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Diversity-oriented approach to linearly fused spirocycles via strategic utilization of a [2+2+2] cycloaddition and the Diels–Alder reaction

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ABSTRACT

We have demonstrated a simple and an efficient protocol for assembling a library of linearly fused spirocycles in a diversity-oriented manner by utilizing two sequential atom-economic reactions such as a [2+2+2] cycloaddition and the Diels–Alder (DA) reaction. Herein, we have used rongalite for the formation of sultine derivatives, which are useful latent diene equivalents suitable for the DA sequence to generate a library of polycycles under mild reaction conditions.

1. Introduction

Designing new synthetic strategies that involve operationally simple, waste-free and atom-economic processes are highly attractive in preparative organic chemistry. Cycloaddition[1] reactions satisfy most of these conditions. They are useful for the construction of multiple bonds as well as stereocenters in a single step. The [2+2+2] cycloaddition process[2] is useful in terms of its applicability to diverse functional groups such as alkynes, diynes, isocyanates, isothiocyanates and imines in the synthesis of various densely functionalized cyclic molecules such as benzenes, pyrones, pyridines, 1,3-cyclohexadienes and pyridones etc.[3] The [2+2+2] cycloaddition protocol is highly atom-economic and tolerate various polar functional groups. Furthermore, it can be used for rapid construction of highly functionalized aromatic compounds.

In 1866, Berthelot first reported[4] a [2+2+2] cyclotrimerization, which is exothermic, despite a loss in entropy and the reaction occurs at high temperature but suffered with a large amount of byproducts formation. In 1949 Reppe reported[5] the first transition metal-mediated [2+2+2] cyclotrimerization, which occurred at low temperature but with fewer byproducts. In recent years, there is an increasing interest in [2+2+2] cycloaddition sequence of alkynes by using various transition metal catalysts (e.g., Wilkinson's catalyst) for the synthesis of diverse and intricate targets.[6] Several complex organic molecules have been synthesized by using a [2+2+2] and the [4+2] cycloaddition reaction. For example, the total synthesis of various natural products such as (±)-estrone, (±)-viridin, taiwanins C and E, (±)-camptothecin and (±)-strychnine etc. involve a [2+2+2] cycloaddition reaction as a key step.[7] Some interesting complex molecules synthesized by the application of a [2+2+2] cycloaddition sequence are shown in Fig. 1.[8]

Spirocycles[9] involving cyclic structure fused at a quaternary center are of great interest because of their structural implications in bioactive substances. Their attractive conformational features combined with the presence of a spiro center is responsible for their biological activity.[10] Due to the presence of an axial chirality, these compounds are useful in designing new chiral ligands and catalysts applicable in the asymmetric synthesis. Although, several methods[11] are available in the literature for the synthesis of spirocycles, simple and atom-economic protocols are still desirable. To this end, we have developed a new approach, which involve two sequential atom-economic reactions such as [2+2+2] and the [4+2] cycloadditions to generate a range of linearly fused spirocycles in a diversity-oriented fashion.[12]

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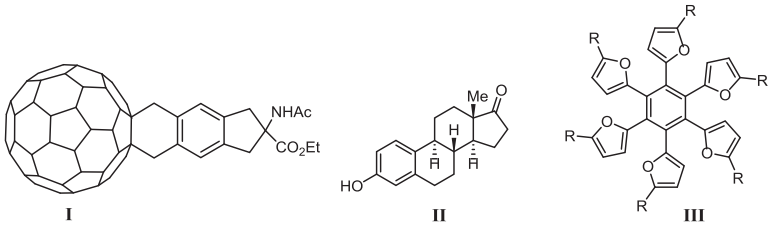


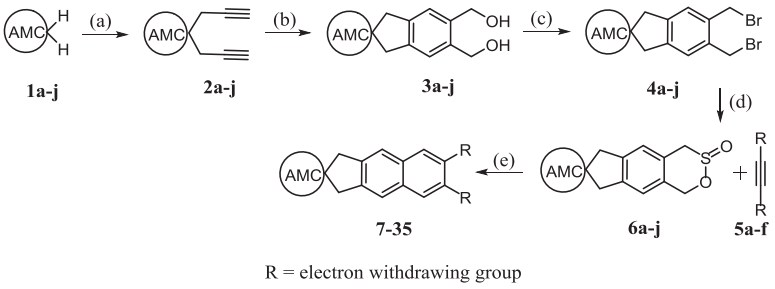
Fig. 1. Some interesting molecules assembled via a [2+2+2] cycloaddition sequence.

2. Results and discussion

Our synthetic approach to the linearly annulated spirocycles shown in Scheme 1, began with the di-propargylation of inexpensive and commercially available active methylene compounds (AMCs) **1a**–**j** (Fig. 2). The selection of the bases employed for the di-propargylation step rely on the acidity of the AMCs and in some instances, we have modified the literature conditions to improve the yields of the desired alkylation products. In our preliminary report,[9a] we have shown a simple approach for the synthesis of indane-based spirocycles by using a [2+2+2] cycloaddition and the DA reaction as key steps.[13] This strategy is simple for the construction of a range of linearly fused spirocycles. So, we extended this methodology to other interesting AMCs including fluorenes to assemble a library of linearly annulated spirocycles in a diversity-oriented fashion. Fluorenes are a unique class of blue-emitting molecular entities used in polymer light-emitting diodes (PLEDs). Moreover, they also found useful applications as sensors and their remarkable quantum efficiency have made them important in the field of optoelectronics. Recently, much attention has been paid towards the synthesis of ladder-type oligomers and polymers of fluorenes with rigid spiro linkage in their structures. Therefore, we are interested in expanding the chemical space of the fluorene derivatives by assembling these molecules via a [2+2+2] co-trimerization followed by the [4+2] cycloaddition reaction.

We started our journey with the di-propargylation of diethyl malonate **1a** to deliver the known compound **2a** in 94% yield (Table 1 and Fig. 3). The compound **2a** was further subjected to a [2+2+2] cycloaddition sequence with the aid of Wilkinson's catalyst and a catalytic amount of titanium isopropoxide in dry EtOH at refluxing temperature to afford the diol **3a** (Fig. 4), which on treatment with PBr_3 delivered the di-bromo compound **4a** in 75% yield (Table 1 and Fig. 5). Next, the di-bromo compound **4a** was reacted with rongalite in DMF to deliver the sultine derivative **6a** in 88% yield (Fig. 6). Having the sultine derivative **6a** in hand, it was treated with dienophiles (e.g., **5a** and **5b**, Fig. 7) in DA fashion to deliver the cycloadducts. The DA adduct derived from compound **6a** with dienophile **5b** on dehydrogenation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing toluene delivered the corresponding aromatized product **8** (Fig. 8).

Reagents and conditions: (a) i) aq NaOH (12.5 N), benzyltriethyammonium chloride (BTEAC), propargyl bromide, rt, 15 h, 94% (compound **2a**); ii) K_2CO_3, tetrabutylammonium hydrogen sulfate (TBAHS), MeCN, propargyl bromide, rt, 15–16 h, 68–78% (compounds **2b** and **2e**); iii) NaH, THF, propargyl bromide, rt, 10–12 h, 70–83% (compounds **2c**, **2d** and **2j**); iv) 50% aq NaOH, BTEAC, propargyl bromide, rt, 10–15 h, 65–86% (compounds



Scheme 1. General strategy to linearly fused spirocycles.

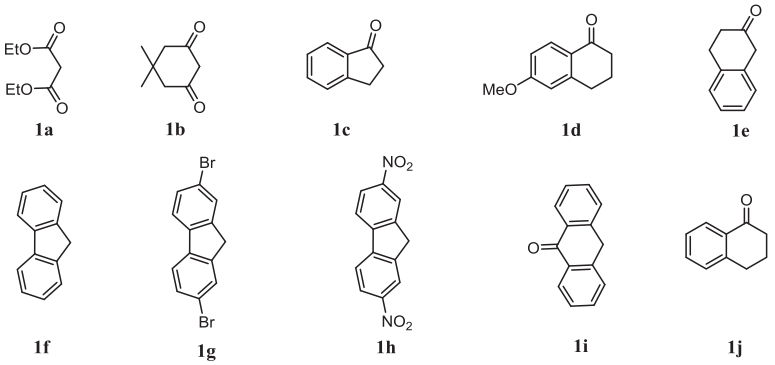


Fig. 2. Different active methylene compounds used in our strategy.

Table 1
Diverse building blocks assembled during the synthesis of spirocycles

1a–j	**2a–j** (%yields)	Time (h)	**3a–j** (%yields)	Time (h)	**4a–j** (%yields)	Time (h)	**6a–j** (%yields)	Time (h)
1a	**2a** (94)	15	**3a** (68)	12	**4a** (75)	10	**6a** (88)	3
1b	**2b** (68)	15	**3b** (NI)	16	**4b** (49)[a]	15	**6b** (77)	6
1c	**2c** (83)	12	**3c** (NI)	24	**4c** (58)[a]	14	**6c** (66)	4
1d	**2d** (70)	10	**3d** (NI)	18	**4d** (52)[a]	15	**6d** (81)	6
1e	**2e** (78)	16	**3e** (NI)	15	**4e** (60)[a]	12	**6e** (92)	5
1f	**2f** (72)	15	**3f** (NI)	24	**4f** (62)[a]	18	**6f** (82)	4
1g	**2g** (86)	10	**3g** (NI)	24	**4g** (57)[a]	14	**6g** (86)	5
1h	**2h** (65)	10	**3h** (NI)	24	**4h** (42)[a]	12	**6h** (70)	5
1i	**2i** (90)	18	**3i** (NI)	18	**4i** (65)[a]	16	**6i** (75)	6
1j	**2j** (81)	12	**3j** (NI)	20	**4j** (69)[a]	12	**6j** (78)	4

NI=Not isolated.
[a] Combined yield of two steps.

2f–**h**); v) 30% aq NaOH, BTEAC, propargyl bromide, rt, 18 h, 90% (compound **2i**); (b) i) 2-butyne-1,4-diol, $Rh(PPh_3)_3Cl$, $Ti(O^iPr)_4$, EtOH, reflux, 24 h, 68% (compound **3a**); ii) 2-butyne-1,4-diol, $Rh(PPh_3)_3Cl$, $Ti(O^iPr)_4$, EtOH, reflux, 15–24 h, not isolated (compounds **3b**–**j**); (c) i) PBr_3, CH_2Cl_2, rt, 10 h, 75% (compound **4a**); ii) PBr_3, CH_2Cl_2, rt, 12–18 h, 42–68% (compounds **4b**–**j**, combined yields of two steps); (d) rongalite, tetrabutylammonium bromide (TBAB), DMF, 0 °C-rt, 3–6 h, (**6a**–**j**, 64–92%); (e) i) dienophiles

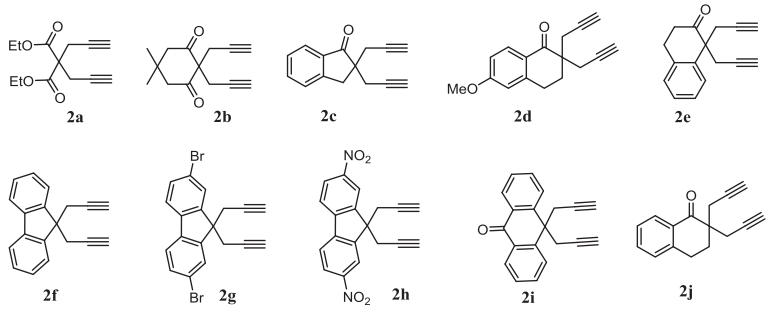


Fig. 3. Structures of di-propargylated building blocks assembled in our study.

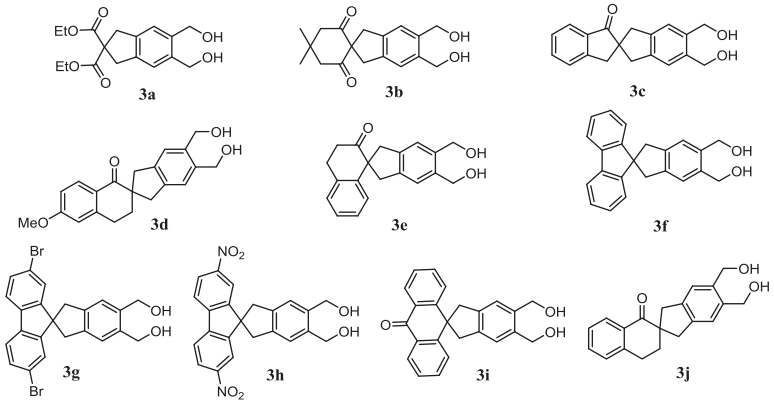


Fig. 4. List of spirodiol building blocks.

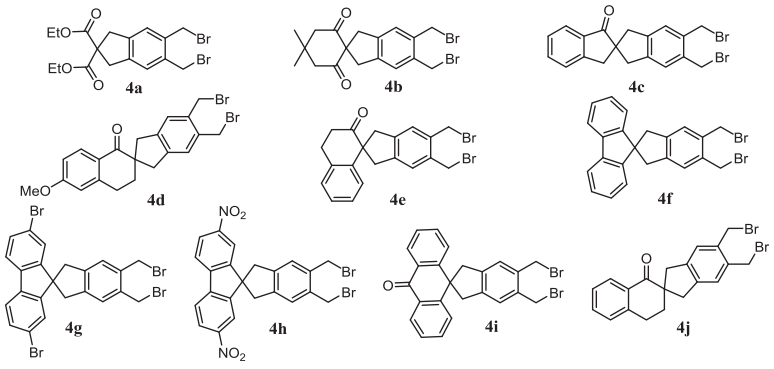


Fig. 5. Diverse di-bromo building blocks assembled in our strategy.

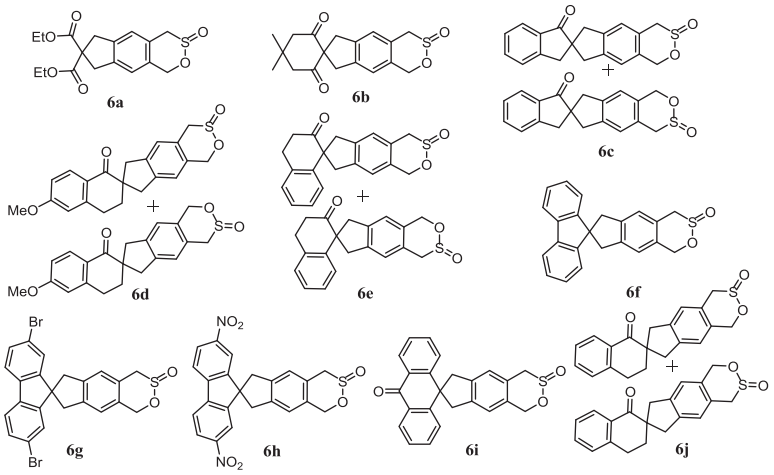


Fig. 6. Structures of sultine derivatives used in DA sequence.

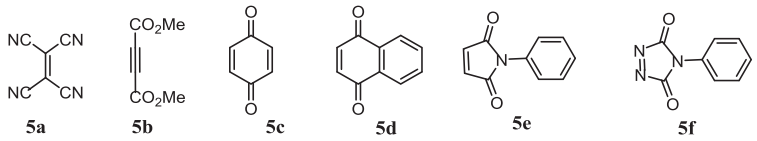


Fig. 7. Different dienophiles used in our methodology.

5a–**f**, toluene, reflux, 12–24 h; ii) DDQ, toluene, reflux, 24 h, (**7**–**35**, 64–90%).

Along similar lines, we have prepared various di-propargylated building blocks **2b**–**j** (Fig. 3) starting from the compounds **1b**–**j** (Fig. 2) by using different bases in good to excellent yields (Table 1 and Fig. 3). Later, these di-propargylated building blocks **2b**–**j** were transformed into the corresponding diols **3b**–**j** (Table 1 and Fig. 4) via a Wilkinson's catalyst mediated [2+2+2] cycloaddition protocol with 2-butyne-1,4-diol and a catalytic amount of titanium isopropoxide as an additive in refluxing EtOH. In most of the cases, we did not isolate the corresponding spirodiols **3b**–**j** (Table 1) because of the overlapping nature of excess amount of 2-butyne-1,4-diol and the product formed (TLC appearance). In such occasions, the crude reaction mixture was directly converted to the corresponding di-bromo compounds **4b**–**j** by treating with PBr_3 in CH_2Cl_2 at room temperature (rt) (Fig. 5). Later, these compounds **4b**–**j** were purified by silica gel column chromatography and further transformed into the corresponding sultine derivatives **6b**–**j** by using rongalite in DMF (Fig. 6).

Since, the sultine derivatives **6b**–**j** are latent diene equivalents, they were treated with various dienophiles **5a**–**f** (Fig. 7) in a DA fashion to afford the corresponding cycloadducts. Subsequently, aromatization of these DA adducts with DDQ in refluxing toluene gave the linearly annulated spirocycles **9**–**35** (Fig. 8). During the DA reaction of compounds **6b** and **6i** with tetracyanoethylene **5a**, we isolated the rearranged products [**12a** (11%) and **33a** (6%)] (Fig. 9) along with the expected DA adducts **12** and **33** (Fig. 8). The structures of compounds **12a** and **33a** have been confirmed by ^1H, ^{13}C NMR spectroscopy and further supported by high resolution mass spectrometric (HRMS) data.

3. Conclusions

In summary, we have established an efficient and versatile synthetic route to a library of linearly fused spirocycles via the application of two sequential atom-economic protocols such as a [2+2+2] cycloaddition and the [4+2] cycloaddition reaction. The present strategy opens up a new and a short synthetic sequence to a range of linearly annulated spirocycles without involvement of protecting groups in a diversity-oriented manner. Our strategy involves a green reagent such as rongalite for the sultine formation and these sultine derivatives acts as latent diene equivalents, which can be trapped with various dienophiles to deliver a number of intricate spirocycles by varying the dienophile components during the DA sequence.

4. Experimental section

All commercially accessible reagents were used without further purification and the reactions involving air sensitive catalysts or reagents were performed in degassed solvents. Moisture sensitive materials were transferred by using 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 a suitable mixture of EtOAc and petroleum ether for development. Column chromatography was performed by using Acme's silica gel (100–200 mesh) with an appropriate mixture of EtOAc and petroleum ether. The coupling constants (*J*) are given in hertz (Hz) and chemical shifts are denoted in parts per million (ppm) downfield from internal standard, tetramethylsilane (TMS). The abbreviations, s, d, t, q, m, dd and td, refer to singlet, doublet, triplet, quartet, multiplet, doublet of doublets, and triplet of doublets, respectively. Wilkinson's catalyst was purchased from Sigma Aldrich. Infrared (IR) spectra were recorded on Nicolet Impact-400 FT IR spectrometer in $CHCl_3$. Proton nuclear magnetic resonance (^1H 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 Veego melting point apparatus.

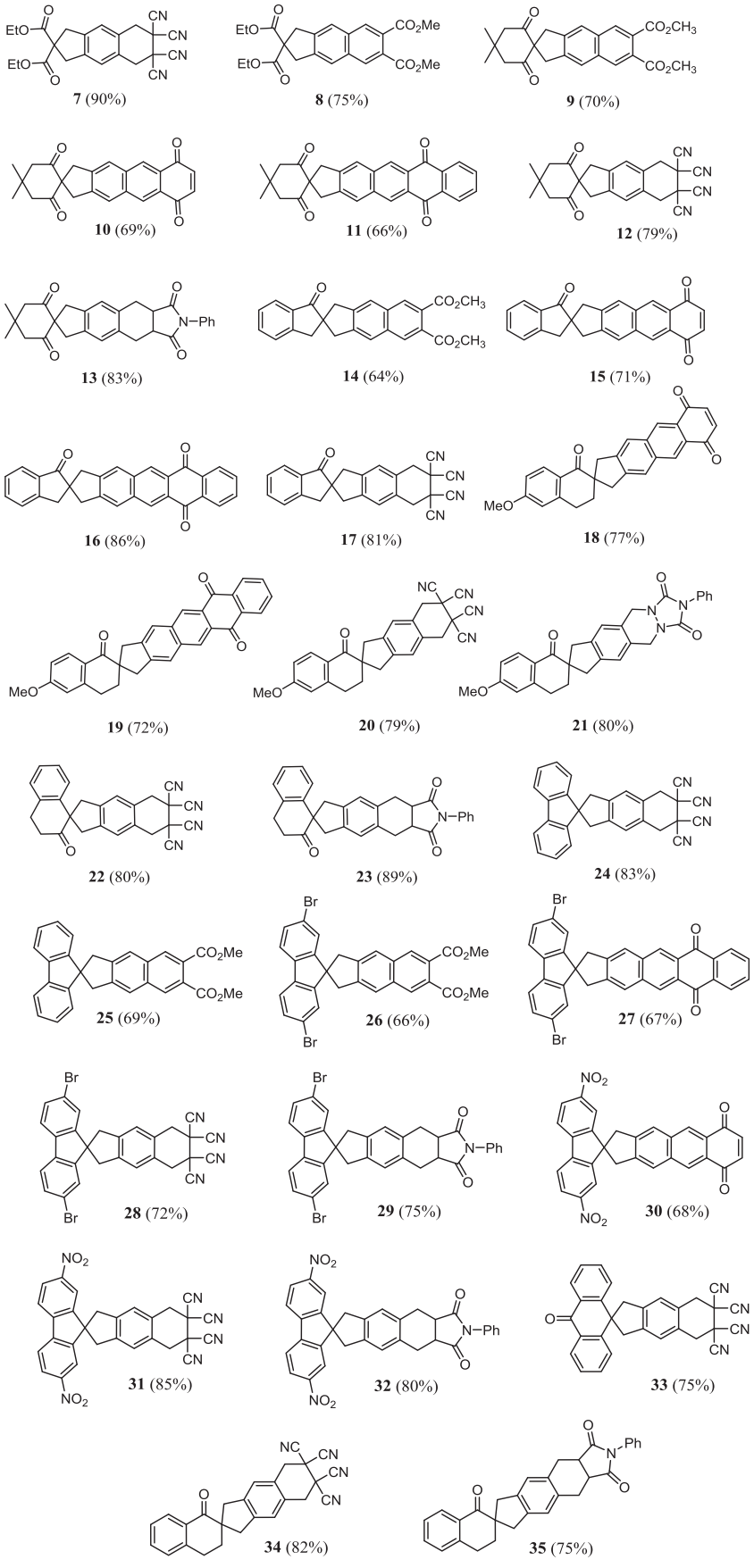


Fig. 8. List of linearly fused spirocycles assembled via a [2+2+2] and [4+2] sequence.

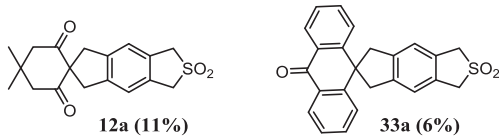


Fig. 9. Structures of sulfones **12a** and **33a** isolated during the DA sequence.

4.1. Preparation of compounds 2a, 2b, 2e, 2f, 2g, 2h and 2i

These compounds have been prepared by the literature procedures and the ^{1}H, ^{13}C NMR data matched with the literature reported spectral data.[14–19]

4.2. General procedure for the synthesis of compounds 2c, 2d and 2j

To a suspension of sodium hydride (4 equiv) in dry THF (~5 mL per mmol), the compounds **1c**, **1d** or **1j** was added and the reaction mixture was stirred at rt for 15 min. Later, propargyl bromide (3 equiv) was added and the stirring was continued at the same temperature for 10–12 h (Table 1). At the conclusion of the reaction (TLC monitoring), the reaction mixture was quenched with EtOAc and the solvent was removed under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 and the crude products were purified by silica gel column chromatography (5% EtOAc-petroleum ether) to deliver the compounds **2c**, **2d** or **2j**.

4.3. Compound 2c

Yellow liquid (83%); R_f=0.69 (silica gel, 10% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.89 (t, J=2.66 Hz, 2H), 2.53, 2.59 (ABq, J=2.60 Hz, 4H), 3.32 (s, 2H), 7.36–7.40 (m, 1H), 7.48–7.50 (m, 1H), 7.60–7.64 (m, 1H), 7.76 (d, J=7.57 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=26.10, 37.19, 50.98, 70.90, 79.92, 124.48, 126.58, 127.71, 135.50, 135.71, 153.16, 207.11; IR (neat): υ_{max}=1608, 1708, 2224, 2840, 2934, 3016, 3310 cm^{-1}; HRMS (ESI, Q-ToF) m/z: calculated for $C_{15}H_{12}NaO$ $[M+Na]^+$ 231.0780, found: 231.0780.

4.4. Preparation of compound 3a

The solution of compound **2a** (1.7 g, 7.2 mmol), and 2-butyne-1,4-diol (1.85 g, 21.60 mmol) in dry ethanol (35 mL) was degassed with nitrogen for 15 min. Later, Wilkinson's catalyst (166 mg, 2.5 mol%) and Ti(O^iPr)$_4$ (511 mg, 25 mol%) were added and the reaction mixture 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 (20% EtOAc-petroleum ether) to deliver compound **3a** (2.14 g, 68%) as a white solid. The ^{1}H and ^{13}C spectra matched with the literature reported spectral data.[20]

4.5. General procedure for the [2+2+2] cycloaddition reaction of 2b–j

The solution of compounds **2b–j** and 2-butyne-1,4-diol (3 equiv) in dry ethanol (~5 mL per mmol) was degassed with nitrogen for 15 min. Later, Wilkinson's catalyst (2.5 mol%) and Ti(O^iPr)$_4$ (25 mol%) was added and the reaction mixture was refluxed for 12–24 h (Table 1). At the conclusion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude products were directly subjected to the next step without further purification.

4.6. Synthesis of compound 4a

To a solution of compound **3a** (1 g, 3.11 mmol) in dry CH_2Cl_2 (25 mL), was added a solution of PBr_3 (0.9 mL, 9.33 mmol) in dry CH_2Cl_2 (10 mL) dropwise by using a dropping funnel at 0 °C and the reaction mixture was stirred at rt for 10 h. At the conclusion of the reaction (TLC monitoring), the reaction mixture was poured into ice-cooled water and the organic layer was extracted with CH_2Cl_2. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (10% EtOAc-petroleum ether) to afford the compound **4a** (1.04 g, 75%) as a white solid.

Mp 162–164 °C; R_f=0.52 (silica gel, 25% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.25 (t, J=7.12 Hz, 6H), 3.57 (s, 4H), 4.20 (q, J_1=7.12 Hz, J_2=14.28 Hz, 4H), 4.63 (s, 4H), 7.20 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.17, 30.54, 40.30, 60.42, 62.06, 127.05, 135.60, 141.95, 171.45; IR (neat): υ_{max}=1446, 1728, 2985, 3055 cm^{-1}; HRMS (ESI, Q-ToF) m/z: calculated for $C_{17}H_{20}^{79}Br_2NaO_4$ $[M+Na]^+$ 468.9621, found: 468.9620 and other isotope peaks are 470.9631 and 472.9695.

4.7. General procedure for the synthesis of 4b–j

To a solution of the diols **3b–j** in CH_2Cl_2 (~8 mL per mmol), was added a solution of PBr_3 (3 equiv) in CH_2Cl_2 (~3 mL per mmol) dropwise by using a dropping funnel at 0 °C. The reaction mixture was stirred at rt for 12–16 h. At the conclusion of the reaction (TLC monitoring), the reaction mixture was poured into ice-cooled water and the organic layer was extracted with CH_2Cl_2. The solvent was removed under reduced pressure and the crude products were purified by silica gel column chromatography by using appropriate mixtures of (EtOAc-petroleum ether) to deliver the desired products **4b–j**.

4.8. Compound 4b

White solid (49%); Mp 103–105 °C; R_f=0.48 (silica gel, 25% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.04 (s, 6H), 2.70 (s, 4H), 3.43 (s, 4H), 4.62 (s, 4H), 7.17 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=28.53, 30.50, 30.79, 38.39, 51.53, 71.31, 127.08, 135.72, 141.38, 202.26; IR (neat): υ_{max}=1602, 1698, 2928, 3019 cm^{-1}; HRMS (ESI, Q-ToF) m/z: calculated for $C_{18}H_{20}^{79}Br_2KO_2$ $[M+K]^+$ 464.9462, found: 464.9457 and other isotope peaks are 466.9440 and 468.9420.

4.9. General procedure for the synthesis of sultine derivatives 6a–j

To a solution of di-bromo compounds **4a–j** and TBAB (1 equiv) in DMF (10 mL), was added rongalite (10 equiv) at 0 °C and the reaction mixture was stirred at 0 °C for 3 h and at r.t. for another 1–3 h (Table 1). At the conclusion of the reaction (TLC monitoring), the aqueous layer was extracted with EtOAc and the organic layer was washed with water (4×30) to remove the excess amount of DMF. The solvent was removed under reduced pressure and the crude products were purified by silica gel column chromatography (40–50% EtOAc-petroleum ether) to deliver the desired sultine derivatives **6a–j**.

4.10. Compound 6a

White solid (88%); Mp 123–124 °C; R_f=0.56 (silica gel, 50% EtOAc-petroleum ether); ^{1}H NMR (400 MHz, $CDCl_3$) δ=1.23–1.27 (m, 6H), 3.50 (d, J=15.25 Hz, 1H), 3.57 (s, 4H), 4.16–4.22 (m, 4H), 4.38 (d, J=15.24 Hz, 1H), 4.90 (d, J=13.48 Hz, 1H), 5.23 (d, J=13.49 Hz, 1H), 7.09 (d, J=13.48 Hz, 2H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ=14.14, 40.24, 40.28, 57.80, 60.51, 62.00, 63.94, 121.97, 125.36, 125.58, 133.09, 140.29, 141.07, 171.37, 171.49; IR (neat): υ_{max}=1657, 1732, 2824, 2934, 2981 cm^{-1}; HRMS (ESI, Q-ToF) *m*/*z*: calculated for $C_{17}H_{20}KO_6S$ $[M+K]^+$ 391.0612, found: 391.0617.

4.11. General procedure for the DA reaction and subsequent aromatization of 6a–j

The solution of compounds **6a–j** and dienophiles **5a–f** (1.5 equiv) in toluene (20 mL) was refluxed for 12–24 h. Later, the DA adducts were aromatized with DDQ (4 equiv) in refluxing toluene for 24 h. The solvent was removed under reduced pressure and the crude products were purified by silica gel column chromatography (40–50% EtOAc-petroleum ether) to deliver the aromatized products **7–35**.

4.12. Compound 7

White solid (90%); Mp 162–164 °C; R_f=0.76 (silica gel, 40% EtOAc-petroleum ether); ^1H NMR (400 MHz, $CDCl_3$) δ=1.27 (t, J=7.12 Hz, 6H), 3.58 (s, 4H), 3.76 (s, 4H), 4.22 (q, J_1=7.12 Hz, J_2=14.24 Hz, 4H), 7.05 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=14.15, 35.76, 38.58, 40.12, 60.47, 62.20, 110.68, 123.92, 124.88, 142.23, 171.21; IR (neat): υ_{max}=1677, 1729, 2246, 2981, 3020 cm^{-1}; HRMS (ESI, Q-ToF) *m*/*z*: calculated for $C_{23}H_{20}N_4NaO_4$ $[M+Na]^+$ 439.1377 found: 439.1376.

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Supplementary data

Supplementary data (Spectral data and the copies of ^1H and ^{13}C NMR for all the new compounds) related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.01.009.

References and notes

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