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DIVERSITY ORIENTED APPROACH TO OXEPINE DERIVATIVES: FURTHER EXPANSION VIA DIELS–ALDER REACTION†

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

Abstract – Oxepine derivatives have been assembled *via* Diels–Alder (DA) reaction as a key step and the latent dienes suitable for the DA reaction have been generated in situ from the sultine derivatives, which in turn were achieved by using commercially available rongalite. The "drug like" molecules assembled here may find useful applications in medicinal as well as bioorganic chemistry.

Heterocycles containing oxygen are prevalent[1] in a number of biologically active substances. They have attracted a great deal of attention of synthetic as well as medicinal chemists. More specifically, unsaturated 7-membered oxacycle (oxepine) frameworks shows a wide range of biological properties such as ion channel blocking, antiplasmodial activity, antiviral, antipsychotic, and antifungal activities.[2] Various natural and marine natural products[3] containing oxepine motif play a vital role in biological processes. Some important natural products containing oxepine structural motif are shown in Figure 1.[4] Since, oxepine containing compounds shows a wide range of applications, several efforts have been directed towards the synthesis of these useful building blocks by different groups using diverse synthetic methods, these include: (a) Lewis-acid and base catalyzed intramolecular cyclization; (b) carbocyclization by rhodium-catalysis; (c) intramolecular acyl radical cyclization and; (d) metathesis sequences etc.[5] Although, the above methods are useful to generate oxepine derivatives, some of these methods have several drawbacks such as use of expensive catalysts, require high temperature, longer reaction time and low yields of the products. To address these problems, complimentary methods involving waste free and environmentally benign strategies are desirable. To this end, we have conceived a very simple methodology to synthesize oxepine derivatives in diversity oriented manner[6] by using DA sequence.

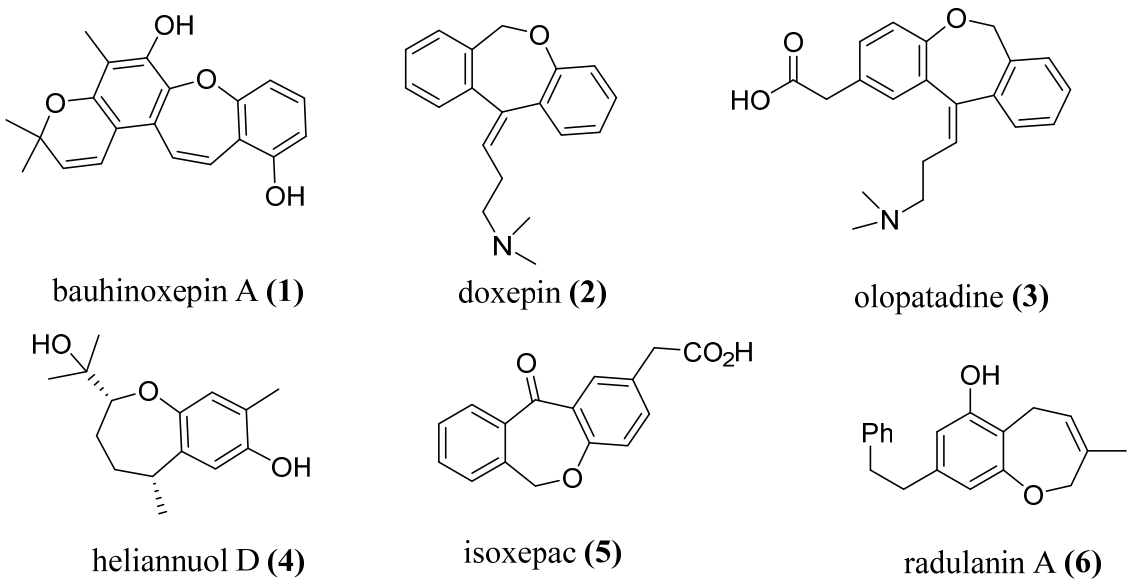
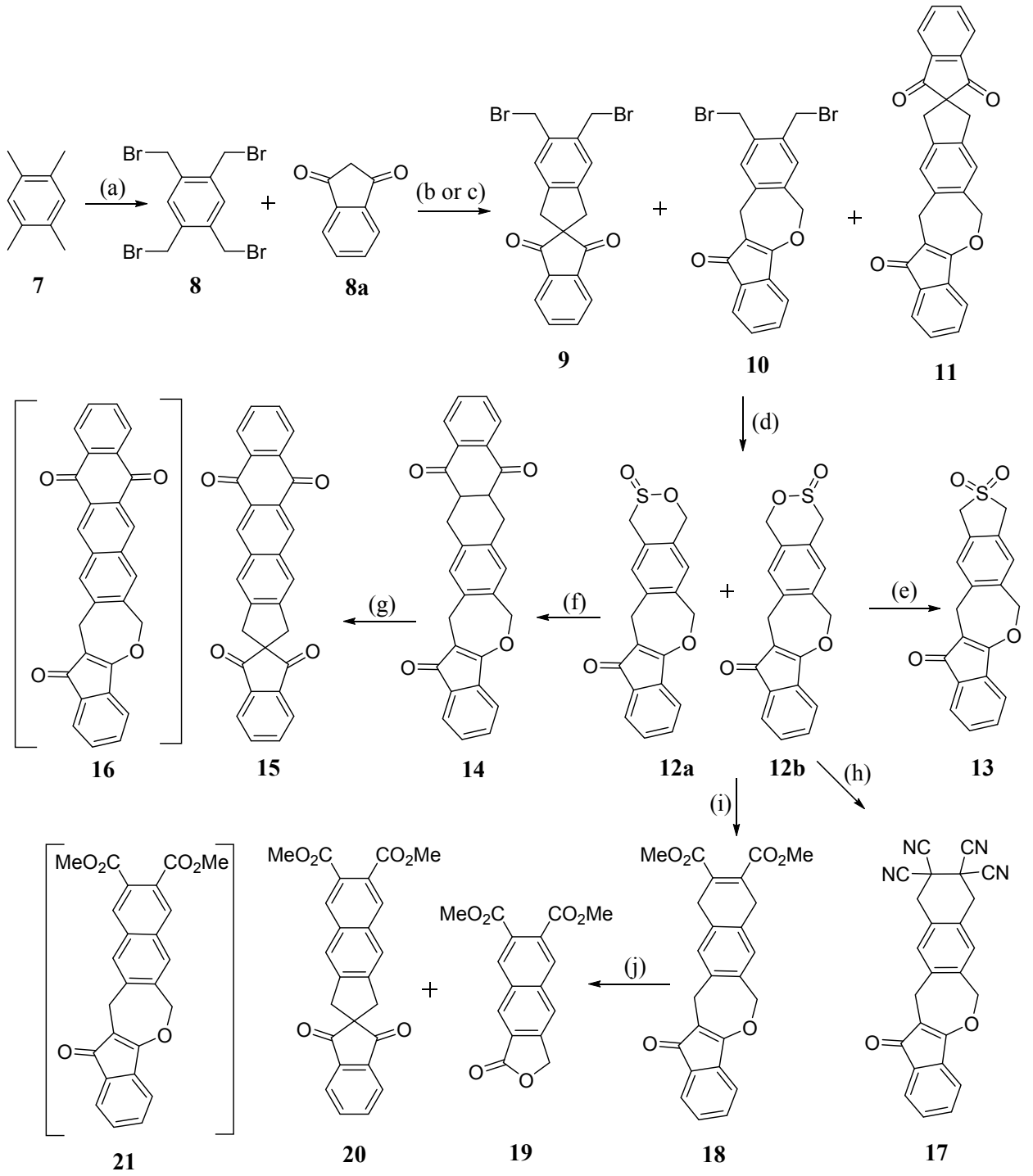
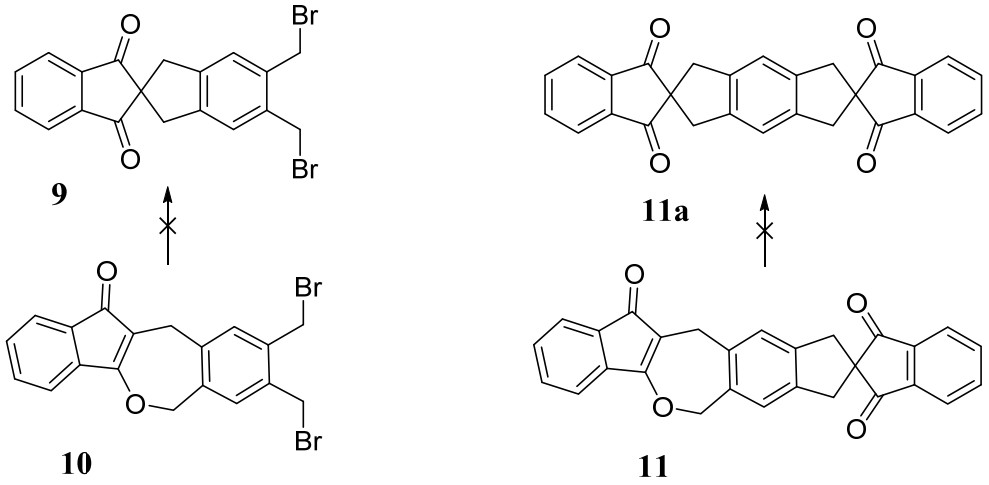


Figure 1. Biologically active substances containing oxepine motif in their structures

Our strategy towards the synthesis of oxepine derivatives began with the preparation of known 1,2,4,5-tetrakis(bromomethyl)benzene **8**.[7] Later, the tetrabromide **8** was treated with indane-1,3-dione **8a** using K_2CO_3 in MeCN to deliver the compounds **9** (8%), and **10** (30%) along with the dimer **11** (18%) (Scheme 1). On the other hand, under Cs_2CO_3 condition, we isolated the compounds **10** (39%) and **11** (14%). Having the compound **10** in hand, it was treated with rongalite in DMF to deliver the inseparable mixture of sultine derivatives **12a** and **12b** in 61% yield. Later, these derivatives **12a** and **12b** were rearranged to sulfone **13** (75%) under toluene reflux conditions. In addition, they were also treated with different dienophiles in a DA fashion to deliver the corresponding DA adducts in **14** (84%), **17** (68%) and **18** (89%) (Scheme 1). When the DA adducts **14** and **18** were treated with MnO_2/DDQ (2,3-dichloro5,6-dicyano-1,4-benzoquinone) in refluxing toluene, we did not observe the corresponding dehydrogenated products **16** and **21**. Surprisingly, the DA adduct **14** on treatment with MnO_2 in toluene under microwave conditions gave [1,3]-sigmatropic rearranged product **15** (51%) instead of expected product **16**. On the other hand, the compound **18** on treatment with MnO_2 in toluene under similar reaction conditions gave unexpected compound **19** (48%) along with the rearranged product **20** (25%) instead of product **21**. The compounds **15**, **19** and **20** were confirmed by ^1H and ^{13}C NMR spectral data and further supported by HRMS. To our surprise, the compounds **10** and **11** under microwave condition did not afford the corresponding [1,3]-sigmatropic rearranged products **9** and **11a** (Scheme 2).



Scheme 1. (a) *N*-bromosuccinimide (NBS), CH_2Cl_2, 500 W lamp, reflux, 20 h, 47%; (b) K_2CO_3, tetrabutylammonium hydrogen sulphate (TBAHS), MeCN, rt, 8 h, **9** (8%), **10** (30%), **11** (18%); (c) Cs_2CO_3, MeCN, rt, 2 h, **10** (39%), **11** (14%); (d) rongalite, tetrabutylammonium bromide (TBAB), DMF, 0 ^{o}C-rt, 6 h, 61%; (e) toluene, reflux, 15 h, (75%); (f) naphthoquinone, toluene, reflux, 24 h, **14** (84%); (g) microwave, MnO_2, toluene, 120 °C, 30 min, **15** (51%); (h) tetracyanoethylene, toluene, reflux, 24 h, **17** (68%); (i) dimethyl acetylenedicarboxylate, toluene, reflux, 24 h, **18** (89%); (j) microwave, MnO_2, toluene, 120 °C, 30 min, **19** (48%), **20** (25%).



Scheme 2. Attempts to [1,3]-sigmatropic rearrangement

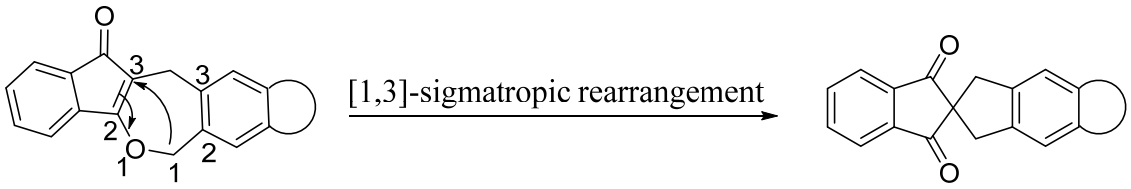
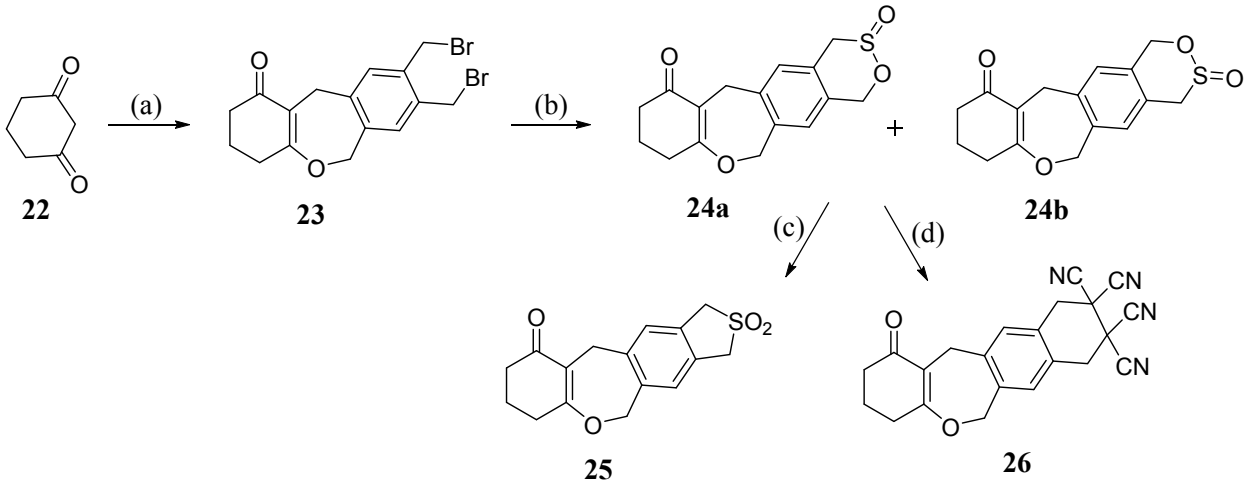
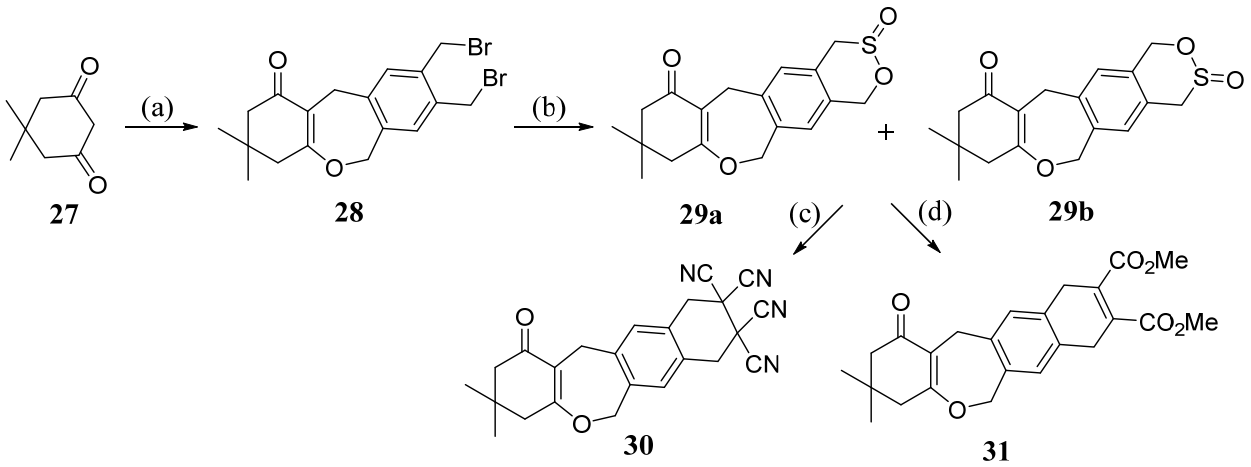


Figure 2. Plausible mechanism for the conversion of oxepine derivative into the spiro system[7]

To generalize our strategy, we have also selected commercially available cyclohexane-1,3-dione **22** and 5,5-dimethylcyclohexane-1,3-dione **27** as a coupling partners with the tetrabromo compound **8** to generate oxepine derivatives. Coupling of the dione **22** with the tetrabromide **8** using Cs_2CO_3 as a base in MeCN delivered the oxepine derivative **23** in 47% yield along with a minor amount of unidentified product. Later, the oxepine derivative **23** was transformed into the inseparable mixture of sultine derivatives **24a** and **24b** by treating with rongalite in DMF, which were further rearranged to sulfone derivative **25** (90%) under toluene reflux conditions (Scheme 3). Later, these sultine derivatives **24a** and **24b** were treated with tetracyanoethylene to deliver the cycloadduct **26** in 89% (Scheme 3). Along similar lines, treatment of 5,5-dimethylcyclohexane-1,3-dione **27** with the tetrabromide **8** using Cs_2CO_3 as a base in MeCN gave the compound **28** in 58% yield (Scheme 4). Later, the compound **28** was treated with rongalite in DMF to deliver the inseparable mixture of sultine derivatives **29a** and **29b** in 75% yield. Having the sultine derivatives **29a** and **29b** in hand, they were treated with tetracyanoethylene and dimethyl acetylenedicarboxylate (DMAD) to deliver the corresponding DA adducts **30** (95%) and **31** (72%) respectively (Scheme 4).



Scheme 3. (a) 1,2,4,5-tetrakis(bromomethyl)benzene **8**, Cs_2CO_3, MeCN, rt, 30 min, 47%; (b) rongalite, TBAB, DMF, 0 ^oC-rt, 6 h, 79%; (c) toluene, reflux, 10 h, 90%; (d) tetracyanoethylene, toluene, reflux, 12 h, 89%.



Scheme 4. (a) 1,2,4,5-tetrakis(bromomethyl)benzene **8**, Cs_2CO_3, MeCN, rt, 45 min, 58%; (b) rongalite, TBAB, DMF, 0 ^oC-rt, 4 h, 75%; (c) tetracyanoethylene, toluene, reflux, 12 h, 95%; (d) DMAD, toluene, reflux, 20 h, 72%.

In summary, we have developed a very simple and useful method for the synthesis of oxepine derivatives *via* DA reaction as a key step. Our strategy involves the use of rongalite for the sultine formation and the sultine derivatives act as latent diene equivalents in the DA sequence. These sultine derivatives can be trapped with various dienophile to generate a range of complex oxepine derivatives and also these can be rearranged to sulfone derivatives.[8] Since oxepine derivatives are valuable in medicinal chemistry, our approach is useful to generate a library of "drug like" molecules by varying the diene and dienophile components in DA reaction. Moreover, these sulfones can be used to expand the library by the alkylation of the active methylene of sulfones and also by desulfonation sequence.

EXPERIMENTAL

Commercially available reagents were used without purification and reactions involving air sensitive reagents or catalysts were performed in degassed solvents. Moisture sensitive materials were transferred by using standard syringe-septum techniques and the reactions were maintained under nitrogen atmosphere. Analytical thin layer chromatography (TLC) was performed on (7.5×2.5 cm) glass plates coated with Acme's silica gel GF 254 (containing 13% calcium sulfate as a binder) by using appropriate mixture of ethyl acetate and petroleum ether for development. Column chromatography was performed by using Acme's silica gel (100-200 mesh) with an appropriate mixture of ethyl acetate and petroleum ether. The coupling constants (*J*) are given in hertz (Hz) and chemical shifts are expressed in parts per million (ppm). The abbreviations, s, d, t, q, m, dd and td, refer to singlet, doublet, triplet, quartet, multiplet, doublet of doublet, and triplet of doublet respectively. Reported yields refer to the isolated yields after column chromatography technique. Infrared (IR) spectra were recorded on Nicolet Impact-400 FT IR spectrometer in $CHCl_3$. Proton nuclear magnetic resonance (^{1}H NMR, 400 MHz and 500 MHz) spectra and carbon nuclear magnetic resonance (^{13}C NMR, 100 MHz and 125 MHz) spectra were recorded on a Bruker spectrometer. The high-resolution mass measurements were carried out by using electrospray ionization (ESI, Q-ToF) spectrometer. Melting points were recorded on a Veggo melting point apparatus.

Preparation of compound 8: The ^{1}H and ^{13}C spectra matched with the literature reported spectral data.[9]

Synthesis of compound 10: The solution of the dione **8a** (1.5 g, 10.27 mmol), K_2CO_3 (7.08 g, 51.35 mmol) and TBAHS (870 mg, 2.57 mmol) in dry MeCN (40 mL) was stirred at rt for 15 min. Later, the tetrabromide **8** (4.62 g, 10.27 mmol) was added and the stirring was continue for 8 h at same temperature. At the conclusion of the reaction (TLC monitoring), excess amount of K_2CO_3 was filtered through sintered funnel and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (10% EtOAc-petroleum ether) to afford the spirodibromide **9 (**355 mg, 8%) as a yellow solid and continue elution with 20% EtOAc-petroleum ether gave the oxepine derivatives **10 (**1.33 g, 30%) and **11 (**770 mg, 18%) as yellow solids.

Compound 9: The ^{1}H and ^{13}C spectra matched with the literature reported spectral data.[10]

Compound 10: Mp 187-188 °C; R_f = 0.54 (silica gel, 25% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.75 (s, 2H), 4.60 (s, 2H), 4.64 (s, 2H), 5.39 (s, 2H), 7.09 (d, *J* = 7.04 Hz, 1H), 7.21-7.31 (m, 3H), 7.37-7.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.04, 29.18, 29.35, 71.97, 107.12, 118.18, 121.17, 129.81, 131.30, 131.80, 132.42, 133.08, 134.91, 135.47, 138.20, 139.56, 143.09, 173.21, 194.04; IR ($CHCl_3$): $\upsilon_{max.}$ 1621, 1696, 2925, 3021 cm^{-1}; HRMS (ESI, Q-ToF) *m/z*: calculated for $C_{19}H_{14}Br_2NaO_2$ $[M+Na]^+$ 454.9253, found: 454.9254. and other fragments are 437.1941, 443.1934, 456.9236, 457.9268, 458.9216, 459.9249.

Compound 11: Mp 174-175 °C; R_f = 0.50 (silica gel, 25% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.34 (s, 4H), 3.76 (s, 2H), 5.42 (s, 2H), 7.08-7.13 (m, 2H), 7.22-7.29 (m, 3H), 7.37-7.39 (m, 1H), 7.86-7.89 (m, 2H), 8.00-8.03 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.39, 40.38, 40.77, 58.99, 72.94, 107.96, 118.08, 118.20, 121.02, 123.92, 124.60, 126.37, 129.65, 129.75, 130.62, 132.06, 132.29, 132.40, 132.92, 136.17, 139.31, 139.83, 140.95, 141.59, 142.34, 173.45, 194.32, 202.83; IR ($CHCl_3$): $\upsilon_{max.}$ 1625, 1704, 1736, 2923, 3016 cm^{-1}; HRMS (ESI, Q-ToF) *m/z*: calculated for $C_{28}H_{18}NaO_4$ $[M+Na]^+$ 441.1097, found: 441.1097 and other fragments are 413.2663, 442.1130, 443.1159.

Synthesis of compound 12a and **12b:** To a solution of the oxepine dibromide **10** (600 mg, 1.38 mmol) in DMF (10 mL), was added TBAB (445 mg, 1.38 mmol) and rongalite (2.13 g, 13.8 mmol) at 0 °C and stirred the reaction mixture for 3 h at 0 °C and at rt for another 3 h. At the conclusion of the reaction (TLC monitoring), the compound was extracted with EtOAc and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (40% EtOAc-petroleum ether) to afford the sultine derivatives **12a** and **12b (**284 mg, 61%) as a yellow solid.

Mp 140-142 °C; R_f = 0.58 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.57 (dd, J_1 = 6.12 Hz, J_2 = 15.21 Hz, 1H), 3.75 (s, 2H), 4.32 (d, J = 15.41 Hz, 1H), 4.92-4.97 (m, 1H), 5.24-5.30 (m, 1H), 5.36-5.45 (m, 2H), 7.00-7.13 (m, 2H), 7.21-7.31 (m, 3H), 7.37 (d, J = 6.84 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.93, 55.75, 56.12, 62.45, 72.09, 107.18, 118.07 120.98, 124.47, 125.71, 127.53, 127.59, 129.69, 129.94, 131.66, 131.84, 132.12, 132.31, 133.39, 134.07, 134.69, 139.40, 141.45, 142.08, 173.09, 193.87; IR ($CHCl_3$): $\upsilon_{max.}$ 1625, 1696, 2923, 3016 cm^{-1}; HRMS (ESI, Q-ToF) *m/z*: calculated for $C_{19}H_{14}NaO_4S$ $[M+Na]^+$ 361.0505, found: 361.0505 and other fragments are 242.2845, 274.2744, 296.2562, 318.3005, 340.2825.

Synthesis of sulfone 13: The solution of sultine derivatives **12a** and **12b** (100 mg, 0.29 mmol) in toluene (20 mL) was refluxed for 15 h. At the conclusion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (50% EtOAc-petroleum ether) to afford the sulfone derivative **13** (75 mg, 75%) as a yellow solid.

Mp 157-158 °C; R_f = 0.56 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 2H), 4.36 (d, J = 3.80 Hz, 4H), 5.43 (s, 2H), 7.10 (d, J = 7.00 Hz, 1H), 7.23-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.27, 56.75, 56.91, 72.16, 107.08, 118.22, 121.23, 126.19, 128.00, 129.89, 130.15, 131.77, 132.46, 133.01, 134.67, 139.42, 142.76, 173.18, 193.90; IR ($CHCl_3$): $\upsilon_{max.}$ 1625, 1700, 2929, 3020 cm^{-1}; HRMS (ESI, Q-ToF) *m/z*: calculated for $C_{19}H_{14}NaO_4S$ $[M+Na]^+$ 361.0505, found: 361.0508 and other fragments are 353.2670, 362.0541, 363.0505.

General procedure for DA reaction: The solution of sultine derivatives and dienophiles (1.5 equiv) in toluene (20 mL) was refluxed for 10-24 h. At the conclusion of the reaction (TLC monitoring), the

solvent was removed under reduced pressure and the crude products were purified by silica gel column chromatography (appropriate mixture of EtOAc-petroleum ether) to afford the DA adducts.

Compound 14: The solution of sultine derivatives **12a** and **12b** (50 mg, 0.15 mmol) and naphthoquinone (36 mg, 0.23 mmol) in toluene (20 mL) was refluxed for 24 h. At the conclusion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (40% EtOAc-petroleum ether) to furnish the DA adduct **14** (54 mg, 84%) as a yellow solid.

Mp 170-171 °C; R_f = 0.75 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.95 (d, J = 16.29 Hz, 2H), 3.25 (d, J = 15.12 Hz, 2H), 3.56 (s, 2H), 3.63-3.73 (m, 2H), 5.28-5.40 (m, 2H), 7.00 (s, 1H), 7.06 (d, J = 7.00 Hz, 1H), 7.12 (s, 1H), 7.18-7.25 (m, 2H), 7.35 (d, J = 6.76 Hz, 1H), 7.74-7.79 (m, 2H), 8.03-8.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.94, 28.17, 28.35, 47.10, 47.13, 72.57, 107.87, 118.04, 120.97, 127.10, 127.14, 129.15, 129.61, 131.06, 131.75, 131.94, 132.08, 132.26, 133.96, 134.04, 134.64, 134.68, 134.76, 139.61, 139.77, 173.32, 194.31, 197.72; IR ($CHCl_3$): $\upsilon_{max.}$ 1626, 1696, 2928, 3020 cm^{-1}; HRMS (Q-Tof) *m/z*: calculated for $C_{29}H_{20}NaO_4$ $[M+Na]^+$ 455.1254, found: 455.1254 and other fragments are 318.3008, 330.3372, 346.3320, 362.3269, 437.1937, 456.1289.

Compound 15: The solution of the DA adduct **14** (30 mg, 0.07 mmol) and MnO_2 (61 mg, 0.70 mmol) in toluene (20 mL) was heated at 120 °C for 30 min under microwave condition. At the conclusion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (50% EtOAc-petroleum ether) to deliver the rearranged product **15** (15 mg, 51%) as a yellow solid. The ^{1}H and ^{13}C spectra matched with the literature reported spectral data.[8]

Compound 17: The solution of sultine derivatives **12a** and **12b** (50 mg, 0.15 mmol) and tetracyanoethylene (29 mg, 0.23 mmol) in toluene (20 mL) was refluxed for 24 h. At the conclusion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (50% EtOAc-petroleum ether) to deliver the DA adduct **17** (40 mg, 68%) as a yellow solid.

Mp 150-151 °C; R_f = 0.77 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 2H), 3.80 (s, 2H), 3.81 (s, 2H), 5.42 (s, 2H), 7.10-7.14 (m, 2H), 7.23-7.30 (m, 3H), 7.39 (d, J = 6.88, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.06, 35.36, 35.47, 38.42, 38.45, 71.75, 106.79, 110.46, 110.48, 118.33, 121.31, 124.03, 126.82, 129.10, 129.98, 131.00, 131.70, 132.55, 135.29, 139.35, 143.21, 173.15, 193.90; IR ($CHCl_3$): $\upsilon_{max.}$ 1628, 1701, 2306, 2986, 3054 cm^{-1}; HRMS (Q-Tof) *m/z*: calculated for $C_{25}H_{15}N_4O_2$ $[M+H]^+$ 403.1195, found: 403.1196 and other fragments are 179.0975, 214.0958, 301.1468, 401.1181, 404.1292.

Compound 18: The solution of sultine derivatives **12a** and **12b** (30 mg, 0.09 mmol) and dimethyl acetylenedicarboxylate (0.02 mL, 0.14 mmol) in toluene (20 mL) was refluxed for 24 h. At the conclusion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (60% EtOAc-petroleum ether) to deliver the DA adduct **18** (33 mg, 89%) as a yellow solid.

Mp 163-165 °C; R_f = 0.68 (silica gel, 40% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.69 (s, 4H), 3.72 (s, 2H), 3.83 (s, 6H), 5.38 (s, 2H), 7.04-7.23 (m, 3H), 7.217-7.29 (m, 2H), 7.36 (d, J = 6.92 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.96, 31.05, 31.27, 52.61, 72.49, 107.75, 118.07, 121.00, 128.08, 129.65, 130.00, 130.29, 131.90, 132.29, 132.50, 133.16, 133.24, 139.69, 140.11, 168.07, 168.15, 173.30, 194.26; IR ($CHCl_3$): $\upsilon_{max.}$ 1627, 1710, 1723, 3020 cm^{-1}; HRMS (ESI, Q-ToF) *m/z*: calculated for $C_{25}H_{20}NaO_6$ $[M+Na]^+$ 439.1152, found: 439.1154 and other fragments are 412.3400, 422.3608, 428.3347.

Compound 19: The solution of DA adduct **18** (20 mg, 0.05 mmol) and MnO_2 (44 mg, 0.50 mmol) in toluene (20 mL) was heated at 120 °C for 30 min under microwave condition. At the conclusion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (30% EtOAc-petroleum ether) to deliver the compounds **20** (5 mg, 25%) and further elution gave **19** (7 mg, 48%) as a yellow solid.

Mp 145-146 °C; R_f = 0.59 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.99 (s, 6H), 5.54 (s, 2H), 8.02 (s, 1H), 8.32 (s, 1H), 8.48 (s, 1H), 8.59 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 53.15, 53.19, 69.79, 122.14, 125.70, 126.26, 127.98, 129.55, 130.13, 131.82, 131.95, 132.23, 133.23, 136.34, 142.91, 167.35, 167.83, 170.09; IR ($CHCl_3$): $\upsilon_{max.}$ 1724, 1761, 2924, 3020 cm^{-1}; HRMS (ESI, Q-ToF) *m/z*: calculated for $C_{16}H_{12}NaO_6$ $[M+Na]^+$ 323.0526, found: 323.0527 and other fragments are 320.2037, 324.0561, 325.0595.

Compound 20: The ^{1}H and ^{13}C spectra matched with the literature reported spectral data.[8]

Synthesis of compound 23: The solution of dione **22** (498 mg, 4.44 mmol), Cs_2CO_3 (3.6 g, 11.11 mmol) in dry MeCN (20 mL) was stirred at rt for 15 min. Later, tetrabromo compound **8** (2 g, 4.44 mmol) was added and the stirring was continue for 30 min at same temperature. At the conclusion of the reaction (TLC monitoring), excess amount of Cs_2CO_3 was filtered through sintered funnel and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (25% EtOAc-petroleum ether) to afford the dibromo derivative **23 (**836 mg, 47%) as a white solid.

Mp 180-181 °C; R_f = 0.50 (silica gel, 25% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82-1.89 (m, 2H), 2.05-2.39 (m, 4H), 3.90 (s, 2H), 4.61 (s, 2H), 4.64 (s, 2H), 5.21 (s, 2H), 7.24 (s, 1H), 7.27 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.45, 27.26, 29.49, 29.58, 31.09, 36.99, 70.44, 112.26, 131.16, 131.48, 135.26, 136.17, 137.69, 143.22, 173.12, 198.29; IR ($CHCl_3$): $\upsilon_{max.}$ 1603, 1736, 2942,

3023 cm^{-1}; HRMS (ESI, Q-ToF) *m/z*: calculated for $C_{16}H_{16}Br_2NaO_2$ $[M+Na]^+$ 420.9409, found: 420.9410 and other fragments are 418.0558, 422.9388, 425.3239.

Synthesis of compounds 24a and **24b:** To a solution of dibromo derivative **23** (200 mg, 0.50 mmol) in DMF (10 mL), was added TBAB (161 mg, 0.50 mmol) and rongalite (770 mg, 5.00 mmol) at 0 ^oC and stirred the reaction mixture for 3 h at 0 ^oC and at rt for another 3 h. At the conclusion of the reaction (TLC monitoring), the compound was extracted with EtOAc. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (50% EtOAc-petroleum ether) to afford sultine derivatives **24a** and **24b (**120 mg, 79%) as a yellow sticky liquid.

R_f = 0.55 (silica gel, 50% EtOAc-petroleum ether); ^1H NMR (500 MHz, $CDCl_3$): δ 1.81-1.87 (m, 2H), 2.31-2.38 (m, 4H), 3.57 (dd, J_1 = 6.05 Hz, J_2 = 15.35 Hz, 1H), 3.91 (s, 2H), 4.33 (dd, J_1 = 6.20 Hz, J_2 = 15.50 Hz, 1H), 4.94 (dd, J_1 = 4.65 Hz, J_2 = 13.80 Hz, 1H), 5.21-5.28 (m, 3H), 7.10-7.16 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.33, 27.10, 30.94, 36.84, 55.94, 56.28, 62.59, 62.70, 70.50, 112.27, 112.28, 124.29, 125.69, 125.86, 127.01, 129.87, 130.02, 132.01, 134.32, 134.61, 135.30, 141.60, 142.24, 173.06, 198.21; IR ($CHCl_3$): $\upsilon_{max.}$ 1602, 1711, 2956, 3021 cm^{-1}; HRMS (ESI, Q-ToF) *m/z*: calculated for $C_{16}H_{16}NaO_4S$ $[M+Na]^+$ 327.0662, found: 327.0662 and other fragments are 328.0692, 329.0649.

Synthesis of sulfone 25: The solution of sultine derivatives **24a** and **24b** (30 mg, 0.09 mmol) in toluene (20 mL) was refluxed for 10 h. At the conclusion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (50% EtOAc-petroleum ether) to afford the sulfone derivative **25** (27 mg, 90%) as a yellow sticky liquid.

R_f = 0.53 (silica gel, 50% EtOAc-petroleum ether); ^1H NMR (500 MHz, $CDCl_3$): δ 1.83-1.86 (m, 2H), 2.32-2.38 (m, 4H), 3.92 (s, 2H), 4.33 (s, 2H), 4.34 (s, 2H), 5.25 (s, 2H), 7.20 (s, 1H), 7.22 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.41, 27.32, 30.98, 36.90, 56.72, 56.88, 70.54, 112.22, 126.07, 126.23, 129.86, 132.46, 135.75, 142.78, 173.09, 198.21; IR ($CHCl_3$): $\upsilon_{max.}$ 1604, 1727, 2943, 3002 cm^{-1}; HRMS (ESI, Q-ToF) *m/z*: calculated for $C_{16}H_{16}NaO_4S$ $[M+Na]^+$ 327.0662, found: 327.0662 and other fragments are 242.2861, 305.0854.

Synthesis of compound 26: The solution of sultine derivatives **24a** and **24b** (40 mg, 0.13 mmol) and tetracyanoethylene (25 mg, 0.19 mmol) in toluene (20 mL) was refluxed for 12 h. At the conclusion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (50% EtOAc-petroleum ether) to afford the DA adduct **26** (43 mg, 89%) as a yellow solid.

Mp 203-204 °C; R_f = 0.75 (silica gel, 50% EtOAc-petroleum ether); ^1H NMR (400 MHz, $CDCl_3$): δ 1.86-1.89 (m, 2H), 2.36-2.40 (m, 4H), 3.80 (s, 4H), 3.93 (s, 2H), 5.24 (s, 2H), 7.12 (s, 1H), 7.13 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.42, 27.17, 31.03, 35.49, 35.58, 36.94, 38.48, 38.51, 70.22, 110.55,

112.04, 123.77, 126.31, 129.00, 129.17, 136.43, 143.36, 173.10, 198.21; IR ($CHCl_3$): $\upsilon_{max.}$ 1642, 1725, 2953, 3019 cm^{-1}; HRMS (ESI, Q-ToF) *m/z*: calculated for $C_{22}H_{16}N_4NaO_2$ $[M+Na]^+$ 391.1165, found: 391.1166 and other fragments are 301.1419, 317.1125, 369.1353.

Synthesis of compound 28: The solution of dione **27** (622 mg, 4.44 mmol), Cs_2CO_3 (3.61 g, 11.11 mmol) in dry MeCN (20 mL) was stirred at rt for 15 min. Later, the tetrabromide **8** (2 g, 4.44 mmol) was added and the stirring was continue for 45 min at the same temperature. At the conclusion of the reaction (TLC monitoring), excess amount of Cs_2CO_3 was filtered through sintered funnel and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (20% EtOAc-petroleum ether) to afford the dibromo derivative **28 (**1.10 g, 58%) as a white solid.

Mp 224-225 °C; R_f = 0.57 (silica gel, 25% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.99 (s, 6H), 2.19 (s, 2H), 2.23 (s, 2H), 3.89 (s, 2H), 4.59 (s, 2H), 4.60 (s, 2H), 5.20 (s, 2H), 7.24 (s, 1H), 7.26 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.97, 28.32, 29.49, 29.61, 31.37, 44.62, 50.70, 70.44, 111.03, 131.20, 131.41, 135.19, 136.17, 137.66, 143.27, 171.24, 198.09; IR ($CHCl_3$): $\upsilon_{max.}$ 1670, 1728, 2963, 3018 cm^{-1}; HRMS (ESI, Q-ToF) *m/z*: calculated for $C_{18}H_{21}Br_2O_2$ $[M+H]^+$ 426.9903, found: 426.9904 and other fragments are 353.2665, 379.0850, 428.9883, 430.9799.

Synthesis of compound 29a and **29b:** To a solution of the dibromide **28** (300 mg, 0.70 mmol) in DMF (10 mL), was added TBAB (237 mg, 0.70 mmol) and rongalite (1.08 g, 70.00 mmol) at 0 ^{o}C and stirred the reaction mixture for 3 h at 0 ^{o}C and at rt for another 1 h. At the conclusion of the reaction (TLC monitoring), the compound was extracted with EtOAc and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (50% EtOAc-petroleum ether) to afford the sultine derivatives **29a** and **29b (**174 mg, 75%) as a yellow sticky liquid.

R_f = 0.57 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (s, 6H), 2.16 (s, 2H), 2.19 (s, 2H), 3.52 (dd, J_1 = 5.85 Hz, J_2 = 15.50 Hz, 1H), 3.88 (s, 2H), 4.30 (dd, J_1 = 7.40 Hz, J_2 = 15.50 Hz, 1H), 4.90 (dd, J_1 = 7.40 Hz, J_2 = 15.50 Hz, 1H), 5.12-5.24 (m, 3H), 7.07-7.12 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.91, 28.19, 28.26, 31.33, 44.57, 50.62, 56.01, 56.35, 62.58, 62.71, 70.59, 111.16, 121.95, 124.30, 125.54, 125.78, 125.89, 127.05, 128.45, 129.95, 130.03, 132.02, 134.37, 134.70, 135.41, 141.73, 142.37, 171.29, 198.11; IR ($CHCl_3$): $\upsilon_{max.}$ 1601, 1725, 2987, 3059 cm^{-1}; HRMS (ESI, Q-ToF) *m/z*: calculated for $C_{18}H_{21}O_4S$ $[M+H]^+$ 333.1155, found: 333.1155 and other fragments are 251.1430, 269.1538, 291.1357, 309.1456.

Synthesis of compound 30: The solution of sultine derivatives **29a** and **29b** (50 mg, 0.15 mmol) and tetracyanoethylene (29 mg, 0.23 mmol) in toluene (20 mL) was refluxed for 12 h. At the conclusion of the reaction (TLC monitoring), solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (40% EtOAc-petroleum ether) to afford the DA adduct **30**

(56 mg, 95%) as a white solid.

Mp 240-242 °C; R_f = 0.75 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01 (s, 6H), 2.23 (s, 2H), 2.26 (s, 2H), 3.80 (s, 4H), 3.92 (s, 2H), 5.24 (s, 2H), 7.11 (s, 1H), 7.13 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.86, 28.26, 31.36, 35.34, 35.42, 38.47, 38.50, 44.50, 50.60, 70.18, 110.56, 110.58, 110.79, 123.71, 126.25, 129.01, 129.06, 136.40, 143.30, 171.26, 198.04; IR ($CHCl_3$): $\upsilon_{max.}$ 1603, 1716, 2256, 2962, 3021 cm^{-1}; HRMS (ESI, Q-ToF) *m/z*: calculated for $C_{24}H_{21}N_4O_2$ $[M+H]^+$ 397.1659, found: 397.1662 and other fragments are 398.1691, 399.1724.

Synthesis of compound 31: The solution of sultine derivatives **29a** and **29b** (55 mg, 0.16 mmol) and dimethyl acetylenedicarboxylate (30 mg, 0.24 mmol) in toluene (20 mL) was refluxed for 20 h. At the conclusion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (50% EtOAc-petroleum ether) to afford the DA adduct **31** (49 mg, 72%) as a white semi solid.

R_f = 0.78 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.99 (s, 6H), 2.19 (s, 2H), 2.24 (s, 2H), 3.69 (s, 4H), 3.84 (s, 6H), 3.88 (s, 2H), 5.22 (s, 2H), 7.04 (s, 1H), 7.06 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.96, 28.31, 31.18, 31.38, 31.41, 44.69, 50.76, 52.57, 70.96, 111.63, 123.70, 128.06, 128.17, 130.14, 132.78, 133.21, 133.47, 133.76, 140.37, 168.18, 171.25, 198.27; IR ($CHCl_3$): $\upsilon_{max.}$ 1602, 1725, 2975, 3019 cm^{-1}; HRMS (ESI, Q-ToF) *m/z*: calculated for $C_{24}H_{26}NaO_6$ $[M+Na]^+$ 433.1622, found: 433.1626 and other fragments are 397.0539, 411.1808.

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REFERENCES

1 (a) T. Yasumoto and M. Murata, *Chem. Rev*., 1993, **93**, 1897; (b) P. J. Scheuer, *Tetrahedron*, 1994, **50**, 3; (c) M. Murata and T. Yasumoto, *Nat. Prod. Rep*., 2000, **17**, 293; (d) T. Yasumoto, *Chem. Rec*., 2001, **1**, 228; (e) H. Fuwa, *Bull. Chem. Soc. Jpn*., 2010, **83**, 1401; (f) A. Sharma, P. Appukkuttan, and E. V. Eycken, *Chem. Commun*., 2012, **48**, 1623; (g) D. J. Mack, L. A. Batory, and J. T. Njardarson, *Org. Lett*., 2012, **14**, 378; (h) P. O. Miranda, R. M. Carballo, V. S. Martin, and J. I. Padron, *Org. Lett*., 2009, **11**, 357; (i) J. O. Hoberg, *Tetrahedron*, 1998, **54**, 12631.

2 (a) V. K. Tandon, M. Kumar, A. K. Awasthi, H. O. Saxena, and G. K. Goswamy, *Bioorg, Med. Chem. Lett*., 2004, **14**, 3177; (b) J. R. Vyvyan, J. M. Oaksmith, B. W. Parks, and E. M. Peterson, *Tetrahedron Lett*., 2005, **46**, 2457; (c) H. Kishuku, M. Shindo, and K. Shishido, *Chem. Commun*.,

2003, 350; (d) T. Sugaya, N. Kato, A. Sakaguchi, and S. Tomioka, *Synthesis*, 1995, 1257; (e) L. S. Nicole, M. H. Heather, and W. P. Mark, *Tetrahedron*, 2006, **62**, 9301; (f) C. R. Reddy, P. Ramesh, N. N. Rao, and S. A. Ali, *Eur. J. Org. Chem*., 2011, 2133.

3 (a) M. Kita, O. Ohno, C. Han, and D. Uemura, *Chem. Rec*., 2010, **10**, 57; (b) J. W. Blunt, B. R. Copp, W.-P. Hu, M. H. G. Munro, P. T. Northcote, and M. R. Prinsep, *Nat. Prod. Rep*., 2008, **25**, 35; (c) T. F. Molinski, D. S. Dalisay, S. L. Lievens, and J. P. Saludes, *Nat. Rev. Drug Discovery*, 2009, **8**, 69; (d) V. J. Paul and R. Ritson-Williams, *Nat. Prod. Rep*., 2008, **25**, 662; (e) D. Skropeta, *Nat. Prod. Rep*., 2008, **25**, 1131; (f) K. Nakamura, M. Kitamura, and D. Uemura, *Heterocycles*, 2009, **78**, 1.

4 (a) M. Yoshida, K. Nakatani, and K. Shishido, *Tetrahedron*, 2009, **65**, 5702; (b) N. Ortega, V. S. Martin, and T. Martin, *J. Org. Chem*., 2010, **75**, 6660; (c) K. C. Nicolaou, E. A. Theodorakis, F. P. J. T. Rutjes, M. Sato, J. Tiebes, X.-Y. Xiao, C.-K. Hwang, M. E. Duggan, Z. Yang, E. A. Couladouros, F. Sato, J. Shin, H.-M. He, and T. Bleckman, *J. Am. Chem. Soc*., 1995, **117**, 10239; (d) D. Berger, L. E. Overman, and P. A. Renhowe, *J. Am. Chem. Soc*., 1997, **119**, 2446; (e) G. Doveston, R. Steendam, S. Jones, and R. J. K. Taylor, *Org. Lett*., 2012, **14**, 1122; (f) K. Narita, K. Nakamura, Y. Abe, and T. Katoh, *E. J. Org. Chem*., 2011, 4985; (g) J. R. Vyvyan and R. E. Looper, *Tetrahedron Lett*., 2000, **41**, 1151; (h) J. Bosch, J. Bachs, A. M. Gómez, R. Griera, M. Ecija, and M. Amat, *J. Org. Chem*., 2012, **77**, 6340; (i) M. Stefinovic and V. Snieckus, *J. Org. Chem*., 1998, **63**, 2808.

5 (a) S. Mao, D. Probst, S. Werner, J. Chen, X. Xie, and K. M. Brummond, *J. Comb. Chem*., 2008, **10**, 235; (b) J. Liu and Y. Liu, *Org. Lett*., 2012, **14**, 4742; (c) K. C. Nicolaou, R. Yu, L. Shi, Q. Cai, M. Lu, and P. Heretsch, *Org. Lett*., 2013, **15**, 1994; (d) Y. L Choi, H. S. Lim, H. J. Lim, and J.-N. Heo, *Org. Lett*., 2012, **14**, 5102; (e) Y.-Q. Zhou, N.-X. Wang, S.-B. Zhou, Z. Huang, and L. Cao, *J. Org. Chem*., 2011, **76**, 669; (f) S. Kotha, K. Mandal, A. Tiwari, and S. M. Mobin, *Chem. Eur. J*., 2006, **12**, 8024; (g) S. Kotha, V. Srinivas, and N. G. Krishna, *Heterocycles*, 2012, **86**, 1555; (h) N. L. Snyder, H. M. Haines, and M. W. Peczuh, *Tetrahedron*, 2006, **62**, 9301; (i) A. P. Krapcho, *Synthesis*, 1972, 383.

6 (a) S. Kotha and K. Lahri, *Eur. J. Org. Chem*., 2007, 1221; (b) S. Kotha and P. Khedkar, *Eur. J. Org. Chem*., 2009, 730; (c) S. Kotha, S. Misra, N. G. Krishna, and D. Nagaraju, *Heterocycles*, 2010, **80**, 847; (d) S. Kotha and S. Vittal, *Synlett*, 2011, 2329; (e) S. Kotha, S. Misra, and S.Venu, *Eur. J. Org. Chem*., 2012, 4052; (f) S. Kotha and G. T. Wagule, *J. Org. Chem*., 2012, **77**, 6314; (g) S. L. Schreiber, *Science*, 2000, **287**, 1964; (h) M. D. Burke and S. L. Schreiber, *Angew. Chem. Int. Ed.*, 2004, **43**, 46; (i) D. S. Tan, *Nat. Chem. Biol*., 2005, **1**, 74; (j) P. A. Wender, V. A. Verma, T. J. Paxton, and T. H. Pillow, *Acc. Chem. Res*., 2008, **41**, 40; (k) O. P. Pereshivko, V. A. Peshkov, D. S. Ermolatev, S. V. Hove, K. V. Hecke, L. V. Meervelt, and E. V. Van der Eycken, *Synthesis*, 2011, 1587; (l) R. J. Spandl, A. Bender, and D. R. Spring, *Org. Biomol. Chem*., 2008, **6**, 1149; (m) M. Elena and S. Manfred, *Tetrahedron*, 2005, **61**, 3393; (n) G. C. Micalizio and S. Stuart, *Angew. Chem. Int. Ed*., 2002, **41**, 152.

7 A. V. R. Rao, D. R. Reddy, and V. H. Deshpande, *J. Chem. Soc., Chem. Commun.,* 1984, 1119.

8 (a) F. J. Williams, D. H. Michael, A. L. Finocchio, and D. C. Dittmer, *J. Org. Chem*., 1988, **53***,* 5750; (b) S. Kotha and P. Khedkhar, *Chem. Rev.,* 2012, **112***,* 1650; (c) M. D. Hoey and D. C. Dittmer, *J. Org. Chem*., 1991, **56***,* 1947; (d) W.-S. Chung, W.-J. Lin, W.-D. Liu, and L.-G. Chen, *J. Chem. Soc., Chem. Commun.,* 1995, 2537.

9 H. Kawai, T. Umehara, K. Fujiwara, T. Tsuji, and T. Suzuki, *Angew. Chem*. *Int. Ed.,* 2006, **45**, 4281.

10 S. Kotha, R. Ali, and A. Tiwari, *Synlett*, 2013, **24**, 1921.