JOC Article

Neighboring Group Participation by Sulfonamido Nitrogen

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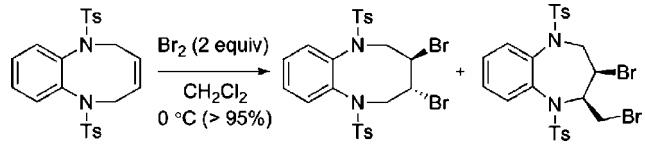
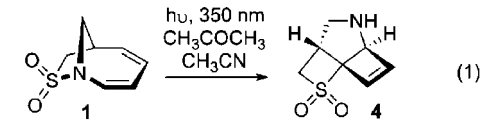


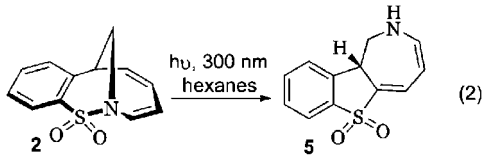
The ability of sulfonamido nitrogen to enter into neighboring group participation was established in two different reaction settings. The first was uncovered during the bromination of benzodiazocine **8** in dichloromethane at 0 °C, and the second during the base treatment of **15a** en route to allene **18**.

Introduction

Doubly unsaturated bridgehead sultams exemplified by **1**−**3** have recently received attention as informative substrates for their response to photochemical activation. The system defined by **1** has been shown to experience isomerization to **4** (eq 1) when irradiated under conditions of acetone sensitization.[1] Noteworthy here is the adoption of a reaction pathway involving unprecedented homolytic cleavage of the customarily robust N-SO_2 bond. This mechanistic option appears to hold some generality as gauged by the conversion of **2** → **5** (eq 2) upon direct irradiation.[2] However this alternative pathway is not followed by **3**, which has the sulfonyl group located at the apex position (eq 3). Instead, this dienyl sulfonamide experiences inefficient conversion to *exo*-cyclobutene **6**.[3]



(1)



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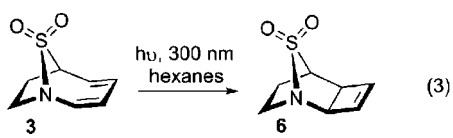
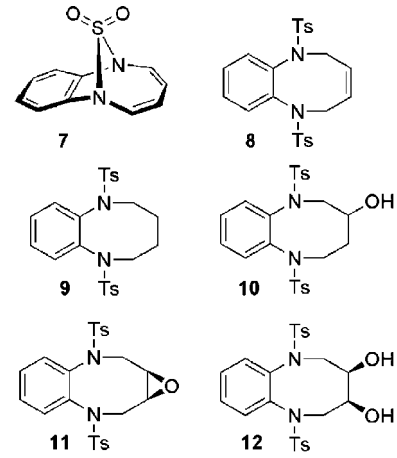


(3)

The lack of any examples of related systems having a nitrogen center at both bridgehead sites has led to an interest in acquiring **7**.[4] The development of a synthetic plan based upon the known 1,6-benzodiazocine **8**[5] was therefore initiated. Preliminary functionalization reactions involving **8** were first accorded attention. The involvement of **8** with such mild reagents as hydrogen over palladium on charcoal, the borane−dimethyl sulfide complex, *m*-chloroperbenzoic acid, and osmium tetroxide/NMO was initially probed and found to give rise to bissulfonamides **9**−**12**, respectively, in good yields. Significantly, no rearrangement of the heterocyclic framework was in evidence with any of these reagents. When recourse was instead made to bromination, however, the same straightforward behavior was not encountered. This result foreshadowed the unanticipated ability of the nitrogen atoms in **8** to engage in neighboring group participation. This and related observations constitute the subject matter of this report.



Results and Discussion

Bromination Results. The four reactions mentioned above share in common a low electrophilic demand. This fact, when coupled with a projected attenuated level of involvement

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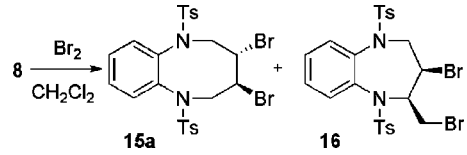
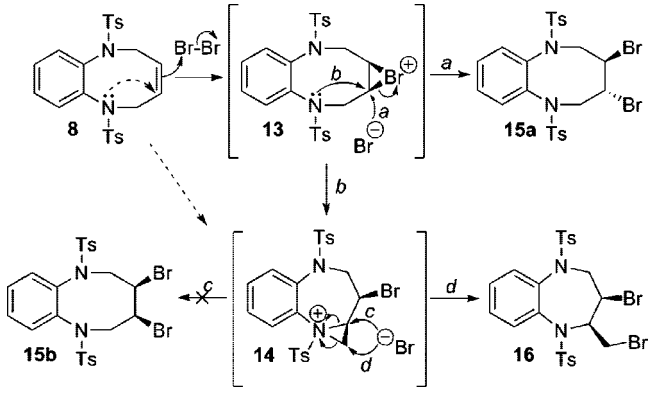
TABLE 1. Results of the Bromination of 8



entry	conditions	temp (°C)	results
1	Br_2 (2.0 equiv)/CH_2Cl_2	rt	>95% yield, 3:1 ratio of **15a**:**16**
2	Br_2 (2.0 equiv)/CH_2Cl_2	0	>95% yield, 2.7:1 ratio of **15a**:**16**
3	liquid Br_2	rt	70% yield, only **16** observed + side products
4	Br_2 (2.0 equiv)/CH_2Cl_2	−78	80% yield, 7:1 ratio of **15a**:**16** some SM remaining
5	Br_2 (2.0 equiv)/CH_2Cl_2 (1 g scale up)	−78 to 0	>95% yield, 6:1 ratio of **15a**:**16**

SCHEME 1. Proposed Mechanism for the Formation of 15a and 16



expected for the sulfonamide functionality, should be met with an absence of neighboring group involvement as has been noted. At issue is whether processes involving higher electron demand would trigger a unique capacity for nitrogen atom participation. The bromination of **8** reveals that its sulfonamide nitrogens do respond positively to the formation of bromonium ion **13** (Scheme 1).

The addition of elemental bromine to **8** dissolved in dichloromethane at 0 °C to room temperature led quantitatively to the formation of **15a** and **16** in a ratio of approximately 3 to 1 (Table 1, entries 1 and 2). X-ray crystallographic analysis of the vicinal dibromide confirmed the trans arrangement of the two halogens in a C_2-symmetric setting (see Supporting Information for ORTEP diagrams of **15a** and **16**). We postulate that **15a** arises from the classical anti dibromination of alkenes involving the precursor bromonium intermediate **13** (path *a*). In contrast, **16** is most likely derived from aziridinium ion **14** (path *b*). The latter highly strained intermediate could have been generated by way of two mechanistic routes. The first originates from **8** by nucleophilic attack of a tosyl nitrogen at an sp^2 carbon, thereby assisting electrophilic addition of bromine across the double bond (dotted path). Alternatively, stereoselective nucleophilic opening of the bromonium ion by the tosyl nitrogen may operate (path *b*). It is presently not possible to differentiate between these two pathways. The heightened levels of **15a** that materialize when the reaction temperature is lowered are consistent with the enhanced direct involvement of **13** (Table 1, entries 4 and 5).

Analysis of the two possible stereoselective aziridinium ring openings by Br^- hold interest. The comparison involves the formation of **16** (path *d*) and the *cis*-dibromide **15b** (path *c*). Although both routes seem to be reasonable, path *c* is considered to be highly disfavored as implied by the total absence of **15b** from the reaction mixture (as confirmed by TLC analysis and high field NMR of the crude products). In this light, preference is given to aziridinium ring opening at the less hindered site to give rise to **16** exclusively. The cisoid arrangement of the Br and CH_2Br functional groups in dibromide **16**, which relative configuration was corroborated by X-ray crystallography, requires the involvement of **14**.

Strikingly, **16** is the very dominant product when the bromination is performed in liquid Br_2 as the reaction medium (Table 1, entry 3). Evidently, the **13** → **14** transition is facilitated under these conditions, with collapse via path *b* materializing subsequently.

Base-Promoted Elimination Studies. As forecasted by the generic response of vicinal medium-ring dibromides to dehydrohalogenations,[6,7] all attempts to effect the conversion of **15a** to the corresponding diene with fluoride ion sources led to degradation or no indication of reaction.[4] Recourse to other bases such as *t*-BuOK, NaOH, DBU, Et_3N, or pyridine proved to be equally problematic over broad temperature ranges. Ultimately uncovered was the successful reaction with silazide bases in THF, most especially the sodium derivative NaHMDS (Table 2).

The first equivalent of NaHMDS was expected to result in abstraction of the proton from the most acidic bromine-substituted carbon in **15a** to generate vinyl bromide **19** (Scheme 2). This intermediate would then find it possible to experience 1,4-elimination of the NTs leaving group by involving a second deprotonation as depicted in the transformation of **19** to **20**. Quenching by a proton source would then deliver **17** whose structural features were confirmed by crystallographic means (for ORTEP diagram, see Supporting Information).

The additional data derived from **15a** indicate that the first equivalent of NaHMDS may also proceed competitively to attack the other side of the eight-membered ring with generation of the neutral 1,6-benzoadiazocine **21** (Scheme 3). The distribution of functional groups in **21** is such as to enable the operation of transannular neighboring group participation eventually leading to formation of the tricyclic ammonium intermediate **22**. A second equivalent of the base can then abstract the vinylic

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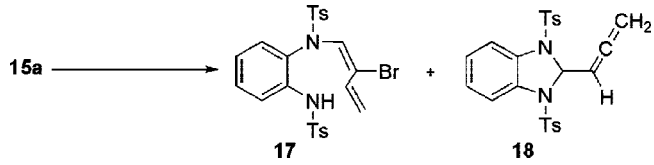
(2) Paquette, L. A.; Dura, R. D.; Fosnaugh, N.; Stepanian, M. *J. Org. Chem.* **2006**, *71*, 8438.
(3) Preston, A. J.; Gallucci, J. C.; Paquette, L. A. *J. Org. Chem.* **2006**, *91*, 6573.
(4) Proust, N. Ph.D. Thesis, The Ohio State University, 2008.
(5) (a) Grasso, S.; Zappala, M.; Chimirri, A. *Heterocycles* **1987**, *26*, 2477. (b) Proust, N.; Preston, A. J.; Paquette, L. A. *Heterocycles* **2009**, 77.
(6) King, P. F.; Paquette, L. A. *Synthesis* **1977**, 279.
(7) Dura, R. D.; Paquette, A. L. *Synthesis* **2006**, 2837.

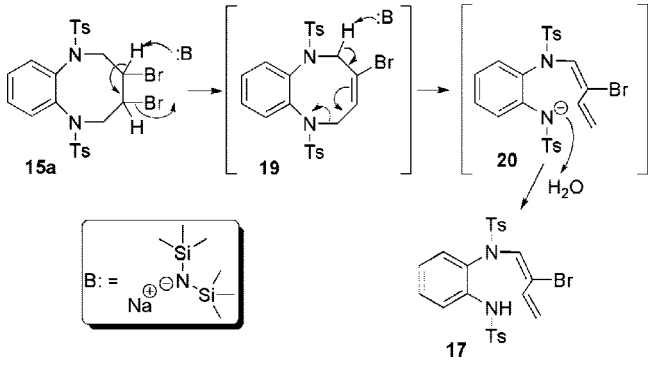
TABLE 2. Dehydrobromination of 15a[a]



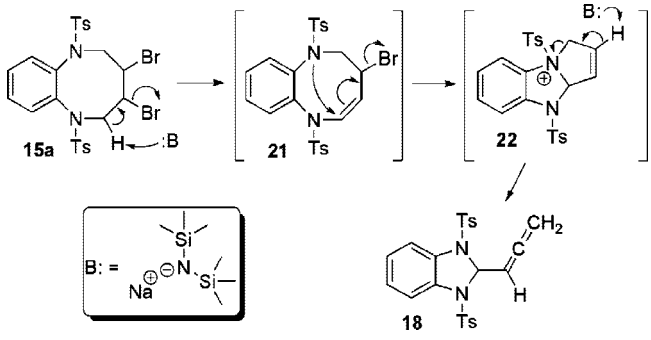
entry	base/solvent	temp (°C)	equiv of base	inverse addition[b]	addition time	product ratio **17**:**18**	total yield (%)
6	NaHMDS/THF	−78	1.0	no	6 min	2:1	43
7	NaHMDS/THF	−78	2.0	no	8 min	4:1	71
8	NaHMDS/THF	−78	2.0	yes	20 min	3:1	54
9	NaHMDS/THF	−78	3.0	no	12 min	4:1	80
10	NaHMDS/THF	−78	5.0	no	20 min	2.1:1	66
11	NaHMDS/THF	−78	2.0	no	15 s	3:1	60
12	NaHMDS/THF	−40	2.0	no	8 min	3:1	58
13	NaHMDS/THF	0	2.0	no	10 min	1.3:1	45
14	KHMDS/THF	−78	2.0	no	8 min	3:1	60
15	LHMDS/THF	−78	2.0	no	9 min	4:1	56
16	DBU/MeCN	0 to rt	2.0	no	5 min	NR	

[a] Reactions performed on 100 mg (0.6 mmol) of **15a** in 5 mL of solvent. [b] Dibromide **15a** was added to a solution of base in THF at −78 °C.

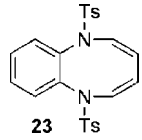
SCHEME 2. Proposed Mechanism for the Formation of 17



SCHEME 3. Proposed Mechanism for the Formation of 18



proton to generate allene **18**, which structure was also corroborated by crystallographic means; see Supporting Information. It is worth noting that under no set of conditions examined was the formation of diene **23** observed.



Conclusion

In our efforts directed toward the synthesis of the benzodiazocine ring system having sulfur at the apex position, we have discovered the latent potential of sulfonamido nitrogens for neighboring group participation in electron-demanding transformations. This capability has been displayed in two processes involving a dibromination and a dehydrobromination reaction. These unprecedented results may well open future discussions regarding the nucleophilicity and basicity of sulfonamide protected nitrogens.

Experimental Section

1,6-Bis(toluene-4-sulfonyl)-1,2,5,6-tetrahydrobenzo[*b*][1,4]diazocine (8). A solution of *N*,*N*′-ditosyl-1,2-diaminobenzene (25 g, 60.1 mmol) and *cis*-1,4-dichloro-2-butene (6.37 mL, 1.0 equiv) in acetonitrile (1500 mL) over K_2CO_3 (41.6 g, 5.0 equiv) was heated to reflux for 24 h. At the end of that period, the reaction mixture was cooled down to room temperature, filtered, and freed of solvent under reduced pressure. The resulting pale yellow solid was purified over silica gel by flash chromatography using CH_2Cl_2/EtOAc (98:2) to provide **8** as a white powder (21.1 g, 75%), mp 215−216 °C (lit.[8] mp 204 °C); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.67 (d, J = 8.4 Hz, 4H), 7.32−7.22 m, 8H), 5.61 (t, J = 4.0 Hz, 2H), 4.23 (d, J = 4.8 Hz, 4H), 2.44 (s, 6H).

1,6-Bis(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydrobenzo[*b*][1,4]-diazocine (9). In a high pressure hydrogenator were loaded **8** (10 mg, 0.02 mmol), MeOH (3 mL), CH_2Cl_2 (1 mL), and Pd/C (10% wet, 2 mg). The reactor was purged with N_2, closed, and placed under 600 psi of H_2. The reaction mixture was maintained overnight with stirring. The reaction mixture was filtered over a pad of Celite and evaporated to leave **9** as a white solid (8.4 mg, 83%), mp 222−225 °C (lit.[9] mp 219 °C); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.86 (d, J = 8.3 Hz, 4H), 7.23 (d, J = 8.3 Hz, 4H), 7.24−7.09 (m, 4H), 3.28−3.27 (m, 4H), 2.34 (s, 6H), 1.33 (m, 4H).

1,6-Bis(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydrobenzo[*b*][1,4]-diazocin-3-ol (10). To a solution of **8** (1.0 g, 2.1 mmol) and THF (50 mL) was added BH_3·THF (1M, 6.4 mL, 3.0 equiv) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 5 h. The reaction mixture was then quenched with NaOH and H_2O_2 at 0 °C and extracted with CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4, and evaporated under reduced pressure to afford **10** as an off-white foam. The alcohol was purified by flash chromatography on silica gel using CH_2Cl_2/MeOH (98:2) to provide **10** as a white solid (0.68 g, 65%), mp 200−202 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.01 (d, J = 8.25 Hz, 2H), 7.93 (d, J = 8.25 Hz, 2H), 7.44−7.29 (m, 6H), 7.27−7.23 (m, 1H), 7.21−7.18

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(m, 1H), 3.78−3.67 (m, 3H), 3.34−3.31 (m, 1H), 3.23−3.18 (m, 1H), 2.46 (s, 6H), 2.42−2.38 (m, 1H), 1.75−1.70 (m, 1H), 1.40−1.32 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.1, 144.0, 141.3, 139.0, 136.9, 136.0, 130.0, 129.9, 129.8, 129.7, 129.4, 128.8, 128.6, 128.2, 68.1, 59.3, 48.1, 31.8, 21.61, 21.59; ES HRMS *m*/*z* $(M + Na)^+$ calcd 509.1175, obsd 509.1149.

1,6-Bis(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydrobenzo[*b*][1,4]-diazocine-3,4-diol (12). In a 25 mL flask, the diazocine **8** (0.25 g, 0.53 mmol), NMO (87 mg, 0.64 mmol), THF (10 mL) and H_2O (1 mL) were added at room temperature. OsO_4 (50 g/l solution, 0.2 equiv) was then added in one portion. The reaction mixture was maintained overnight at room temperature. Five minutes after the end of the addition of OsO_4, the reaction mixture turned progressively pink to red to black. Na_2SO_3 was introduced to the mix to trap the osmium residues. The reaction mixture was filtered, the solvent was evaporated under reduced pressure, and the residue was taken back into CH_2Cl_2, washed with water and brine, dried, and evaporated. The residue was purified on silica gel using EtOAc−hexanes (2:1) to afford **12** as a white crystalline solid (0.22 g, 82%), mp ∼220 °C (decomp observed ∼200 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97 (d, J = 8.0 Hz, 4H), 7.40 (d, J = 6.0 Hz, 4H), 7.39−7.37 (m, 2H), 7.29−7.26 (m, 2H), 3.92 (dd, J = 7.6, 13.6 Hz, 2H), 3.61−3.63 (m, 2H), 3.27 (dd, J = 3.3, 13.6 Hz, 2H), 2.56 (d, J = 9.6 Hz, 2H), 2.49 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.3, 140.1, 136.0, 130.1, 129.9, 128.8, 128.5, 73.4, 54.6, 21.6; ES HRMS *m*/*z* $(M + Na)^+$ calcd 525.1124, obsd 525.1125.

3,4-Dibromo-1,6-bis(toluene-4-sulfonyl)-1,2,3,4,5,6-hexahydrobenzo[*b*][1,4]diazocine (15a) and 3-Bromo-2-bromomethyl-1,5-bis(toluene-4-sulfonyl)-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepine (16). In a 50 mL flask, **8** (1.0 g, 2.14 mmol) and CH_2Cl_2 (20 mL) were loaded at room temperature. The resulting mixture was cooled to −78 °C in an acetone/dry ice bath, and then bromine (2.0 equiv) was added dropwise. The reaction mixture was slowly warmed and maintained at 0 °C for 1 h. Saturated aqueous $NaHSO_3$ solution was added to quench the excess bromine, CH_2Cl_2 and water were added, and the CH_2Cl_2 layer was separated, dried, and evaporated under reduced pressure to afford a white solid in 95% overall yield. The solid was analyzed by ^{1}H NMR and was shown to consiste of **15a** and **16** in a 6:1 ratio. The mixture could be separated on silica gel using CH_2Cl_2 as the eluent.

For **15a**: mp 222−223 °C (degradation observed ∼210 °C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.81 (d, J = 8.5 Hz, 4H), 7.37 (d, J = 8.5 Hz, 4H), 7.35−7.28 (m, 4H), 4.24 (d, J = 14.0 Hz, 2H), 4.11−4.02 (m, 4H), 2.47 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.3, 136.6, 135.7, 129.8, 129.6, 129.1, 128.4, 54.7, 51.5, 21.6; ES HRMS *m*/*z* $(M + Na)^+$ calcd 650.9417, obsd 650.9416.

For **16**: mp 225−226 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.86 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.4 Hz, 2H), 7.52−7.30 (m, 8H), 4.70−4.67 (m, 1H), 4.42−4.33 (m, 2H), 3.83 (dd, J = 2.5, 11.5 Hz, 1H), 3.07−3.02 (m, 1H), 2.51−2.48 (m, 1H), 2.46 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 144.3, 144.1, 138.8, 137.1, 136.9, 132.3, 131.0, 130.0, 129.9, 129.7, 129.5, 128.7, 128.4, 128.1, 127.9, 60.7, 48.8, 48.1, 26.7, 21.6. ES HRMS *m*/*z* $(M + Na)^+$ calcd 650.9423, obsd 650.9395.

***N*-(2-Bromobuta-1,3-dienyl)-*N*,*N*′-di(toluene-4-sulfonyl)benzene-1,2-diamine (17) and 2-Propa-1,2-dienyl-1,3-bis(toluene-4-sulfonyl)-2,3-dihydro-1*H*-benzoimidazole (18).** Into a dry 25 mL flask, dibromide **15a** (100 mg, 0.16 mmol) and THF (5 mL) were loaded at room temperature. The reaction mixture was cooled to −78 °C under N_2, and then NaHMDS (0.5 M in THF, 0.64 mL, 2.0 equiv) was added dropwise very slowly. The colorless reaction mixture was maintained at −78 °C for 2 h and quenched by the addition of 5 mL of water at −78 °C. The temporarily frozen reaction mixture was warmed until stirring was possible (0 °C), and then CH_2Cl_2 was added (30 mL). The separated aqueous layer was extracted again with 10 mL of CH_2Cl_2. The organic layers were then combined, washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to give a pale yellow foam, which was immediately taken back in the minimum amount of CH_2Cl_2 and loaded on a column of silica gel for purification using CH_2Cl_2. Compounds **17** and **18** were obtained as white crystalline solids. The overall yield was 71% with a 4:1 ratio of **17**:**18**.

For **17**: mp 120−127 °C (turned brown at 80 °C); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (s, 1H), 7.79 (d, J = 8.3 Hz, 2H), 7.64 (dd, J = 1.3, 8.3 Hz, 1H), 7.41 (d, J = 8.3 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.82 (td, J = 1.3, 8.0 Hz, 1H), 6.69 (d, J = 0.8 Hz, 1H), 6.26 (dd, J = 1.3, 8.0 Hz, 1H), 5.82−5.93 (ddd, J = 1.0, 10.5, 16.0 Hz, 1H), 5.42 (d, J = 16.0 Hz, 1H), 5.03−5.09 (dt, J = 1.3, 10.5 Hz, 1H), 2.44 (s, 3H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.5, 144.1, 136.7, 136.1, 132.3, 130.0, 129.9, 129.8, 129.7, 128.7, 128.3, 128.2, 127.7, 127.4, 124.5, 122.3, 121.0, 119.7, 21.7, 21.6; ES HRMS *m*/*z* $(M + Na)^+$ calcd 571.0162, obsd 571.0158.

For **18**: mp 115−116 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.5 (d, J = 10.8 Hz, 4H), 7.33−7.37 (m, 2H), 7.1 (d, J = 12.8 Hz, 4H), 7.01−7.05 (m, 2H), 6.41 (dt, J = 2.8, 9.2 Hz, 1H), 5.30 (q, J = 10.4 Hz, 1H), 4.92 (dd, J = 3.2, 10.4 Hz, 2H), 2.37 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.7, 144.5, 134.8, 132.1, 129.8, 127.5, 125.1, 116.0, 91.0, 79.8, 77.5, 21.7; ES HRMS *m*/*z* $(M + Na)^+$ calcd 489.0919, obsd 489.0904.

Acknowledgment. We thank The Ohio State University for partial financial support.

Supporting Information Available: Details of the X-ray crystallographic analyses of **15a**, **16**, **17** and **18** in CIF format and the ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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