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Carbamoyl Functionalized Bent *para*-Phenylenes via an Unexpected Reaction of the Burgess Reagent with α-Ketols

Sydney N. Jackson, Andrew L. Caskey, Natasha K. Narayanan, and Bradley L. Merner*

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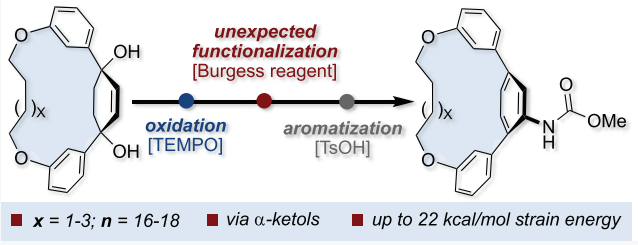
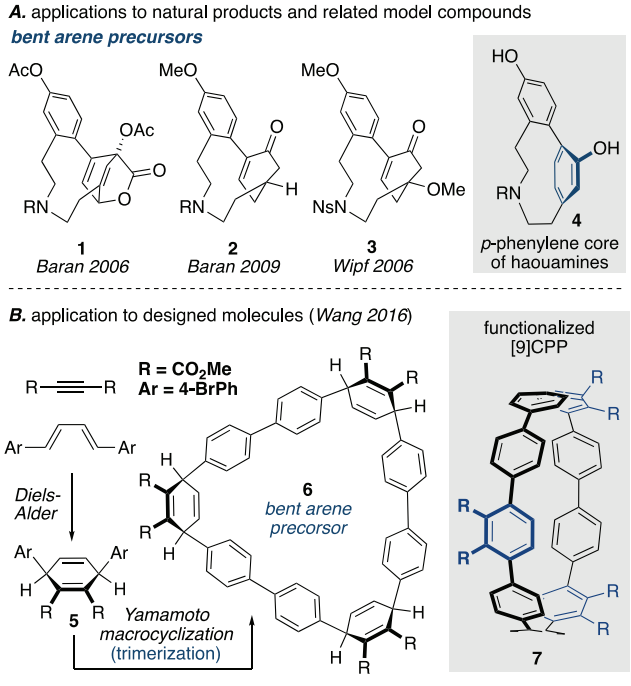
ABSTRACT: The attempted dehydration of macrocyclic α-ketols with the Burgess reagent has resulted in the unexpected synthesis of carbamoylated, bent *para*-phenylene units. The same reaction with an acyclic analogue affords the intended dehydration product, indicating that the change in reactivity is conformationally controlled and a result of the bifunctional nature of the Burgess reagent.



The synthesis of functionalized, bent *para*-phenylene rings has only been achieved on a few occasions. Notable, recent examples include Baran's total syntheses of haouamine A (**1** and **2** to **4**, Scheme 1A),[1−3] Wipf's approach to the strained phenol unit of the same natural product (**3** to **4**, Scheme 1A),[4] and Wang and co-workers Diels−Alder based approach to 2,3-carbomethoxy-1,4-cyclohexadiene units,[5] which were subsequently aromatized to furnish functionalized [*n*]CPP derivatives (e.g., **7**, Scheme 1B). Access to functionalized bent *para*-phenylene rings would provide a platform from which π-extended, curved aromatic systems could be synthesized. Direct π-extension of bent, unfunctionalized benzenoid systems has been recently achieved;[5,6] however, these examples are limited to modestly strained arene units. Indeed, the aforementioned work has led to the synthesis of challenging targets such as carbon nanobelts (CNBs);[7] however, access to smaller, more strained CNBs using oxidative arylation reactions have not been reported. With the latter in mind, and our interest in synthesizing haouamine A-type scaffolds, we report here a synthetic strategy for accessing strained, carbamoyl functionalized, *para*-phenylene rings that result from unexpected reactions with the Burgess reagent.

Scheme 1. Arene Precursors for the Synthesis of Functionalized, Bent *para*-Phenylenes



We have recently reported on the synthesis of several highly strained *para*-phenylene-containing macrocycles using a dehydrative aromatization reaction of macrocyclic cyclohex-2-ene-1,4-diols (Scheme 2).[8] This core (pre-arene) structure, bearing tertiary allylic alcohol units, presented the opportunity to explore oxidative transformations to functionalize the cyclohexene nucleus of **8**−**10**, en route to functionalized strained arene units. Initial focus was directed toward allylic alcohol transposition, followed by oxidation, to furnish macrocyclic α-ketols, or α′-hydroxy (α,β-unsaturated) enones, such as **13**−**15** (Table 1). Conversion of macrocyclic cyclohex-2-ene-1,4-diols **8**−**10** to the desired α-ketols proved to be sensitive to the oxidative conditions employed. For instance,

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Scheme 2. Previous Dehydrative Aromatization Reactions of Macrocyclic Cyclohex-2-ene-1,4-diols and New Oxidative Transformations

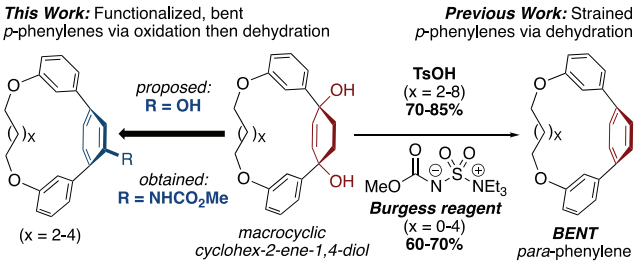
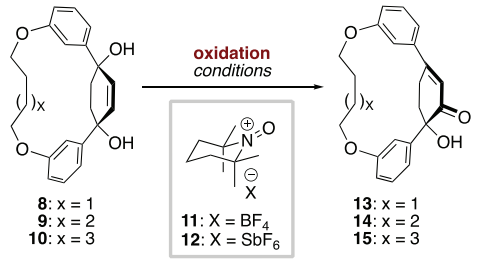
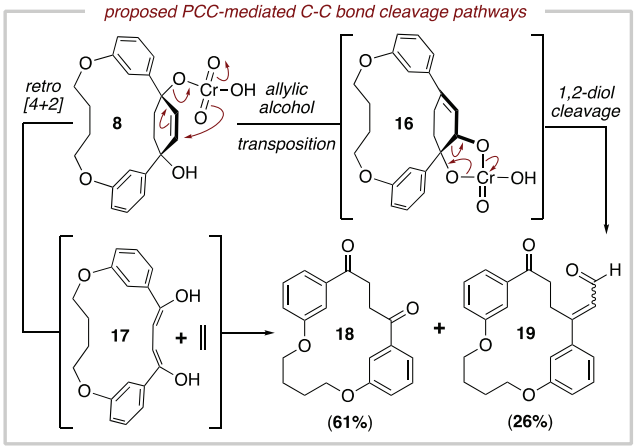


Table 1. Oxidative Transformations of Cyclohex-2-ene-1,4-diols and Proposed Mechanism for Oxidative Cleavage Products



entry	compd	conditions	product	yield
1	**8**	PCC, CH_2Cl_2, 23 °C, 3 h	**13**	0%[a]
2	**8**	IBX, DMSO, 50 °C, 24 h	**13**	0%
3	**8**	DMP, CH_2Cl_2, 23 °C, 24 h	**13**	0%
4	**8**	**11**, MeCN, 50 °C, 24 h	**13**	67%
5	**8**	**12**, MeCN, 50 °C, 24 h	**13**	94%
6	**9**	**11**, MeCN, 50 °C, 24h	**14**	62%
7	**9**	**12**, MeCN, 50 °C, 24 h	**14**	73%
8	**10**	**11**, MeCN, 50 °C, 24 h	**15**	75%
9	**10**	**12**, MeCN, 50 °C, 24 h	**15**	67%

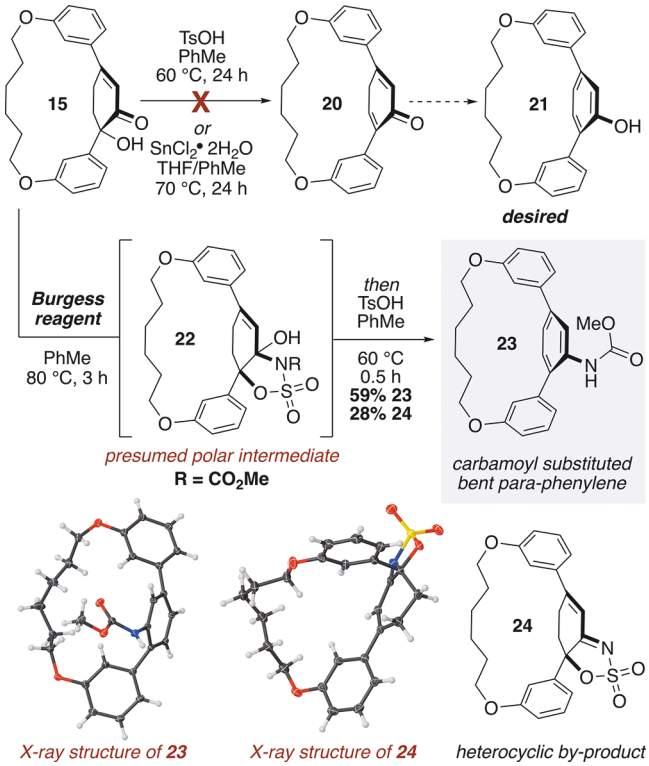
[a]Ring opened products **18** and **19**, 61% and 26% respectively.



standard chromium-based reaction conditions resulted in the formation of 1,4-diketone **18**, and a mixture of enals **19** (entry 1, Table 1). Formation of the 1,4-diketone byproduct can be explained by a formal retro-[4 + 2] cycloaddition reaction (**8** to **17**, Table 1), while the ring-opened enal byproducts could arise from initial allylic alcohol transposition to furnish 1,2-diol **16**, which subsequently undergoes oxidative cleavage rather than secondary alcohol oxidation (proposed mechanism, Table 1). Bis-allylic-1,4-diol **8** was resistant to hypervalent iodine-mediated oxidations (entries 2 and 3, Table 1); however, TEMPO-based oxoammonium salts **11** and **12**, previously reported by Iwabuchi and co-workers,[9] proved to be ideally suited for the synthesis of α-ketol **13** (entries 4 and 5, Table 1). Application of these conditions to larger macrocyclic cyclohex-2-ene-1,4-diols **9** and **10** furnished α-ketols **14** and **15** in 62−73% and 67−75% yield, respectively (entries 6−9, Table 1).

With three homologous α-ketols in hand, focus was shifted toward their conversion into bent phenol units. These studies commenced with the largest macrocyclic system **15**, which would yield the least strained central *para*-phenylene unit. It was envisaged that dehydration of **15** would afford dienone **20**, which could undergo tautomerization to give the strained phenol unit of **21** (Scheme 3). Previous work from our

Scheme 3. Attempted Dehydration Reactions of 15, Unexpected Functionalization with the Burgess Reagent, and X-ray Crystal Structures of 23 and 24



laboratory delineated several different dehydrative aromatization reaction conditions for synthesizing moderately to highly strained arene units.[10] In the case of α-ketol **15**, containing 18 backbone carbon atoms in its macrocyclic structure, protic acid mediated conditions seemed well suited to achieve the desired transformation; however, treatment of **15** with TsOH in toluene at 80 °C resulted in no conversion of the starting material. Likewise, Lewis acid-mediated dehydration with $SnCl_2$, which had been previously employed as a mild alternative to TsOH,[10−12] did not furnish **20**, but rather recovered **15**. Similar results were obtained using other dehydration protocols.[13] When **15** was subjected to the Burgess reagent,[14] a new, more polar product formed. This compound was isolable; however, broadened peaks and poorly resolved ^1H and ^{13}C NMR spectra precluded detailed analysis

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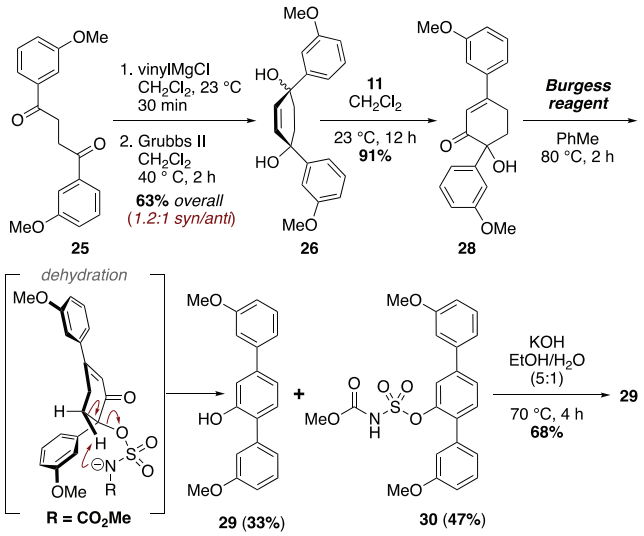
of its structure. Directly subjecting the crude material obtained from the reaction of **15** with the Burgess reagent to TsOH in toluene resulted in the formation of carbamoyl substituted *para*-phenylene **23** and heterocycle **24** in 59% and 28% yield, respectively (Scheme 3). The structure of **23** was easily assigned on the basis of ^{1}H, ^{13}C NMR and HRMS analyses; however, recrystallization of **23** from dichloromethane gave crystals suitable for X-ray crystallography (see X-ray structure, Scheme 3). The structure of **24** was difficult to unambiguously assign from ^{1}H and ^{13}C NMR analyses, as the newly formed heterocyclic portion of **24** is NMR silent. Fortunately, crystals suitable for X-ray analysis were obtained (from dichloromethane) and the heterocyclic ring present in **24** was assigned as a 5*H*-[1,2,3]-oxathiazole-2,2-dioxide unit (see X-ray structure, Scheme 3).[15]

This unexpected functionalization of α-ketol **15** led us to investigate the same reaction with an acyclic analogue. 1,4-Diketone **25** was treated with vinylmagnesium chloride in dichloromethane to afford a mixture of diastereomers, which were directly subjected to ring-closing metathesis with the Grubbs second-generation catalyst to furnish cyclohex-2-ene-1,4-diols **26** (1.2:1 *syn*/*anti*) in 63% yield over two steps (Scheme 4). Oxidation of the mixture of diols with **11** in

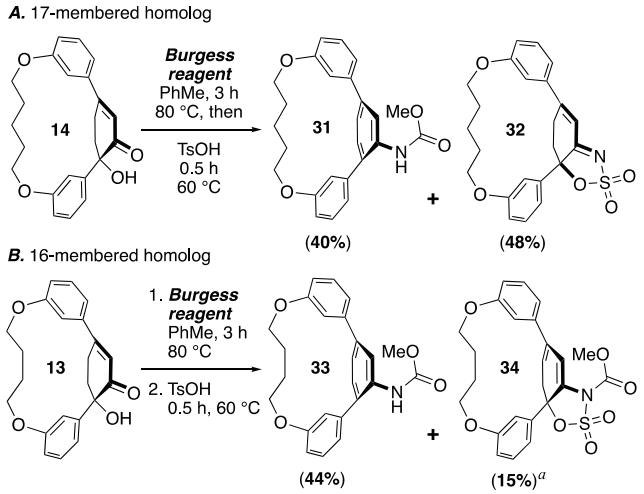
Scheme 4. Synthesis of Phenol 29 via Dehydration of Acyclic Enone 28



dichloromethane furnished enone **28** in 91% yield. At this juncture, dehydration with the Burgess reagent using the same conditions described above for macrocyclic analogue **15** gave phenol **29** in 33% yield and sulfamic acid derivative **30** (47% yield). Phenols are known to undergo sulfamic acid formation in the presence of the Burgess reagent,[16] and complete conversion of **28** to **29** and **30** required 2.4 equiv of the Burgess reagent. Treatment of **30** with KOH in aqueous ethanol afforded **29** in 68% yield.

Applying the same reaction conditions that led to the unexpected formation of **23** and **24** from **15**, to α-ketols **14** and **13** gave similar results, indicating that conformational bias within the macrocyclic framework of the α-ketols presents an alternative reaction pathway that is not observed in the acyclic α-ketol analog **28**. In both cases, the carbamoyl functionalized bent *para*-phenylenes **31** and **33** were produced in 40% and 44% yield, respectively; however, in the case of **14** more of the 5*H*-[1,2,3]-oxathiazole-2,2-dioxide-contaning heterocycle **32** was produced (48% yield, Scheme 5A). A different heterocyclic

Scheme 5. Synthesis of Carbamoyl Functionalized, Bent *para*-Phenylenes 31 and 33



[a]Isolated after step 1. **34** has the same R_f value as **33**.

byproduct, **34**, was produced during the reaction of **13** under these conditions (Scheme 5B). The lower yields obtained for **31** and **33**, compared to that of **23**, are not surprising, as the resulting *para*-phenylenes are increasingly strained, but the formation of a different heterocyclic byproduct is. The stability of **33** under these acidic conditions is noteworthy. Previously, we have reported that the unfunctionalized analogue of **33** was susceptible to a protic acid mediated rearrangement under the conditions with which **33** is generated.[10] It seems that the carbamoyl unit of **33** protects the highly strained *para*-phenylene unit (*ca.* 20 kcal/mol of strain energy) from bridgehead protonation.[17]

In conclusion, an unexpected transformation with the Burgess reagent upon attempted dehydration of a series of macrocyclic α-ketols has resulted in the synthesis of carbamoyl substituted, bent *para*-phenylene units. This outcome is attributed to conformational bias within the macrocycle framework of the α-ketol units, as an acyclic analogue succumbs to dehydration and aromatization directly. These findings represent a rare occasion where a functionalized, strained *para*-phenylene ring has been afforded from a pre-arene unit. The carbamoyl group seems to provide increased stability to the highly strained *para*-phenylene ring of **33**, which, in the absence of this functional group, was susceptible to TsOH-mediated rearrangement.[10] *N*-Aryl carbamates have been employed as directing groups in C−H functionalization and *ortho*-lithiation reactions to furnish selectively substituted aromatics. We hope to use the carbamoyl group in a similar regard to synthesize polyfunctionalized, bent *para*-phenylene units, which can be subjected to future skeletal building reactions, namely π-extension to furnish curved PAHs. Further investigation of the mechanism of this Burgess reagent-mediated reaction and reactions of macrocyclic α-ketols that lead to functionalized, bent *para*-phenylenes are ongoing in our laboratories.

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EXPERIMENTAL SECTION

General Experimental Conditions. All reactions were run in flame- or oven-dried (120 °C) glassware and cooled under a positive pressure of ultra high pure nitrogen or argon gas. All chemicals were used as received from commercial sources, unless otherwise stated. Anhydrous reaction solvents were purified and dried by passing HPLC grade solvents through activated columns of alumina (Glass Contour SDS). All solvents used for chromatographic separations were HPLC grade (hexanes, ethyl acetate, and dichloromethane). Chromatographic separations were performed using flash chromatography, as originally reported by Still and co-workers, on silica gel 60 (particle size 43−60 μm), and all chromatography conditions have been reported as diameter × height in centimeters. Reaction progress was monitored by thin layer chromatography (TLC), on glass-backed silica gel plates (pH = 7.0). TLC plates were visualized using a hand-held UV lamp (254 or 365 nm) and stained using an aqueous ceric ammonium molybdate (CAM) solution. Plates were dipped, wiped clean, and heated from the back. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at 400, 500, or 600 MHz, calibrated using residual undeuterated solvent as an internal reference ($CHCl_3$, δ 7.27 and 77.2 ppm), reported in parts per million relative to trimethylsilane (TMS, δ 0.00 ppm), and presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, ddt = doublet of doublet of triplets, bs = broad singlet, m = multiplet), coupling constants (J, Hz), and integration. X-ray diffraction was recorded on a Bruker D8 VENTURE diffractometer system. Single crystals were obtained from slow evaporation of dicholoromethane. High-resolution mass spectrometric (HRMS) data were obtained using a quadrupole time-of-flight (Q-TOF) spectrometer and electron impact (EI) or electrospray ionization (ESI). Reactions carried out above room temperature were heated using a ceramic heat block unless otherwise stated.

α-Ketol ***13***. Oxoammonium salt **11** (TEMPO-BF_4, 0.31 g, 1.3 mmol) was added to a stirred 50 °C solution of cyclohex-2-ene-1,4-diol **8** (0.30 g, 0.85 mmol) in acetonitrile (4.2 mL). After 24 h, the reaction was cooled to room temperature, poured into water (5 mL), and further diluted with dichloromethane (5 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (1.3 cm × 18 cm; 30% EtOAc/hexanes) to afford **13** as a light yellow oil (0.20 g, 67%): R_f = 0.34 (30% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39−7.38 (m, 2H), 7.31−7.28 (m, 1H), 6.95 (s, 1H), 6.90−6.89 (m, 2H), 6.88.6.86 (m, 1H), 6.59 (s, 1H), 6.42 (s, 1H), 4.25−4.14 (m, 3H), 4.13−4.05 (m, 1H), 4.04−3.94 (m, 1H), 2.63 (m, 1H), 2.40−2.36 (m, 2H), 2.22−2.03 (m, 2H), 1.77−1.67 (m, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 199.2, 165.4, 157.6, 157.5, 143.4, 141.8, 130.4, 130.2, 126.6, 119.7, 118.7, 117.1, 115.4, 113.5, 109.8, 76.8, 67.7, 66.7, 35.2, 30.6, 24.1, 22.9; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calculated for $C_{22}H_{22}O_4Na$ 373.1402; found 373.1416.

Synthesis of ***13*** *Using Oxoammonium Salt* ***12***. Oxoammonium salt **12** (TEMPO-SbF_6) (9.1 mg, 0.021 mmol) was added to a stirred 50 °C solution of cyclohex-2-ene-1,4-diol **8** (5.0 mg 0.017 mmol) in acetonitrile (0.5 mL). After 24 h, the reaction was cooled to room temperature, poured into water (1 mL), and further diluted with dichloromethane (1 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 1 mL). The combined organic extracts were washed with water (2 mL) and brine (2 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (1.3 cm × 18 cm; 30% EtOAc/hexanes) to afford **13** as a light yellow oil (4.7 mg, 94%).

α-Ketol ***14***. Oxoammonium salt **11** (TEMPO-BF_4, 50 mg, 0.21 mmol) was added to a stirred 50 °C solution of cyclohex-2-ene-1,4-diol **9** (5.0 mg, 0.14 mmol) in acetonitrile (1.1 mL). After 24 h, the reaction was cooled to room temperature, poured into water (5 mL), and further diluted with dichloromethane (5 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (1.3 cm × 18 cm; 30% EtOAc/hexanes) to afford **14** as a light yellow oil (32 mg, 62%): R_f = 0.35 (30% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34−7.30 (m, 3H) 6.99−6.96 (m, 2H), 6.84−6.82 (m, 1H), 6.80−6.78 (m, 2H), 6.54−6.53 (m, 1H), 4.21−4.15 (m, 3H), 4.10−4.06 (m, 1H), 3.81−3.77 (m, 1H), 2.86−2.82 (m, 1H), 2.54−2.51 (m, 1H), 2.44−2.40 (m, 1H), 2.21−2.16 (m, 1H), 1.96−1.92 (m, 1H), 1.72−1.52 (m, 5H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 200.1, 164.8, 158.1, 157.9, 142.6, 140.8, 130.2, 130.0, 124.8, 119.9, 119.1, 118.4, 114.3, 113.7, 112.6, 76.5, 68.3, 67.5, 34.8, 29.4, 27.4, 25.9, 20.7; HRMS (ESI-TOF) m/z: [M + Na]$^+$ calculated for $C_{23}H_{24}O_4Na$ 387.1565; found 387.1572.

Synthesis of ***14*** *Using Oxoammonium Salt* ***12***. Oxoammonium salt **12** (TEMPO-SbF_6, 15 mg, 0.040 mmol) was added to a stirred 50 °C solution of cyclohex-2-ene-1,4-diol **9** (10 mg, 0.027 mmol) in acetonitrile (1.0 mL). After 24 h, the reaction was cooled to room temperature, poured into water (2 mL), and further diluted with dichloromethane (2 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 2 mL). The combined organic extracts were washed with water (3 mL) and brine (3 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (1.3 cm × 18 cm; 30% EtOAc/hexanes) to afford **14** as a light yellow oil (7.2 mg, 73%).

α-Ketol ***15***. Oxoammonium salt **11** (TEMPO-BF_4, 120 mg, 0.53 mmol) was added to a stirred 50 °C solution of cyclohex-2-ene-1,4-diol **10** (100 mg, 0.26 mmol) in acetonitrile (1.5 mL). After 24 h, the reaction was cooled to room temperature, poured into water (15 mL), and further diluted with dichloromethane (15 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were washed with water (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (2.5 cm × 15 cm; 20% EtOAc/hexanes) to afford **15** as a light yellow solid (74 mg, 75%): R_f = 0.27 (20% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36−7.32 (m, 3H), 7.08 (d, J = 7.6 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 6.93−6.92 (m, 1H), 6.82−6.81 (m, 1H), 6.76 (s, 1H), 6.61 (s, 1H), 4.27−4.19 (m, 1H), 4.17−4.11 (m, 1H), 3.96 (s, 1H), 3.94−3.91 (m, 1H), 3.85−3.82 (m, 1H), 2.85−2.83 (m, 1H), 2.47−2.40 (m, 3H), 1.76−1.63 (m, 4H), 1.51−1.43 (m, 4H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 200.0, 164.4, 158.9, 158.1, 142.9, 140.5, 130.3, 125.2, 119.8, 118.7, 115.0, 113.3, 110.9, 76.7, 68.6, 67.7, 36.1, 28.3, 27.88, 27.86, 25.3, 24.6; HRMS (ESI-TOF) m/z: [M + H]$^+$ calculated for $C_{24}H_{27}O_4$379.1906; found 379.1909.

Synthesis of ***15*** *Using Oxoammonium Salt* ***12***. Oxoammonium salt **12** (TEMPO-SbF_6, 9.1 mg, 0.019 mmol) was added to a stirred 50 °C solution of cyclohex-2-ene-1,4-diol **10** (5.0 mg, 0.013 mmol) in acetonitrile (0.1 mL). After 24 h, the reaction was cooled to room temperature, poured into water (1 mL), and further diluted with dichloromethane (1 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 1 mL). The combined organic extracts were washed with water (2 mL) and brine (2 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (1.3 cm × 15 cm; 20% EtOAc/hexanes) to afford **15** as a light yellow solid (3.3 mg, 67%).

Diketone ***18***. PCC (0.056 g, 0.26 mmol) was added to a stirred solution of cyclohex-2-ene-1,4-diol **8** (0.050 g, 0.13 mmol) in dichloromethane (2.0 mL) at room temperature. After 12 h, the reaction was filtered through a pad of Celite and rinsed with ether (3 × 5 mL). The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (1.3 cm × 18 cm; 20% EtOAc/hexanes) to afford **18** (0.028 g, 61%): R_f = 0.36 (40% EtOAc/hexanes) and **19** (0.013g, 26%): R_f = 0.42 (40% EtOAc/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (dd, J = 7.8, 1.3 Hz,

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2H), 7.42−7.35 (m, 2H), 7.25−7.21 (m, 2H), 7.11 (ddd, J = 8.2, 2.5, 1.0 Hz, 2H), 4.22−4.17 (m, 4H), 3.09 (s, 4H), 2.00−1.93 (m, 4H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 199.8, 158.6, 137.6, 130.4, 120.9, 120.1, 115.9, 68.4, 36.2, 25.9; HRMS (ESI-TOF) m/z: ($[M + H]^+$) calculated for $C_{20}H_{21}O_4$ 325.1440, found 325.1436.

Carbamate ***23***. Burgess reagent (12 mg, 0.050 mmol) was added to a stirred solution of **15** (15 mg, 0.041 mmol) in toluene (5 mL) and heated to 80 °C. After 3 h, the reaction was cooled to room temperature, poured into water (5 mL), and diluted with 1 M HCl (5 mL). The resulting mixture was extracted with dichloromethane (3 × 5 mL), and the combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in toluene (4.5 mL) and heated to 60 °C, followed by addition of TsOH (0.015 g, 0.082 mmol). After 0.5 h, the reaction was cooled to room temperature, poured into water (5 mL), and diluted with dichloromethane (5 mL). The resulting mixture was extracted with dichloromethane (3 × 5 mL), and the combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford **23** as a white solid (11 mg, 59%) and **24** as a light yellow oil (5.2 mg, 28%): R_f = 0.48 (30% EtOAc/hexanes); ^1H NMR (600 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.42−7.38 (m, 1H), 7.37−7.33 (m, 1H), 7.27−7.24 (m, 1H), 7.22−7.14 (m, 3H), 6.89 (dd, J = 8.4, 2.6 Hz, 1H), 6.83 (dd, J = 8.3, 2.6 Hz, 1H), 6.50 (bs, 1H), 6.10 (bs, 1H), 5.83 (bs, 1H), 4.20−4.14 (m, 1H), 4.06−3.97 (m, 2H), 3.93−3.85 (m, 1H), 3.70 (s, 3H), 1.70−1.48 (m, 4H), 1.33−1,19 (m, 2H), 1.16−0.98 (m, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 157.7, 156.6, 153.9, 145.3, 144.1, 139.9, 135.8, 131.5, 130.4, 130.1, 123.3, 120.2, 118.2, 117.1, 116.9, 116.4, 115.7, 68.8, 67.8, 52.2, 27.6, 27.4, 27.2 (23 of 26 C's reported); HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_{26}H_{27}NO_4Na$ 440.1838; found 440.1822.

Heterocycle ***24***. R_f = 0.30 (30% EtOAc/hexanes); ^1H NMR (600 MHz, $CDCl_3$) δ 7.42−7.34 (m, 2H), 7.25−7.21 (m, 1H), 7.08−7.04 (m, 2H), 7.02 (d, J = 2.6 Hz, 1H), 6.96−6.93 (m, 1H), 6.89 (dd, J = 8.4, 2.5 Hz, 1H), 6.77 (s, 1H), 4.30−4.23 (m, 1H), 4.21−4.15 (m, 1H), 3.98−3.93 (m, 1H), 3.90−384 (m, 1H), 3.06 (dd, J = 20.5, 4.1 Hz, 1H), 2.78−2.72 (m, 1H), 2.57 (ddd, J = 12.4, 7.2, 5.1, 1H), 2.42−2.31 (m, 1H), 1.77−1.62 (m, 4H), 1.54−1.42 (m, 4H; $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 176.9, 165.2, 159.1, 158.4, 139.5, 136.2, 131.0, 130.6, 120.7, 118.9, 118.4, 117.5, 116.4, 113.3, 111.2, 92.5, 68.6, 67.8, 34.4, 28.4, 27.75, 27.69, 25.4, 24.7; HRMS (ESI-TOF) m/z: $[M-H]^-$ calculated for $C_{24}H_{25}NO_5S$ 438.1472; found 438.1480.

Cyclohex-2-ene-1,4-diols ***26***. VinylMgCl (0.09 mL, 0.2 mmol) was added to a stirred solution of diketone **25** (0.02 g, 0.06 mmol) in dichloromethane (1 mL) at room temperature. After 20 min, water (2 mL) and 1 M HCl (2 mL) were added and the resulting mixture was extracted with dichloromethane (3 × 2 mL). The combined organic extracts were washed with a saturated solution of sodium bicarbonate (5 mL) and brine (5 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in dichloromethane (41 mL) and stirred, followed by the addition of a Hoveyda−Grubbs second-generation catalyst (1.1 mg, 0.0017 mmol). The reaction was heated for 2 h at 40 °C, then cooled to room temperature, and concentrated under reduced pressure. The residue was purified by flash chromatography (1.3 cm × 18 cm; 20% EtOAc/hexanes) to afford **26** as a mixture of diastereomers (1.2:1 *syn*/*anti*, 14 mg, 63%).

*anti-***26**. R_f = 0.41 (40% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, J = 7.7 Hz, 2H), 7.16−7.09 (m, 4H), 6.83 (dd, J = 7.5, 1.9 Hz, 2H), 6.06 (s, 2H), 3.83 (s, 6H), 2.23−2.17 (m, 2H), 2.19−2.13 (m, 2H), 1.98−1.90 (m, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.7, 148.6, 134.2, 129.3, 117.8, 112.5, 111.3, 71.9, 55.2, 36.0; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_{20}H_{22}O_4Na$ 349.1415; found 349.1422.

*syn-***26**. R_f = 0.21 (40% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.32−7.27 (m, 2H), 7.12−7.04 (m, 4H), 6.84−6.83 (m, 2H), 6.06 (s, 2H), 3.83 (s, 6H), 2.24−2.14 (m, 4H), 1.98−1.90 (m, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 159.7, 147.8, 134.5, 129.3, 117.7, 112.9, 111.3, 72.5, 55.2, 36.2; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_{20}H_{22}O_4Na$ 349.1414; found 349.1416.

α-Ketol ***28***. Oxoammonium salt **11** (TEMPO-BF_4, 58 mg, 0.24 mmol) was added to a stirred solution of cyclohex-2-ene-1,4-diols **26** (64 mg, 0.19 mmol) in dichloromethane (20 mL) at room temperature. After 12 h, the reaction was poured into water (5 mL) and further diluted with dichloromethane (10 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with water (10 mL) and brine (15 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (1.3 cm × 18 cm; 20% EtOAc/hexanes) to afford **28** as a light yellow oil (58 mg, 91%): R_f = 0.40 (30% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, J = 8.0 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 7.13 (d, J = 8.6 Hz, 1H), 7.07−6.99 (m, 2H), 7.01−6.92 (m, 2H), 6.85 (dd, J = 8.3, 2.4 Hz, 1H), 6.71 (d, J = 2.5 Hz, 1H), 4.05 (s, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 2.84 (ddd, J = 18.3, 4.7, 2.5 Hz, 1H), 2.69 (ddd, J = 13.1, 4.3, 2.5 Hz, 1H), 2.61−2.50 (m, 1H), 2.46−2.36 (m, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 200.8, 161.4, 159.83, 159.77, 142.6, 139.2, 129.8, 129.5, 123.5, 118.6, 118.1, 115.9, 113.4, 112.0, 111.8, 76.6, 55.3, 55.2, 36.2, 26.9; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_{20}H_{20}O_4Na$ 347.1259; found 347.1269.

2,5-Bis(3-methoxyphenyl)phenol ***29***. Burgess reagent (17 mg, 0.071 mmol) was added to a stirred solution of **28** (20 mg, 0.06 mmol) in toluene (6.5 mL) and heated to 80 °C. After 30 min, additional Burgess reagent (17 mg, 0.07 mmol) was added to the stirred solution. After 2 h, the reaction was cooled to room temperature, poured into water (10 mL), and diluted with 1 M HCl (5 mL). The resulting mixture was extracted with dichloromethane (3 × 5 mL), and then the combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (1.3 cm × 18 cm; 30% EtOAc/hexanes) to afford **29** as a white solid (6.2 mg, 33%) and **30** as a tan solid (12.5 mg, 47%).

2,5-Bis(3-methoxyphenyl)phenol ***29***. R_f = 0.45 (**29**, 35% EtOAc/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (t, J = 7.9 Hz, 1H), 7.38 (t, J = 7.9 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.26−7.22 (m, 3H), 7.17 (s, 1H), 7.10 (d, J = 8.1 Hz, 1H), 7.04 (s, 1H), 6.97 (dd, J = 8.4, 2.5 Hz, 1H), 6.93 (dd, J = 8.3, 2.4 Hz, 1H), 5.40 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 160.4, 160.0, 152.7, 142.3, 142.0, 138.1, 130.5, 130.4, 129.8, 127.0, 121.1, 119.65, 119.56, 114.48, 114.46, 113.7, 113.1, 112.7, 55.37, 55.33; HRMS (EI-TOF) m/z: $[M^+]$ calculated for $C_{20}H_{18}O_3$ 306.1255; found 306.1283.

p-Terphenyl ***30***. R_f = 0.27 (5% MeOH/EtOAc); ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.63 (d, J = 7.9 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.43−7.35 (m, 2H), 7.21 (d, J = 7.7 Hz, 1H), 7.16−7.08 (m, 3H), 6.95 (d, J = 8.3 Hz, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.60 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 160.1, 159.5, 147.1, 142.2, 140.5, 137.4, 133.7, 131.8, 130.1, 129.58, 126.50, 122.1, 121.8, 119.6, 114.7, 113.9, 113.5, 112.9, 55.38, 55.32, 54.0; HRMS (ESI-TOF) m/z: $[M - H]^-$ calculated for $C_{22}H_{20}NO_7S$ 442.0966; found 442.0968.

2,5-Bis(3-methoxyphenyl)phenol ***(29)***. Potassium hydroxide (88 mg, 1.6 mmol) was added to a stirred solution of **30** (6.8 mg, 0.02 mmol) in a 5:1 mixture of ethanol/water (0.5 mL) and heated to 70 °C. After 4 h, the reaction was cooled to room temperature, poured into water (5 mL), and diluted with dichloromethane (3 mL). The resulting mixture was extracted with dichloromethane (3 × 3 mL). Afterward, the organic extracts were combined and washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (1.0 cm × 18 cm; 35% EtOAc/hexanes) to afford **29** as a white solid (3.1 mg, 68%).

Carbamate ***31***. Burgess reagent (13 mg, 0.056 mmol) was added to a stirred solution of **14** (17 mg, 0.047 mmol) in toluene (5.0 mL) at room temperature and then heated to 80 °C. After 3 h, the reaction was cooled to room temperature, poured into water (5 mL), and diluted with 1 M HCl (10 mL). The resulting mixture was extracted with dichloromethane (3 × 10 mL), and the combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The

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residue was dissolved in toluene (4 mL) and stirred, followed by the addition of TsOH (15 mg, 0.055 mmol). The reaction was heated for 0.5 h at 60 °C, then cooled to room temperature, poured into water (5 mL), and diluted with dichloromethane (3 mL). The layers were separated, the aqueous phase was extracted with dichloromethane (3 × 5 mL), and the combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (1.3 cm × 18 cm; 30% EtOAc/hexanes) to afford **31** as a white solid (7.5 mg, 40%) and **32** (9.5 mg, 48%) as a light yellow oil: R_f = 0.46 (30% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (bs, 1H), 7.39−7.31 (m, 1H), 7.34−7.32 (m, 1H), 7.26−7.25 (m, 1H), 7.26−7.24 (m, 1H), 7.21 (d, J = 7.4 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.11 (dd, J = 7.9, 1.8 Hz, 1H), 6.81 (dd, J = 8.4, 2.7 Hz, 1H), 6.78 (dd, J = 8.4, 2.7 Hz, 1H), 6.69 (bs, 1H) 6.02 (s, 1H), 5.83 (s, 1H), 4.19−4.03 (m, 3H), 3.89−3.81 (m, 1H), 3.75 (s, 3H), 1.57−1.54 (m, 1H), 1.43−1.38 (m, 2H), 1.24−1.18 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 158.0, 156.7, 154.6, 145.7, 144.2, 140.9, 136.1, 130.8, 130.6, 130.3, 125.6, 118.1, 117.4, 117.3, 116.1, 115.7, 115.3, 69.0, 68.1, 52.5, 29.7, 26.8, 26.4, 22.6; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{25}H_{26}NO_4$ 404.1865; found 404.1862.

Heterocycle ***32***. R_f = 0.34 (30% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41−7.36 (m, 1H), 7.35−7.31 (m, 1H), 7.25−7.22 (m, 1H), 7.02 (dd, J = 8.3, 2.5 Hz, 1H), 6.99−6.96 (m, 1H), 6.94 (d, J = 2.5 Hz, 1H), 6.91 (dd, J = 8.2, 2.5 Hz, 1H), 6.84−6.81 (m, 1H), 6.80−6.77 (m, 1H), 4.26−4.16 (m, 2H), 4.13−4.08 (m, 1H), 3.84−3.77 (m, 1H), 3.03 (dd, J = 20.4, 4.9 Hz, 1H), 2.83−2.76 (m, 1H), 2.60−2.50 (m, 1H), 2.22−2.11 (m, 3H), 2.02−1.95 (m, 1H), 1.73−1.63 (m, 2H), 1.59−1.54 (m, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) 176.8, 165.5, 158.5, 158.4, 140.0, 136.0, 130.8, 130.5, 121.0, 118.9, 118.6, 117.3, 116.0, 114.6, 112.9, 92.1, 68.5, 67.6, 33.2, 29.5, 27.4, 26.0, 20.8; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_{23}H_{23}NO_5SNa$ 448.1194; found 448.1189.

Carbamate ***33***. Burgess reagent (20 mg, 0.085 mmol) was added to a stirred solution of **13** (25 mg, 0.071 mmol) in toluene (7 mL) at room temperature, and then the reaction was heated to 80 °C. After 3 h, the reaction was cooled to room temperature, poured into water (5 mL), and diluted with 1 M HCl (10 mL). The resulting mixture was extracted with dichloromethane (3 × 10 mL), and the combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (1.3 cm × 18 cm; 30% EtOAc/hexanes) to afford **34** as a light yellow oil (4.1 mg, 15%): R_f = 0.47 (30% EtOAc/hexanes) and a polar compound, R_f = 0.08 (5% MeOH/EtOAc) isolated as a colorless oil, that was directly subjected to aromatization. The residue was dissolved in toluene (4 mL) and stirred at room temperature, followed by the addition of TsOH (15 mg, 0.055 mmol). The reaction was then heated for 0.5 h at 60 °C, cooled to room temperature, poured into water (5 mL), and diluted with dichloromethane (2 mL). The layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography (1.3 cm × 18 cm; 30% EtOAc/hexanes) to afford **33** as a white solid (12 mg, 44% from **13**): R_f = 0.47 (30% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (bs, 1H), 7.38−7.35 (m, 1H), 7.34−7.30 (m, 1H), 7.26−7.19 (m, 3H), 7.15 (d, J = 8.5 Hz, 1H), 6.82 (dd, J = 8.5, 2.7 Hz, 1H), 6.77 (dd, J = 8.3, 2.7 Hz, 1H), 6.53 (bs, 1H), 5.52 (s, 1H), 5.38 (s, 1H), 4.09−4.01 (m, 1H), 3.96−3.80 (m, 3H), 3.69 (s, 3H), 1.53−1.41 (m, 4H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 157.4, 156.1, 154.0, 147.2, 144.7, 141.1, 137.6, 131.5, 130.4, 130.2, 125.3, 117.71, 117.68, 116.6, 116.5, 115.63, 115.59, 67.8, 66.9, 52.3, 22.9, 22.5; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calculated for $C_{24}H_{23}NO_4Na$ 412.1524; found 412.1503.

Heterocycle ***34***. R_f = 0.47 (30% EtOAc/hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 (t, J = 7.9 Hz, 1H), 7.30−7.27 (m, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.07−7.04 (m, 1H), 6.96 (dd, J = 8.1, 2.5 Hz, 1H), 6.91 (d, J = 7.5 Hz, 1H), 6.87 (dd, J = 8.1, 2.5 Hz, 1H), 6.76 (s, 1H), 6.61 (s, 1H), 5.52 (dd, J = 7.1, 2.7 Hz, 1H), 4.26−4.19 (m, 1H), 4.17−4.04 (m, 3H), 3.99 (s, 3H), 3.23 (dd, J = 15.5, 2.7 Hz, 1H), 2.83 (dd, J = 15.5, 7.1 Hz, 1H), 2.21−2.12 (m, 1H), 1.75−1.61 (m, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 158.0, 157.5, 148.8, 141.4, 141.1, 135.1, 130.8, 130.1, 129.8, 118.9, 118.3, 117.7, 117.3, 116.1, 115.6, 112.6, 108.8, 90.9, 68.0, 66.7, 54.9, 37.9, 24.2, 23.1; HRMS (ESI-TOF) m/z: $[M + H]^+$ calculated for $C_{24}H_{24}NO_7S$ 470.1274; found 470.1282.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02979.

^{1}H and ^{13}C NMR spectra for all new compounds, and crystallographic data (PDF)

Accession Codes

CCDC 1961283 and 2010184 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Bradley L. Merner − *Department of Chemistry and Biochemistry, Auburn University, Auburn, Alabama 36849, United States;* orcid.org/0000-0002-0543-3708; Email: blm0022@auburn.edu

Authors

Sydney N. Jackson − *Department of Chemistry and Biochemistry, Auburn University, Auburn, Alabama 36849, United States*

Andrew L. Caskey − *Department of Chemistry and Biochemistry, Auburn University, Auburn, Alabama 36849, United States*

Natasha K. Narayanan − *Department of Chemistry and Biochemistry, Auburn University, Auburn, Alabama 36849, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.0c02979

Notes

The authors declare no competing financial interest.

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