

HETEROCYCLES, Vol. 90, No. 1, 2015, pp. 226 - 237. © 2015 The Japan Institute of Heterocyclic Chemistry  
Received, 18th February, 2014, Accepted, 9th May, 2014, Published online, 19th May, 2014  
DOI: 10.3987/COM-14-S(K)9

## DIVERSITY ORIENTED APPROACH TO PHENYLALANINE DERIVATIVES VIA THE DIELS–ALDER REACTION INVOLVING SULFOLENE INTERMEDIATES†

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†This paper is dedicated to Prof. Isao Kuwajima on the occasion of his 77<sup>th</sup> birthday.

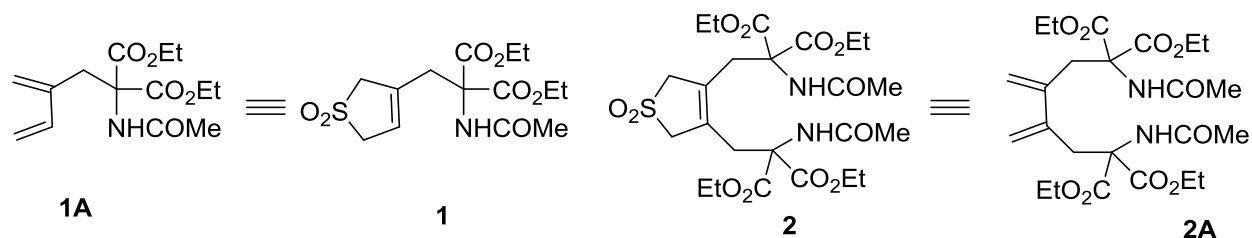
**Abstract** – We report a new synthetic approach to highly functionalized phenylalanine derivatives via sulfolenes as latent diene equivalents. Here, the Diels–Alder reaction has been used as a key step to assemble diverse unusual amino acid derivatives.

### INTRODUCTION

Unusual  $\alpha$ -amino acids (AAAs) play a critical role in modulating the stability and the activity of therapeutically useful peptides.<sup>1</sup> In this regard, development of general methods to a library of unusual AAA derivatives with varied electronic and steric properties is warranted for structure activity or conformational activity relationships.<sup>2-4</sup> In view of limited reports available for the synthesis of unusual AAA derivatives using Diels–Alder (DA) reaction as a key step, we envisioned a major program based on DA approach that can deliver a series of unusual AAA derivatives.<sup>5-7</sup> Sulfolene derivatives are known to be useful for the synthesis of natural products.<sup>8</sup> For example, alkylation of 3-sulfolenes followed by desulfonylation generate a facile stereoselective method for the synthesis of (*E*)-, (*E*)(*Z*)-, and (*E*)(*E*)-conjugated dienes.<sup>9,10</sup> Although, a number of methods are available to generate conjugated dienes based on organometallic reagents,<sup>11</sup> thermal desulfonylation of 3-sulfolenes has been a well established method for this purpose.<sup>12</sup> Here, we report a new method to generate phenylalanine derivatives using sulfolenes as a diene equivalent.

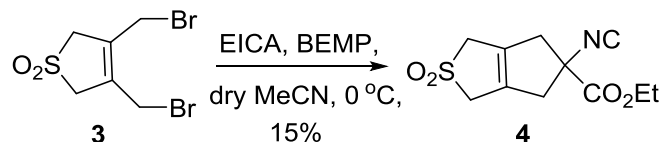
## RESULTS AND DISCUSSION

Two sulfolene based AAA derivatives **1**, and **2** were chosen as our initial targets. These sulfolene derivatives on DA reaction with a suitable dienophile followed by aromatization can deliver highly functionalized phenylalanine based AAA derivatives (Figure 1).



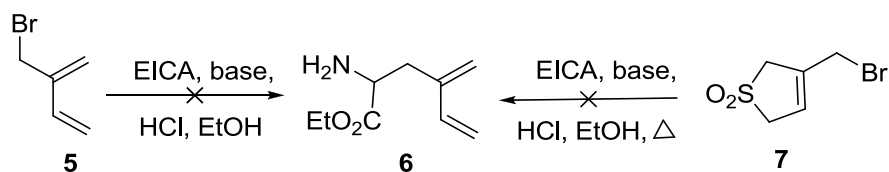
**Figure 1.** Sulfolene based AAA derivatives

We have shown that the (dibromomethyl)sulfolene **3** on coupling with ethyl isocyanoacetate (EICA) in the presence of 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) gave the isonitrile derivative **4** in low yields (Scheme 1). Efforts to improve the yields of the coupling product **4** were not successful.<sup>13</sup>



**Scheme 1.** Alkylation of dibromide **3** with ethyl isocyanoacetate

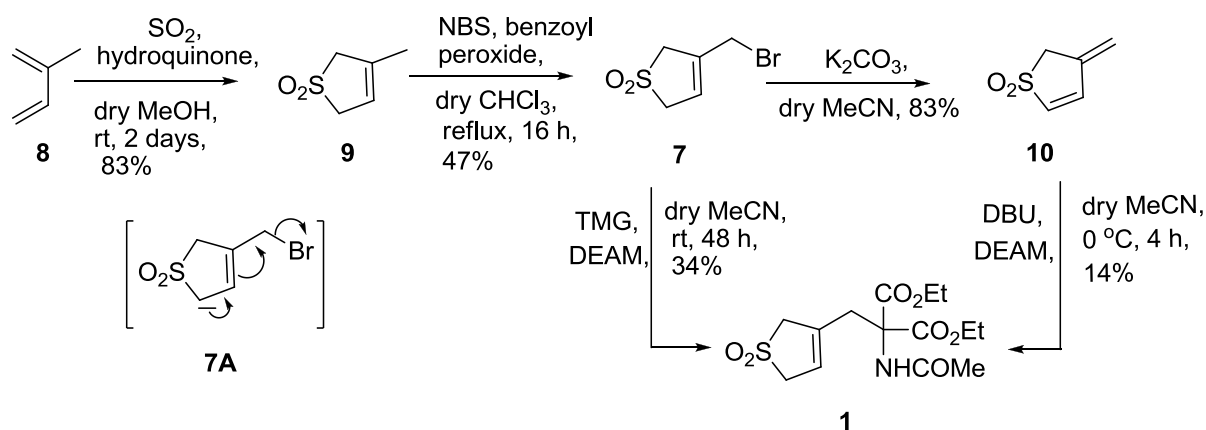
In another occasion, attempts to alkylate ethyl isocyanoacetate with 2-bromomethyl-1,3-butadiene **5** or (bromomethyl)sulfolene **7** failed to give the alkylated product, and therefore, the amino acid based diene **6** could not be realized (Scheme 2).<sup>14</sup>



**Scheme 2.** Attempted synthesis of amino acid based diene **6**

Although sulfolene involvement in DA chemistry is well established, from the two examples **3** and **7** discussed earlier it is clear that attaching amino acid fragment to sulfolene moiety is not a simple task. Therefore, the challenge is: creation of C-C bond with glycine equivalent and sulfolene moiety.


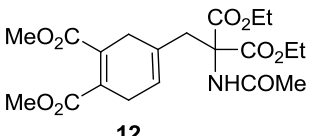
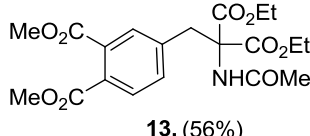
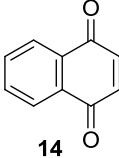
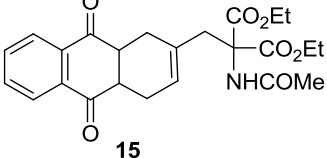
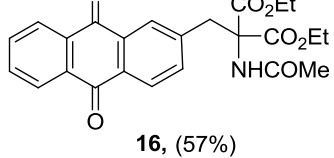
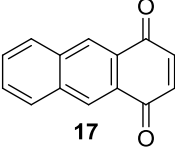
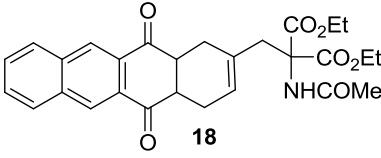
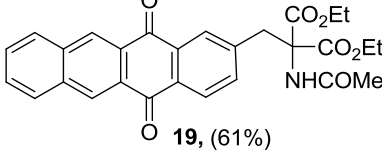
To begin with, cheletropic addition of  $\text{SO}_2$  to 2-methyl-1,3-butadiene **8** gave the known sulfolene derivative **9** in 83% yield.<sup>15</sup> Allylic bromination of the sulfolene **9** with *N*-bromosuccinimide (NBS) in dry  $\text{CHCl}_3$  in the presence of benzoyl peroxide gave the bromo compound **7** (47%), which on treatment with  $\text{K}_2\text{CO}_3$  in dry acetonitrile furnished the unsaturated compound **10** via an intermediate **7A**. Since most of the reactions of **7** with base resulted in the low yields of **10** caused to the side-reaction. Coupling of sulfone **10** with diethyl acetamidomalonate (DEAM) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the corresponding conjugate addition product **1** in 14% yield. Several other reaction conditions to obtain amino acid derivative **1** or its equivalent involving various bases and other glycine equivalents were not successful. After considerable amount of experimentation, we found that the bromo derivative **7** on treatment with DEAM in the presence of 1,1,3,3-tetramethylguanidine (TMG) in dry acetonitrile gave the required product **1** in 34% yield. During this sequence, we obtained the formation of **10** as an intermediate which is indicated by TLC. However, **10** have been used to generate **1** (Scheme 3).



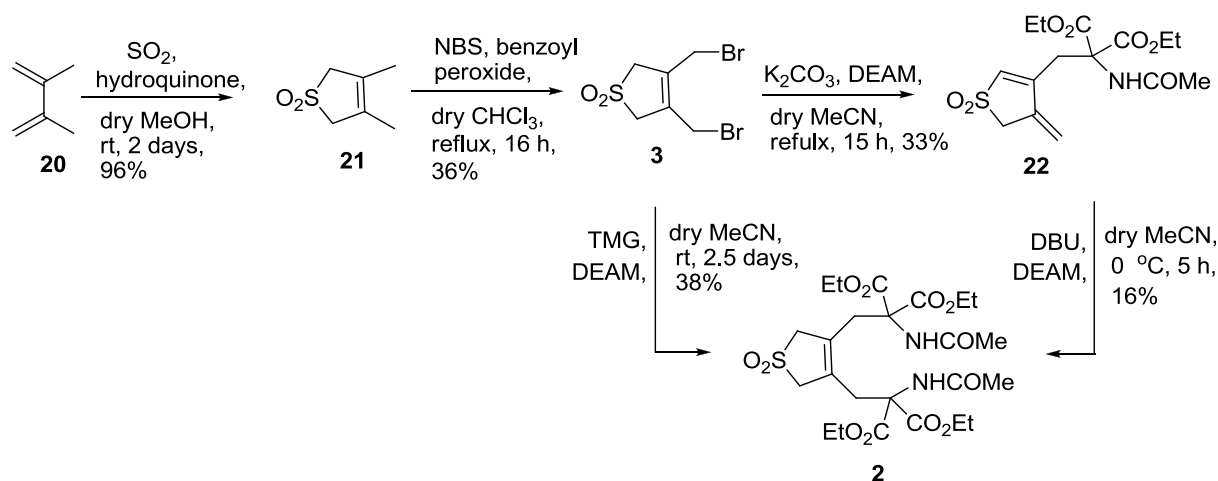
**Scheme 3.** Synthetic route to the amino acid derivative **1**

Sulfolene based amino acid derivative **1** on DA reaction under microwave conditions with dimethyl acetylenedicarboxylate (DMAD) in 1,2-dichlorobenzene at 150 °C gave **12**. However, naphthoquinone **14**, and anthraquinone **17** on DA with **1** in 1,2-dichlorobenzene at 160 °C furnished the corresponding DA adducts **15** and **18** under microwave irradiation conditions. We did not characterize the DA adducts, because some of these adducts were contaminated with partially aromatized products. Therefore, these DA adducts were directly treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to deliver the corresponding aromatized products **13**, **16**, and **19** respectively (Table 1).

**Table 1.** List of unusual AAA derivatives prepared by DA strategy via **1**

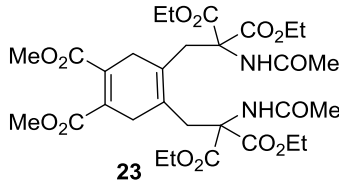
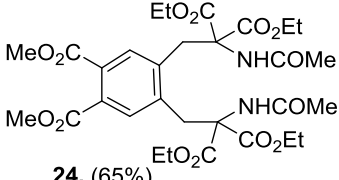
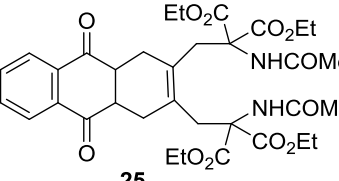
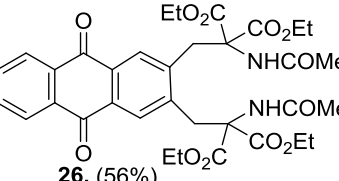
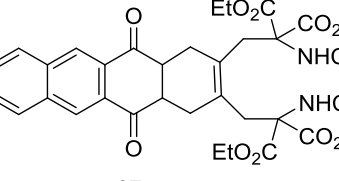
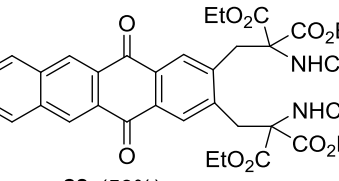
S. No	Dienophile	DA adduct	Aromatised product & Yield
1			 <b>13, (56%)</b>
2			 <b>16, (57%)</b>
3			 <b>19, (61%)</b>

Along similar lines, the reaction of 2,3-dimethyl-1,3-butadiene **20** with SO<sub>2</sub> in the presence of hydroquinone in dry methanol gave the (dimethyl)sulfolene **21** (96%) which on allylic bromination with NBS in dry CHCl<sub>3</sub> in the presence of benzoyl peroxide gave the dibromide **3** in 36% yield.<sup>16</sup> Later, treatment of the dibromide **3** with DEAM in the presence of K<sub>2</sub>CO<sub>3</sub> in dry acetonitrile gave the unsaturated compound **22** in 33% yield.

**Scheme 4.** Synthetic route to amino acid derivative **2**

Coupling of the conjugated sulfolene **22** with DEAM in the presence of DBU in dry acetonitrile gave the coupling product **2** (16%). To improve the yield of the desired bis armed amino acid derivative **2**, we had investigated an alternate protocol and found that the dibromide **3** on coupling with DEAM in the presence of TMG in dry acetonitrile gave the dialkylated product **2** in a better yield (Scheme 4).

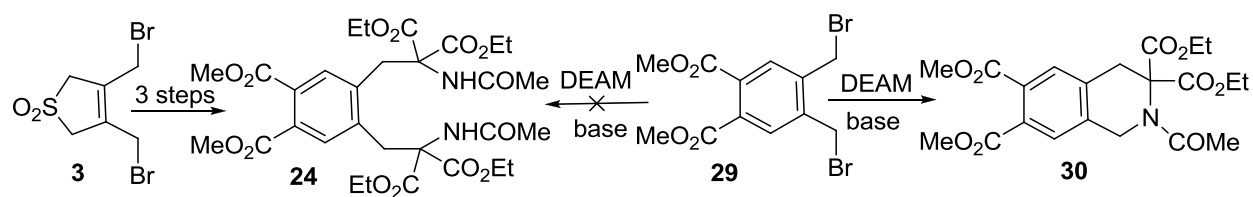
**Table 2.** List of unusual AAA derivatives prepared by DA strategy via **2**

S. No	dienophile	DA adduct	Aromatised product & Yield
1	<b>11</b>		
2	<b>14</b>		
3	<b>17</b>		

DA reaction of sulfolene derivative **2** on DA reaction under microwave conditions with DMAD **11** in 1,2-dichlorobenzene at 150 °C gave **23**, whereas naphthoquinone **14** and anthraquinone **17** on DA with **2** in 1,2-dichlorobenzene at 160 °C furnished the corresponding DA adducts **25** and **27**, these DA adducts were contaminated with aromatized products, respectively. The corresponding mixtures were subsequently treated with DDQ to obtain **24**, **26**, and **28**, respectively (Table 2).

Although the yields of the alkylation step are somewhat low, the starting materials are readily available and also inexpensive, the overall process to prepare unusual AAA derivatives is a useful addition to the existing methods to prepare these unusual AAA derivatives. Moreover, the length of the sequence involved to assemble the key building blocks **1** and **2** is short. In view of these considerations, our DA approach to unusual AAA is likely to play important role in design of peptidomimetics.

In summary, we have synthesized a series of highly functionalized unusual phenylalanines by DA reaction of sulfolenes derived from DEAM as the glycine equivalent. Various points for diversification are embedded in our strategy and thus provide opportunity to generate a library of unusual phenylalanine derivatives. By our methodology, these unusual AAAs are readily accessible from easily available starting materials such as **3** and **7** in three steps. The strategy demonstrated here can provide access to bis-armed AAA derivatives such as **24**, which are not accessible by conventional coupling strategies. For example, dibromo compound **29** on coupling with DEAM gave 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic) derivative **30**.<sup>17</sup> DA strategy can deliver bis armed AAA derivatives such as **24**.



**Scheme 5.** Preparation of Tic containing AAA derivatives

## EXPERIMENTAL

All the reactions were monitored by using TLC technique with appropriate solvents for the development. Oxygen sensitive reagents reactions were performed in dry solvents. Acetonitrile was distilled over  $\text{CaH}_2$ . Dry toluene was obtained by distillation over sodium benzophenone ketyl freshly prior to use. Reported yields are isolated yields of the products after purification. All the commercial grade reagents were used without any further purification. Generally NMR samples were made in chloroform-*d* solvent and chemical shifts were reported in  $\delta$  scale using tetramethylsilane (TMS) as an internal standard. The standard abbreviation s, d, t, q and m, refer to singlet, doublet, triplet, quartet, and multiplet, respectively. Coupling constants (*J*) were reported in Hertz. All microwave irradiated reactions were performed with a Discover SP CEM Microwave apparatus. The reactions were carried out in 10 mL glass tubes, sealed with Teflon™ septum and placed in the microwave cavity. The reaction mixture was irradiated at a required ceiling temperature using maximum power for the stipulated time; the reaction mixture temperatures were measured by an external IR sensor.

### Compound 1

**Procedure A.** To a solution of diethyl acetamidomalonate (108 mg, 0.49 mmol) in dry MeCN (5 mL) was added DBU (88 mg, 0.57 mmol) at 0 °C and was added compound **10** (50 mg, 0.38 mmol) in dry MeCN (5 mL) and the reaction mixture was stirred at rt for 4 h. At the conclusion of the reaction (TLC monitoring), MeCN was removed and the reaction mixture was quenched with cold water. The product was extracted with  $\text{CHCl}_3$  and the organic layer was dried over  $\text{MgSO}_4$ . The crude product was purified by silica gel column chromatography. Elution of the column with 40% EtOAc/petroleum ether gave the desired product (18 mg, 14%) as a colorless solid.

**Procedure B.** To a solution of diethyl acetamidomalonate (372 mg, 1.71 mmol) in MeCN (10 mL) was added 1,1,3,3-tetramethylguanidine (362 mg, 3.14 mmol) and then the compound **7** (300 mg, 1.42 mmol) dissolved in MeCN (5 mL) was added drop wise and the reaction mixture was stirred at rt for 48 h. At the conclusion of the reaction (TLC monitoring), the MeCN was removed and the reaction mixture was quenched with cold water. The product was extracted with EtOAc and the organic layer was dried over  $\text{MgSO}_4$ . The crude product was purified by silica gel column chromatography. Elution of the column with 40% EtOAc/ petroleum ether gave the desired product **1** (168 mg, 34%) as a colorless solid.

Mp 102 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ = 1.27 (t, *J* = 7.1 Hz, 6H), 2.05 (s, 3H), 3.30 (s, 2H), 3.63 (s, 2H), 3.75 (s, 2H), 4.23-4.30 (m, 4H), 5.77 (s, 1H), 6.85 (s, 1H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ = 169.8, 167.4, 133.4, 122.8, 65.8, 63.3, 58.0, 56.6, 36.5, 23.1, 14.1; IR (KBr): *v*<sub>max</sub> = 3403, 3054, 2986, 1740, 1684, 896, 740 cm<sup>-1</sup>; “accurate mass” electrospray ionization (ESI), (Q-Tof) calculated for C<sub>14</sub>H<sub>22</sub>NO<sub>7</sub>S [M+H]<sup>+</sup> 348.1111, found: 348.1119.

### Compound 13

To a solution of compound **1** (100 mg, 0.28 mmol) in 1,2-dichlorobenzene (1.3 mL) was added DMAD **11** (245 mg, 1.72 mmol) and was irradiated in a microwave oven at 150 °C for 15 min. At the conclusion of the reaction (TLC monitoring), the crude product was purified by column chromatography to give the mixture of DA adduct and aromatized product (90 mg). The adduct was dissolved in dry toluene (10 mL), added DDQ (96 mg) and then refluxed for 22 h. At the conclusion of the reaction (TLC monitoring), toluene was removed and the reaction mixture was quenched with 2% KOH solution. The product was extracted with EtOAc and the organic layer was washed with water and brine solution. The organic layer was dried over MgSO<sub>4</sub> and the crude product was purified by silica gel column chromatography. Elution of the column with 40% EtOAc/ petroleum ether gave the aromatized product **13** (68.4 mg, 56%).

Mp 98 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ = 1.30 (t, *J* = 7.1 Hz, 6H), 2.04 (s, 3H), 3.73 (s, 2H), 3.89 (s, 3H), 3.90 (s, 3H), 4.27 (q, *J* = 7.1 Hz, 4H), 6.54 (s, 1H), 7.17 (dd, *J*<sub>1</sub> = 7.9 Hz, *J*<sub>2</sub> = 1.6 Hz, 1H), 7.37 (d, *J* = 1.5 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ = 168.2, 166.6, 166.5, 165.9, 137.9, 131.3, 130.8, 129.6, 129.2, 127.8, 65.7, 61.8, 51.4, 36.2, 21.8, 12.8; IR (KBr): *v*<sub>max</sub> = 3401, 3019, 2977, 1739, 1675, 1216, 760, 669 cm<sup>-1</sup>; “accurate mass” electrospray ionization (ESI), (Q-Tof) calculated for C<sub>20</sub>H<sub>26</sub>NO<sub>9</sub> [M+H]<sup>+</sup> 424.1602, found: 424.1613.

### Compound 16

To a solution of compound **1** (30 mg, 0.08 mmol) in 1,2-dichlorobenzene (1.2 mL) was added naphthoquinone **14** (20.7 mg, 0.13 mmol) and was irradiated in a microwave oven at 160 °C for 15 min. At the conclusion of the reaction (TLC monitoring), the crude product was purified by column chromatography to give a mixture of partially aromatized DA adduct (24 mg). The adduct was dissolved in dry toluene (10 mL), added DDQ (49.3 mg) and the reaction mixture was refluxed for 24 h. At the conclusion of the reaction (TLC monitoring), toluene was removed and the reaction mixture was quenched with 2% KOH solution. The product was extracted with EtOAc and the organic layer was washed with water and brine solution. The organic layer was dried over MgSO<sub>4</sub> and the crude product was purified by silica gel column chromatography. Elution of the column with 40% EtOAc/ petroleum ether gave the aromatized product **16** (21.6 mg, 57%) as a colorless solid.

Mp 209 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ = 1.34 (t, *J* = 7.1 Hz, 6H), 2.09 (s, 3H), 3.85 (s, 2H), 4.31 (q,

$J = 7.1$  Hz, 4H), 6.57 (s, 1H), 7.45 (dd,  $J_1 = 7.9$  Hz,  $J_2 = 1.6$  Hz, 1H), 7.79-7.83 (m, 2H), 7.96 (d,  $J = 1.4$  Hz, 1H), 8.22 (d,  $J = 7.8$  Hz, 1H), 8.27-8.32 (m, 2H);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 183.1, 183.0, 169.6, 167.3, 142.6, 135.9, 134.4, 134.3, 133.6, 133.5, 133.5, 132.6, 128.4, 127.5, 127.4, 127.3, 67.1, 63.3, 38.0, 29.8, 23.2, 14.2$ ; IR (KBr):  $\nu_{\text{max}} = 3406, 3019, 2950, 1735, 1679, 758, 1216, 669$   $\text{cm}^{-1}$ ; “accurate mass” electrospray ionization (ESI), (Q-Tof) calculated for  $\text{C}_{24}\text{H}_{24}\text{NO}_7$   $[\text{M}+\text{H}]^+$  438.1547, found: 438.1549.

### Compound 19

To a solution of compound **1** (30 mg, 0.08 mmol) in 1,2-dichlorobenzene (1.2 mL) was added anthraquinone **17** (36 mg, 0.17 mmol) and was irradiated in a microwave oven at 160 °C for 15 min. At the conclusion of the reaction (TLC monitoring), the crude product was purified by column chromatography to give the mixture of DA and partially aromatized adduct (29 mg), which was dissolved in dry toluene (10 mL), added DDQ (53.4 mg) and the reaction mixture was irradiated in a microwave oven at 120 °C for 1 h. At the conclusion of the reaction (TLC monitoring), toluene was removed and quenched with 2% KOH solution. The product was extracted with EtOAc and the organic layer was washed with water and brine solution. The organic layer was dried over  $\text{MgSO}_4$  and the crude product was purified by silica gel column chromatography. Elution of the column with 50% EtOAc/ petroleum ether gave the aromatized product **19** (26 mg, 61%) as a yellow solid.

Mp 265 °C;  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 1.36$  (t,  $J = 7.1$  Hz, 6H), 2.11 (s, 3H), 3.86 (s, 2H), 4.34-4.31 (m, 4H), 6.60 (s, 1H), 7.47 (dd,  $J_1 = 7.9$  Hz,  $J_2 = 1.6$  Hz, 1H), 7.69-7.71 (m, 2H), 8.04-8.12 (m, 3H), 8.29 (d,  $J = 7.9$  Hz, 1H), 8.83 (d,  $J = 8.3$  Hz, 2H);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 183.0, 182.8, 169.7, 167.3, 142.7, 136.0, 135.3, 135.3, 134.5, 133.6, 130.3, 129.9, 129.8, 129.7, 128.7, 127.8, 67.2, 63.3, 38.1, 29.8, 23.2, 14.2$ ; IR (KBr):  $\nu_{\text{max}} 3247, 3049, 2928, 1745, 1668, 758, 702$   $\text{cm}^{-1}$ ; “accurate mass” electrospray ionization (ESI), (Q-Tof) calculated for  $\text{C}_{28}\text{H}_{25}\text{NNaO}_7$   $[\text{M}+\text{Na}]^+$  510.1523, found: 510.1519.

### Compound 22

To a solution of diethyl acetamidomalonate (360 mg, 1.65 mmol) in dry MeCN (20 mL) was added  $\text{K}_2\text{CO}_3$  (565 mg, 4.09 mmol) and refluxed for 15 min. Then compound **3** (250 mg, 0.82 mmol) was added and refluxed for 4 h. At the conclusion of the reaction (TLC monitoring), the reaction mixture was filtered through celite pad and acetonitrile was removed to get the crude compound, which was purified by silica gel column chromatography. Elution of the column with 40% EtOAc/ petroleum ether gave the desired product **22** (98 mg, 33%).

Mp 123 °C;  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta = 1.27$  (t,  $J = 7.1$  Hz, 6H), 2.03 (s, 3H), 3.55 (s, 2H), 3.91 (s, 2H), 4.19-4.31 (m, 4H), 5.36 (s, 1H), 5.59 (s, 1H), 6.41 (s, 1H), 6.84 (s, 1H);  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta = 170.1, 167.0, 145.6, 137.0, 131.5, 114.6, 65.5, 63.5, 53.9, 29.4, 23.1, 14.1$ ; IR (KBr):  $\nu_{\text{max}}$

3407, 3019, 1741, 1680, 851, 759, 669  $\text{cm}^{-1}$ ; “accurate mass” electrospray ionization (ESI), (Q-Tof) calculated for  $\text{C}_{15}\text{H}_{21}\text{NNaO}_7\text{S} [\text{M}+\text{Na}]^+$  382.0931, found: 382.0932.

### Compound 2

**Procedure A.** To a solution of diethyl acetamidomalonate (26.5 mg, 0.12 mmol) in dry MeCN (10 mL) was added DBU (20.3 mg, 0.13 mmol) at 0 °C and then added compound **22** (40 mg, 0.11 mmol) dissolved in dry MeCN drop wise and stirred the reaction mixture for 5 h. At the conclusion of the reaction (TLC monitoring), MeCN was removed and quenched with cold water. The product was extracted with EtOAc and the organic layer dried over  $\text{MgSO}_4$ . The crude product was purified by silica gel column chromatography. Elution of the column with 40% EtOAc/ petroleum ether gave the desired product **2** (10 mg, 16%) as a colorless solid.

**Procedure B.** To a solution of diethyl acetamidomalonate (428 mg, 1.97 mmol) and MeCN (10 mL) was added 1,1,3,3-tetramethylguanidine (303 mg, 2.63 mmol). Then, the compound **3** (200 mg, 0.65 mmol) dissolved in MeCN (5 mL) was added drop wise and the reaction mixture was stirred at rt for 2.5 days. At the conclusion of the reaction (TLC monitoring), MeCN was removed and quenched with cold water. The product was extracted with EtOAc and the organic layer dried over  $\text{MgSO}_4$ . The crude product was purified by silica gel column chromatography. Elution of the column with 40% EtOAc/ petroleum ether gave the desired product **2** (136 mg, 38%) as a colorless solid.

Mp 178 °C;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  = 1.27 (t,  $J$  = 7.1 Hz, 12H), 2.05 (s, 6H), 3.25 (s, 4H), 3.65 (s, 4H), 4.21-4.32 (m, 8H), 6.85 (s, 2H);  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  = 170.0, 167.3, 130.6, 65.7, 63.4, 58.6, 31.8, 23.1, 14.0; IR (KBr):  $\nu_{\text{max}}$  = 3405, 3020, 1740, 1680, 858, 758, 669  $\text{cm}^{-1}$ . “accurate mass” electrospray ionization (ESI), (Q-Tof) calculated for  $\text{C}_{24}\text{H}_{37}\text{N}_2\text{O}_{12}\text{S} [\text{M}+\text{H}]^+$  577.2067, found: 577.2078.

### Compound 24

To a solution of compound **2** (50 mg, 0.08 mmol) in 1,2-dichlorobenzene (1.2 mL) was added DMAD **11** (24.62 mg, 0.17 mmol) and was irradiated in a microwave oven at 150 °C for 15 min. At the conclusion of the reaction (TLC monitoring), crude product was purified by stirring with 20 mL of petroleum ether and kept in refrigerator for 10 h followed by decantation and reprecipitated the product with EtOAc/petroleum ether to give the mixture of DA and aromatized adducts (41 mg). The adduct was dissolved in dry toluene (10 mL), added DDQ (24.4 mg) and the reaction mixture was refluxed for 27 h. At the conclusion of the reaction (TLC monitoring), the toluene was removed and quenched with 2% KOH solution. The product was extracted with DCM and the organic layer was washed with water and brine solution. The organic layer dried over  $\text{MgSO}_4$  and the crude product was purified by silica gel column chromatography. Elution of the column with 45% EtOAc/ petroleum ether gave the aromatized product **24** (36.9 mg, 65%) as a colorless solid.

Mp 166 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ = 1.30 (t, *J* = 3.5 Hz, 12H), 2.07 (s, 6H), 3.63 (s, 4H), 3.87 (s, 6H), 4.24-4.30 (m, 8H), 6.45 (s, 2H), 7.26 (s, 2H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ = 169.8, 167.6, 167.2, 138.2, 132.2, 130.4, 66.5, 63.2, 52.8, 33.2, 23.0, 14.0; IR (KBr): *v*<sub>max</sub> 3368, 2925, 2851, 1738, 1666, 741 cm<sup>-1</sup>; “accurate mass” electrospray ionization (ESI), (Q-Tof) calculated for C<sub>30</sub>H<sub>41</sub>N<sub>2</sub>O<sub>14</sub> [M+H]<sup>+</sup> 653.2552, found: 653.2556.

### Compound 26

To a solution of compound **2** (40 mg, 0.06 mmol) in 1,2-dichlorobenzene (1.2 mL) was added naphthoquinone **14** (14.2 mg, 0.09 mmol) and was irradiated in a microwave oven at 160 °C for 20 min. At the conclusion of the reaction (TLC monitoring), the crude product was purified by column chromatography to give the mixture of DA adduct and partially aromatized adduct (36 mg). The mixture was dissolved in dry toluene (1.2 mL), added DDQ (16.4 mg) and the reaction mixture was irradiated in a microwave oven at 120 °C for 1 h. At the conclusion of the reaction (TLC monitoring), toluene was removed and quenched with 2% KOH solution. The product was extracted with EtOAc and the organic layer was washed with water and brine solution. The organic layer dried over MgSO<sub>4</sub> and the crude product was purified by silica gel column chromatography. Elution of the column with 50% EtOAc/petroleum ether gave the aromatized product **26** (25.9 mg, 56%) as a pale yellow solid.

Mp 228 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ = 1.26 (t, *J* = 7.1 Hz, 12H), 2.06 (s, 6H), 3.72 (s, 4H), 4.18-4.26 (m, 8H), 6.43 (s, 2H), 7.72 (dd, *J*<sub>1</sub> = 5.8 Hz, *J*<sub>2</sub> = 3.3 Hz, 2H), 7.84 (s, 2H), 8.19 (dd, *J*<sub>1</sub> = 5.7 Hz, *J*<sub>2</sub> = 3.3 Hz, 2H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ = 182.9, 169.9, 167.3, 141.8, 134.3, 133.6, 131.8, 130.1, 127.3, 66.7, 63.3, 33.5, 23.1, 14.0; IR (KBr): *v*<sub>max</sub> = 3379, 3054, 2851, 1749, 1673, 803, 743 cm<sup>-1</sup>; “accurate mass” electrospray ionization (ESI), (Q-Tof) calculated for C<sub>34</sub>H<sub>39</sub>N<sub>2</sub>O<sub>12</sub> [M+H]<sup>+</sup> 667.2498, found: 667.2494.

### Compound 28

To a solution of compound **2** (50 mg, 0.08 mmol) in 1,2-dichlorobenzene (1.3 mL) was added anthraquinone **17** (36 mg, 0.17 mmol) and was irradiated in a microwave oven at 160 °C for 30 min. At the conclusion of the reaction (TLC monitoring), the crude product was purified by column chromatography (60% EtOAc/petroleum ether) to give the mixture of DA adduct and partially aromatized product (45 mg). The mixture was dissolved in dry toluene (2 mL), added DDQ (50.3 mg) and the reaction mixture was irradiated in a microwave oven at 120 °C for 2 h. At the conclusion of the reaction (TLC monitoring), toluene was removed and quenched with 2% KOH solution. The product was extracted with EtOAc and the organic layer was washed with water and brine solution. The organic layer dried over MgSO<sub>4</sub> and the crude product was purified by silica gel column chromatography. Elution of the column with 60% EtOAc/petroleum ether gave the aromatized product **28** (36 mg, 58%) as a yellow

solid.

Mp decomposed at 262 °C; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ = 1.28 (t, *J* = 7 Hz, 12H), 2.09 (s, 6H), 3.74 (s, 4H), 4.20-4.27 (m, 8H), 6.45 (s, 2H), 7.64 (dd, *J*<sub>1</sub> = 3.1 Hz, *J*<sub>2</sub> = 6.2 Hz, 2H), 7.93 (s, 2H), 8.02 (dd, *J*<sub>1</sub> = 3.1 Hz, *J*<sub>2</sub> = 6.2 Hz, 2H), 8.75 (s, 2H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ = 182.7, 169.9, 167.3, 141.9, 135.3, 132.7, 130.4, 130.3, 129.9, 129.7, 66.8, 63.3, 33.6, 23.1, 14.0; IR (KBr): *v*<sub>max</sub> = 3362, 2956, 2923, 1739, 1670, 877, 762 cm<sup>-1</sup>; “accurate mass” electrospray ionization (ESI), (Q-Tof) calculated for C<sub>38</sub>H<sub>40</sub>N<sub>2</sub>NaO<sub>12</sub> [M+Na]<sup>+</sup> 739.2473, found: 739.2477.

## ACKNOWLEDGEMENTS

We thank Department of Science and Technology and Council for Scientific and Industrial Research, New Delhi for financial support. S. K. thanks DST-New Delhi for the award of a J. C. Bose fellowship.

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