmagnesium compound **8** or by an attack of an allenylmagnesium compound, which is formed during the generation of the Grignard reagent **8**.[16] We observed that more of the allenylmethyl compound **12** was formed when the halogen-substituted aldimines **10b–d** were used as substrates.



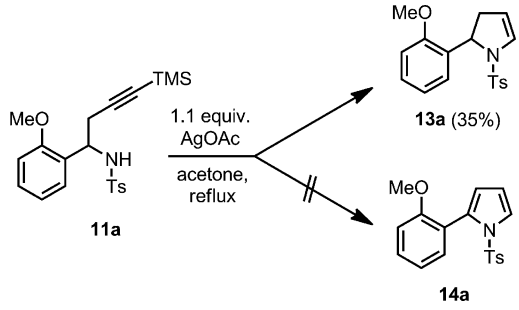
Scheme 3. Synthesis of the *N*-(homopropargyl)toluenesulfonamides **11a–d** and *N*-(allenylmethyl)toluenesulfonamides **12a–d**.

Table 1. Synthesis of aldimines **10a–d** and results from the addition of Grignard reagent **8**.

	X	% Yield **10**[a]	% Yield **11**[a]	% Yield **12**[a]	**11/12**
a	H	94	76	8	9.5:1
b	F	81	52	25	2.1:1
c	Cl	70	50	27	1.9:1
c	Cl	70	34[b]	45[b]	1:1.3[b]
d	Br	79	55	32	1.7:1

[a] Isolated yields. [b] Addition of **8** at –10 °C.

Using stoichiometric amounts of silver(I) acetate for the cyclization of **11a** did not afford the *N*-tosylpyrrole **14a**, but instead it led to the 2,3-dihydro-2-arylpyrrole **13a** in moderate yield (see Scheme 4). The structure of compound **13a** was unequivocally confirmed by an X-ray crystal structure determination (see Figure 2). The yield of **13a** was considerably improved by removing the silyl group at the terminal position of the alkyne prior to the cyclization (see Scheme 5 and Table 2). Further improvement of the yield was achieved by the use of only catalytic amounts (5–15 mol-%) of silver(I) acetate. Thus, homopropargyl compound **15a** can be cyclized to give 2,3-dihydropyrrole **13a** in up to 97% yield. Using less than 5 mol-% of silver(I) acetate resulted in a low turnover of the catalyst. Other metal salts were ineffective. Catalytic amounts of copper(I) acetate afforded **13a** in only 23% yield. Using palladium(II) acetate or gold(I) chloride as catalyst led to the recovery of starting material and some decomposition, whereas treatment of **15a** with gold(III) chloride only resulted in decomposition.



Scheme 4. Silver(I)-promoted cyclization of the *N*-(homopropargyl)toluenesulfonamide **11a**.

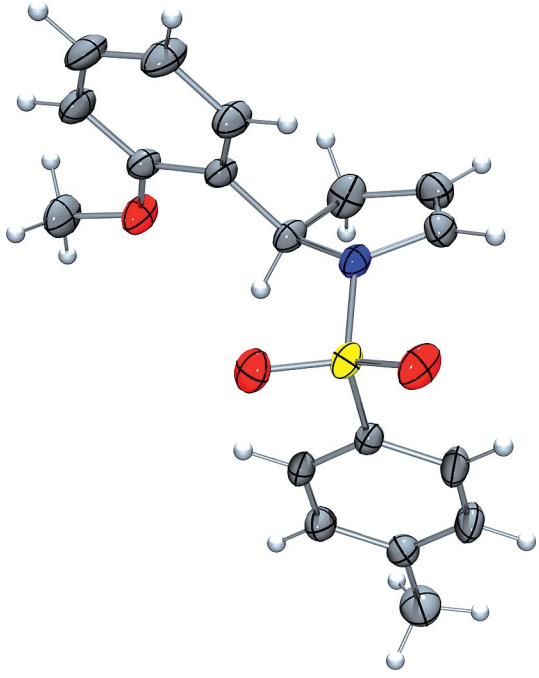
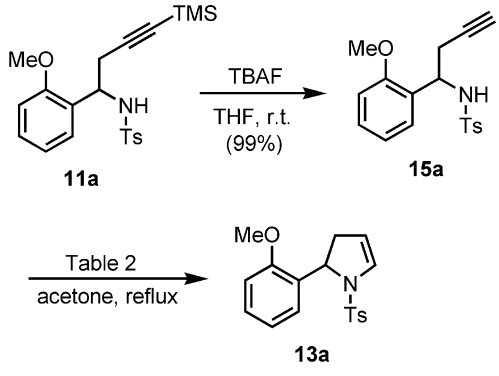


Figure 2. Molecular structure of the 2,3-dihydro-2-arylpyrrole **13a** in the crystal.



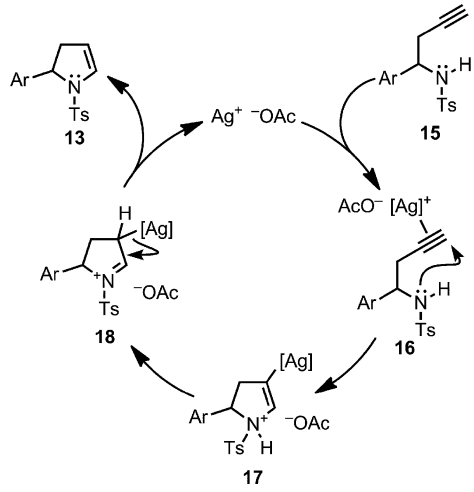
Scheme 5. Desilylation of **11a** and transition-metal-catalyzed cycloisomerization of *N*-(homopropargyl)toluenesulfonamide **15a** to give 2,3-dihydro-2-arylpyrrole **13a** (TBAF = tetra-*n*-butylammonium fluoride, THF = tetrahydrofuran).

The silver(I)-catalyzed cycloisomerization of *N*-(homopropargyl)toluenesulfonamides **15** leading to the *N*-tosyl-2,3-dihydropyrroles **13** probably starts with the initial formation of the silver(I)–alkyne π-complex **16** (see Scheme 6).[17] Activated alkynes that are generated by complexation to silver(I) have found diverse applications in heterocyclization reactions.[18] The nucleophilic attack of the amide nitrogen atom leads to the 2,3-dihydropyrrol-4-ylsilver(I) compound **17** through a 5-*endo*-*dig* cyclization.[19] The tautomerization of **17** to give the iminium salt **18** followed by deargentation provides the 2,3-dihydropyrrole **13** and regenerates the silver(I) salt.

Table 2. Variation of the catalyst for the cycloisomerization of **15a** to give 2,3-dihydro-2-arylpyrrole **13a**.

Catalyst	Equiv.	Reaction time [d]	% Yield **13a**
AgOAc	1.10	2	77
AgOAc	0.15	2.5	96
AgOAc	0.10	3	97
AgOAc	0.05	4	86
AgOAc	0.02	7	22
CuOAc	0.10	8	23
$Pd(OAc)_2$	0.10	4	_[a]
AuCl	0.10	4	_[b]
$AuCl_3$	0.10	2	_[c]

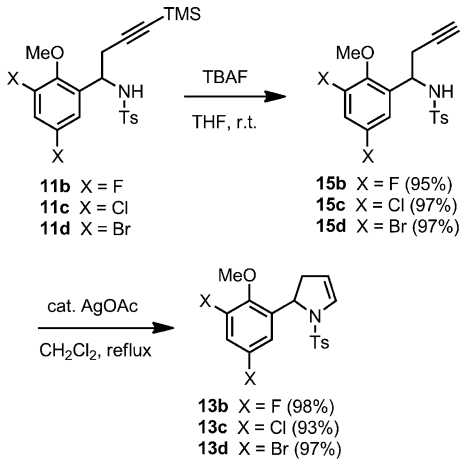
[a] 20% of **15a** recovered. [b] 85% of **15a** recovered. [c] Decomposition occurred.



Scheme 6. Mechanism proposed for the silver(I)-catalyzed cycloisomerization of *N*-(homopropargyl)toluenesulfonamide **15**.

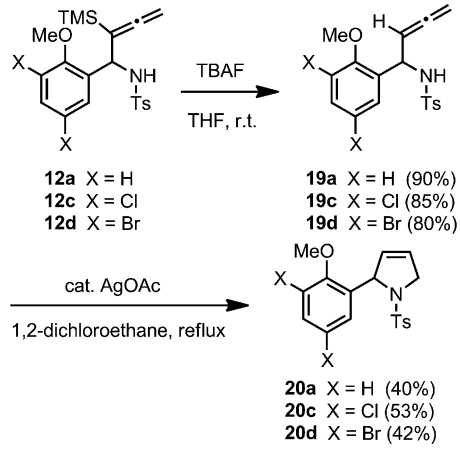
The silver(I)-catalyzed cycloisomerization was then applied to the corresponding halo-substituted precursors (see Scheme 7). The protodesilylation of **11b–d** by treatment with TBAF afforded the terminal alkynes **15b–d**. Because of better solubility, dichloromethane was used as solvent, instead of acetone, for the subsequent cycloisomerization. Thus, treatment of the homopropargyl compounds **15b–d** with a catalytic amount (10–15 mol-%) of silver(I) acetate in dichloromethane at reflux temperature provided halo-substituted 2,3-dihydro-2-arylpyrroles **13b–d** in excellent yields (93–98%).

We also envisaged the cycloisomerization of the *N*-(allenylmethyl)toluenesulfonamides **19a**, **19c**, and **19d** (see Scheme 8). Such a transformation was first reported by Claesson and co-workers who used catalytic amounts of sil-



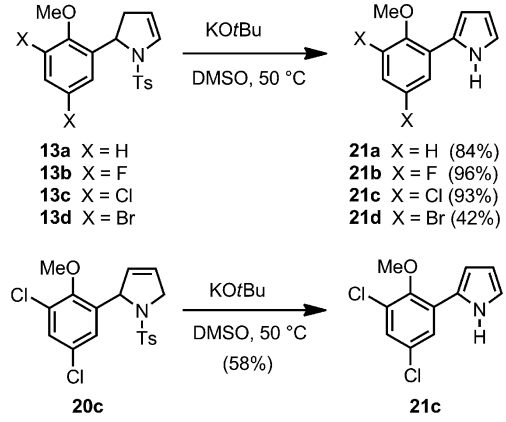
Scheme 7. Synthesis of the halo-substituted 2,3-dihydro-2-arylpyrroles **13b–d**.

ver(I) tetrafluoroborate in chloroform at room temperature.[20] Compounds **19a**, **19c**, and **19d** were obtained by protodesilylation of the silyl derivatives **12a**, **12c**, and **12d**, respectively, which were formed as byproducts during the synthesis of the *N*-(homopropargyl)toluenesulfonamides **11** (cf. Scheme 3). Similar to their propargylic counterparts **15c** and **15d**, allenylmethyl derivatives **19c** and **19d** proved to be insufficiently soluble in acetone. Furthermore, the treatment of **19c** with silver(I) acetate in refluxing dichloromethane led only to the isolation of starting material. The desired cyclizations of **19a**, **19c**, and **19d** giving the 2,5-dihydro-2-arylpyrroles **20a**, **20c**, and **20d**, respectively, were finally achieved by heating them at reflux in 1,2-dichloroethane in the presence of a catalytic amount of silver(I) acetate.



Scheme 8. Synthesis of the 2,5-dihydro-2-arylpyrroles **20**.

The next step for the total synthesis of natural and non-natural halogenated 2-arylpyrroles involved the aromatization of the 2,3-dihydropyrroles **13a–d** (see Scheme 9). The base-induced elimination of *p*-toluenesulfinic acid by treatment of *N*-tosyl-2,3-dihydropyrroles **13a–d** with 4 equiv. of potassium *tert*-butoxide in dimethyl sulfoxide (DMSO) at 50 °C led to the desired 2-arylpyrroles **21a–c** in good to excellent yields. However, the brominated compound **21d** was only obtained in moderate yield. An alternative route to the 2-arylpyrroles **21** involved the base-induced aromatization of the 2,5-dihydropyrroles **20**.[20b] This has been demonstrated for the conversion of **20c** into **21c** (see Scheme 9). Thus, the combined overall yield for 2-arylpyrrole **21c** based on benzaldehyde **9c** is 34% over five steps.

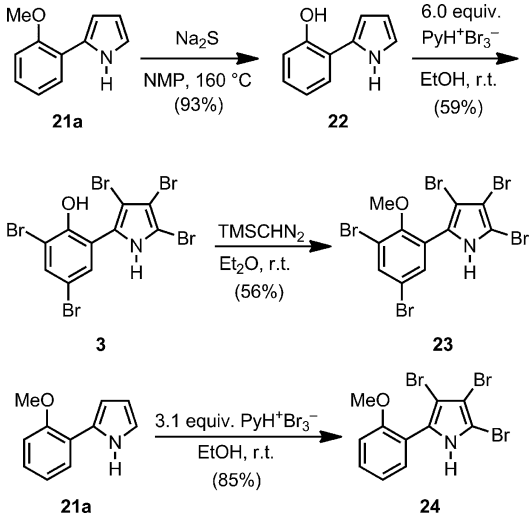


Scheme 9. Aromatization of the 2,3-dihydro-2-arylpyrroles **13a–d** and 2,5-dihydro-2-arylpyrrole **20c**.

The non-halogenated 2-arylpyrrole **21a** (*O*-methylpseudilin) then served as precursor for the synthesis of pentabromopseudilin (**3**) and the corresponding *O*-methyl and *N*-methyl derivatives. The cleavage of the methyl ether moiety by heating **21a** with sodium sulfide in *N*-methylpyrrolidone (NMP) provided pseudilin (**22**) in 93% yield (see Scheme 10).[13e] Attempts to employ boron tribromide at low temperatures (–78 °C) for the cleavage of the ether only resulted in decomposition. The pentabromination of pseudilin (**22**) by using 6 equiv. of freshly recrystallized pyridinium tribromide afforded the natural product pentabromopseudilin (**3**) in 59% yield. This yield for this pentabromination corresponds to an average yield of 90% for each C–Br bond formation. Our synthesis provided pentabromopseudilin (**3**) in seven steps and 32% overall yield based on the commercial starting materials **9a** and *p*-toluenesulfonamide.

To study the structure–activity relationship of pseudilin derivatives, we transformed the natural product **3** into its corresponding methyl ether **23** (see Scheme 10). The attempted *O*-methylation of **3** by sequential treatment with potassium *tert*-butoxide and iodomethane was unsuccessful and resulted in decomposition, and the reaction with dimethyl sulfate and potassium carbonate mainly led to the isolation of the starting material. Finally, pentabromopseudilin (**3**) was converted into the methyl ether **23** by treatment with trimethylsilyldiazomethane in diethyl ether at room temperature. The reaction of *O*-methylpseudilin (**21a**) with 3.1 equiv. of pyridinium tribromide in ethanol at room temperature provided the tribromo-substituted compound **24** by chemoselective bromination of the pyrrole ring. Unfortunately, all attempts to cleave the methyl ether of **24** led either to decomposition or isolation of the starting

material. The chemoselective bromination of the pyrrole ring of pseudilin (**22**) was unsuccessful as well and resulted in decomposition.

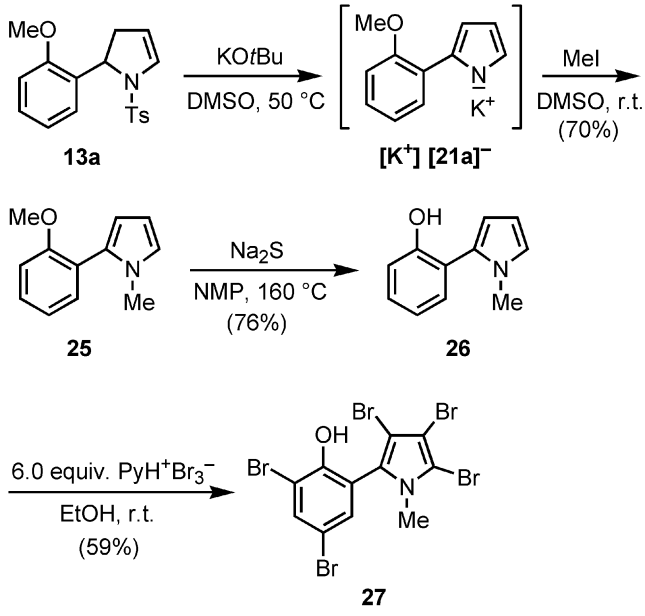


Scheme 10. Synthesis of pentabromopseudilin (**3**) and its derivatives.

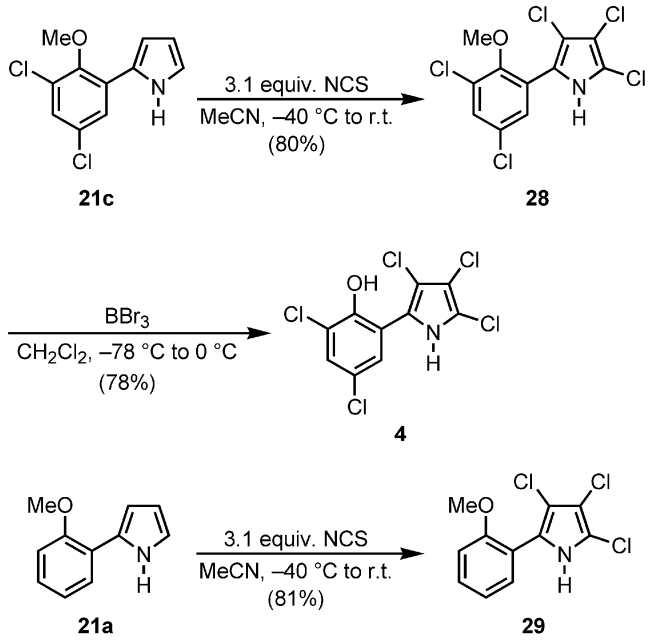
For the investigation of the structure–activity relationship, we also devised the synthesis of *N*-methylpentabromopseudilin (**27**, see Scheme 11). The alkylation at the nitrogen atom was most efficiently achieved by trapping the potassium salt of **21a** in situ with iodomethane to afford *N*,*O*-dimethylpseudilin (**25**). This procedure proved to be superior to the alkylation of isolated *O*-methylpseudilin (**21a**). The potassium salt of **21a** is an intermediate in the potassium *tert*-butoxide promoted aromatization of dihydropyrrole **13a** (cf. Scheme 9). The cleavage of the methyl ether of compound **25** by heating with sodium sulfide in *N*-methylpyrrolidone afforded *N*-methylpseudilin (**26**). The bromination of **26** by treatment with 6 equiv. of pyridinium tribromide provided *N*-methylpentabromopseudilin (**27**) in 59% yield (corresponding to an average yield of 90% for each C–Br bond formation).

The pentachlorination of either *O*-methylpseudilin (**21a**) or pseudilin (**22**) could not be achieved. Thus, pentachloropseudilin (**4**) was prepared starting from the dichloro-substituted compound **21c** (see Scheme 12). The electrophilic trichlorination of the pyrrole ring by reaction of **21c** with 3.1 equiv. of *N*-chlorosuccinimide (NCS) at low temperature led to *O*-methylpentachloropseudilin (**28**) in 80% yield (corresponding to 93% yield for each C–Cl bond formation). Cleavage of the methyl ether of **28** provided pentachloropseudilin (**4**). Our approach provides access to pentachloropseudilin (**4**) in seven steps and 21% overall yield based on the starting material benzaldehyde **9c**. The chlorination of *O*-methylpseudilin (**21a**) using the same reaction conditions as described above for **21c** afforded the corresponding trichloro-substituted compound **29**. All attempts to cleave the methyl ether of **29** led to decomposition.

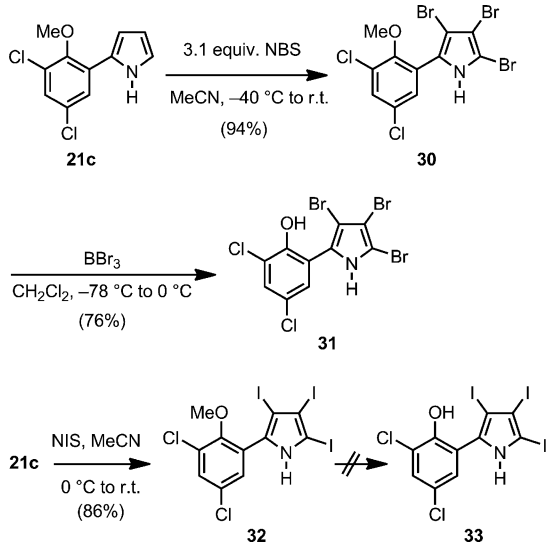
The dichloro-substituted compound **21c** was also employed in the syntheses of non-natural mixed halogenated pseudilin analogues of **3** and **4** (see Scheme 13). The electrophilic tribromination of **21c** by treatment with *N*-bromosuccinimide (NBS) at low temperature provided 2,3,4-tribromo-5-(3,5-dichloro-2-methoxyphenyl)pyrrole (**30**). Cleavage of the methyl ether moiety using boron tribromide at low temperature afforded tribromodichloropseudilin (**31**). The triiodination of **21c** was achieved by a reaction with *N*-iodosuccinimide (NIS) and led to 2,3,4-triiodo-5-(3,5-dichloro-2-methoxyphenyl)pyrrole (**32**) in 86% yield (corresponding to 95% yield for each C–I bond formation). Unfortunately, we could not cleave the methyl ether of **32**.



Scheme 11. Synthesis of *N*-methylpentabromopseudilin (**27**).

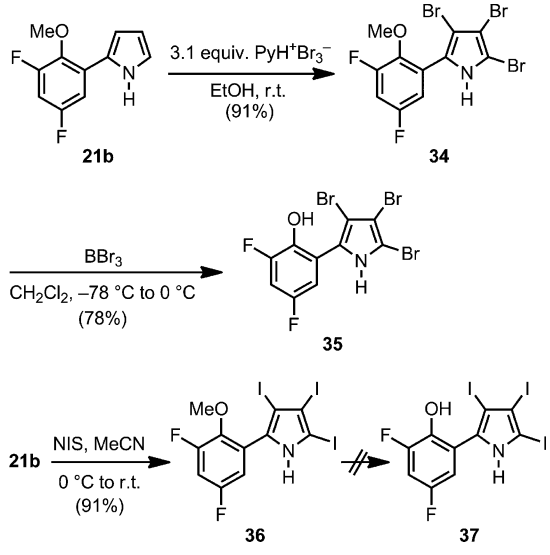


Scheme 12. Synthesis of pentachloropseudilin (**4**) and *O*-methyltrichloropseudilin (**29**).



Scheme 13. Synthesis of mixed halogenated pseudilin derivatives **30**–**32**.

A fluorinated analogue of pentabromopseudilin (**3**) was obtained starting from the difluoro-substituted compound **21b** (see Scheme 14). The tribromination of the pyrrole ring of **21b** using pyridinium tribromide afforded compound **34**. Cleavage of the methyl ether unit finally led to tribromodifluoropseudilin (**35**). The iodination of **21b** using *N*-iodosuccinimide provided triiodo-substituted compound **36**. However, similar to compound **32**, cleavage of the methyl ether of **36** was unsuccessful.



Scheme 14. Synthesis of the fluorinated pseudilin derivatives **34**–**36**.

Myosins are a family of ATP-dependent molecular motor proteins that move along actin filaments. Myosin activity plays a pivotal role in a range of biological processes such as chemo-mechanical signal transduction and in many diseases such as cancer, malaria, cardiovascular failure, and disorders of the sensory organs and nervous system. A wide range of different myosin isoforms are known. We found that the pentahalogenated pseudilins **3** and **4** represent a new class of allosteric inhibitors for different myosins.[14] Pentabromopseudilin (**3**), pentachloropseudilin (**4**), and some of the non-natural derivatives described above were tested for their potency as inhibitors of myosin motor activity. Using an assay for the inhibition of the activity of skeletal muscle myosin-2 ATPase (see Figure 3), these compounds were compared with the previously known inhibitors (*S*)-(–)-blebbistatin (**38**) and *N*-benzyl-*p*-toluenesulfonamide (**39**, see Figure 4).

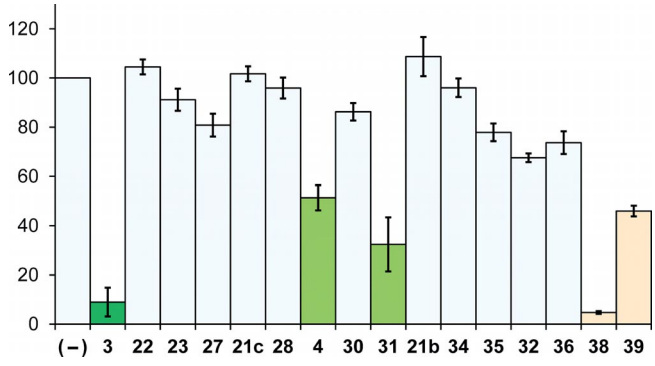
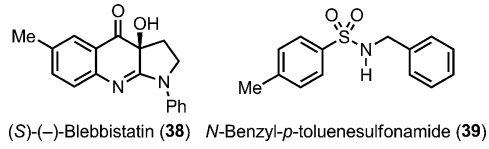


Figure 3. Inhibition of basal skeletal muscle myosin-2 ATPase activity relative to control [no inhibitor added (–): 100%]. The bars represent mean values of three independent measurements. All compounds were tested at a concentration of 25 μM.



(*S*)-(–)-Blebbistatin (**38**) *N*-Benzyl-*p*-toluenesulfonamide (**39**)

Figure 4. Previously known myosin ATPase inhibitors.

The inhibition of skeletal muscle myosin-2 ATPase activity by pentabromopseudilin (**3**) is in the same range as that of (–)-blebbistatin (**38**). The corresponding *O*-methyl and *N*-methyl derivatives **23** and **27**, respectively, were significantly less active. In the presence of a concentration of 25 μM, the residual ATPase activity of basal skeletal muscle myosin-2 ATPase decreased to less than 10%, whereas at the same concentration, 90% of the myosin-2 ATPase activity was retained with *O*-methylpentabromopseudilin (**23**) and 80% with *N*-methylpentabromopseudilin (**27**). The inhibitory activity of pentachloropseudilin (**4**) towards basal skeletal muscle myosin-2 ATPase was comparable to that of *N*-benzyl-*p*-toluenesulfonamide (**39**), approximately 50% of the activity was retained. The inhibition of myosin-2 ATPase activity by tribromodichloropseudilin (**31**) (approximately 30% of activity was retained) was between that of pentabromopseudilin (**3**) and pentachloropseudilin (**4**). The other derivatives tested, pseudilin (**22**), the *O*-methyl compounds **21b**, **21c**, **28**, **30**, **32**, **34**, and **36**, and tribromodifluoropseudilin (**35**), showed little or no inhibition of myosin-2 ATPase activity. The binding affinities of the pentahalogenated pseudilins **3**, **4**, and **31** to the *Dictyostelium discoideum* (*Dd*) myosin-2 motor domain were deter-

mined by microscale thermophoresis (see Figure 5). The obtained binding affinities correlate well with the IC_{50} values for the inhibition of basal myosin-2 ATPase activity.

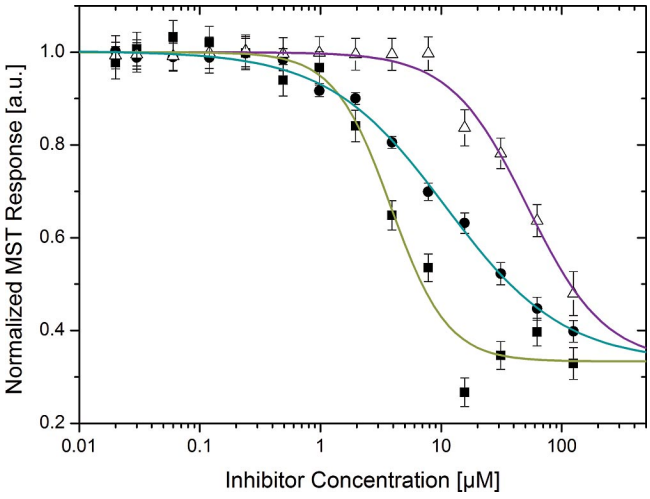


Figure 5. Binding of the pentahalogenated pseudilins **3**, **4**, and **31** to the fluorescent labeled *Dd* myosin-2 motor domain determined by microscale thermophoresis at different inhibitor concentrations (MST = microscale thermophoresis). Sigmoidal fit of the normalized data gave binding affinities of $K_d = 3.81 \pm 0.59$ μM [for **3** (■)], $K_d = 10.89 \pm 1.68$ μM [for **31** (●)], $K_d = 52.22 \pm 17.59$ μM [for **4** (Δ)].

X-ray crystallographic analysis of the *Dictyostelium discoideum* myosin-2 motor domain complexes with magnesium(II)–ADP–metavanadate (ADP = adenosine diphosphate) and the three pseudilin inhibitors **3**, **4**, and **31** allowed us to identify the crucial interactions and revealed that the pseudilins bind to a previously unknown allosteric binding pocket (for the X-ray crystal structure of the corresponding complex with tribromodichloropseudilin **31**, see Figure 6). The pseudilin binding pocket is 16 Å away from the nucleotide binding site and 7 Å from the allosteric binding pocket of (*S*)-(–)-blebbistatin (**38**). The X-ray crystal structures for all three complexes confirm that the free O–H and N–H groups of pseudilins **3**, **4**, and **31** are required for the formation of the crucial hydrogen bonds in the pseudilin binding pocket. This observation explains why the corresponding *O*-methyl and *N*-methyl derivatives (**23**, **27**, **28** and **30**) exhibit significantly lower inhibition activities.

The mode of action for the inhibition of myosin by pentahalogenated pseudilins **3**, **4**, and **31** was identified by X-ray crystallographic studies of the corresponding protein–inhibitor complexes. The binding of pseudilins **3**, **4**, and **31** at the allosteric site leads to conformational changes of the amino acid residues along the relay path and prevents the proper positioning of the lytic water, which is required in the active site for ATP hydrolysis by an in-line attack (vide infra).

A comparative structural analysis of the three known high resolution myosin-2–inhibitor complex structures with the X-ray structure of unbound myosin-2 in the prepower

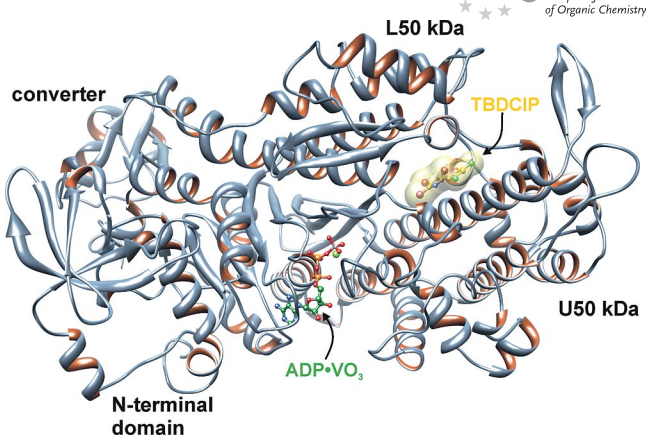
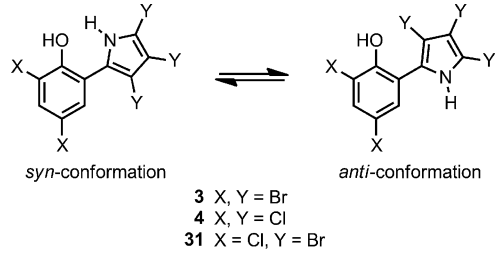


Figure 6. Ribbon presentation of the X-ray crystal structure of the *Dd* myosin-2 motor domain complex with Mg^{2+}–ADP–metavanadate and tribromodichloropseudilin (TBDClP, **31**), PDB ID: 2XO8 (overview).

stroke state (PDB ID: 2JJ9, 1VOM) revealed a communication pathway between the allosteric binding pocket and the active site of the myosin (see Figures 7, a–c). The pentahalogenated pseudilins exhibit their inhibitory activity through a cascade of small conformational changes along the signal relay path, which leads to the inability of the myosin to stabilize the lytic water molecule in the active site for an in-line nucleophilic attack of the ATP γ-phosphate, and, thus, efficiently inhibits the enzymatic ATPase function. We also observed a substituent-dependent conformational change in the pseudilin–myosin-2 complex. In the pentabromopseudilin–myosin-2 complex, the O–H and N–H groups of **3** adopt an almost *syn*-periplanar arrangement, whereas in the myosin-2 complexes with pentachloropseudilin (**4**) and tribromodichloropseudilin (**31**), the O–H and N–H groups are in an *anti*-periplanar conformation (see Scheme 15 and cf. Figures 7, a–c).



Scheme 15. Different conformations of pentahalopseudilins **3**, **4**, and **31** with respect to the biaryl axis.

A further study revealed that the magnitude and order of the inhibition activity of the pentahalogenated pseudilins **3**, **4**, and **31** for the different myosin-isoforms varied significantly. Pentabromopseudilin (**3**) displayed a high binding affinity towards class 5 myosins. The highest binding affinity of compound **3** was observed for chicken myosin-5a with a half-maximal inhibitory concentration (IC_{50}) of 1.2 μM, which is much lower than the IC_{50} value for class-2 myosins (approximately 25 μM) and *Dd* myosin-1E (approximately 50 μM). Pentachloropseudilin (**4**) revealed very different

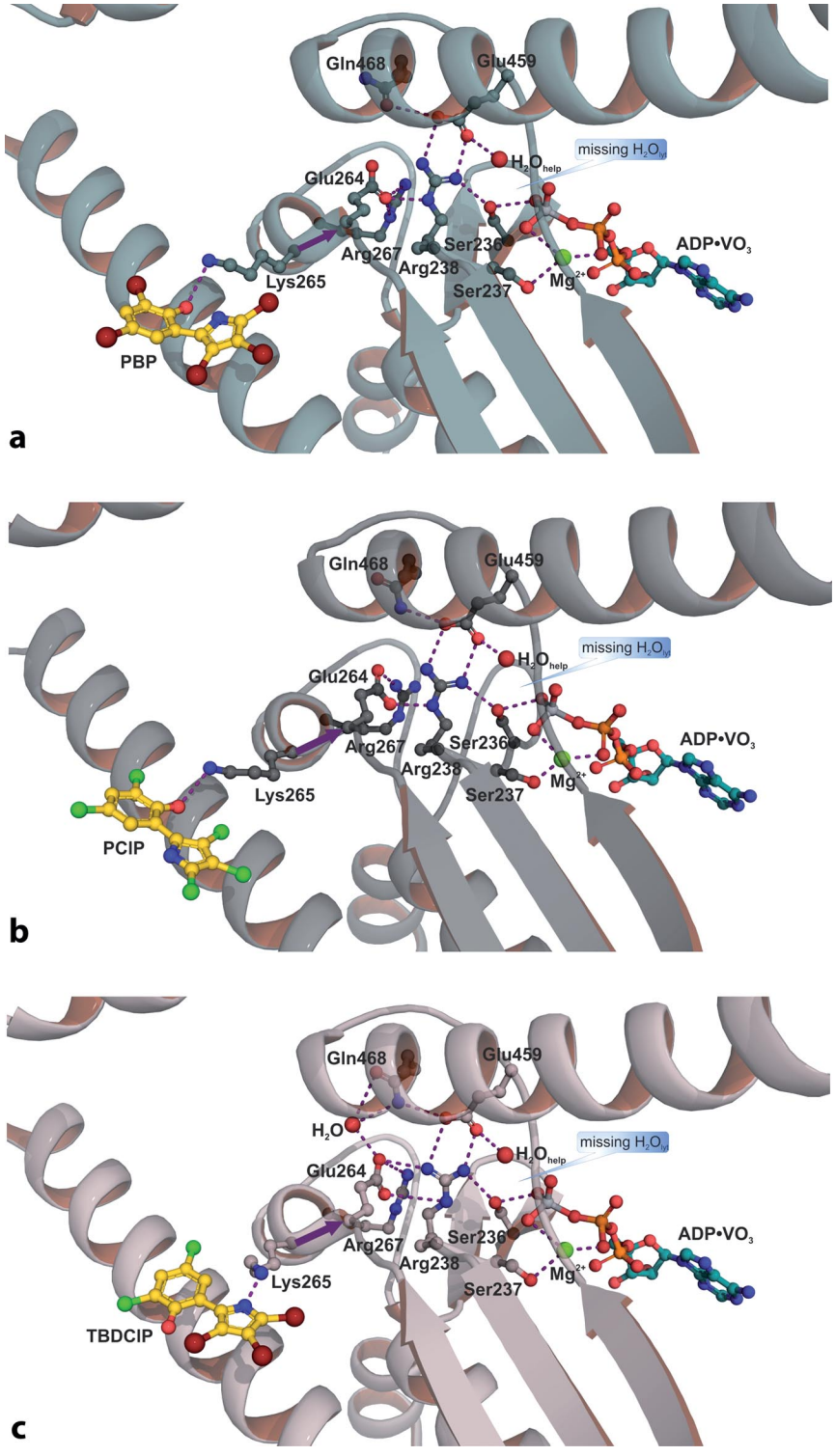


Figure 7. (a) Close-up of the communication pathway in the structure of the myosin-2 complex with Mg^{2+}–ADP–metavanadate and pentabromopseudilin (PBP, **3**), PDB ID: 2JHR. (b) Close-up of the communication pathway in the structure of the myosin-2 complex with Mg^{2+}–ADP–metavanadate and pentachloropseudilin (PClP, **4**), PDB ID: 2XEL. (c) Close-up of the communication pathway in the structure of the myosin-2 complex with Mg^{2+}–ADP–metavanadate and tribromodichloropseudilin (TBDClP, **31**), PDB ID: 2XO8.

binding preferences with the highest affinity towards mammalian class 1 myosins ($IC_{50} \approx 1$ μM for *Dd* myosin-1B) and a significantly reduced affinity towards class 2 and 5 myosins ($IC_{50} \approx 100$ μM). This different behavior was attributed to the different polarities of the binding pockets of the proteins. The more polar binding pocket of class 1 myosins better accommodates the more electronegative chlorine substituents, whereas pentabromopseudilin (**3**) shows a

preference for the less polar binding pocket of class 2 and 5 myosins. Thus, the different pseudilins may serve as potent and isoform-specific myosin ATPase inhibitors, depending on their halogenation pattern. The observed specificity for the inhibition of class 1 myosins that is exhibited by pentachloropseudilin (**4**) is very useful for the investigation of myosin-1 dependent biological processes.[21] More recently, the pentahalogenated pseudilins **3**, **4**, **31**, and **35** were also shown to function as allosteric inhibitors of IspD, an enzyme of the non-mevalonate (deoxyxylulose) pathway for the biogenesis of terpenes in plants and microorganisms.[22]

Conclusions

Using a silver(I)-catalyzed cycloisomerization of *N*-(homopropargyl)toluenesulfonamides as the key step, we developed very efficient routes for the syntheses of the pentahalogenated 2-arylpyrrole alkaloids pentabromopseudilin (**3**, seven steps and 32% overall yield based on **9a**) and pentachloropseudilin (**4**, seven steps and 21% overall yield based on **9c**) as well as several mixed halogenated analogues. The pentahalogenated 2-arylpyrroles were shown to represent a new class of isoform-specific allosteric inhibitors for different myosin ATPases. Their mode of action for the inhibition of myosin was deduced by X-ray crystallographic studies of the corresponding protein–inhibitor complexes.

Experimental Section

General Methods: All reactions were carried out in oven-dried glassware using dry solvents under argon, unless stated otherwise. Dichloromethane, acetonitrile, tetrahydrofuran, and diethyl ether were dried using a solvent purification system (MBraun-SPS). All other chemicals were used as received from their commercial sources. Flash chromatography was performed on silica gel from Acros Organics (0.035–0.070 mm). Thin layer chromatography was performed with TLC plates from Merck (60 F_{254}) and by using UV light for visualization. Melting points were measured with a Gallenkamp MPD 350 melting point apparatus. Ultraviolet spectra were recorded with a Perkin–Elmer 25 UV/Vis spectrometer. Infrared spectra were recorded with a Thermo Nicolet Avatar 360 FT-IR spectrometer using the ATR method (attenuated total reflectance). NMR spectroscopic data were recorded with Bruker Avance III 600 and DRX 500 spectrometers. Chemical shifts (δ) are reported in parts per million with the nondeuterated residual solvent as the internal standard. The abbreviations used to report the data are s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br. (broad). Mass spectrometry data were recorded with a Finnigan MAT-95 spectrometer (electron impact, 70 eV) or by GC–MS coupling using an Agilent Technologies 6890 N GC System equipped with a 5973 mass selective detector (electron impact, 70 eV). ESI-MS spectra were recorded on an Esquire LC with an ion trap detector from Bruker. Positive and negative ions were detected. Elemental analyses were measured with a EuroVector EuroEA3000 elemental analyzer. X-ray crystal structure analysis was performed with a Bruker-Nonius Kappa CCD equipped with a 700 series cryostream low temperature device from Oxford Cryosystems and with SHELXS-97[23] (G. M. Sheldrick, 1997), SADABS[24] version 2.10 (G. M. Sheldrick, Bruker AXS Inc., 2002), SHELXL-97[25] (G. M. Sheldrick, 1997), and ORTEP-3 for Windows software.[26]

3,5-Dichloro-2-methoxybenzaldehyde (9c): Potassium carbonate (2.38 g, 17.3 mmol) and iodomethane (1.29 mL, 2.94 g, 20.7 mmol) were added at room temperature to a solution of 3,5-dichloro-2-hydroxybenzaldehyde (2.64 g, 13.8 mmol) in *N*,*N*-dimethylformamide (DMF, 25 mL), and the mixture was heated at 70 °C for 2 d. Water (50 mL) was added, and the mixture was extracted with diethyl ether (3× 50 mL). The combined organic layers were washed with aqueous 2 N NaOH (2× 50 mL), water (50 mL), and brine and then dried with sodium sulfate. The solvent was evaporated to provide **9c** (2.25 g, 80% yield) as a light yellow solid; m.p. 88–89 °C. UV (MeOH): λ = 250, 277, 285, 313 nm. IR (ATR): $\tilde{\nu}$ = 3360, 3074, 3021, 2948, 2873, 2743, 1688, 1583, 1562, 1462, 1451, 1419, 1402, 1380, 1272, 1244, 1216, 1161, 1088, 1053, 974, 918, 899, 879, 840, 759, 744, 651 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.99 (s, 3 H), 7.62 (d, J = 2.7 Hz, 1 H), 7.71 (d, J = 2.7 Hz, 1 H), 10.30 (s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 63.37 (CH_3), 126.73 (CH), 129.83 (C), 130.53 (C), 131.23 (C), 135.82 (CH), 157.73 (C), 187.71 (CHO) ppm. MS (EI): *m*/*z* (%) = 208 (12), 206 (66), 204 (100) $[M]^+$, 191 (44), 189 (82), 97 (52). $C_8H_6Cl_2O_2$ (205.04): calcd. C 46.86, H 2.95; found C 47.07, H 3.00.

***N*-(2-Methoxybenzylidene)-4-methylbenzenesulfonamide (10a):** Tetraethyl orthosilicate (5.15 mL, 4.81 g, 23.1 mmol), 2-methoxybenzaldehyde (**9a**, 3.00 g, 22.0 mmol), and *p*-toluenesulfonamide (3.77 g, 22.0 mmol) were heated at 160 °C for 6 h in a distillation apparatus under argon (EtOH was distilled off). Ethyl acetate (20 mL) and pentane (250 mL) were added, and the suspension was cooled in a refrigerator for 24 h. The resulting precipitate was collected by filtration, washed thoroughly with pentane (400 mL), and dried under vacuum to provide **10a** (5.97 g, 94% yield) as a yellow solid; m.p. 105–109 °C. UV (MeOH): λ = 222, 275, 342 nm. IR (ATR): $\tilde{\nu}$ = 3357, 3260, 2974, 2842, 1586, 1563, 1483, 1439, 1357, 1315, 1301, 1252, 1151, 1084, 1043, 1014, 809, 759, 674 cm^{-1}. ^1H NMR (500 MHz, CD_2Cl_2): δ = 2.43 (s, 3 H), 3.93 (s, 3 H), 7.01 (m, 2 H), 7.36 (d, J = 8.2 Hz, 2 H), 7.59 (m, 1 H), 7.84 (d, J = 8.3 Hz, 2 H), 8.01 (dd, J = 8.0, 1.8 Hz, 1 H), 9.48 (s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, CD_2Cl_2): δ = 21.70 (CH_3), 56.20 (CH_3), 112.05 (CH), 121.19 (C), 121.21 (CH), 128.16 (2 CH), 129.25 (CH), 130.10 (2 CH), 135.99 (C), 137.35 (CH), 144.93 (C), 162.18 (C), 166.65 (*C*H=NTs) ppm. MS (EI): *m*/*z* (%) = 289 (2.5) $[M]^+$, 171 (9), 155 (17), 134 (75), 133 (65), 119 (16), 118 (15), 107 (12), 91 (100), 77 (12), 65 (17). HRMS (EI): calcd. for $C_{15}H_{15}NO_3S^+$ $[M]^+$ 289.0773; found 289.0772.

***N*-(3,5-Difluoro-2-methoxybenzylidene)-4-methylbenzenesulfonamide (10b):** Tetraethyl orthosilicate (1.59 mL, 1.48 g, 7.12 mmol), 3,5-difluoro-2-methoxybenzaldehyde (**9b**, 1.17 g, 6.78 mmol) and *p*-toluenesulfonamide (1.16 g, 6.78 mmol) were heated at 160 °C for 6 h in a distillation apparatus under argon (EtOH was distilled off). Ethyl acetate (10 mL) and pentane (175 mL) were added, and the suspension was cooled in a refrigerator for 15 h. The resulting precipitate was collected by filtration, washed carefully with pentane, and dried under vacuum to provide **10b** (1.80 g, 81% yield) as an off-white solid; m.p. 105 °C. UV (MeOH): λ = 224, 269 nm. IR (ATR): $\tilde{\nu}$ = 3093, 2996, 2949, 2882, 2845, 1644, 1579, 1489, 1450, 1431, 1360, 1330, 1316, 1290, 1239, 1194, 1179, 1162, 1124, 1086, 1003, 873, 827, 810, 758, 730, 708, 694, 650 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 4.04 (d, $^5J_{H,F}$ = 2.5 Hz, 3 H), 7.08 (ddd, $^3J_{H,F}$ = 11.2, 7.9 Hz, $^4J_{H,H}$ = 3.2 Hz, 1 H), 7.35 (d, J = 8.1 Hz, 2 H), 7.52 (m, 1 H), 7.87 (d, J = 8.3 Hz, 2 H), 9.36 (d, $^5J_{H,F}$ = 2.2 Hz, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ

= 21.68 (CH_3), 62.59 (d, $^4J_{C,F}$ = 7.1 Hz, CH_3), 109.91 (dd, $^2J_{C,F}$ = 23.9 Hz, $^4J_{C,F}$ = 3.7 Hz, CH), 111.61 (dd, $^2J_{C,F}$ = 27.3, 22.8 Hz, CH), 126.68 (m, C), 128.20 (2 CH), 129.87 (2 CH), 134.69 (C), 144.91 (C), 147.00 (m, C), 154.94 (dd, $^1J_{C,F}$ = 252.4 Hz, $^3J_{C,F}$ = 11.6 Hz, C), 157.13 (dd, $^1J_{C,F}$ = 246.9 Hz, $^3J_{C,F}$ = 11.0 Hz, C), 164.30 (d, $^4J_{C,F}$ = 3.2 Hz, *C*H=NTs) ppm. MS (EI): *m*/*z* (%) = 325 (0.5) $[M]^+$, 170 (65), 169 (38), 155 (34), 154 (98), 91 (100), 65 (17).

***N*-(3,5-Dichloro-2-methoxybenzylidene)-4-methylbenzenesulfonamide (10c):** Tetraethyl orthosilicate (1.28 mL, 1.19 g, 5.71 mmol), 3,5-dichloro-2-methoxybenzaldehyde (**9c**, 1.12 g, 5.44 mmol), and *p*-toluenesulfonamide (931 mg, 5.44 mmol) were heated at 160 °C for 6 h in a distillation apparatus under argon (EtOH was distilled off). Ethyl acetate (10 mL) and pentane (200 mL) were added, and the suspension was cooled in a refrigerator for 24 h. The resulting precipitate was collected by filtration, washed carefully with pentane, and dried under vacuum to provide **10c** (1.37 g, 70% yield) as a yellow solid; m.p. 103 °C. UV (MeOH): λ = 222 nm. IR (ATR): $\tilde{\nu}$ = 3349, 3258, 3062, 2972, 2921, 2865, 1597, 1561, 1520, 1464, 1418, 1385, 1323, 1302, 1246, 1223, 1183, 1154, 1085, 1017, 988, 945, 901, 874, 808, 761, 711, 679 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 3.95 (s, 3 H), 7.36 (d, *J* = 8.1 Hz, 2 H), 7.59 (d, *J* = 2.6 Hz, 1 H), 7.88 (d, *J* = 8.2 Hz, 2 H), 7.93 (d, *J* = 2.6 Hz, 1 H), 9.28 (s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.69 (CH_3), 63.26 (CH_3), 127.21 (CH), 128.26 (2 CH), 128.29 (C), 129.57 (C), 129.93 (2 CH), 130.46 (C), 134.47 (C), 136.21 (CH), 145.06 (C), 157.54 (C), 164.23 (*C*H=NTs) ppm. MS (EI): *m*/*z* (%) = 357 (0.3) $[M]^+$, 206 (4), 205 (6), 204 (22), 203 (29), 202 (36) $[M - C_7H_7SO_2]^+$, 201 (41) $[M - C_7H_8SO_2]^+$, 155 (20), 91 (100).

***N*-(3,5-Dibromo-2-methoxybenzylidene)-4-methylbenzenesulfonamide (10d):** Tetraethyl orthosilicate (1.25 mL, 1.17 g, 5.61 mmol), 3,5-dibromo-2-methoxybenzaldehyde (**9d**, 1.50 g, 5.10 mmol), and *p*-toluenesulfonamide (874 mg, 5.10 mmol) were heated at 160 °C for 5 h in a distillation apparatus under argon (EtOH was distilled off). Ethyl acetate (10 mL) and pentane (200 mL) were added, and the suspension was cooled in a refrigerator for 24 h. The resulting precipitate was collected by filtration, washed carefully with pentane, and dried under vacuum to provide **10d** (1.81 g, 79% yield) as a yellow solid; m.p. 81–82 °C. UV (MeOH): λ = 222, 262 nm. IR (ATR): $\tilde{\nu}$ = 3354, 3259, 3064, 1598, 1575, 1528, 1458, 1410, 1387, 1353, 1300, 1228, 1182, 1155, 1088, 1019, 987, 904, 875, 816, 792, 756, 707, 693, 665 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.44 (s, 3 H), 3.92 (s, 3 H), 7.36 (d, *J* = 8.2 Hz, 2 H), 7.87 (d, *J* = 8.3 Hz, 2 H), 7.89 (d, *J* = 2.2 Hz, 1 H), 8.11 (d, *J* = 2.3 Hz, 1 H), 9.25 (s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.69 (CH_3), 63.49 (CH_3), 118.10 (C), 118.83 (C), 128.26 (2 CH), 128.71 (C), 129.94 (2 CH), 130.98 (CH), 134.37 (C), 141.79 (CH), 145.08 (C), 159.08 (C), 164.23 (*C*H=NTs) ppm.

***N*-[1-(2-Methoxyphenyl)-4-(trimethylsilyl)but-3-ynyl]-4-methylbenzenesulfonamide (11a) and *N*-[1-(Methoxyphenyl)-2-(trimethylsilyl)-buta-2,3-dienyl]-4-methylbenzenesulfonamide (12a):** 3-Bromo-1-(trimethylsilyl)-1-propyne (7.62 mL, 8.92 g, 46.7 mmol) was added dropwise at room temperature to a mixture of magnesium turnings (1.24 g, 51.0 mmol) and diethyl ether (30 mL) at such a rate that the mixture was gently boiling. After the complete addition, the mixture was stirred at room temperature for 15 min. The supernatant solution was removed by a syringe and added at room temperature to a solution of tosylimine **10a** (4.50 g, 15.6 mmol) in dichloromethane (80 mL), and the mixture was stirred at room temperature for 15 h. Aqueous ammonium chloride (150 mL) was added, and the layers were separated. The aqueous layer was extracted with dichloromethane (3 × 100 mL), and the combined organic layers were dried with magnesium sulfate. The solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 4:1) provided **12a** (519 mg, 8% yield) as light yellow crystals; m.p. 114–115 °C. UV (MeOH): λ = 204, 226 nm. IR (ATR): $\tilde{\nu}$ = 3306, 3028, 2952, 2893, 2843, 1932, 1620, 1600, 1494, 1456, 1442, 1419, 1321, 1287, 1246, 1211, 1184, 1159, 1117, 1095, 1073, 1050, 1030, 1003, 926, 840, 808, 760, 720, 700, 666 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = –0.07 (s, 9 H), 2.31 (s, 3 H), 3.67 (s, 3 H), 4.35 (dd, *J* = 11.0, 3.3 Hz, 1 H), 4.42 (dd, *J* = 11.0, 3.1 Hz, 1 H), 5.12 (dt, *J* = 9.6, 3.2 Hz, 1 H), 5.52 (d, *J* = 9.6 Hz, 1 H), 6.59 (d, *J* = 8.2 Hz, 1 H), 6.73 (dt, *J* = 0.8, 7.4 Hz, 1 H), 6.95 (dd, *J* = 7.5, 1.6 Hz, 1 H), 7.03 (d, *J* = 8.0 Hz, 2 H), 7.08 (m, 1 H), 7.49 (d, *J* = 8.3 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = –1.44 (3 CH_3), 21.36 (CH_3), 53.82 (CH), 55.07 (CH_3), 72.94 (CH_2), 97.80 (C), 110.66 (CH), 120.23 (CH), 127.02 (2 CH), 127.63 (C), 128.70 (CH), 128.77 (2 CH), 128.97 (CH), 137.81 (C), 142.47 (C), 156.58 (C), 207.97 (C) ppm. $C_{21}H_{27}NO_3SSi$ (401.60): calcd. C 62.81, H 6.78, N 3.49, S 7.98; found C 62.55, H 6.87, N 3.45, S 7.77. Compound **11a** was obtained from the more polar fraction as colorless crystals (4.76 g, 76% yield); m.p. 129–130 °C. UV (MeOH): λ = 222, 273 nm. IR (ATR): $\tilde{\nu}$ = 3275, 2996, 2958, 2836, 2181, 1932, 1600, 1492, 1464, 1439, 1417, 1347, 1323, 1287, 1247, 1216, 1159, 1120, 1095, 1075, 1045, 1031, 967, 940, 897, 837, 818, 758, 686, 658 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 0.04 (s, 9 H), 2.31 (s, 3 H), 2.68 (d, *J* = 6.8 Hz, 2 H), 3.73 (s, 3 H), 4.60 (dt, *J* = 9.4, 6.8 Hz, 1 H), 5.61 (d, *J* = 9.4 Hz, 1 H), 6.67 (d, *J* = 8.1 Hz, 1 H), 6.74 (dt, *J* = 0.9, 7.4 Hz, 1 H), 6.97 (dd, *J* = 7.5, 1.6 Hz, 1 H), 7.07 (d, *J* = 8.0 Hz, 2 H), 7.12 (m, 1 H), 7.53 (d, *J* = 8.3 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = –0.13 (3 CH_3), 21.40 (CH_3), 27.24 (CH_2), 54.48 (CH), 55.11 (CH_3), 88.02 (C), 102.43 (C), 110.31 (CH), 120.16 (CH), 126.57 (C), 126.88 (2 CH), 128.69 (CH), 129.14 (2 CH), 129.29 (CH), 137.42 (C), 142.88 (C), 156.00 (C) ppm. MS (EI): *m*/*z* (%) = 401 (0.01) $[M]^+$, 386 (0.3), 290 (100) $[M - C_6H_{11}Si]^+$, 155 (16), 91 (21). HRMS (EI): calcd. for $C_{15}H_{16}NO_3S^+$ $[M - C_6H_{11}Si]^+$ 290.0851; found 290.0830. $C_{21}H_{27}NO_3SSi$ (401.60): calcd. C 62.81, H 6.78, N 3.49, S 7.98; found C 62.75, H 6.78, N 3.43, S 7.85.

***N*-[1-(3,5-Difluoro-2-methoxyphenyl)-4-(trimethylsilyl)but-3-ynyl]-4-methylbenzenesulfonamide (11b) and *N*-[1-(3,5-Difluoro-2-methoxyphenyl)-2-(trimethylsilyl)buta-2,3-dienyl]-4-methylbenzenesulfonamide (12b):** 3-Bromo-1-(trimethylsilyl)-1-propyne (2.48 mL, 2.91 g, 15.2 mmol) was added dropwise at room temperature to a mixture of magnesium turnings (407 mg, 16.7 mmol) and diethyl ether (10 mL) at such a rate that the mixture was gently boiling. After the complete addition, the mixture was stirred at room temperature for 15 min. The supernatant solution was removed by a syringe and added at room temperature to a solution of tosylimine **10b** (1.65 g, 5.07 mmol) in dichloromethane (50 mL), and the mixture was stirred at room temperature for 15 h. Aqueous ammonium chloride (100 mL) was added, and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 50 mL), and the combined organic layers were dried with magnesium sulfate. The solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 8:1) provided **12b** (558 mg, 25% yield) as a yellow oil. UV (MeOH): λ = 235, 269 nm. IR (ATR): $\tilde{\nu}$ = 3250, 3025, 2961, 2894, 2836, 2173, 1928, 1598, 1491, 1436, 1424, 1340, 1325, 1248, 1225, 1155, 1121, 1080, 993, 947 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = –0.02 (s, 9 H), 2.35 (s, 3 H), 3.86 (d, $^5J_{H,F}$ = 1.9 Hz, 3 H), 4.37 (dd, *J* = 11.5, 3.3 Hz, 1 H), 4.48 (dd, *J* = 11.5, 3.1 Hz, 1 H), 5.15 (dt, *J* = 9.2, 3.2 Hz, 1 H), 5.37 (d, *J* = 9.3 Hz, 1 H), 6.42 (ddd, $^3J_{H,F}$ = 8.6 Hz, $^4J_{H,H}$ = 2.9 Hz, $^5J_{H,F}$ = 1.8 Hz, 1 H), 6.61 (ddd, $^3J_{H,F}$ =

11.4, 8.2 Hz, $^4J_{H,H}$ = 3.1 Hz, 1 H), 7.13 (d, J = 8.1 Hz, 2 H), 7.55 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = –1.43 (3 CH_3), 21.38 (CH_3), 52.30 (CH), 61.32 (d, $^4J_{C,F}$ = 6.3 Hz, CH_3), 73.88 (CH_2), 98.28 (C), 104.09 (dd, $^2J_{C,F}$ = 26.7, 23.2 Hz, CH), 110.38 (dd, $^2J_{C,F}$ = 23.1 Hz, $^4J_{C,F}$ = 3.3 Hz, CH), 127.07 (2 CH), 129.11 (2 CH), 135.40 (dd, $^3J_{C,F}$ = 7.9, 3.0 Hz, C), 137.40 (C), 141.16 (dd, $^2J_{C,F}$ = 11.0 Hz, $^4J_{C,F}$ = 3.8 Hz, C), 143.20 (C), 155.00 (dd, $^1J_{C,F}$ = 250.5 Hz, $^3J_{C,F}$ = 12.3 Hz, C), 157.14 (dd, $^1J_{C,F}$ = 244.8 Hz, $^3J_{C,F}$ = 11.7 Hz, C), 207.69 (C) ppm. Compound **11b** was obtained from the more polar fraction as colorless crystals (1.15 g, 52% yield); m.p. 122 °C. UV (MeOH): λ = 233, 269 nm. IR (ATR): $\tilde{\nu}$ = 3269, 3070, 2958, 2828, 2178, 1601, 1488, 1437, 1417, 1328, 1249, 1226, 1187, 1165, 1124, 1090, 1061, 1002, 944, 907, 842, 811, 760, 710, 700, 665 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.08 (s, 9 H), 2.36 (s, 3 H), 2.59 (m, 2 H), 3.88 (d, $^5J_{H,F}$ = 2.1 Hz, 3 H), 4.67 (dt, J = 8.2, 6.3 Hz, 1 H), 5.36 (d, J = 8.3 Hz, 1 H), 6.58 (ddd, $^3J_{H,F}$ = 8.7 Hz, $^4J_{H,H}$ = 2.8 Hz, $^5J_{H,F}$ = 1.8 Hz, 1 H), 6.67 (ddd, $^3J_{H,F}$ = 11.4, 8.2 Hz, $^4J_{H,H}$ = 3.1 Hz, 1 H), 7.18 (d, J = 8.0 Hz, 2 H), 7.60 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = –0.21 (3 CH_3), 21.44 (CH_3), 27.74 (CH_2), 51.73 (CH), 61.42 (d, $^4J_{C,F}$ = 6.8 Hz, CH_3), 89.62 (C), 100.64 (C), 104.26 (dd, $^2J_{C,F}$ = 26.5, 23.5 Hz, CH), 110.55 (dd, $^2J_{C,F}$ = 23.8 Hz, $^4J_{C,F}$ = 3.2 Hz, CH), 127.01 (2 CH), 129.45 (2 CH), 134.31 (dd, $^3J_{C,F}$ = 8.3, 3.4 Hz, C), 136.97 (C), 140.75 (dd, $^2J_{C,F}$ = 11.1 Hz, $^4J_{C,F}$ = 4.0 Hz, C), 143.59 (C), 154.62 (dd, $^1J_{C,F}$ = 249.7 Hz, $^3J_{C,F}$ = 12.2 Hz, C), 157.06 (dd, $^1J_{C,F}$ = 244.8 Hz, $^3J_{C,F}$ = 11.8 Hz, C) ppm. MS (EI): m/z (%) = 326 (100) [M – $C_6H_{11}Si$]$^+$, 155 (44), 91 (48). $C_{21}H_{25}F_2NO_3SSi$ (437.58): calcd. C 57.64, H 5.76, N 3.20, S 7.33; found C 57.35, H 5.88, N 3.16, S 7.33.

***N*-[1-(3,5-Dichloro-2-methoxyphenyl)-4-(trimethylsilyl)but-3-ynyl]-4-methylbenzenesulfonamide (11c) and *N*-[1-(3,5-Dichloro-2-methoxyphenyl)-2-(trimethylsilyl)buta-2,3-dienyl]-4-methylbenzenesulfonamide (12c):** 3-Bromo-1-(trimethylsilyl)-1-propyne (2.06 mL, 2.41 g, 12.6 mmol) was added dropwise at room temperature to a mixture of magnesium turnings (337 mg, 13.9 mmol) and diethyl ether (10 mL) at such a rate that the mixture was gently boiling. After the complete addition, the mixture was stirred at room temperature for 15 min. The supernatant solution was removed by a syringe and added at room temperature to a solution of tosylimine **10c** (1.50 g, 4.20 mmol) in dichloromethane (40 mL), and the mixture was stirred at room temperature for 15 h. Aqueous ammonium chloride (100 mL) was added, and the layers were separated. The aqueous layer was extracted with dichloromethane (2× 50 mL), and the combined organic layers were dried with magnesium sulfate. The solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 8:1) provided **12c** (526 mg, 27% yield) as a yellow oil. UV (MeOH): λ = 227 nm. IR (ATR): $\tilde{\nu}$ = 3274, 3074, 2954, 2849, 1932, 1598, 1567, 1466, 1422, 1335, 1289, 1248, 1217, 1158, 1092, 1061, 996, 895, 836, 813, 756, 720, 702, 665 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.03 (s, 9 H), 2.35 (s, 3 H), 3.87 (s, 3 H), 4.34 (dd, J = 11.6, 3.3 Hz, 1 H), 4.46 (dd, J = 11.6, 3.2 Hz, 1 H), 5.18 (dd, J = 9.2, 6.2 Hz, 1 H), 5.30 (d, J = 9.2 Hz, 1 H), 6.72 (d, J = 2.5 Hz, 1 H), 7.12 (m, 3 H), 7.51 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = –1.34 (3 CH_3), 21.40 (CH_3), 52.50 (CH), 61.20 (CH_3), 74.00 (CH_2), 98.73 (C), 126.97 (2 CH), 127.30 (CH), 128.37 (C), 128.90 (C), 129.13 (2 CH), 129.18 (CH), 136.19 (C), 137.18 (C), 143.32 (C), 151.90 (C), 207.98 (C) ppm. MS (EI): m/z (%) = 360 (8), 358 (12) [M – $C_6H_{11}Si$]$^+$, 253 (3), 155 (24), 91 (100). Compound **11c** was obtained from the more polar fraction as colorless crystals (998 mg, 50% yield); m.p. 132 °C. UV (MeOH): λ = 225 nm. IR (ATR): $\tilde{\nu}$ = 3267, 3066, 2958, 2820, 2180, 1599, 1566, 1495, 1468, 1422, 1344, 1327, 1269, 1249, 1229, 1186, 1164, 1108, 1093, 1083, 1055, 1006, 972, 941, 912, 865, 840, 809, 758 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.10 (s, 9 H), 2.37 (s, 3 H), 2.54 (dd, J_{AB} = 17.1 Hz, J = 5.4 Hz, 1 H), 2.61 (dd, J_{AB} = 17.1 Hz, J = 6.2 Hz, 1 H), 3.86 (s, 3 H), 4.72–4.75 (m, 1 H), 5.32 (d, J = 7.9 Hz, 1 H), 6.92 (d, J = 2.4 Hz, 1 H), 7.18 (m, 3 H), 7.58 (d, J = 8.1 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = –0.19 (3 CH_3), 21.46 (CH_3), 27.94 (CH_2), 50.75 (CH), 61.27 (CH_3), 90.25 (C), 100.15 (C), 126.93 (2 CH), 127.18 (CH), 128.11 (C), 129.05 (C), 129.39 (CH), 129.50 (2 CH), 135.32 (C), 136.86 (C), 143.73(C), 151.64 (C) ppm. MS (EI): m/z (%) = 362 (14), 360 (69), 358 (100) [M – $C_6H_{11}Si$]$^+$, 155 (71), 91 (79), 65 (10). $C_{21}H_{25}Cl_2NO_3SSi$ (470.49): calcd. C 53.61, H 5.36, N 2.98, S 6.82; found C 53.74, H 5.33, N 2.96, S 6.83.

***N*-[1-(3,5-Dibromo-2-methoxyphenyl)-4-(trimethylsilyl)but-3-ynyl]-4-methylbenzenesulfonamide (11d) and *N*-[1-(3,5-Dibromo-2-methoxyphenyl)-2-(trimethylsilyl)buta-2,3-dienyl]-4-methylbenzenesulfonamide (12d):** 3-Bromo-1-(trimethylsilyl)-1-propyne (683 μL, 800 mg, 4.21 mmol) was added dropwise at room temperature to a mixture of magnesium turnings (122 mg, 5.04 mmol) and diethyl ether (4 mL) at such a rate that the mixture was gently boiling. After the complete addition, the mixture was stirred at room temperature for 15 min. The supernatant solution was removed by a syringe and added at room temperature to a solution of tosylimine **10d** (624 mg, 1.39 mmol) in dichloromethane (20 mL), and the mixture was stirred at room temperature for 15 h. Aqueous ammonium chloride (50 mL) was added, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3× 25 mL), and the combined organic layers were dried with magnesium sulfate. The solvent was removed, and the resulting residue was purified by chromatography on a silica gel column (pentane/diethyl ether, 9:1) to provide **12d** (249 mg, 32% yield) as yellow oil. UV (MeOH): λ = 229 nm. IR (ATR): $\tilde{\nu}$ = 3280, 2956, 2175, 1931, 1599, 1462, 1418, 1335, 1249, 1160, 1092, 1053, 996, 918, 840 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.04 (s, 9 H), 2.35 (s, 3 H), 3.86 (s, 3 H), 4.33 (dd, J = 11.7, 3.2 Hz, 1 H), 4.45 (dd, J = 11.7, 3.2 Hz, 1 H), 5.19 (dt, J = 9.3, 3.2 Hz, 1 H), 5.28 (d, J = 9.3 Hz, 1 H), 6.88 (d, J = 2.3 Hz, 1 H), 7.12 (d, J = 8.1 Hz, 2 H), 7.41 (d, J = 2.3 Hz, 1 H), 7.50 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = –1.30 (3 CH_3), 21.46 (CH_3), 52.59 (CH), 61.34 (CH_3), 74.01 (CH_2), 98.87 (C), 116.71 (C), 117.82 (C), 126.94 (2 CH), 129.17 (2 CH), 130.96 (CH), 134.78 (CH), 136.66 (C), 137.13 (C), 143.34 (C), 153.43 (C), 208.13 (C) ppm. Compound **11d** was obtained from the more polar fraction as colorless crystals (426 mg, 55% yield); m.p. 122 °C. UV (MeOH): λ = 225 nm. IR (ATR): $\tilde{\nu}$ = 3266, 3061, 3011, 2953, 2179, 1736, 1598, 1556, 1494, 1465, 1456, 1417, 1343, 1326, 1248, 1227, 1164, 1141, 1092, 1051, 1003, 965, 940, 912, 864, 838, 807, 758, 713, 670 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.11 (s, 9 H), 2.38 (s, 3 H), 2.53 (dd, J_{AB} = 17.1 Hz, J = 5.3 Hz, 1 H), 2.63 (dd, J_{AB} = 17.1 Hz, J = 6.1 Hz, 1 H), 3.85 (s, 3 H), 4.76 (dt, J = 7.8, 5.8 Hz, 1 H), 5.31 (d, J = 7.9 Hz, 1 H), 7.10 (d, J = 2.4 Hz, 1 H), 7.18 (d, J = 8.2 Hz, 2 H), 7.48 (d, J = 2.4 Hz, 1 H), 7.57 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = –0.14 (3 CH_3), 21.51 (CH_3), 28.01 (CH_2), 50.56 (CH), 61.37 (CH_3), 90.40 (C), 100.01 (C), 116.87 (C), 117.52 (C), 126.89 (2 CH), 129.54 (2 CH), 130.74 (CH), 135.00 (CH), 135.80 (C), 136.85 (C), 143.75 (C), 153.19 (C) ppm. MS (EI): m/z (%) = 450 (53), 448 (100), 446 (50) [M – $C_6H_{11}Si$]$^+$, 155 (89), 91 (95), 65 (11). $C_{21}H_{25}Br_2NO_3SSi$ (559.39): calcd. C 45.09, H 4.50, N 2.50, S 5.73; found C 45.23, H 4.49, N 2.55, S 5.81.

***N*-[1-(2-Methoxyphenyl)-but-3-ynyl]-4-methylbenzenesulfonamide (15a):** TBAF (1.0 M solution in THF, 440 μL, 0.440 mmol) was added at room temperature to a solution of **11a** (149 mg,

0.370 mmol) in THF (10 mL), and the mixture was stirred at room temperature for 16 h. Water (50 mL) was added, and the reaction mixture was extracted with diethyl ether (3× 50 mL). The combined organic layers were dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 3:1) provided **15a** (121 mg, 99% yield) as yellow crystals; m.p. 120–121 °C. UV (MeOH): λ = 222, 272 nm. IR (ATR): $\tilde{\nu}$ = 3285, 3250, 2922, 2841, 1960, 1923, 1599, 1494, 1454, 1439, 1421, 1338, 1320, 1305, 1292, 1247, 1216, 1188, 1154, 1118, 1091, 1065, 1026, 941, 862, 839, 815, 781, 750, 706, 667 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.88 (t, J = 2.6 Hz, 1 H), 2.31 (s, 3 H), 2.68 (dd, J = 2.5, 1.6 Hz, 1 H), 2.69 (d, J = 2.6 Hz, 1 H), 3.73 (s, 3 H), 4.61 (dt, J = 9.6, 6.8 Hz, 1 H), 5.65 (d, J = 9.6 Hz, 1 H), 6.67 (d, J = 8.1 Hz, 1 H), 6.75 (dt, J = 0.8, 7.4 Hz, 1 H), 6.98 (dd, J = 7.5, 1.6 Hz, 1 H), 7.07 (d, J = 8.1 Hz, 2 H), 7.13 (m, 1 H), 7.54 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.38 (CH_3), 25.78 (CH_2), 54.58 (CH), 55.11 (CH_3), 71.07 (CH), 80.03 (C), 110.41 (CH), 120.31 (CH), 126.42 (C), 126.90 (2 CH), 128.87 (CH), 129.10 (3 CH), 137.37 (C), 142.89 (C), 156.02 (C) ppm. MS (EI): m/z (%) = 329 (0.1) $[M]^+$, 290 (100), 155 (21), 91 (35). HRMS (EI): calcd. for $C_{15}H_{16}NO_3S^+$ $[M - C_3H_3]^+$ 290.0851; found 290.0833. $C_{18}H_{19}NO_3S$ (329.41): calcd. C 65.63, H 5.81, N 4.25, S 9.73; found C 65.86, H 5.93, N 4.20, S 9.43.

***N*-[1-(3,5-Difluoro-2-methoxyphenyl)-but-3-ynyl]-4-methylbenzenesulfonamide (15b):** TBAF (1.0 M solution in THF, 2.60 mL, 2.60 mmol) was added at room temperature to a solution of **11b** (1.03 g, 2.35 mmol) in THF (50 mL), and the mixture was stirred at room temperature for 15 h. Water (100 mL) was added, and the reaction mixture was extracted with diethyl ether (3× 100 mL). The combined organic layers were dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 3:1) provided **15b** (814 mg, 95% yield) as light orange crystals; m.p. 128 °C. UV (MeOH): λ = 230, 270 nm. IR (ATR): $\tilde{\nu}$ = 3289, 3245, 3013, 2984, 2951, 2925, 2841, 1597, 1491, 1461, 1442, 1422, 1328, 1319, 1306, 1289, 1264, 1224, 1189, 1156, 1120, 1084, 1048, 1019, 998, 971, 941, 862, 845, 815, 779, 740, 703, 666, 650 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.96 (t, J = 2.6 Hz, 1 H), 2.36 (s, 3 H), 2.59 (m, 2 H), 3.88 (d, $^5J_{H,F}$ = 2.1 Hz, 3 H), 4.69 (dt, J = 8.5, 6.4 Hz, 1 H), 5.41 (d, J = 8.6 Hz, 1 H), 6.58 (m, 1 H), 6.67 (ddd, $^3J_{H,F}$ = 11.4, 8.2 Hz, $^4J_{H,H}$ = 3.1 Hz, 1 H), 7.18 (d, J = 8.1 Hz, 2 H), 7.61 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.42 (CH_3), 26.33 (CH_2), 51.92 (CH), 61.40 (d, $^4J_{C,F}$ = 7.1 Hz, CH_3), 72.30 (CH), 78.59 (C), 104.44 (dd, $^2J_{C,F}$ = 26.6, 23.3 Hz, CH), 110.40 (dd, $^2J_{C,F}$ = 23.6 Hz, $^4J_{C,F}$ = 2.9 Hz, CH), 127.02 (2 CH), 129.41 (2 CH), 134.08 (m, C), 136.95 (C), 140.76 (dd, $^2J_{C,F}$ = 10.9 Hz, $^4J_{C,F}$ = 3.5 Hz, C), 143.60 (C), 154.63 (dd, $^1J_{C,F}$ = 249.8 Hz, $^3J_{C,F}$ = 12.3 Hz, C), 157.12 (dd, $^1J_{C,F}$ = 244.8 Hz, $^3J_{C,F}$ = 11.8 Hz, C) ppm. MS (EI): m/z (%) = 326 (100) $[M - C_3H_3]^+$, 155 (51), 91 (73). $C_{18}H_{17}F_2NO_3S$ (365.39): calcd. C 59.17, H 4.69, N 3.83, S 8.78; found C 59.45, H 4.99, N 3.88, S 8.71.

***N*-[1-(3,5-Dichloro-2-methoxyphenyl)-but-3-ynyl]-4-methylbenzenesulfonamide (15c):** TBAF (1.0 M solution in THF, 2.20 mL, 2.20 mmol) was added at room temperature to a solution of **11c** (945 mg, 2.01 mmol) in THF (25 mL), and the mixture was stirred at room temperature for 15 h. Water (100 mL) was added, and the reaction mixture was extracted with diethyl ether (3× 100 mL). The combined organic layers were dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 3:1) provided **15c** (779 mg, 97% yield) as colorless crystals; m.p. 111 °C. UV (MeOH): λ = 264, 270, 275, 286 nm. IR (ATR): $\tilde{\nu}$ = 3278, 3245, 2946, 1595, 1569, 1493, 1466, 1421, 1331, 1305, 1283, 1265, 1240, 1217, 1186, 1157, 1120, 1092, 1072, 1018, 998, 943, 916, 885, 866, 844, 816, 766, 726, 704, 665 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.01 (t, J = 2.6 Hz, 1 H), 2.37 (s, 3 H), 2.54 (ddd, J_{AB} = 17.0 Hz, J = 6.0, 2.6 Hz, 1 H), 2.61 (ddd, J_{AB} = 17.0 Hz, J = 6.4, 2.6 Hz, 1 H), 3.87 (s, 3 H), 4.73 (m, 1 H), 5.32 (d, J = 8.0 Hz, 1 H), 6.91 (d, J = 2.5 Hz, 1 H), 7.175 (d, J = 2.6 Hz, 1 H), 7.177 (d, J = 8.1 Hz, 2 H), 7.58 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.47 (CH_3), 26.54 (CH_2), 51.23 (CH), 61.29 (CH_3), 72.78 (CH), 78.28 (C), 126.98 (2 CH), 128.23 (C), 129.26 (C), 129.46 (3 CH), 129.60 (CH), 135.23 (C), 136.78 (C), 143.76 (C), 151.73 (C) ppm. MS (EI): m/z (%) = 362 (10), 360 (50), 358 (73) $[M - C_3H_3]^+$, 155 (67), 91 (100), 65 (16). $C_{18}H_{17}Cl_2NO_3S$ (398.30): calcd. C 54.28, H 4.30, N 3.52, S 8.05; found C 54.30, H 4.26, N 3.52, S 7.86.

***N*-[1-(3,5-Dibromo-2-methoxyphenyl)-but-3-ynyl]-4-methylbenzenesulfonamide (15d):** TBAF (1.0 M solution in THF, 1.24 mL, 1.24 mmol) was added at room temperature to a solution of **11d** (634 mg, 1.13 mmol) in THF (25 mL), and the mixture was stirred at room temperature for 15 h. Water (100 mL) was added, and the reaction mixture was extracted with diethyl ether (3× 100 mL). The combined organic layers were dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 2:1) provided **15d** (533 mg, 97% yield) as yellow crystals; m.p. 147–148 °C. UV (MeOH): λ = 226 nm. IR (ATR): $\tilde{\nu}$ = 3311, 3246, 3073, 2923, 2853, 1730, 1599, 1558, 1493, 1461, 1420, 1325, 1310, 1299, 1261, 1228, 1182, 1156, 1093, 1080, 1017, 991, 954, 938, 886, 864, 842, 830, 811, 764, 710, 699, 675, 651, 637 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.01 (t, J = 2.6 Hz, 1 H), 2.38 (s, 3 H), 2.53 (ddd, J_{AB} = 17.0 Hz, J = 6.0, 2.6 Hz, 1 H), 2.62 (ddd, J_{AB} = 17.0 Hz, J = 6.3, 2.6 Hz, 1 H), 3.86 (s, 3 H), 4.76 (m, 1 H), 5.36 (d, J = 7.9 Hz, 1 H), 7.09 (d, J = 2.3 Hz, 1 H), 7.18 (d, J = 8.0 Hz, 2 H), 7.48 (d, J = 2.3 Hz, 1 H), 7.57 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.51 (CH_3), 26.60 (CH_2), 51.05 (CH), 61.37 (CH_3), 72.84 (CH), 78.22 (C), 117.08 (C), 117.63 (C), 126.93 (2 CH), 129.48 (2 CH), 130.49 (CH), 135.18 (CH), 135.74 (C), 136.73 (C), 143.75 (C), 153.27 (C) ppm. MS (EI): m/z (%) = 450 (31), 448 (58), 446 (29) $[M - C_3H_3]^+$, 155 (68), 91 (100), 65 (15). $C_{18}H_{17}Br_2NO_3S$ (487.21): calcd. C 44.37, H 3.52, N 2.87, S 6.58; found C 44.51, H 3.50, N 2.91, S 6.48.

2-(2-Methoxyphenyl)-1-(*p*-tolylsulfonyl)-2,3-dihydro-1*H*-pyrrole (13a): Silver acetate (177 mg, 1.06 mmol) was added at room temperature to a solution of **15a** (3.50 g, 10.6 mmol) in acetone (150 mL), and the mixture was heated at reflux for 72 h. The solvent was evaporated, and the residue was purified by chromatography on a silica gel column (pentane/ethyl acetate, 3:1) to provide **13a** (3.39 g, 97% yield) as light yellow crystals; m.p. 142–145 °C. UV (MeOH): λ = 220, 264, 270, 277 nm. IR (ATR): $\tilde{\nu}$ = 3099, 2924, 2839, 1923, 1731, 1620, 1593, 1491, 1466, 1438, 1398, 1359, 1342, 1287, 1262, 1243, 1194, 1156, 1115, 1096, 1053, 1028, 987, 962, 931, 895, 873, 840, 815, 804, 782, 752, 720, 664 cm^{-1}. ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 2.22–2.26 (m, 1 H), 2.45 (s, 3 H), 2.87 (ddt, J = 16.8, 10.9, 2.4 Hz, 1 H), 3.82 (s, 3 H), 5.04 (dd, J = 10.9, 6.1 Hz, 1 H), 5.10 (dt, J = 4.4, 2.4 Hz, 1 H), 6.49 (m, 1 H), 6.90 (d, J = 8.2 Hz, 1 H), 6.98 (dt, J = 0.7, 7.5 Hz, 1 H), 7.27 (dt, J = 1.7, 7.8 Hz, 1 H), 7.36 (d, J = 8.0 Hz, 2 H), 7.47 (dd, J = 7.6, 1.6 Hz, 1 H), 7.67 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, CD_2Cl_2): δ = 21.67 (CH_3), 40.09 (CH_2), 55.66 (CH_3), 57.90 (CH), 110.69 (CH), 111.58 (CH), 120.80 (CH), 127.17 (CH), 128.04 (2 CH), 128.62 (CH), 129.93 (2 CH), 130.80 (CH), 131.76 (C), 133.93 (C), 144.32 (C), 156.28 (C) ppm. MS (EI): m/z (%) =

329 (20) $[M]^+$, 290 (5), 174 (100), 159 (12), 149 (12), 91 (15). HRMS (EI): calcd. for $C_{18}H_{19}NO_3S^+$ $[M]^+$ 329.1086; found 329.1092. $C_{18}H_{19}NO_3S$ (329.41): calcd. C 65.63, H 5.81, N 4.25, S 9.73; found C 65.21, H 5.73, N 4.23, S 9.34.

Crystallographic Data for 13a: $C_{18}H_{19}NO_3S$, M = 329.40 g mol^{-1}, crystal size: 0.45 × 0.16 × 0.16 mm^3, monoclinic, space group $P2_1/c$, a = 7.7320(10) Å, b = 20.232(2) Å, c = 12.8800(10) Å, β = 126.540(10)°, V = 1618.8(3) Å^3, Z = 4, $\rho_{calcd.}$ = 1.352 g cm^{-3}, μ = 0.214 mm^{-1}, λ = 0.71073 Å, T = 198(2) K, θ range = 3.28–30.00°, reflections collected: 39066, independent: 4697 (R_{int} = 0.0598), 210 parameters. The structure was solved by direct methods and refined by full-matrix least-squares on F^2, final R indices [$I > 2\sigma(I)$]: R_1 = 0.0414, wR_2 = 0.1092, maximal residual electron density: 0.416 e Å^{-3}. CCDC-738984 (for **13a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2-(3,5-Difluoro-2-methoxyphenyl)-1-(*p*-tolylsulfonyl)-2,3-dihydro-1*H*-pyrrole (13b): Silver acetate (4.6 mg, 27 μmol) was added at room temperature to a solution of **15b** (100 mg, 274 μmol) in dichloromethane (10 mL), and the mixture was heated at reflux for 48 h. The solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 6:1) provided **13b** (98 mg, 98% yield) as colorless crystals; m.p. 125 °C. UV (MeOH): λ = 258 nm. IR (ATR): $\tilde{\nu}$ = 3103, 2996, 2949, 2918, 2841, 1618, 1606, 1490, 1476, 1448, 1432, 1358, 1339, 1306, 1290, 1265, 1229, 1198, 1158, 1120, 1106, 1087, 1068, 1025, 1004, 984, 957, 915, 900, 848, 811, 768, 748, 705, 665 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.24–2.30 (m, 1 H), 2.44 (s, 3 H), 2.91 (ddt, J = 16.7, 11.1, 2.4 Hz, 1 H), 3.91 (d, $^5J_{H,F}$ = 1.6 Hz, 3 H), 4.99 (dd, J = 11.1, 6.3 Hz, 1 H), 5.09 (dt, J = 4.4, 2.2 Hz, 1 H), 6.50 (m, 1 H), 6.75 (ddd, $^3J_{H,F}$ = 11.3, 8.2 Hz, $^4J_{H,H}$ = 3.1 Hz, 1 H), 6.96 (ddd, $^3J_{H,F}$ = 9.0 Hz, $^4J_{H,H}$ = 2.9 Hz, $^5J_{H,F}$ = 1.9 Hz, 1 H), 7.33 (d, J = 8.0 Hz, 2 H), 7.67 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.60 (CH_3), 40.05 (CH_2), 57.09 (d, $^4J_{C,F}$ = 2.8 Hz, CH), 61.43 (d, $^4J_{C,F}$ = 6.0 Hz, CH_3), 104.00 (dd, $^2J_{C,F}$ = 26.7, 23.0 Hz, CH), 109.17 (dd, $^2J_{C,F}$ = 23.9 Hz, $^4J_{C,F}$ = 3.0 Hz, CH), 110.56 (CH), 127.71 (2 CH), 129.71 (2 CH), 130.60 (CH), 133.21 (C), 138.64 (dd, $^3J_{C,F}$ = 8.5, 3.4 Hz, C), 140.43 (dd, $^2J_{C,F}$ = 11.5 Hz, $^4J_{C,F}$ = 4.0 Hz, C), 144.09 (C), 154.99 (dd, $^1J_{C,F}$ = 249.5 Hz, $^3J_{C,F}$ = 12.9 Hz, C), 157.94 (dd, $^1J_{C,F}$ = 244.4 Hz, $^3J_{C,F}$ = 12.0 Hz, C) ppm. MS (EI): *m/z* (%) = 365 (18) $[M]^+$, 210 (100), 195 (32), 170 (15), 155 (10), 91 (33). $C_{18}H_{17}F_2NO_3S$ (365.39): calcd. C 59.17, H 4.69, N 3.83, S 8.78; found C 59.38, H 4.84, N 3.75, S 8.47.

2-(3,5-Dichloro-2-methoxyphenyl)-1-(*p*-tolylsulfonyl)-2,3-dihydro-1*H*-pyrrole (13c): Silver acetate (42 mg, 0.25 mmol) was added at room temperature to a solution of **15c** (670 mg, 1.68 mmol) in dichloromethane (40 mL), and the mixture was heated at reflux for 48 h. The solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 5:1) provided **13c** (623 mg, 93% yield) as colorless crystals; m.p. 105 °C. UV (MeOH): λ = 221, 257 nm. IR (ATR): $\tilde{\nu}$ = 3098, 3079, 2918, 2850, 1920, 1730, 1625, 1596, 1569, 1470, 1449, 1427, 1349, 1320, 1308, 1293, 1260, 1226, 1163, 1150, 1107, 1089, 1055, 999, 983, 947, 918, 891, 865, 851, 828, 812, 765, 713, 665 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.28 (ddt, J = 16.7, 6.3, 2.3 Hz, 1 H), 2.44 (s, 3 H), 2.94 (ddt, J = 16.6, 11.3, 2.5 Hz, 1 H), 3.89 (s, 3 H), 4.97 (dd, J = 11.1, 6.3 Hz, 1 H), 5.10 (m, 1 H), 6.52 (m, 1 H), 7.27 (d, J = 2.5 Hz, 1 H), 7.29 (d, J = 2.5 Hz, 1 H), 7.32 (d, J = 8.0 Hz, 2 H), 7.65 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.62 (CH_3), 40.24 (CH_2), 57.34 (CH), 61.13 (CH_3), 110.34 (CH), 126.20 (CH), 127.66 (2 CH), 128.27 (C), 129.23 (CH), 129.74 (2 CH), 129.93 (C), 130.62 (CH), 133.27 (C), 139.45 (C), 144.18 (C), 151.31 (C) ppm. MS (EI): *m/z* (%) = 401 (2), 399 (11), 397 (16) $[M]^+$, 246 (10), 244 (63), 242 (100), 231 (4), 229 (21), 227 (33), 155 (13), 91 (65), 65 (18). $C_{18}H_{17}Cl_2NO_3S$ (398.30): calcd. C 54.28, H 4.30, N 3.52, S 8.05; found C 54.37, H 4.24, N 3.51, S 8.07.

2-(3,5-Dibromo-2-methoxyphenyl)-1-(*p*-tolylsulfonyl)-2,3-dihydro-1*H*-pyrrole (13d): Silver acetate (38 mg, 0.23 mmol) was added at room temperature to a solution of **15d** (729 mg, 1.50 mmol) in dichloromethane (40 mL), and the mixture was heated at reflux for 60 h. The solvent was evaporated. The residue was purified by chromatography on a silica gel column (petroleum ether/diethyl ether, 5:1) to provide **13d** (706 mg, 97% yield) as light yellow crystals; m.p. 134 °C. UV (MeOH): λ = 225 nm. IR (ATR): $\tilde{\nu}$ = 3492, 3108, 3025, 2922, 2849, 1724, 1614, 1594, 1557, 1492, 1459, 1420, 1398, 1349, 1325, 1271, 1255, 1217, 1168, 1139, 1100, 1060, 991, 965, 908, 877, 847, 818, 761, 733, 696, 660 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.28 (m, 1 H), 2.44 (s, 3 H), 2.95 (m, 1 H), 3.87 (s, 3 H), 4.98 (dd, J = 11.1, 6.3 Hz, 1 H), 5.10 (m, 1 H), 6.52 (m, 1 H), 7.32 (d, J = 8.1 Hz, 2 H), 7.45 (d, J = 2.3 Hz, 1 H), 7.57 (d, J = 2.3 Hz, 1 H), 7.65 (d, J = 8.1 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.62 (CH_3), 40.32 (CH_2), 57.39 (CH), 61.19 (CH_3), 110.26 (CH), 117.70 (C), 117.79 (C), 127.63 (2 CH), 129.74 (2 CH), 129.81 (CH), 130.60 (CH), 133.31 (C), 134.83 (CH), 139.90 (C), 144.19 (C), 152.85 (C) ppm. MS (EI): *m/z* (%) = 489 (16), 487 (29), 485 (15) $[M]^+$, 334 (57), 332 (100), 330 (57), 319 (13), 317 (26), 315 (13), 155 (18), 91 (49). HRMS (EI): calcd. for $C_{18}H_{17}Br_2NO_3S^+$ $[M]^+$ 484.9296; found 484.9285. $C_{18}H_{17}Br_2NO_3S$ (487.21): calcd. C 44.37, H 3.52, N 2.87, S 6.58; found C 44.31, H 3.61, N 2.85, S 6.20.

***N*-[1-(2-Methoxyphenyl)buta-2,3-dienyl]-4-methylbenzenesulfonamide (19a):** TBAF (1.0 M solution in THF, 327 μL, 327 μmol) was added at room temperature to a solution of **12a** (110 mg, 274 μmol) in THF (10 mL), and the mixture was stirred at room temperature for 16 h. Water (50 mL) was added, and the reaction mixture was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (pentane/ethyl acetate, 3:1) provided **19a** (80.8 mg, 90% yield) as yellow crystals; m.p. 98–99 °C. UV (MeOH) λ = 193, 197 (sh), 208, 223, 273 nm. IR (ATR): $\tilde{\nu}$ = 3281, 3007, 2939, 2840, 1954, 1600, 1493, 1464, 1428, 1324, 1292, 1247, 1188, 1157, 1091, 1061, 1025, 948, 915, 863, 814, 782, 749, 706, 674 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 3.74 (s, 3 H), 4.65–4.75 (m, 2 H), 5.08 (ddt, J = 9.4, 6.2, 2.9 Hz, 1 H), 5.34 (q, J = 6.5 Hz, 1 H), 5.53 (d, J = 9.5 Hz, 1 H), 6.70 (d, J = 8.2 Hz, 1 H), 6.80 (dt, J = 1.0, 7.4 Hz, 1 H), 7.03 (dd, J = 1.7, 7.4 Hz, 1 H), 7.12 (d, J = 8.2 Hz, 2 H), 7.16 (dt, J = 1.7, 7.8 Hz, 1 H), 7.58 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.42 (CH_3), 54.59 (CH), 55.21 (CH_3), 78.36 (CH_2), 92.10 (CH), 110.70 (CH), 120.64 (CH), 127.03 (2 CH), 127.37 (C), 128.50 (CH), 128.92 (CH), 129.06 (2 CH), 137.73 (C), 142.79 (C), 156.33 (C), 207.22 (C) ppm. MS (EI): *m/z* (%) = 290 (100) $[M - C_3H_3]^+$, 155 (19), 91 (45). $C_{18}H_{19}NO_3S$ (329.41): calcd. C 65.63, H 5.81, N 4.25, S 9.73; found C 66.24, H 5.97, N 4.35, S 9.26.

***N*-[1-(3,5-Dichloro-2-methoxyphenyl)buta-2,3-dienyl]-4-methylbenzenesulfonamide (19c):** TBAF (1.0 M solution in THF, 987 μL, 987 μmol) was added at room temperature to a solution of **12c** (422 mg, 897 μmol) in THF (10 mL), and the mixture was stirred at room temperature for 16 h. A saturated solution of sodium chloride in water (30 mL) was added, and the reaction mixture was

extracted with diethyl ether (3× 20 mL). The combined organic layers were dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 4:1) provided **19c** (302 mg, 85%) as colorless crystals; m.p. 88–90 °C. UV (MeOH) λ = 263, 270, 277, 287 nm. IR (ATR): $\tilde{\nu}$ = 3256, 3070, 2926, 1958, 1597, 1568, 1499, 1468, 1450, 1422, 1320, 1221, 1153, 1139, 1095, 995, 946, 921, 902, 858, 817, 768, 698, 661 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.36 (s, 3 H), 3.84 (s, 3 H), 4.77 (dd, J = 11.3, 6.6, 3.8 Hz, 1 H), 4.85 (ddd, J = 11.2, 6.7, 3.7 Hz, 1 H), 5.13–5.17 (m, 1 H), 5.24–5.27 (m, 1 H), 5.35 (d, J = 8.3 Hz, 1 H), 6.85 (d, J = 2.4 Hz, 1 H), 7.147 (d, J = 2.3 Hz, 1 H), 7.153 (d, J = 8.2 Hz, 2 H), 7.56 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.44 (CH_3), 51.78 (CH), 61.35 (CH_3), 80.23 (CH_2), 92.62 (CH), 126.99 (3 CH), 128.43 (2 C), 129.30 (2 CH), 129.46 (CH), 135.73 (C), 136.96 (C), 143.51 (C), 152.01 (C), 206.61 (C) ppm. MS (EI): m/z (%) = 246 (9), 244 (65), 242 (100) $[M - C_7H_7SO_2]^+$, 231 (3), 229 (18), 227 (24), 155 (16). $C_{18}H_{17}Cl_2NO_3S$ (398.30): calcd. C 54.28, H 4.30, N 3.52, S 8.05; found C 54.41, H 4.21, N 3.39, S 7.89.

***N*-[1-(3,5-Dibromo-2-methoxyphenyl)buta-2,3-dienyl]-4-methylbenzenesulfonamide (19d):** TBAF (1.0 M solution in THF, 1.50 mL, 1.50 mmol) was added at room temperature to a solution of **12d** (676 mg, 1.21 mmol) in THF (15 mL), and the mixture was stirred at room temperature for 15 h. Water (100 mL) was added, and the reaction mixture was extracted with diethyl ether (3× 100 mL). The combined organic layers were dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 2:1) provided **19d** (471 mg, 80% yield) as colorless crystals; m.p. 114 °C. UV (MeOH): λ = 264, 270, 279, 287 nm. IR (ATR): $\tilde{\nu}$ = 3276, 3078, 3004, 2943, 1960, 1598, 1558, 1494, 1460, 1416, 1384, 1330, 1308, 1290, 1213, 1166, 1150, 1091, 1070, 994, 933, 850, 812, 761, 705, 685, 659 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.37 (s, 3 H), 3.84 (s, 3 H), 4.79 (ddd, J = 11.3, 6.6, 3.8 Hz, 1 H), 4.86 (ddd, J = 11.3, 6.6, 3.7 Hz, 1 H), 5.17 (m, 1 H), 5.24–5.29 (m, 2 H), 7.01 (d, J = 2.3 Hz, 1 H), 7.15 (d, J = 8.0 Hz, 2 H), 7.45 (d, J = 2.3 Hz, 1 H), 7.54 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.50 (CH_3), 51.70 (CH), 61.50 (CH_3), 80.38 (CH_2), 92.72 (CH), 117.11 (C), 117.91 (C), 126.96 (2 CH), 129.34 (2 CH), 130.63 (CH), 135.10 (CH), 136.18 (C), 136.88 (C), 143.54 (C), 153.58 (C), 206.57 (C) ppm. MS (EI): m/z (%) = 334 (60), 332 (100), 330 (59) $[M - C_7H_7SO_2]^+$, 319 (13), 317 (28), 315 (12), 155 (23), 91 (51), 65 (11). $C_{18}H_{17}Br_2NO_3S$ (487.21): calcd. C 44.37, H 3.52, N 2.87, S 6.58; found C 44.39, H 3.52, N 2.78, S 6.43.

2-(2-Methoxyphenyl)-1-(*p*-tolylsulfonyl)-2,5-dihydro-1*H*-pyrrole (20a): Silver acetate (2.5 mg, 15 μmol) was added at room temperature to a solution of **19a** (48.9 mg, 148 μmol) in acetone (5 mL), and the mixture was heated at reflux for 3 d. The solvent was evaporated. Purification of the residue by chromatography on a silica gel column (pentane/ethyl acetate, 8:1) provided **20a** (19.5 mg, 40% yield) as colorless crystals; m.p. 167–168 °C. UV (MeOH): λ = 194, 203, 223, 272 nm. IR (ATR): $\tilde{\nu}$ = 3091, 3048, 3005, 2920, 2862, 1736, 1596, 1490, 1464, 1396, 1335, 1282, 1243, 1196, 1155, 1088, 1050, 1030, 983, 849, 818, 784, 751, 707, 661, 624 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.41 (s, 3 H), 3.80 (s, 3 H), 4.31 (m, 2 H), 5.62 (dq, J = 6.2, 2.0 Hz, 1 H), 5.68 (dq, J = 6.2, 2.0 Hz, 1 H), 5.86 (m, 1 H), 6.81 (dd, J = 8.2, 0.5 Hz, 1 H), 6.94 (dt, J = 0.9, 7.5 Hz, 1 H), 7.22 (dt, J = 1.7, 7.8 Hz, 1 H), 7.26 (d, J = 8.2 Hz, 2 H), 7.40 (dd, J = 7.6, 1.6 Hz, 1 H), 7.66 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.50 (CH_3), 55.31 (CH_3), 55.61 (CH_2), 65.31 (CH), 110.27 (CH), 120.83 (CH), 123.43 (CH), 127.47 (2 CH), 127.67 (CH), 128.49 (CH), 129.20 (C), 129.49 (2 CH), 130.24 (CH), 134.94 (C), 143.15 (C), 155.89 (C) ppm. MS (EI): m/z (%) = 329 (1) $[M]^+$, 174 (100), 159 (18), 155 (12), 130 (11), 91 (31).

2-(3,5-Dichloro-2-methoxyphenyl)-1-(*p*-tolylsulfonyl)-2,5-dihydro-1*H*-pyrrole (20c): Silver acetate (3.4 mg, 20 μmol) was added at room temperature to a solution of **19c** (80.8 mg, 203 μmol) in 1,2-dichloroethane (8 mL), and the mixture was heated at reflux for 3 d. The solvent was evaporated. Purification of the residue by chromatography on a silica gel column (pentane/diethyl ether, 9:1) provided **20c** (42.6 mg, 53% yield) as light yellow crystals; m.p. 167–168 °C. IR (ATR): $\tilde{\nu}$ = 3082, 3025, 2921, 2877, 1728, 1597, 1564, 1456, 1424, 1336, 1315, 1289, 1256, 1239, 1219, 1191, 1158, 1119, 1089, 1057, 997, 891, 867, 853, 834, 815, 768, 744, 709, 665, 635 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 3.96 (s, 3 H), 4.34 (m, 2 H), 5.57 (dq, J = 6.2, 2.1 Hz, 1 H), 5.73 (dq, J = 6.2, 2.1 Hz, 1 H), 5.80 (m, 1 H), 7.09 (d, J = 2.6 Hz, 1 H), 7.25 (d, J = 2.6 Hz, 1 H), 7.29 (d, J = 8.2 Hz, 2 H), 7.65 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.54 (CH_3), 55.69 (CH_2), 61.28 (CH_3), 64.81 (CH), 124.67 (CH), 126.93 (CH), 127.31 (2 CH), 128.33 (C), 129.31 (CH), 129.74 (2 CH), 129.80 (CH), 129.82 (C), 134.68 (C), 137.60 (C), 143.81 (C), 151.52 (C) ppm. MS (EI): m/z (%) = 246 (11), 244 (62), 242 (100), 229 (17), 227 (27), 155 (16), 91 (44), 65 (12). $C_{18}H_{17}Cl_2NO_3S$ (398.30): calcd. C 54.28, H 4.30, N 3.52, S 8.05; found C 53.96, H 4.46, N 3.27, S 7.54.

2-(3,5-Dibromo-2-methoxyphenyl)-1-(*p*-tolylsulfonyl)-2,5-dihydro-1*H*-pyrrole (20d): Silver acetate (12 mg, 72 μmol) was added at room temperature to a solution of **19d** (230 mg, 472 μmol) in 1,2-dichloroethane (10 mL), and the mixture was heated at reflux for 3 d. The solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 7:1) provided **20d** (96 mg, 42% yield) as colorless crystals; m.p. 157–158 °C. UV (MeOH): λ = 230 nm. IR (ATR): $\tilde{\nu}$ = 3072, 2921, 2873, 2851, 1921, 1734, 1597, 1559, 1492, 1461, 1449, 1420, 1397, 1378, 1334, 1313, 1290, 1252, 1223, 1190, 1158, 1118, 1089, 1056, 1016, 998, 963, 890, 865, 846, 814, 764, 731, 708, 687, 665 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.42 (s, 3 H), 3.94 (s, 3 H), 4.33 (m, 2 H), 5.57 (dq, J = 6.3, 2.1 Hz, 1 H), 5.72 (dq, J = 6.1, 2.0 Hz, 1 H), 5.79 (m, 1 H), 7.23 (d, J = 2.4 Hz, 1 H), 7.28 (d, J = 8.1 Hz, 2 H), 7.54 (d, J = 2.4 Hz, 1 H), 7.63 (d, J = 8.3 Hz, 2 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 21.56 (CH_3), 55.68 (CH_2), 61.36 (CH_3), 64.90 (CH), 117.67 (C), 117.79 (C), 124.70 (CH), 127.27 (2 CH), 129.74 (2 CH), 129.83 (CH), 130.60 (CH), 134.74 (C), 134.88 (CH), 138.05 (C), 143.81 (C), 153.06 (C) ppm. MS (EI): m/z (%) = 334 (48), 332 (100), 330 (54) $[M - C_7H_7SO_2]^+$, 319 (11), 317 (21), 315 (12), 222 (14), 155 (21), 91 (42). $C_{18}H_{17}Br_2NO_3S$ (487.21): calcd. C 44.37, H 3.52, N 2.87, S 6.58; found C 45.17, H 3.42, N 2.77, S 6.14.

2-(2-Methoxyphenyl)-1*H*-pyrrole (21a): 2,3-Dihydropyrrole **13a** (535 mg, 1.62 mmol) was added to a solution of potassium *tert*-butoxide (729 mg, 6.50 mmol) in DMSO (30 mL), and the solution was heated at 50 °C for 3.5 h. A saturated aqueous solution of ammonium chloride (50 mL) was added, and the mixture was extracted with diethyl ether (3× 50 mL). The combined organic layers were washed with brine and then dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 6:1) provided **21a** (236 mg, 84% yield) as colorless crystals; m.p. 70 °C; ref.[7] m.p. 65 °C. UV (MeOH): λ = 232, 283, 307 nm. IR (ATR): $\tilde{\nu}$ = 3440, 3003, 2978, 2944, 2839, 2022, 1935, 1898, 1862, 1780, 1725, 1597, 1581, 1514, 1491, 1466, 1435, 1407, 1313,

1273, 1233, 1182, 1166, 1126, 1109, 1056, 1041, 1021, 932, 919, 882, 855, 787, 751, 640 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.96 (s, 3 H), 6.29 (m, 1 H), 6.62 (m, 1 H), 6.86 (m, 1 H), 6.97 (m, 2 H), 7.15 (dt, J = 0.7, 7.8 Hz, 1 H), 7.66 (dd, J = 7.8, 1.6 Hz, 1 H), 9.82 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 55.65 (CH_3), 106.06 (CH), 108.80 (CH), 111.60 (CH), 117.74 (CH), 121.08 (C), 121.42 (CH), 126.59 (CH), 126.63 (CH), 129.82 (C), 154.66 (C) ppm. MS (EI): *m/z* (%) = 173 (100) $[M]^+$, 158 (58), 130 (57), 115 (11), 103 (15), 77 (16). $C_{11}H_{11}NO$ (173.21): calcd. C 76.28, H 6.40, N 8.09; found C 75.68, H 6.23, N 7.66.

2-(3,5-Difluoro-2-methoxyphenyl)-1*H*-pyrrole (21b): 2,3-Dihydropyrrole **13b** (400 mg, 1.09 mmol) was added to a solution of potassium *tert*-butoxide (491 mg, 4.38 mmol) in DMSO (20 mL), and the solution was stirred at room temperature for 16 h. A saturated aqueous solution of ammonium chloride (100 mL) was added, and the mixture was extracted with diethyl ether (3× 100 mL). The combined organic layers were washed with brine and then dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 10:1) provided **21b** (218 mg, 96% yield) as colorless crystals; m.p. 53–54 °C. UV (MeOH): λ = 229, 287, 303 nm. IR (ATR): $\tilde{\nu}$ = 3400, 3097, 2949, 2922, 2849, 2180, 1735, 1699, 1614, 1598, 1561, 1489, 1453, 1430, 1399, 1346, 1282, 1244, 1216, 1176, 1158, 1113, 1080, 1041, 993, 982, 962, 885, 847, 803, 770, 727 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.90 (d, $^5J_{H,F}$ = 1.2 Hz, 3 H), 6.30 (dt, J = 3.5, 2.7 Hz, 1 H), 6.60 (ddd, J = 3.7, 2.4, 1.4 Hz, 1 H), 6.66 (ddd, $^3J_{H,F}$ = 11.1, 8.1 Hz, $^4J_{H,H}$ = 3.0 Hz, 1 H), 6.91 (dt, J = 1.5, 2.6 Hz, 1 H), 7.08 (ddd, $^3J_{H,F}$ = 9.8 Hz, $^4J_{H,H}$ = 3.0 Hz, $^5J_{H,F}$ = 2.0 Hz, 1 H), 9.70 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 61.57 (d, $^4J_{C,F}$ = 5.4 Hz, CH_3), 101.85 (dd, $^2J_{C,F}$ = 27.2, 23.4 Hz, CH), 107.58 (dd, $^2J_{C,F}$ = 24.1 Hz, $^4J_{C,F}$ = 3.3 Hz, CH), 108.08 (CH), 109.39 (CH), 119.51 (CH), 127.11 (dd, $^3J_{C,F}$ = 10.3, 3.8 Hz, C), 127.78 (t, $^4J_{C,F}$ = 3.3 Hz, C), 139.39 (dd, $^2J_{C,F}$ = 12.7 Hz, $^4J_{C,F}$ = 3.7 Hz, C), 156.15 (dd, $^1J_{C,F}$ = 248.1 Hz, $^3J_{C,F}$ = 13.6 Hz, C), 158.31 (dd, $^1J_{C,F}$ = 242.9 Hz, $^4J_{C,F}$ = 12.8 Hz, C) ppm. MS (EI): *m/z* (%) = 209 (98) $[M]^+$, 194 (100), 167 (34), 166 (15), 139 (11), 119 (12). $C_{11}H_9F_2NO$ (209.19): calcd. C 63.16, H 4.34, N 6.70; found C 63.33, H 4.57, N 6.69.

2-(3,5-Dichloro-2-methoxyphenyl)-1*H*-pyrrole (21c)

Method A: 2,3-Dihydropyrrole **13c** (532 mg, 1.34 mmol) was added to a solution of potassium *tert*-butoxide (601 mg, 5.36 mmol) in DMSO (35 mL), and the solution was stirred at room temperature for 16 h. A saturated aqueous solution of ammonium chloride (50 mL) was added, and the mixture was extracted with diethyl ether (3× 100 mL). The combined organic layers were washed with brine and then dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 10:1) provided **21c** (301 mg, 93% yield) as colorless crystals; m.p. 105 °C; ref.[7] m.p. 105 °C; ref.[9] m.p. 107–108 °C. UV (MeOH): λ = 221, 242, 249, 300 nm. IR (ATR): $\tilde{\nu}$ = 3401, 3105, 2980, 2933, 2849, 1736, 1682, 1581, 1545, 1470, 1441, 1431, 1409, 1379, 1301, 1229, 1172, 1118, 1100, 1060, 1041, 971, 884, 872, 840, 812, 739, 693 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.77 (s, 3 H), 6.30 (m, 1 H), 6.60 (m, 1 H), 6.92 (m, 1 H), 7.18 (d, J = 2.5 Hz, 1 H), 7.47 (d, J = 2.5 Hz, 1 H), 9.65 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 60.72 (CH_3), 108.46 (CH), 109.54 (CH), 119.78 (CH), 125.23 (CH), 126.89 (CH), 127.01 (C), 128.15 (C), 129.48 (C), 130.13 (C), 149.72 (C) ppm. MS (EI): *m/z* (%) = 245 (11), 243 (65), 241 (100) $[M]^+$, 230 (10), 228 (62), 226 (99), 200 (22), 198 (34), 193 (19), 191 (55), 99 (13). $C_{11}H_9Cl_2NO$ (242.10): calcd. C 54.57, H 3.75, N 5.79; found C 54.65, H 3.88, N 5.69.

Method B: A solution of potassium *tert*-butoxide (37 mg, 0.33 mmol) in DMSO (6 mL) was added to 2,5-dihydropyrrole **20c** (33 mg, 82.8 μmol), and the mixture was stirred at 50 °C for 2 h. A saturated aqueous solution of ammonium chloride (10 mL) was added, and the mixture was extracted with diethyl ether (5× 10 mL). The combined organic layers were washed with water (2× 20 mL) and then dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (pentane/diethyl ether, 9:2) provided **21c** (11.6 mg, 58% yield) as colorless crystals. For spectroscopic data, see above.

2-(3,5-Dibromo-2-methoxyphenyl)-1*H*-pyrrole (21d): A solution of potassium *tert*-butoxide (20 mg, 0.18 mmol) in DMSO (8 mL) was added to 2,3-dihydropyrrole **13d** (30 mg, 61 μmol), and the mixture was stirred at room temperature for 70 min. Water (15 mL) was added, and the mixture was extracted with diethyl ether (4× 15 mL). The combined organic layers were dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (pentane/diethyl ether, 3:2) provided **21d** (8.5 mg, 42% yield) as colorless crystals. IR (ATR): $\tilde{\nu}$ = 3457, 3405, 3104, 3065, 2969, 2934, 2846, 1729, 1678, 1574, 1532, 1459, 1408, 1375, 1231, 1179, 1110, 1043, 984, 883, 837, 806, 753, 720, 665, 632 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.74 (s, 3 H), 6.30 (dt, J = 3.6, 2.7 Hz, 1 H), 6.60 (ddd, J = 3.6, 2.5, 1.4 Hz, 1 H), 6.92 (dt, J = 1.5, 2.7 Hz, 1 H), 7.49 (d, J = 2.4 Hz, 1 H), 7.66 (d, J = 2.4 Hz, 1 H), 9.62 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 60.68 (CH_3), 108.55 (CH), 109.57 (CH), 117.97 (C), 119.05 (C), 119.83 (CH), 126.77 (C), 128.67 (C), 129.07 (CH), 132.49 (CH), 151.19 (C) ppm. MS (EI): *m/z* (%) = 333 (49), 331 (100) $[M]^+$, 329 (53), 318 (38), 316 (81), 314 (46), 290 (11), 288 (20), 286 (11), 237 (35), 235 (36), 209 (12), 207 (12), 170 (11), 141 (14), 140 (10), 128 (43), 101 (10), 75 (11), 74 (11), 64 (16). $C_{11}H_9Br_2NO$ (331.01): calcd. C 39.91, H 2.74, N 4.23; found C 39.74, H 2.80, N 3.90.

2-(2-Hydroxyphenyl)-1*H*-pyrrole (22): Sodium sulfide (323 mg, 4.14 mmol) was added at room temperature to a solution of **21a** (120 mg, 0.693 mmol) in NMP (10 mL), and the mixture was heated at 160 °C for 2.5 h. Diluted aqueous hydrochloric acid was added at room temperature, and the mixture was extracted with diethyl ether (3× 50 mL). The combined organic layers were dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 4:1) provided **22** (103 mg, 93% yield) as dark blue-grey crystals; m.p. 99 °C; ref.[13e] m.p. 99–101 °C. UV (MeOH): λ = 229, 282, 307 nm. IR (ATR): $\tilde{\nu}$ = 3419, 3100, 3040, 2922, 2851, 1933, 1668, 1604, 1586, 1493, 1464, 1403, 1328, 1289, 1248, 1202, 1175, 1160, 1123, 1097, 1047, 1037, 972, 931, 921, 816, 799, 745, 731, 675, 643 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.30 (br. s, 1 H), 6.31 (q, J = 2.9 Hz, 1 H), 6.57 (m, 1 H), 6.83 (d, J = 8.0 Hz, 1 H), 6.90 (m, 1 H), 6.96 (t, J = 7.5 Hz, 1 H), 7.09 (m, 1 H), 7.53 (dd, J = 7.8, 0.7 Hz, 1 H), 9.38 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 106.25 (CH), 109.24 (CH), 116.20 (CH), 118.51 (CH), 119.64 (C), 121.45 (CH), 127.06 (CH), 127.20 (CH), 128.65 (C), 150.92 (C) ppm. MS (EI): *m/z* (%) = 159 (100) $[M]^+$, 131 (35), 130 (63), 103 (11), 77 (13). $C_{10}H_9NO$ (159.19): calcd. C 75.45, H 5.70, N 8.80; found C 75.34, H 6.18, N 7.99.

Pentabromopseudilin (3): Pyridinium tribromide (1.05 g, 3.29 mmol) was added at room temperature to a solution of **22** (87 mg, 546 μmol) in ethanol (5 mL), and the mixture was stirred at room temperature for 3 d. The solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 9:1) provided **3** (179 mg, 59% yield) as

purple crystals; m.p. 152 °C (decomp.); ref.[7] m.p. 152 °C (decomp.). UV (MeOH): λ = 226, 287, 309, 357 nm. IR (ATR): $\tilde{\nu}$ = 3471, 3456, 3413, 3061, 2921, 2851, 1723, 1600, 1561, 1546, 1467, 1434, 1411, 1344, 1319, 1285, 1269, 1250, 1229, 1162, 1127, 997, 976, 884, 861, 750, 733, 696, 655 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.03 (s, 1 H), 7.57 (d, J = 2.3 Hz, 1 H), 8.10 (d, J = 2.3 Hz, 1 H), 9.48 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 99.36 (C), 100.97 (C), 103.85 (C), 111.90 (C), 113.21 (C), 119.29 (C), 125.05 (C), 130.86 (CH), 133.13 (CH), 147.19 (C) ppm. MS (EI): m/z (%) = 559 (7), 557 (38), 555 (77), 553 (79), 551 (40), 549 (8) $[M]^+$, 478 (17), 476 (66), 474 (100), 472 (67), 470 (17), 451 (5), 449 (21), 447 (33), 445 (23), 443 (6), 397 (22), 395 (59), 393 (57), 391 (19). HRMS (EI): calcd. for $C_{10}H_4Br_5NO^+$ $[M]^+$ 548.6210; found 548.6209.

***O*-Methylpentabromopseudilin [2,3,4-Tribromo-5-(3,5-dibromo-2-methoxyphenyl)-1*H*-pyrrole, 23]:** Trimethylsilyldiazomethane (2 M solution in hexane, 92 µL, 0.18 mmol) was added at room temperature to a solution of **3** (68 mg, 0.12 µmol) in diethyl ether (5 mL), and the mixture was stirred at room temperature for 15 h. Glacial acetic acid (3 mL) was added, and the solvent was removed. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 9:1) provided **23** (39 mg, 56% yield) as dark crystals; m.p. 125 °C; ref.[7] m.p. 124 °C; ref.[13a] m.p. 124–125 °C. UV (MeOH): λ = 226, 290 nm. IR (ATR): $\tilde{\nu}$ = 3381, 3323, 3074, 2923, 2852, 1792, 1721, 1690, 1613, 1580, 1558, 1460, 1413, 1343, 1282, 1242, 1152, 1053, 983, 921, 869, 818, 750, 717, 657 cm^{-1}. ^1H NMR (500 MHz, [D$_6$]acetone): δ = 3.57 (s, 3 H), 7.73 (d, J = 2.3 Hz, 1 H), 7.89 (d, J = 2.4 Hz, 1 H), 11.57 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, [D$_6$]acetone): δ = 61.05 (CH_3), 99.66 (C), 102.06 (C), 102.36 (C), 117.10 (C), 119.35 (C), 126.66 (C), 128.16 (C), 134.27 (CH), 136.47 (CH), 155.37 (C) ppm. MS (EI): m/z (%) = 573 (9), 571 (45), 569 (98), 567 (100), 565 (48), 563 (10) $[M]^+$, 477 (15), 475 (61), 473 (97), 471 (64), 469 (16). HRMS (EI): calcd. for $C_{11}H_6Br_5NO^+$ $[M]^+$ 562.6366; found 562.6344.

2,3,4-Tribromo-5-(2-methoxyphenyl)-1-methyl-1*H*-pyrrole (24): Pyridinium tribromide (332 mg, 1.04 mmol) was added at room temperature to a solution of **21a** (58.0 mg, 335 µmol) in ethanol (2.5 mL), and the mixture was stirred at room temperature for 30 min. The solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 4:1) provided **24** (117 mg, 85% yield) as dark crystals; m.p. 123 °C. UV (MeOH): λ = 272, 291 nm. IR (ATR): $\tilde{\nu}$ = 3303, 2935, 2838, 1604, 1582, 1554, 1491, 1458, 1360, 1295, 1241, 1180, 1165, 1135, 1112, 1046, 1012, 956, 791, 756 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.90 (s, 3 H), 6.98 (d, J = 8.3 Hz, 1 H), 7.04 (t, J = 7.6 Hz, 1 H), 7.31 (m, 1 H), 7.91 (dd, J = 7.7, 1.5 Hz, 1 H), 9.36 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 55.83 (CH_3), 97.80 (C), 99.13 (C), 103.06 (C), 111.41 (CH), 118.59 (C), 121.02 (CH), 127.84 (C), 129.31 (CH), 129.42 (CH), 155.76 (C) ppm. MS (EI): m/z (%) = 413 (30), 411 (97), 409 (100), 407 (32) $[M]^+$, 317 (43), 315 (91), 313 (44), 251 (18), 250 (15), 249 (19), 248 (13), 170 (15), 115 (9), 100 (9). HRMS (EI): calcd. for $C_{11}H_8Br_3NO^+$ $[M]^+$ 406.8156; found 406.8170. $C_{11}H_8Br_3NO$ (409.90): calcd. C 32.23, H 1.97, N 3.42; found C 32.31, H 1.98, N 3.42.

2-(2-Methoxyphenyl)-1-methyl-1*H*-pyrrole (25): Dihydropyrrole **13a** (267 mg, 811 µmol) was added to a solution of potassium *tert*-butoxide (363 mg, 3.24 mmol) in DMSO (15 mL), and the solution was heated at 50 °C for 3.5 h. The heating source was turned off, and iodomethane (1.15 g, 504 µL, 8.10 mmol) was added dropwise. The mixture was stirred at room temperature for 15 h. Water was added (100 mL), and the mixture was extracted with diethyl ether (3 × 100 mL). The combined organic layers were washed with water (2 × 50 mL) and then dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 6:1) provided **25** (107 mg, 70% yield) as a yellow oil. UV (MeOH): λ = 271 nm. IR (ATR): $\tilde{\nu}$ = 3099, 3000, 2938, 2835, 1693, 1600, 1579, 1546, 1494, 1462, 1436, 1409, 1310, 1278, 1247, 1230, 1180, 1161, 1117, 1088, 1056, 1022, 981, 936, 886, 852, 793, 750, 706 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.49 (s, 3 H), 3.81 (s, 3 H), 6.14 (dd, J = 3.5, 1.8 Hz, 1 H), 6.22 (m, 1 H), 6.73 (t, J = 2.1 Hz, 1 H), 6.95 (d, J = 8.4 Hz, 1 H), 6.99 (dt, J = 7.4, 1.0 Hz, 1 H), 7.28 (dd, J = 7.4, 1.7 Hz, 1 H), 7.34 (m, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 34.52 (CH_3), 55.32 (CH_3), 107.47 (CH), 108.87 (CH), 110.64 (CH), 120.46 (CH), 122.41 (CH), 122.47 (C), 129.14 (CH), 131.12 (C), 132.34 (CH), 157.32 (C) ppm. MS (EI): m/z (%) = 187 (100) $[M]^+$, 186 (60), 172 (30), 144 (22), 131 (18), 115 (10). HRMS (EI): calcd. for $C_{12}H_{13}NO^+$ $[M]^+$ 187.0997; found 187.1009.

2-(2-Hydroxyphenyl)-1-methyl-1*H*-pyrrole (26): Sodium sulfide (243 mg, 3.11 mmol) was added at room temperature to a solution of **25** (97 mg, 0.52 mmol) in NMP (10 mL), and the mixture was heated at 160 °C for 2 h. Dilute aqueous hydrochloric acid was added at room temperature, and the mixture was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL) and then dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 5:1) provided **26** (68 mg, 76% yield) as a yellow oil. UV (MeOH): λ = 258, 285 nm. IR (ATR): $\tilde{\nu}$ = 3412, 3099, 2946, 2804, 2714, 1639, 1612, 1577, 1544, 1479, 1450, 1429, 1409, 1344, 1310, 1286, 1246, 1211, 1180, 1153, 1105, 1089, 1054, 1029, 982, 941, 887, 825, 754, 716 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.51 (s, 3 H), 5.71 (s, 1 H), 6.26 (m, 2 H), 6.81 (t, J = 2.2 Hz, 1 H), 6.95 (m, 1 H), 7.00 (d, J = 8.0 Hz, 1 H), 7.18 (dd, J = 7.6, 1.6 Hz, 1 H), 7.28 (m, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 34.38 (CH_3), 108.23 (CH), 109.18 (CH), 115.35 (CH), 118.95 (C), 120.04 (CH), 124.19 (CH), 127.12 (C), 129.69 (CH), 130.85 (CH), 154.06 (C) ppm. MS (EI): m/z (%) = 173 (100) $[M]^+$, 172 (40), 144 (15), 131 (12). HRMS: calcd. for $C_{11}H_{11}NO^+$ $[M]^+$ 173.0841; found 173.0824.

***N*-Methylpentabromopseudilin [2,3,4-Tribromo-5-(3,5-dibromo-2-hydroxyphenyl)-1-methyl-1*H*-pyrrole, 27]:** Pyridinium tribromide (852 mg, 2.66 mmol) was added at room temperature to a solution of **26** (77 mg, 445 µmol) in ethanol (5 mL), and the mixture was stirred at room temperature for 2.5 d. The solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 10:1) provided **27** (148 mg, 59%) as brown crystals; m.p. 149–150 °C. UV (MeOH): λ = 210, 229 nm. IR (ATR): $\tilde{\nu}$ = 3475, 3071, 2922, 2851, 1688, 1594, 1561, 1524, 1465, 1434, 1406, 1364, 1321, 1255, 1233, 1221, 1150, 1091, 1053, 991, 902, 865, 828, 795, 746, 720, 695, 656 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 3.46 (s, 3 H), 5.66 (s, 1 H), 7.33 (d, J = 2.3 Hz, 1 H), 7.71 (d, J = 2.3 Hz, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 35.62 (CH_3), 99.75 (C), 101.29 (C), 105.79 (C), 111.52 (C), 112.50 (C), 119.79 (C), 127.16 (C), 134.86 (CH), 135.55 (CH), 150.13 (C) ppm. MS (EI): m/z (%) = 572 (6), 570 (33), 568 (74), 566 (76), 564 (35), 562 (7) $[M - H]^+$. HRMS (EI): calcd. for $C_{11}H_6Br_5NO^+$ $[M]^+$ 562.6366; found 562.6347. $C_{11}H_6Br_5NO$ (567.69): calcd. C 23.27, H 1.07, N 2.47; found C 23.97, H 1.32, N 2.27.

***O*-Methylpentachloropseudilin [2,3,4-Trichloro-5-(3,5-dichloro-2-methoxyphenyl)-1*H*-pyrrole, 28]:** A solution of *N*-chlorosuccinimide

(278 mg, 2.08 mmol) in acetonitrile (5 mL) was added at –40 °C to a solution of **21c** (162 mg, 669 μmol) in acetonitrile (5 mL), and the mixture was stirred at –40 °C for 5 min. The mixture was warmed to room temperature and then stirred for 15 h, and the solvent was evaporated. Purification of the residue by chromatography on silica gel column (petroleum ether/diethyl ether, 40:1) provided **28** (186 mg, 80% yield) as yellow crystals; m.p. 123–124 °C; ref.[9] m.p. 118–121 °C. UV (MeOH): λ = 221, 292 nm. IR (ATR): $\tilde{\nu}$ = 3363, 3108, 2953, 1575, 1561, 1540, 1485, 1447, 1413, 1361, 1234, 1211, 1184, 1130, 1103, 1039, 1006, 969, 871, 850, 844, 795, 756, 704, 669 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.71 (s, 3 H), 7.32 (d, J = 2.5 Hz, 1 H), 7.84 (d, J = 2.5 Hz, 1 H), 9.44 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 61.07 (CH_3), 110.35 (C), 110.60 (C), 112.75 (C), 120.28 (C), 125.09 (C), 126.76 (CH), 129.13 (CH), 129.56 (C), 130.37 (C), 150.73 (C) ppm. MS (EI): m/z (%) = 351 (3), 349 (19), 347 (62), 345 (100), 343 (59) $[M]^+$, 336 (3), 334 (17), 332 (56), 330 (90), 328 (53), 309 (6), 307 (16), 305 (44), 303 (72), 301 (43). HRMS (EI): calcd. for $C_{11}H_6Cl_5NO^+$ $[M]^+$ 342.8892; found 342.8872. $C_{11}H_6Cl_5NO$ (345.44): calcd. C 38.25, H 1.75, N 4.05; found C 38.36, H 1.77, N 4.10.

Pentachloropseudilin (4): Boron tribromide (1 M solution in dichloromethane, 420 μL, 420 μmol) was added at –78 °C to a solution of **28** (132 mg, 382 μmol) in dichloromethane (10 mL), and the mixture was stirred at 0 °C for 2 h. Methanol (1 mL) and water (25 mL) were added at 0 °C, and the mixture was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 5:1) provided **4** (99 mg, 78% yield) as grey crystals; m.p. 131–132 °C; ref.[9] m.p. 126–130 °C. UV (MeOH): λ = 223, 283, 310, 355 nm. IR (ATR): $\tilde{\nu}$ = 3485, 3398, 3107, 3077, 2920, 2851, 1707, 1592, 1573, 1545, 1486, 1425, 1362, 1327, 1235, 1165, 1141, 1039, 1004, 871, 853, 789, 743, 727 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.12 (s, 1 H), 7.28 (d, J = 2.4 Hz, 1 H), 8.00 (d, J = 2.4 Hz, 1 H), 9.55 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 110.38 (C), 110.43 (C), 112.32 (C), 118.57 (C), 120.48 (C), 121.31 (C), 126.33 (CH), 126.36 (C), 127.06 (CH), 145.42 (C) ppm. MS (EI): m/z (%) = 337 (3), 335 (18), 333 (61), 331 (100), 329 (58) $[M]^+$, 300 (8), 298 (34), 296 (77), 294 (59), 273 (6), 271 (26), 269 (59), 267 (47), 263 (6), 261 (18), 259 (18). HRMS (EI): calcd. for $C_{10}H_4Cl_5NO^+$ $[M]^+$ 328.8735; found 328.8723. $C_{10}H_4Cl_5NO$ (331.41): calcd. C 36.24, H 1.22, N 4.23; found C 36.39, H 1.10, N 4.27.

2,3,4-Trichloro-5-(2-methoxyphenyl)-1*H*-pyrrole (29): A solution of *N*-chlorosuccinimide (227 mg, 1.70 mmol) in acetonitrile (6 mL) was added at –40 °C to a solution of **21a** (96 mg, 554 μmol) in acetonitrile (7 mL), and the mixture was stirred at –40 °C for 5 min. The mixture was warmed to room temperature and then stirred for 15 h, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 19:1) provided **29** (124 mg, 81% yield) as a brown oil. UV (MeOH): λ = 272, 290 nm. IR (ATR): $\tilde{\nu}$ = 3304, 3067, 3028, 2924, 2842, 1666, 1600, 1583, 1568, 1504, 1461, 1437, 1380, 1295, 1270, 1244, 1182, 1165, 1143, 1117, 1047, 1031, 1014, 967, 940, 812, 794, 755 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.92 (s, 3 H), 6.99 (d, J = 8.3 Hz, 1 H), 7.05 (m, 1 H), 7.28 (m, 1 H), 8.00 (dd, J = 7.8, 1.6 Hz, 1 H), 9.39 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 55.85 (CH_3), 108.74 (C), 109.66 (C), 110.56 (C), 111.45 (CH), 118.11 (C), 121.27 (CH), 123.07 (C), 128.54 (CH), 128.81 (CH), 155.44 (C) ppm. MS (EI): m/z (%) = 279 (30), 277 (93), 275 (100) $[M]^+$, 264 (12), 262 (36), 260 (37), 242 (14), 240 (23), 237 (24), 235 (71), 233 (72), 232 (19), 227 (34), 225 (53), 204 (30).

2,3,4-Tribromo-5-(3,5-dichloro-2-methoxyphenyl)-1*H*-pyrrole (30): *N*-Bromosuccinimide (226 mg, 1.27 mmol) was added at –40 °C to a solution of **21c** (99.5 mg, 411 μmol) in acetonitrile (10 mL). The mixture was warmed to room temperature and then stirred for 15 h, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 40:1) provided **30** (186 mg, 94% yield) as dark crystals, m.p. 105 °C; ref, m.p.[7] 109 °C. UV (MeOH): λ = 293 nm. IR (ATR): $\tilde{\nu}$ = 3370, 3279, 3069, 2951, 2923, 2851, 1721, 1587, 1558, 1545, 1466, 1414, 1341, 1291, 1236, 1209, 1180, 1123, 1005, 982, 969, 885, 865, 842, 776, 760, 708, 697, 665 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.67 (s, 3 H), 7.35 (d, J = 2.5 Hz, 1 H), 7.82 (d, J = 2.5 Hz, 1 H), 9.48 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 61.08 (CH_3), 99.46 (C), 101.32 (C), 103.68 (C), 124.98 (C), 125.69 (C), 127.50 (CH), 129.47 (CH), 129.54 (C), 130.12 (C), 151.06 (C) ppm. MS (EI): m/z (%) = 485 (2), 483 (15), 481 (53), 479 (88), 477 (63), 475 (17) $[M]^+$, 387 (30), 385 (88), 383 (100), 381 (36). HRMS (EI): calcd. for $C_{11}H_6Br_3Cl_2NO$ $[M]^+$ 474.7377; found 474.7360.

2,3,4-Tribromo-5-(3,5-dichloro-2-hydroxyphenyl)-1*H*-pyrrole (31): Boron tribromide (1 M solution in dichloromethane, 240 μL, 240 μmol) was added at –78 °C to a solution of **30** (103 mg, 215 μmol) in dichloromethane (10 mL), and the mixture was stirred at –78 °C for 15 min and then at 0 °C for 2.5 h. Methanol (1 mL) and water (25 mL) were added at 0 °C, and the mixture was extracted with diethyl ether (3 × 50 mL). The combined organic layers were dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 5:1) provided **31** (76 mg, 76% yield) as grey crystals, m.p. 170 °C; ref, m.p.[7] 170 °C (decomp.). UV (MeOH): λ = 226, 284, 306 nm. IR (ATR): $\tilde{\nu}$ = 3482, 3439, 3411, 3095, 3070, 2922, 2851, 1704, 1674, 1591, 1464, 1422, 1344, 1319, 1230, 1192, 1160, 1117, 1058, 1006, 981, 928, 882, 854, 801, 777, 754, 740, 722, 702 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.07 (s, 1 H), 7.31 (d, J = 2.4 Hz, 1 H), 7.96 (d, J = 2.4 Hz, 1 H), 9.53 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 99.30 (C), 100.98 (C), 103.87 (C), 118.94 (C), 121.30 (C), 125.12 (C), 126.05 (C), 127.17 (CH), 127.58 (CH), 145.89 (C) ppm. MS (EI): m/z (%) = 471 (2), 469 (18), 467 (62), 465 (100), 463 (73), 461 (20) $[M]^+$, 390 (5), 388 (32), 386 (86), 384 (93), 382 (35), 361 (14), 359 (40), 357 (45), 355 (18), 309 (8), 307 (41), 305 (84), 303 (50). HRMS (EI): calcd. for $C_{10}H_4Br_3Cl_2NO$ $[M]^+$ 460.7220; found 460.7220.

2,3,4-Triiodo-5-(3,5-dichloro-2-methoxyphenyl)-1*H*-pyrrole (32): *N*-Iodosuccinimide (113 mg, 502 μmol) was added at 0 °C to a solution of **21c** (39 mg, 161 μmol) in acetonitrile (5 mL). The mixture was warmed to room temperature and stirred for 15 h. A saturated aqueous solution of sodium hydrogensulfite (20 mL) was added, and the mixture was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 20:1) provided **32** (85 mg, 86% yield) as dark crystals; m.p. 147 °C. UV (MeOH): λ = 227, 255, 303 nm. IR (ATR): $\tilde{\nu}$ = 3394, 3068, 2922, 2853, 1726, 1587, 1561, 1529, 1456, 1428, 1412, 1394, 1320, 1239, 1175, 1136, 1028, 985, 950, 884, 861, 843, 780, 764, 711 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.59 (s, 3 H), 7.35 (d, J = 2.5 Hz, 1 H), 7.66 (d, J = 2.5 Hz, 1 H), 9.34 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 61.11 (CH_3), 74.88 (C), 75.69 (C), 90.11 (C), 126.99 (C), 128.82 (CH), 129.39 (C), 129.68 (C), 129.88 (CH), 133.24 (C), 151.52 (C) ppm.

2,3,4-Tribromo-5-(3,5-difluoro-2-methoxyphenyl)-1*H*-pyrrole (34): Pyridinium tribromide (248 mg, 0.775 mmol) was added at room temperature to a solution of **21b** (53.0 mg, 253 μmol) in ethanol (5 mL), and the mixture was stirred at room temperature for 30 min. The solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 20:1) provided **34** (102 mg, 91% yield) as colorless crystals; m.p. 79 °C. UV (MeOH): λ = 287 nm. IR (ATR): $\tilde{\nu}$ = 3403, 3365, 3123, 3088, 2950, 2836, 1618, 1587, 1535, 1479, 1453, 1426, 1392, 1357, 1321, 1280, 1222, 1199, 1179, 1142, 1117, 1083, 1044, 1001, 984, 969, 857, 826, 792, 767, 735, 669 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.82 (d, $^5J_{H,F}$ = 1.2 Hz, 3 H), 6.83 (ddd, $^3J_{H,F}$ = 10.9, 7.9 Hz, $^4J_{H,H}$ = 3.0 Hz, 1 H), 7.57 (ddd, $^3J_{H,F}$ = 9.7 Hz, $^4J_{H,H}$ = 3.0 Hz, $^5J_{H,F}$ = 2.0 Hz, 1 H), 9.66 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 61.97 (d, $^4J_{C,F}$ = 5.0 Hz, CH_3), 99.24 (C), 101.10 (C), 103.88 (C), 104.44 (dd, $^2J_{C,F}$ = 26.8, 23.1 Hz, CH), 110.21 (dd, $^2J_{C,F}$ = 25.3 Hz, $^4J_{C,F}$ = 3.4 Hz, CH), 124.68 (dd, $^3J_{C,F}$ = 10.8, 3.4 Hz, C), 125.41 (m, C), 140.61 (m, C), 155.84 (dd, $^1J_{C,F}$ = 249.7 Hz, $^3J_{C,F}$ = 13.5 Hz, C), 157.82 (dd, $^1J_{C,F}$ = 245.6 Hz, $^3J_{C,F}$ = 12.2 Hz, C) ppm. MS (EI): *m/z* (%) = 449 (23), 447 (81), 445 (84), 443 (24) $[M]^+$, 353 (46), 351 (100), 349 (48). HRMS (EI): calcd. for $C_{11}H_6Br_3F_2NO$ $[M]^+$ 442.7968; found 442.7960. $C_{11}H_6Br_3F_2NO$ (445.88): calcd. C 29.63, H 1.36, N 3.14; found C 29.94, H 1.38, N 3.17.

2,3,4-Tribromo-5-(3,5-difluoro-2-hydroxyphenyl)-1*H*-pyrrole (35): Boron tribromide (1 M solution in dichloromethane, 341 μL, 341 μmol) was added at –78 °C to a solution of **34** (138 mg, 310 μmol) in dichloromethane (10 mL), and the mixture was stirred at 0 °C for 90 min. Methanol (1 mL) and water (25 mL) were added at 0 °C, and the layers were separated. The aqueous layer was extracted with dichloromethane (2× 50 mL). The combined organic layers were dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 7:1) provided **35** (104 mg, 78% yield) as light green crystals; m.p. 132 °C (decomp.). UV (MeOH): λ = 278, 299 nm. IR (ATR): $\tilde{\nu}$ = 3557, 3417, 3361, 3096, 2922, 2853, 1629, 1606, 1548, 1485, 1455, 1406, 1369, 1347, 1309, 1267, 1228, 1200, 1156, 1109, 1033, 987, 855, 827, 787, 728 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.47 (d, $^4J_{H,F}$ = 4.6 Hz, 1 H), 6.85 (ddd, $^3J_{H,F}$ = 10.2, 7.7 Hz, $^4J_{H,H}$ = 2.7 Hz, 1 H), 7.68 (dt, $^3J_{H,F}$ = 10.0 Hz, $^4J_{H,H}$ = 2.4 Hz, $^5J_{H,F}$ = 2.4 Hz, 1 H), 9.68 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 99.09 (C), 101.02 (C), 102.99 (dd, $^2J_{C,F}$ = 27.6, 22.4 Hz, CH), 104.00 (C), 109.85 (dd, $^2J_{C,F}$ = 25.7 Hz, $^4J_{C,F}$ = 3.2 Hz, CH), 118.78 (m, C), 125.31 (m, C), 136.23 (m, C), 150.70 (dd, $^1J_{C,F}$ = 237.6 Hz, $^3J_{C,F}$ = 13.2 Hz, C), 155.49 (dd, $^1J_{C,F}$ = 241.3 Hz, $^3J_{C,F}$ = 12.2 Hz, C) ppm. MS (EI): *m/z* (%) = 435 (29), 433 (95), 431 (98), 429 (30) $[M]^+$, 354 (47), 352 (100), 350 (47), 327 (25), 325 (54), 323 (27). 273 (75), 271 (74), 192 (49). HRMS (EI): calcd. for $C_{10}H_4Br_3F_2NO$ $[M]^+$ 428.7811; found 428.7793.

2,3,4-Triiodo-5-(3,5-difluoro-2-methoxyphenyl)-1*H*-pyrrole (36): *N*-Iodosuccinimide (370 mg, 1.64 mmol) was added at 0 °C to a solution of **21b** (110 mg, 526 μmol) in acetonitrile (10 mL). The mixture was warmed to room temperature and then stirred for 17 h. A saturated aqueous solution of sodium hydrogensulfite (25 mL) was added, and the mixture was extracted with diethyl ether (3× 50 mL). The combined organic layers were dried with magnesium sulfate, and the solvent was evaporated. Purification of the residue by chromatography on a silica gel column (petroleum ether/diethyl ether, 20:1) provided **36** (281 mg, 91% yield) as grey crystals; m.p. 112 °C. UV (MeOH): λ = 297 nm. IR (ATR): $\tilde{\nu}$ = 3387, 3077, 2984, 2925, 1698, 1611, 1588, 1542, 1470, 1433, 1417, 1353, 1297, 1247, 1227, 1180, 1161, 1118, 1035, 986, 950, 867, 846, 828, 776, 744, 684 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.75 (d, $^5J_{H,F}$ = 1.1 Hz, 3 H), 6.85 (ddd, $^3J_{H,F}$ = 10.9, 8.0 Hz, $^4J_{H,H}$ = 2.9 Hz, 1 H), 7.40 (ddd, $^3J_{H,F}$ = 9.4 Hz, $^4J_{H,H}$ = 2.9 Hz, $^5J_{H,F}$ = 2.0 Hz, 1 H), 9.41 (br. s, 1 H) ppm. ^{13}C NMR and DEPT (125 MHz, $CDCl_3$): δ = 61.97 (d, $^4J_{C,F}$ = 4.8 Hz, CH_3), 74.54 (C), 75.54 (C), 90.59 (C), 104.94 (dd, $^3J_{C,F}$ = 26.7, 23.2 Hz, CH), 111.56 (dd, $^3J_{C,F}$ = 24.8 Hz, $^5J_{C,F}$ = 3.4 Hz, CH), 125.94 (dd, $^3J_{C,F}$ = 10.6, 3.6 Hz, C), 133.51 (m, C), 141.10 (m, C), 155.81 (dd, $^1J_{C,F}$ = 249.6 Hz, $^3J_{C,F}$ = 13.3 Hz, C), 157.45 (dd, $^1J_{C,F}$ = 244.9 Hz, $^3J_{C,F}$ = 12.3 Hz, C) ppm. $C_{11}H_6F_2I_3NO$ (586.88): calcd. C 22.51, H 1.03, N 2.39; found C 23.08, H 0.93, N 2.34.

Myosin-2 ATPase Assay: Heavy meromyosin (HMM, 0.02 mg mL^{-1}), which was prepared from rabbit muscle myosin-2,[27] was dissolved in an assay buffer (50 mM KCl, 5 mM $CaCl_2$, 25 mM Tris-HCl pH = 7.5), and the resulting solution was mixed with various concentrations of test compounds in a 96-well plate. The solutions were incubated for 20 min at 37 °C. After the addition of ATP (50 μM), the solutions were further incubated for 20 min at 20 °C, and the amount of liberated phosphate in the solution was measured by the colorimetric method using BIOMOL Green™ reagent (Biomol GmbH, Hamburg, Germany). The absorbance was determined at 640 nm in an Infinite™ microplate reader (Tecan, Crailsheim, Germany).

Protein Preparation and Microscale Thermophoresis: Proteins were prepared as described earlier[14] and labeled with a fluorescent RED-NHS dye. Measurements were carried out using hydrophobic capillaries in a NanoTemper Monolith™ instrument according to Duhr et al.[28]

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra for compounds **9c**–**36**.

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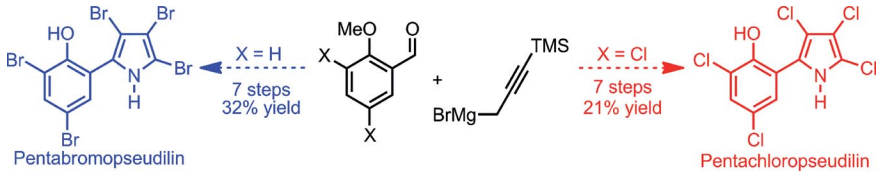

The alkaloids pentabromopseudilin and pentachloropseudilin represent a new class of isoform-specific allosteric inhibitors of myosin ATPase. Herein, we describe an application of the silver(I)-catalyzed cycloisomerization of *N*-(homopropargyl)-toluenesulfonamides to the syntheses of these alkaloids and their non-natural analogues as well as a study of their inhibition of myosin ATPase activity.

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Silver(I)-Catalyzed Route to Pyrroles: Synthesis of Halogenated Pseudilins as Allosteric Inhibitors for Myosin ATPase and X-ray Crystal Structures of the Protein–Inhibitor Complexes

Keywords: Synthetic methods / Nitrogen heterocycles / Alkaloids / Cyclization / Halogenation / Inhibitors / Silver

