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Step-Economical Synthesis of the Marine Ascidian Antibiotics Cadiolide A, B, and D

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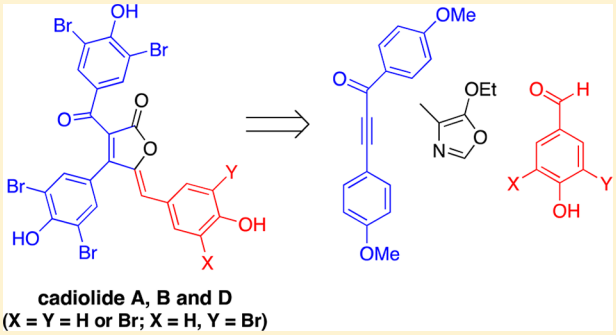
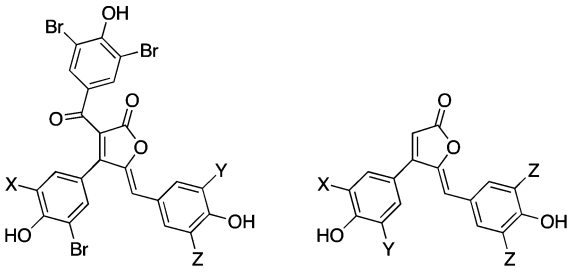
Supporting Information

ABSTRACT: A concise, modular and efficient synthesis of the title natural products is reported. Prominent steps include (i) one-pot assembly of a key β-aryl-α-benzoylbutenolide building block by regiocontrolled "click–unclick" oxazole–ynone Diels–Alder cycloaddition/cycloreversion and ensuing 2-alkoxyfuran hydrolysis and (ii) a protecting group-free vinylogous Knoevenagel condensation enabling rapid access to cadiolides A, B, and D from a common precursor.



The continuing emergence of drug-resistant microorganisms has become a major global threat to public health.[1,2] Among bacterial pathogens, the most deadly is methicillin-resistant *Staphylococcus aureus* (MRSA) causing an alarming number of infections worldwide, not only to hospitalized patients but also to healthy individuals.[3] In the US, for instance, more people die from MRSA than from HIV/AIDS, Parkinson's disease, and homicide combined.[4] Nature's privileged structures have been the basis of nearly all antibiotics in clinical use.[5] However, new classes of compounds are urgently needed to combat the rising tide of resistance.[6] As such, small-molecule natural products possessing anti-MRSA activity and novel structural features represent compelling targets for synthesis and leads par excellence for chemical and pharmacological exploration.



1 X = Br, Y = Z = H (cadiolide A)
2 X = Y = Z = Br (cadiolide B)
3 X = Y = H, Z = Br (cadiolide C)
4 X = Y = Br, Z = H (cadiolide D)
5 X = H, Y = Z = Br (cadiolide E)

6 X = Y = Z = Br (rubrolide A)
7 X = Y = H, Z = Br (rubrolide C)
8 X = Y = Z = H (rubrolide E)
9 X = Z = Br, Y = H (rubrolide J)

Figure 1. Structures of cadiolides and rubrolides.

Cadiolides A–E (**1**–**5**, Figure 1) comprise a group of noncytotoxic, densely functionalized butenolides isolated in 1998 and 2012 from Indonesian and Korean ascidians, respectively.[7−9] Only recently, however, were their significant in vitro antibacterial activities brought to light.[8,9] Against MRSA strains in particular, cadiolides C and D are several-fold more potent than linezolid and at least as potent as the injectable last-resort drug vancomycin.[8] Another study revealed that cadiolide E strongly inhibits *Candida albicans* isocitrate lyase (ILC), suggesting that the cadiolides may also possess antifungal activity.[10] Furthermore, in 2014, cadiolide B was shown to inhibit Japanese encephalitis virus (JEV) at a concentration of 1 μg/mL.[11]

Given the limited availability of these compounds from marine ascidia, where recollection and resupply is often difficult, if not impossible, future biological studies will likely depend on total synthesis. Structurally and biogenetically, the cadiolides are closely related to rubrolides (e.g., **6**–**9**),[12] as both co-occur in ascidia and share a common β-aryl-γ-benzylidene-butenolide unit.[7,8] However, the former are clearly distinguished by an unusual α-benzoyl appendage which makes their carbon skeleton unprecedented (Figure 1). While the "extra" benzoyl substituent appears to improve antibacterial and antiviral activity,[8,11] it also poses some specific challenges to their synthesis.[13] Indeed, compared to rubrolides,[14,15] synthetic accomplishments in the cadiolide area have been few and far between. The first total synthesis of a cadiolide (cf. **2**), reported from these laboratories in 2005,[16] relies on furanolate chemistry and Suzuki cross-coupling to generate intermediates **10** and **11** (Scheme 1). Recently, Franck and Leleu described a new

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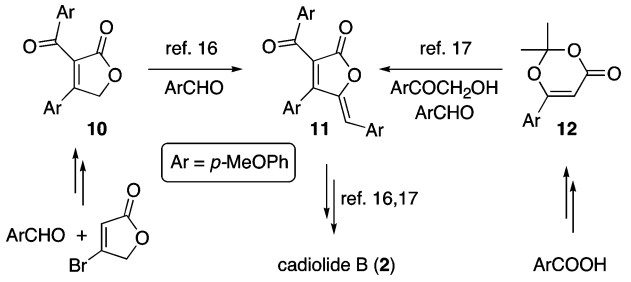
Scheme 1. Previous Syntheses of Cadiolide B



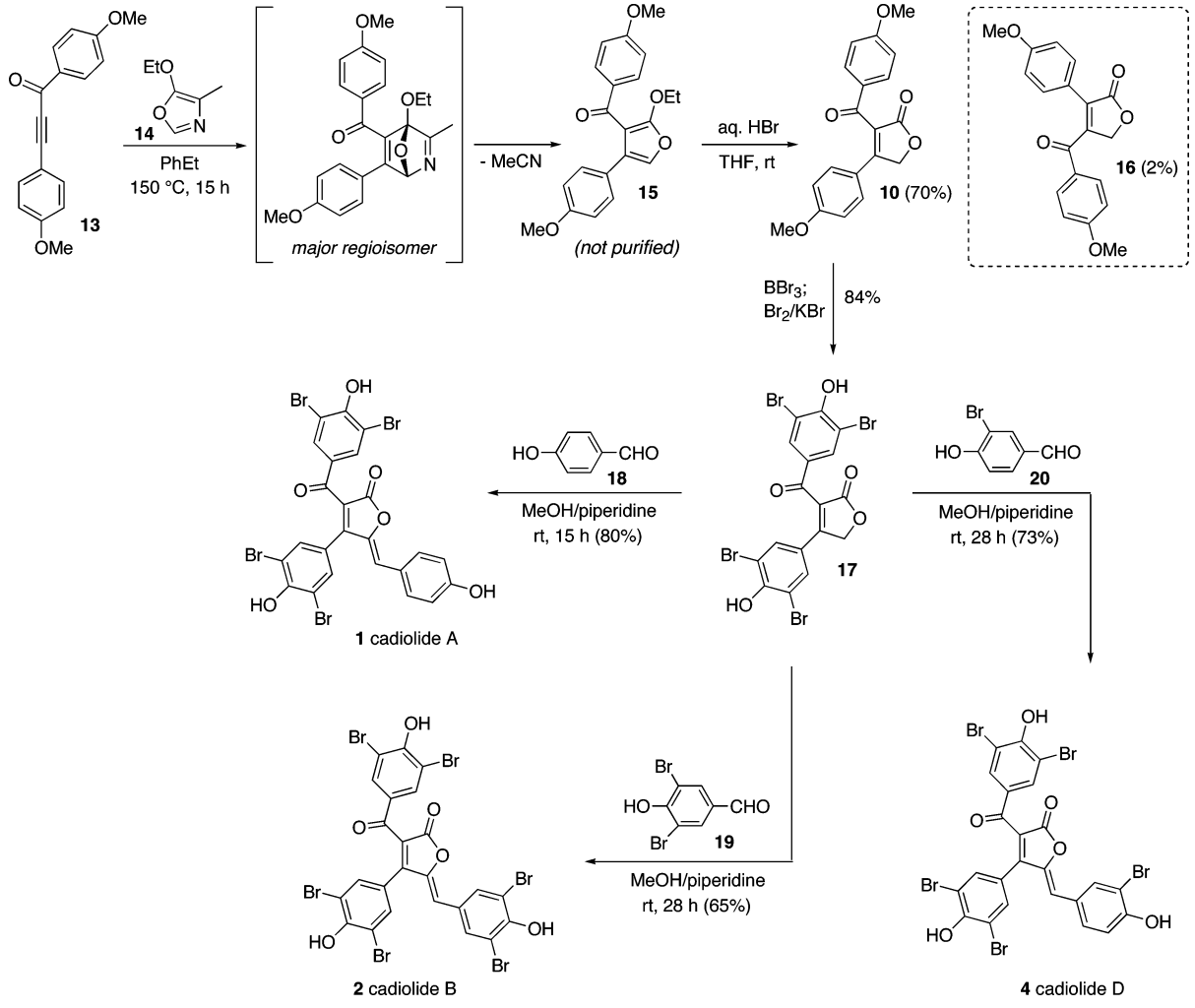
approach to **11** utilizing a multicomponent process as the prominent step.[17] On both occasions, crafting **11** into cadiolide B (**2**) was achieved in two steps by demethylation and bromination of the three identical aryl substituents.[16,17]

Notwithstanding the individual merits of these strategies, as yet, none have been shown to be applicable to the preparation of cadiolides bearing nonidentical aryls, such as the highly potent anti-MRSA agents cadiolide C and D. Herein, therefore, we report a distinctly different, concise and modular generic approach to these targets, illustrated by de novo acquisition of butenolide **10** and a flexible end-game strategy enabling the assembly of cadiolides A, B, and D from a common precursor.

As outlined in Scheme 2, the synthesis began from easily prepared ynone **13**[18] and commercial 5-ethoxy-4-methyloxazole **14**.[19] Heating **13** with an excess of **14** in ethylbenzene accomplished regioselective "click–unclick" Diels–Alder cycloaddition–cycloreversion[20,21] leading mainly to furan **15**. The product mixture was not purified but directly treated with aqueous HBr/THF to give butenolides **10** and **16** in a ratio approximating 9:1. Pleasingly, a single recrystallization of the so obtained solid provided analytically pure **10** in a respectable 70% yield. Though of no consequence to the ensuing synthetic operations, a small amount of isomer **16**, arising from the regioisomer of furan **15** (not shown), was also isolated for characterization purposes by subjecting the filtrate to flash chromatography. The serviceability of this ploy in generating **10** in a single operation is notable given the paucity and limitations of existing pathways to such α,β-disubstituted butenolides.[13,16,17]

Next, elaboration of the cadiolide progenitor **17** necessitated cleavage of the methyl aryl ether groups in **10** with boron tribromide and ensuing bromination of the phenolic moieties with in situ generated[16,22] KBr_3 (Scheme 2). Once again, this two-step transformation was swiftly realized in one-pot fashion, without the need for chromatographic purification, to deliver **17** (84%) after a simple recrystallization.

Scheme 2. Total Synthesis of Cadiolides A, B, and D



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At this point, the plan called for a vinylogous Knoevenagel condensation of **17** with commercially available aldehydes **18**–**20** to install the appropriate γ-arylmethylidene substituent (Scheme 2). To accomplish this as economically as possible, it was imperative that the phenol groups in both partners remain unprotected. Although related reactions have been used in the synthesis of (*Z*)-γ-benzylidenebutenolides,[23] including cadiolide B[16] and rubrolides,[14b−i,15a−c] protecting group free variants have yet to be reported. In the present instance, the α-benzoyl substituent was considered advantageous because of the increased acidity of the γ-methylene protons[24] and, more importantly, the enhanced reactivity of the corresponding carbanion toward aldehydes.[25] Indeed, under classical Knoevenagel conditions (piperidine, MeOH, rt), butenolide **17** smoothly underwent *Z*-selective condensation[23] with aldehyde **18** to afford isomerically pure cadiolide A (**1**, 80%), whose structure was confirmed by X-ray diffraction analysis.[26] Likewise, cadiolides B and D, **2** and **4**, were obtained from **17** and the corresponding aldehyde in yields of 65 and 73%, respectively (Scheme 2).

In conclusion, the first synthesis of cadiolide A and D and a new synthesis of cadiolide B have been achieved in three operational steps and overall yields of 47, 43, and 38% from ynone **13**. The foregoing work serves to demonstrate the power of click-unclick Diels–Alder chemistry for constructing β-aryl-α-benzoylbutenolides and a versatile late-stage strategy enabling direct access to cadiolides from a single precursor.

EXPERIMENTAL SECTION

General Protocols. All commercial reagents were used as received. Methylene chloride and methanol were distilled from calcium hydride. Flash chromatography was performed on an automated system (UV–vis detector) using silica gel as stationary phase. Melting points are uncorrected. NMR spectra were recorded at room temperature in $CDCl_3$ or $(CD_3)_2CO$. Chemical shifts are reported relative to chloroform (δ_H 7.26; δ_C 72.2) or acetone (δ_H 2.05; δ_C 29.8). ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. High-resolution mass spectra were obtained on a time-of-flight instrument using electrospray ionization (ESI).

3-(4-Methoxybenzoyl)-4-(4-methoxyphenyl)furan-2(5*H*)-one (10) and 4-(4-Methoxybenzoyl)-3-(4-methoxyphenyl)-furan-2(5*H*)-one (16). To a solution of ynone **13**[18] (170.4 mg, 0.64 mmol) in anhydrous ethylbenzene (5 mL) was added 5-ethoxy-4-methyloxazole (446.5 mg, 3.51 mmol). The vial was capped, subjected to strong vacuum under agitation, and then purged with nitrogen. This process was repeated three times. The vial was covered with aluminum paper, magnetically stirred, and heated in an oil bath maintained at 145–150 °C for 15 h. After cooling, the volatiles were evaporated under vacuum at 60 °C. The crude product was dissolved in THF (6.5 mL), and aq 48% HBr (34.5 μL, 0.31 mmol) was slowly added. After being stirred for 8 h at rt, the mixture was quenched with brine (10 mL) and extracted with EtOAc. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. ^{1}H NMR analysis of the crude product indicated a 9:1 ratio of regioisomers **10**/**16**. The crude mixture was recrystallized from chloroform/light petroleum ether to afford **10** (145.0 mg, 70%) as a yellow solid: mp 166–168 °C (lit.[16] mp 166–167 °C); IR (NaCl, film) 3007, 2936, 2841, 1748, 1598, 1253, 1166, 1025, 834 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.9 Hz, 2H) 7.35 (d, *J* = 9.0 Hz, 2H) 6.91 (d, *J* = 9.0 Hz, 2H) 6.84 (d, *J* = 8.9 Hz, 2H) 5.29 (s, 2H) 3.84 (s, 3H) 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.4, 171.4, 164.9, 162.6, 160.0, 132.2, 129.8, 129.0, 123.6, 121.7, 114.8, 114.3, 70.5, 55.7, 55.6; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{17}O_5$ 325.1076, found 325.1075. Anal. Calcd for $C_{19}H_{16}O_5$: C, 70.36; H, 4.97. Found: C, 70.62; H, 4.74. The filtrate was chromatographed (CH_2Cl_2) to provide the minor regioisomer **16** (4.2 mg, 2%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.9 Hz, 2H) 7.46 (d, *J* = 8.9 Hz, 2H) 6.81 (d, *J* = 8.9 Hz, 2H) 6.77 (d, *J* = 8.9 Hz, 2H) 5.10 (s, 2H) 3.82 (s, 3H) 3.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 172.2, 164.9, 160.7, 152.4, 132.2, 130.7, 129.6, 127.3, 121.2, 114.4, 114.1, 70.4, 55.7, 55.4; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{16}O_5Na$ 347.0895, found 347.0901.

3-(3,5-Dibromo-4-hydroxybenzoyl)-4-(3,5-dibromo-4-hydroxyphenyl)furan-2(5*H*)-one (17). To a solution of butenolide **10** (286.9 mg, 0.89 mmol) in freshly distilled and degassed CH_2Cl_2 (7 mL) was added BBr_3 in CH_2Cl_2 (1 M, 3.55 mL, 3.55 mmol) dropwise at −78 °C. After 15 min, the mixture was slowly warmed to rt, stirred for 24 h, and quenched with brine (10 mL) at 0 °C. The aqueous layer was extracted with EtOAc, and the organic phase was dried ($NaSO_4$) and concentrated in vacuo. The crude product was triturated with Et_2O to give a beige solid, which was dissolved in a mixture of water (1.5 mL) and 1,4-dioxane (7.5 mL) "solution A". Next, KBr (1.5 g) and Br_2 (0.32 mL, 1 g) were dissolved in nanopure water (10 mL) to form KBr_3 "solution B". At this point, 5.66 mL (3.54 mmol) of solution B were added dropwise to solution A. The mixture was allowed to stir at rt for 2 h and then quenched with brine (15 mL), and the aqueous layer was extracted with EtOAc. The organic phase was successively washed with a saturated solution of sodium thiosulfate (2 × 25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated in vacuo. The crude product was triturated with EtOAc, filtered and rinsed with cold Et_2O to furnish **17** (454.5 mg, 84%) as a yellow solid: mp 226–229 °C dec; IR (NaCl, film) 3348, 1743, 1656, 1578, 1476, 1327, 1234, 1150, 1067, 738 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.15 (s, 2H) 7.75 (s, 2H) 5.52 (s, 2H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 188.6, 171.1, 161.5, 156.9, 154.5, 134.7, 133.1, 131.3, 125.3, 124.9, 111.9, 111.8, 71.8; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{17}H_9O_5Br_4$ 614.7122, found 614.7128.

Cadiolide A (1). To a solution of **17** (50.7 mg, 0.08 mmol) in freshly distilled methanol (1.5 mL) was added piperidine (41.0 μL, 0.41 mmol), and the mixture was allowed to stir for 30 min at rt. A solution of 4-hydroxybenzaldehyde (15.2 mg, 0.12 mmol) in methanol (0.5 mL) was then added. After 15 h, the reaction was quenched with aqueous 1 M HCl (5 mL) and extracted with EtOAc. The organic phase was dried with sodium sulfate and concentrated in vacuo. Flash chromatography (100:0:0 to 39:60:1 hexanes/Et_2O/AcOH) provided cadiolide A (47.3 mg, 80%) as a red solid: mp 245–250 °C dec; IR (NaCl, film) 3397, 1740, 1598, 1165, 741 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 8.05 (s, 2H) 7.84 (d, *J* = 8.8 Hz, 2H) 7.69 (s, 2H) 6.97 (d, *J* = 8.8 Hz, 2H) 6.48 (s, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 186.0, 166.3, 160.6, 156.7, 156.4, 153.3, 146.2, 134.8, 134.4, 134.1, 131.4, 125.9, 124.3, 123.0, 118.8, 117.0, 111.6, 111.4; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{13}O_6Br_4$ 716.7405, found 716.7396. Anal. Calcd for $C_{24}H_{12}O_6Br_4$: C, 40.26; H, 1.69. Found: C, 40.29; H, 1.36. Suitable crystals for X-ray crystallography were obtained by partial evaporation of the eluent (hexanes/Et_2O/AcOH) over 9 days.

Cadiolide B (2). To a solution of **17** (37.3 mg, 0.06 mmol) in freshly distilled methanol (1 mL) were added three molecular sieves and piperidine (24.0 μL, 0.24 mmol), and the mixture was allowed to stir for 30 min at rt. A solution of 3,5-dibromo-4-hydroxybenzaldehyde (17.9 mg, 0.06 mmol) in methanol (0.5 mL) was then added. After 28 h, the reaction was quenched with aqueous 1 M HCl (10 mL) and extracted with EtOAc. The organic phase was dried ($MgSO_4$), concentrated in vacuo, and the residue was purified by flash column chromatography (100% hexanes to 60:38:1:1 hexanes/Et_2O/MeOH/AcOH) to give cadiolide B (34.5 mg, 65%) as a yellow solid: mp 253–257 °C dec; IR (NaCl, film) 3477, 3067, 1758, 1475, 1296, 1250, 1153, 739 cm^{-1}; ^{1}H NMR (400 MHz, $(CD_3)_2CO$) 8.16 (s, 2H) 8.06 (s, 2H) 7.70 (s, 2H) 6.52 (s, 1H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) 185.9, 165.8, 156.4, 156.3, 153.5, 152.9, 147.9, 135.7, 134.8, 134.2, 131.3, 128.9, 124.4, 123.8, 114.8, 111.8, 111.7, 111.4; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{11}O_6Br_6$ 874.5595, found 874.5589.

Cadiolide D (4). Using a procedure similar to that described above, **17** (38.5 mg, 0.06 mmol) and 3-bromo-4-hydroxybenzaldehyde (13.3

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mg, 0.07 mmol) were stirred in distilled MeOH (0.5 mL), and three molecular sieves were added. The mixture was cooled to 0 °C, and piperidine (25.0 μL, 0.25 mmol) was added. After being stirred for 10 min at 0 °C, the mixture was slowly warmed to rt and stirring continued for 28 h. Usual workup and flash chromatography (100% hexanes to 60:38:1:1 hexanes/Et_2O/MeOH/AcOH) afforded cadiolide D (36.5 mg, 73%) as an orange solid: mp 244−245 °C dec; IR-ATR (ZnSe, neat) 3190, 3078, 2923, 1738, 1538, 1371, 1292, 1148, 741 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2CO$) 8.14 (d, J = 1.9 Hz, 1H) 8.05 (s, 2H) 7.84 (dd, J = 8.6, 1.8 Hz, 1H) 7.70 (s, 2H) 7.14 (d, J = 8.6 Hz, 1H) 6.50 (s, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$) 186.0, 166.1, 156.7, 156.5, 156.4, 153.4, 147.0, 137.0, 134.8, 134.2, 133.1, 131.4, 127.6, 124.1, 123.8, 117.7, 116.8, 111.7, 111.4, 111.0; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{24}H_{12}O_6Br_5$ 794.6510, found 794.6507.

■ ASSOCIATED CONTENT

Supporting Information

Proton and carbon NMR spectra of all isolated compounds, and full crystallographic data for **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(26) The solid-state structure of synthetic **1** (cocrystallized with two molecules of water) further reveals that the brominated aromatic rings undergo intra- and intermolecular π-stacking; see the Supporting Information for details.