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Sequential Enyne-Metathesis/Diels-Alder Strategy: Rapid Access to the Novel Sugar-oxasteroid-quinone Hybrids

Ashik A. Sayyad and Krishna P. Kaliappan*

Abstract Sequential enyne metathesis/Diels-Alder strategy is herein reported to synthesize a novel class of sugar-oxasteroid-quinone hybrid molecules. For the synthesis of series of sugar-oxasteroid-quinone hybrid analogues, 1,2,5,6-diisopropylidine-D-glucose was chosen as the chiral pool starting material. Varieties of sugar derived enynes are synthesized from common starting precursor and their treatment with various quinone dienophiles in Diels-Alder reaction conditions resulted in the library of sugar-oxasteroid-quinone hybrids.

Introduction

Nature has been the main source of structurally diverse and complex natural products from long time; some of these natural products are found to exhibit interesting biological activities.[1] It has long been recognized that natural product structures possess high chemical diversity and biological specificity that makes them favourable as lead structures for drug discovery. Steroids represent an important class of natural products, which plays critical role in a number of disorders, including malignancies like prostate cancer, where steroid production inside and outside the tumor promotes cancer cell aggressiveness.[2]

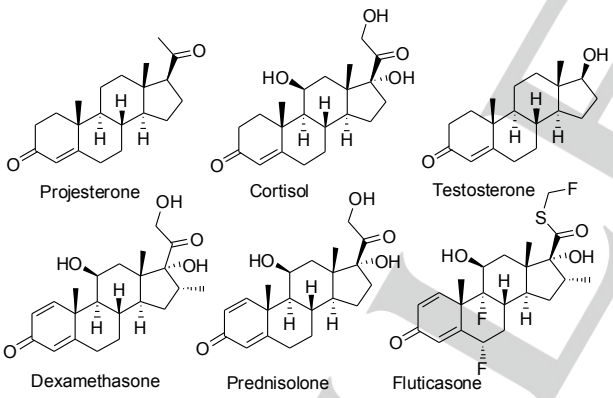

Fig.1 Glucocorticoids

Synthetic steroid hybrids have attracted significant attention for the purpose of drug development.[3] A few interesting strategies have been reported for the synthesis of different types of steroid hybrids.[4,5] Treatment of inflammatory diseases (Rheumatoid arthritis, COPD and related autoimmune diseases) has been achieved with powerful glucocorticoids such as dexamethasone, prednisolone, fluticasone (Fig. 1) etc. However, prolonged use of Glucocorticoids in the treatment of chronic conditions causes various serious side effects including diabetes and osteoporosis.[6,7] Therefore, there is a great need to synthesize steroid-like molecules with desired biological activity and lacking the serious side-effects. Quinones are ubiquitous in nature and constitute of natural and synthetic compounds that have several beneficial as well as toxicological effects.[8a-f] Anthracycline antibiotics consists of quinone unit are well known for their important antineoplastic activity. Out of the various anthracyclines daunorubicin and doxorubicin (Fig. 2) were initially isolated from *Streptomyces peucetius* and were found to exhibit the widest spectrum of antitumor activity against human cancers.[8g-j] Because of the promising anticancer activity of these molecules, there has been a lot of interest in chemically modifying them to minimize their cardiotoxic side effects.

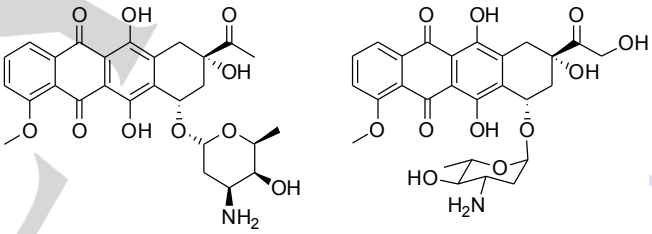

Fig. 2 Daunorubicin and Doxorubicin

The chemical synthesis of hybrid natural product provides rapid access to structurally diverse chemical substances for pharmacological testing in short span of time. The novel class of hybrid natural products, which are potentially bioactive, can be designed by combining structural units of two or more classes of natural products. As a part of our research programme aimed at the synthesis of biologically active compounds,[9] we earlier reported our preliminary attempts towards design and synthesis of new class of sugar–oxasteroid–quinone hybrids with the purpose of combining the reactivity of the acetal moiety of furanose and the quinone unit with the steroidal backbone, as outlined in Scheme 1.[10] Our strategy consists of sequential enyne metathesis and Diels–Alder reaction[11] of an enyne **1** derived from a sugar unit with a variety of 1,4-quinones to provide hybrid molecule **3** as outlined in Scheme 1. Herein, we disclose a comprehensive account on our endeavours for the synthesis of sugar–oxasteroid–quinone hybrids through a sequential intramolecular enyne metathesis/Diels–Alder[11] /aromatization reaction strategy (Scheme 1).

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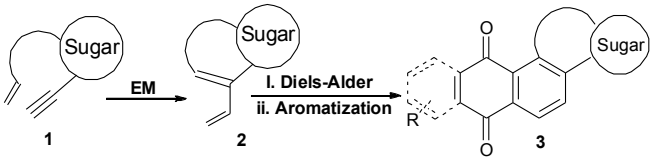
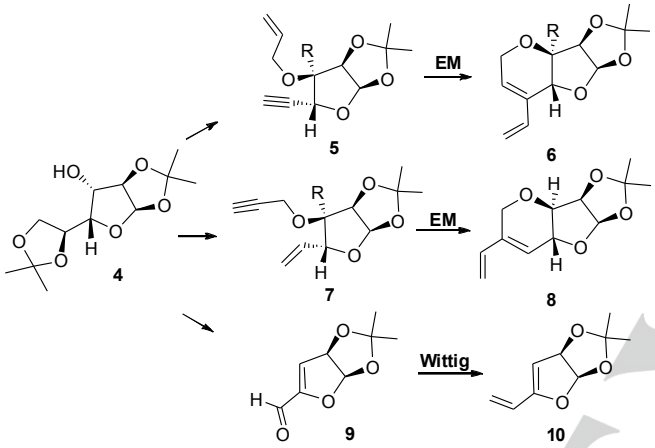


Scheme 1. General enyne metathesis/Diels-Alder/aromatization strategy

The diversity for the synthesis of various sugar–oxasteroid–quinone hybrids could be accomplished by treating different dienes derived from carbohydrate precursor with a variety of dienophiles in the Diels–Alder reaction. 1,2,5,6-diisopropylidine-D-glucose **4** was used as the chiral pool starting material.[10b]



Scheme 2. Diversity in the synthesis of dienes

Varieties of enynes were synthesized in few steps from common starting precursor **4**. Treatment of these various enynes with Grubb's first generation catalyst afforded reactive dienes (Scheme 2). These dienes on treatment with various quinone dienophiles[12] resulted in a library of sugar–oxasteroid–quinone hybrids with different scaffolds as shown in the Figure 3.

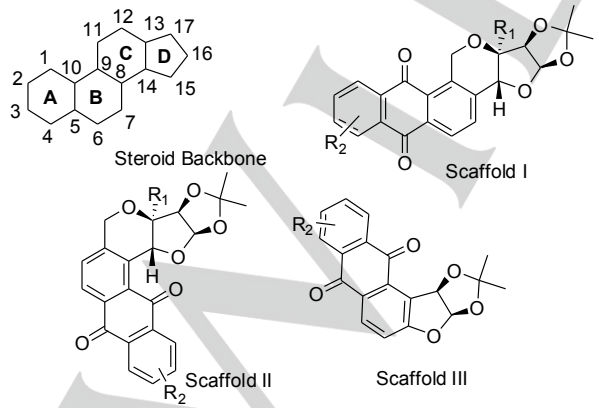


Figure 3. Various scaffolds of oxasteroid-quinone hybrids

The major difference in these scaffolds is in the **A**-**B** and **B**-**C** ring fusion with respect to the steroidal backbone, thus providing the access to array of hybrids with significant variety in the ring fusion of the steroid skeleton (Scaffold I-III, Fig. 3). To test our planned strategy, we designed a set of dienes (**17**-**21**) that could be synthesised from the common starting precursor 1,2,5,6-diisopropylidine-D-glucose **4** by using enyne metathesis. Later, these dienes could be used in the Diels–Alder reaction[11] with 1, 4-naphthoquinone (**11**), 5, 8-dihydroxy-1,4-naphthoquinone (**12**), 1,4-anthraquinone (**13**), 5-hydroxy-1,4-naphthoquinone (**14**), 5-nitro-1,4-naphthoquinone (**15**),[13a] and DMAD (**16**) as dienophiles (Fig.4) for the synthesis of respective sugar oxasteroid-quinone hybrids.

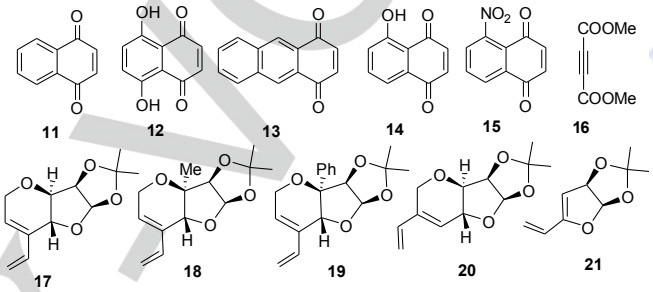
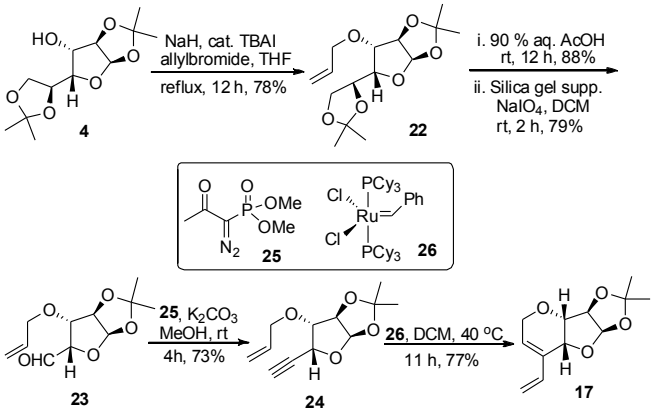


Figure 4. Various dienes and quinone dienophiles

Results and Discussion

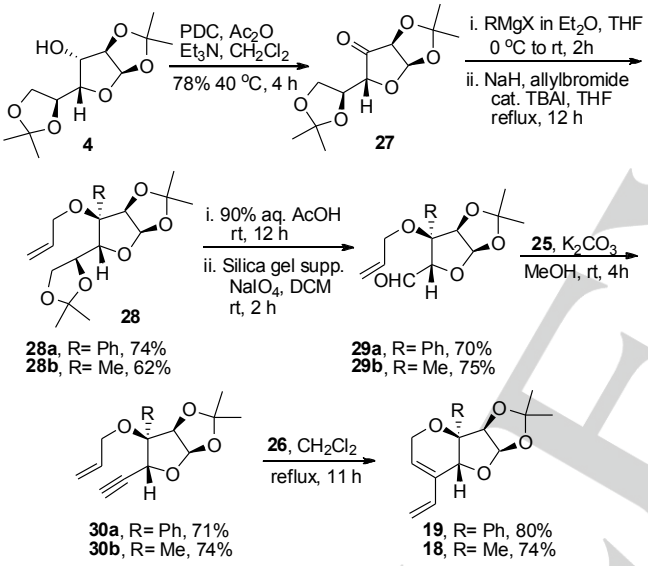
Synthesis of sugar-oxasteroid-quinone hybrids

The building blocks for the synthesis of sugar-oxasteroid-quinone hybrids are enynes, which were derived from the secondary alcohol **4** (Scheme 3). Our synthetic journey towards the sugar–oxasteroid–quinone hybrid molecules was started with the synthesis of diene **17** in a convergent manner from the 1,2,5,6-diisopropylidine-D-glucose **4**. Allylation of precursor **4** resulted in to the allyl ether **22** in good yield. Selective deprotection of the more exposed *5,6-O*-isopropylidene group of **22** afforded a diol, which was subsequently cleaved by silica gel supported $NaIO_4$ to provide the aldehyde **23**.[13b-c]



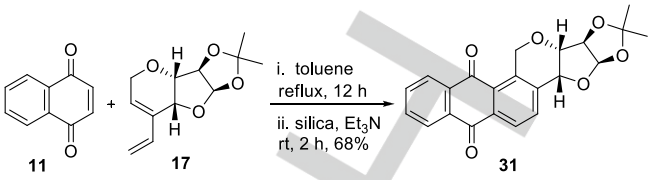
Scheme 3. Synthesis of diene **17**

The aldehyde **23** was then easily converted into the key enyne precursor **24** by Ohira-Bestmann's protocol[14] in a single step by treating aldehyde **23** with the diazo compound **25** in presence of K_2CO_3 in MeOH in 73% yield. The synthesis of enyne **24** allowed us to attempt the key enyne metathesis reaction. As planned, the enyne **24** underwent a smooth intramolecular enyne metathesis[15] with the Grubbs' first generation catalyst **26** to yield the diene **17** in good yield. However, synthesis of dienes **18** and **19** were commenced with the ketone **27** which could be obtained from precursor **4** (Scheme 4) by PDC oxidation.[16] Addition of phenyl[17] and methyl magnesium bromide[10] separately to the ketone **27** resulted in respective tertiary alcohols in moderate yields. Allylation of resulting tertiary alcohols yielded allyl ethers **28a** and **28b**, which on cleavage of more exposed *5,6-O*-isopropylidene group furnished respective diols[10] in quantitative yields, further treatment with silica supported $NaIO_4$ afforded aldehydes **29a** and **29b**. Aldehydes were converted into desired enynes **30a** and **30b** in single step by using Ohira-Bestmann's protocol[14] (Scheme 4).



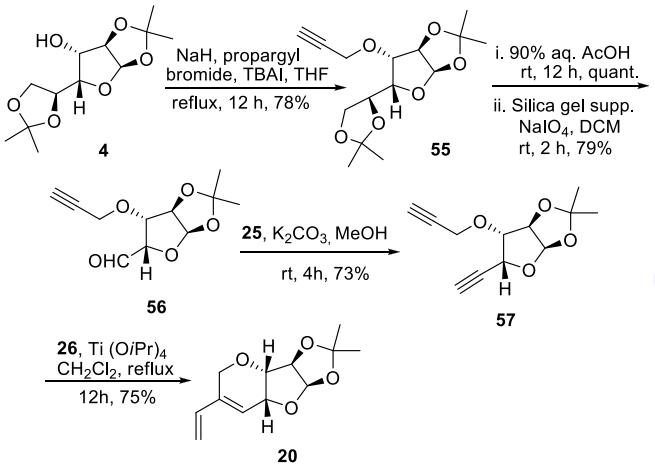
Scheme 4. Synthesis of diene **18** and **19**

Finally enyne metathesis[15] of above enynes with Grubbs' first generation catalyst **26** yielded dienes **19** and **18** in good yields. After synthesizing the dienes **17**, **18** and **19**, the stage was set to carry out the intermolecular Diels–Alder reaction[11] with 1,4-quinones as dienophiles to generate sugar-oxasteroid quinone hybrids. As expected and based on our earlier experience[10] Diels-alder reaction of diene **17** with 1,4-napthoquinone underwent smoothly under thermal conditions. However, the cycloadduct seemed to be unstable and found to undergo aromatization/oxidation on a silica gel column without any oxidizing agent. Thus we treated the crude cycloaddition product immediately with triethylamine[10] and silica gel without purification which resulted in the aromatised product **31** in 68% yield (Scheme 5).



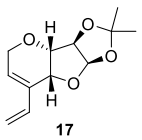
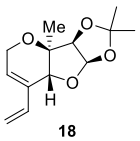
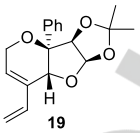
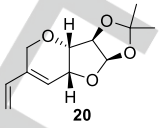
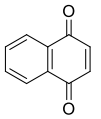
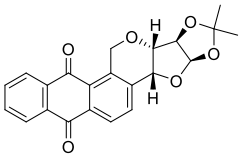
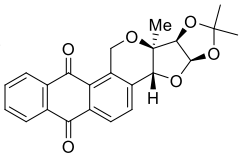
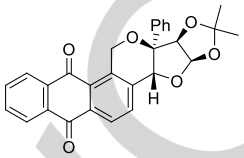
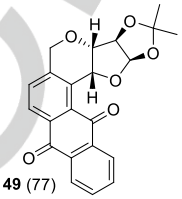
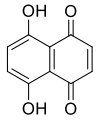
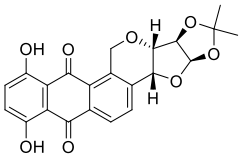
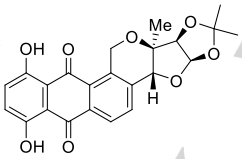
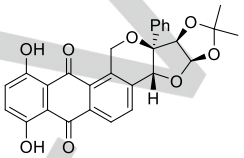
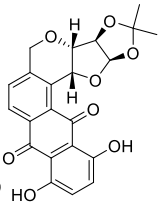
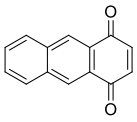
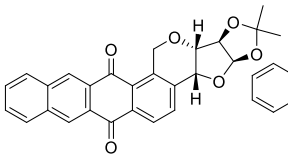
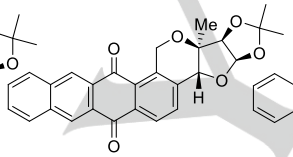
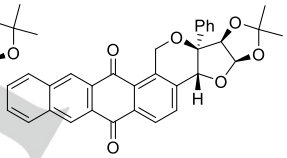
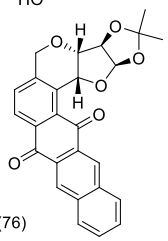
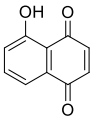
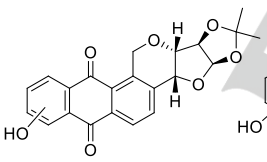
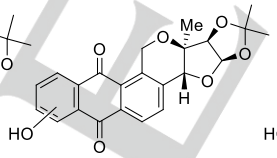
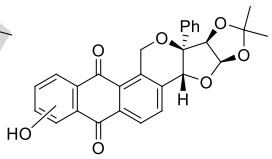
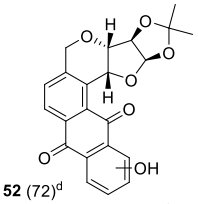
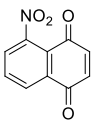
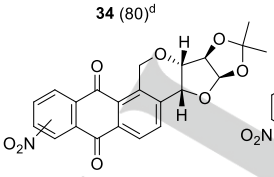
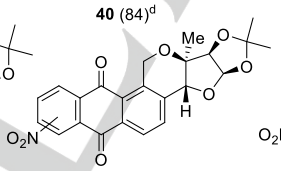
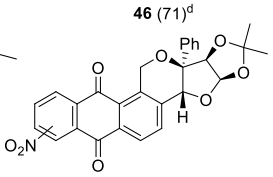
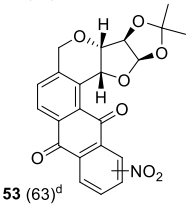
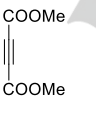
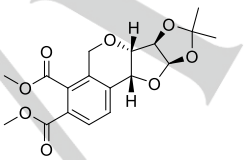
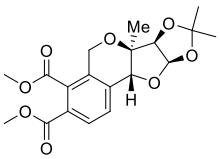
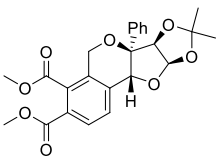
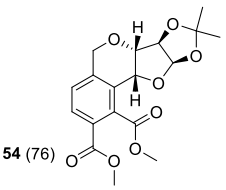
Scheme 5. Diels-Alder/aromatization strategy

This sequence was then repeated with 5,8-dihydroxy 1,4-naphthoquinone **12**, 1,4-anthraquinone **13**, 5-hydroxy 1,4-napthoquinone **14** and 5-nitro 1,4-napthoquinone **15** to obtain the respective hybrid molecules **32**, **33**, **34** and **35** with scaffold-I structure (Table 1) in moderate to good overall yields. As expected mixture of inseparable regeoisomers was obtained in case of substituted quinones **14** and **15**. We were sceptical about reactivity of our sugar dienes with dienophiles other than quinone and hence we treated diene **17** with DMAD. Unlike quinone dienophiles Diels-Alder adducts, the adduct with DMAD was reluctant to undergo aromatization with triethyl amine/basified silica gel, however treatment with oxidant MnO_2[18] in refluxing toluene resulted in the desired aromatised product **36** in 73% yield. In similar manner diene **18** and **19** were subjected to Diels–Alder reaction/aromatization[10] reaction sequence with quinone dienophiles **11** to **15** as well as DMAD, reactions proceeded smoothly and the respective aromatization reactions led to the corresponding sugar–oxasteroid–quinone hybrids **37-48** in 62-89% yields (Table 1). Synthesis of diene **20**[19] was commenced with propargylation of precursor **4** followed by selective deprotection of the more exposed 5,6-O-isopropylidene group of **55** to give diol in quantitative yield, which on treatment with silica supported $NaIO_4$ resulted in aldehyde **56** in 79% yield (Scheme 6). Further treatment of aldehyde with methyl triphenyl phosphonium bromide in basic condition furnished enyne **57** in 73% yield. The treatment of enyne **57** with Grubbs' first generation catalyst **26** afforded diene **20**.[19]



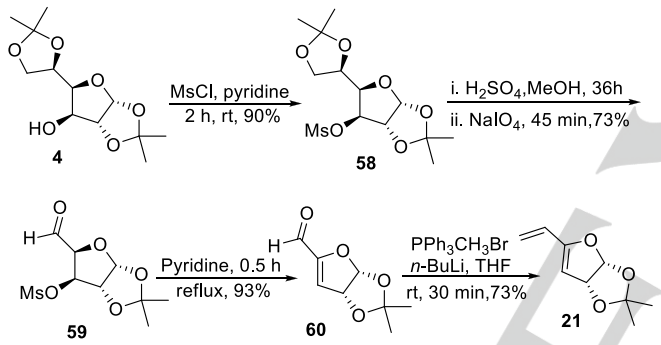
Scheme 6. Synthesis of diene **20**

Table 1. Synthesis of sugar-oxasteroid quinone hybrids. [a,b,c,d,e]

Dienophile/1,3 Diene[a]	 **17**	 **18**	 **19**	 **20**
 **11**	 **31** (68)	 **37** (75)	 **43** (82)	 **49** (77)
 **12**	 **32** (67)	 **38** (62)	 **44** (63)	 **50** (64)
 **13**	 **33** (71)	 **39** (76)	 **45** (89)	 **51** (76)
 **14**	 **34** (80)[d]	 **40** (84)[d]	 **46** (71)[d]	 **52** (72)[d]
 **15**	 **35** (75)[d]	 **41** (81)[d]	 **47** (84)[d]	 **53** (63)[d]
 **16**	 **36** (73)	 **42** (69)	 **48** (75)	 **54** (76)

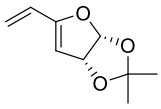
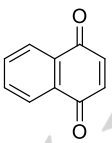
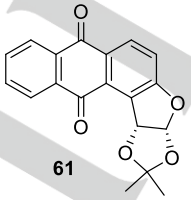
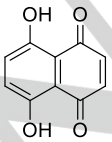
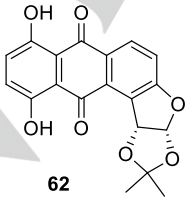
(a) The dienes were synthesised from the respective alkynes by using Grubbs' first-generation catalyst (7 mol%) under an Ar atmosphere in CH_2Cl_2 at 40 °C. (b) All the Diels–Alder reactions were carried out in toluene at 80°C followed by aromatization with basic (Et_3N) silica in $CHCl_3$ at RT. (c) Overall yield for two steps. (d) Mixture of regioisomers was obtained. (e) Yields are given in parenthesis.

In this event, the Diels–Alder reaction[11] of the diene **20** proceeded smoothly with dienophiles **11**-**16**, and the respective aromatization reactions led to the corresponding sugar-oxasteroid-quinone hybrids **49**-**54** with scaffold-II in good yields (Table 1), where symmetric quinones yielded single product but in case of substituted quinones (**14** and **15**) inseparable mixture of regeoisomers (**52** and **53** respectively) were obtained. The synthetic journey towards diene **21** was commenced with same precursor **4** by using known protocol.[20] Precursor **4** was subjected to mesylation condition to obtain mesyl ether **58**. The selective deprotection of more exposed 5,6-O-isopropylidene group of **58** with dil. H_2SO_4 afforded a diol, which was further cleaved by silica gel supported $NaIO_4$ to provide the aldehyde **59**. Treatment of aldehyde **59** with pyridine in refluxing conditions afforded aldehyde **60** in 93% yield. Finally aldehyde **60** was treated with methyl triphenyl phosphonium bromide in basic condition furnished diene **21** (Scheme 7) in 73% yield. The diene **21** is structurally different from the other dienes of **6** and **8** types. Also the Diels-Alder/aromatization[10] reaction sequence in this case of diene **21** will essentially lead to the sugar oxa-steroid quinone hybrids



Scheme 7. Synthesis of diene **21**

Table 2. Synthesis of sugar-oxasteroid-quinone hybrids with scaffold III[a,b,c,]

1,3 Diene[a]	Dienophile	Hybrid	Yield
 21	 11	 61	64%
21	 12	 62	52%

(a) All the Diels–Alder reactions were carried out in toluene at 80 °C followed by aromatization with basic (Et_3N) silica in $CHCl_3$ at RT. (b) Overall yield for two steps. (c) Yields are given in parenthesis.

with new scaffold III. Surprisingly, diene **21** was found to be less reactive towards the Diels–Alder reaction[11] with 1,4 quinones than the diene **17**-**20** and required longer time for completion of the reaction, however after refluxing the diene **21** with 1,4-naphthoquinone for 48 to 72 hours in toluene, desired hybrid **61** with scaffold-III (Fig. 3) was obtained in 64% yield (Table 2). The reaction of diene **21** with 5,8-dihydroxy-1,4 naphthoquinone effortlesssely yielded hybrid **62** in 52% yield. However, Diels Alder reactions with 5-hydroxy, 1,4-naphthoquinone, 5-nitro 1,4-naphthoquinone and DMAD were not clean and only traces of product formed, which could be attributed to the low reactivity of diene **21** towards Diels-Alder reaction.

Conclusion

We have disclosed a simple, versatile and efficient strategy for the synthesis of a novel class of sugar–oxa–steroid quinone hybrids. The choice of different types of sugar dienes derived from the common precursor on Diels-Alder/aromatization reaction sequence has led us to novel sugar oxa-steroid quinone hybrids with three different steroidal scaffolds. During this course, Diels-alder/aromatization strategy for six different dienophiles against five different dienes was investigated. Also, these sugar derived dienes undergo smooth reaction with DMAD, this proves scope of our methodology is not only limited to quinone dienophiles but could be extended to non-quinone dienophiles as well. Thus, library of hybrid molecules which has steroid-like backbone (scaffold-I) and modified steroidal backbone (scaffold II and III) can be synthesized by using this methodology, which provides a rapid access to number of steroid hybrids.

Experimental Section

General: All starting materials and reagents were obtained from commercial suppliers and used after further purification as detailed below. All solvents for routine isolation of products and chromatography were reagent-grade and glass-distilled. Reaction flasks were dried in oven at 130 °C for 12 h. Air and moisture-sensitive reactions were performed under an argon/UHP nitrogen atmosphere. Column chromatography was performed using silica gel (100−200 mesh size) with indicated solvents. Thin-layer chromatography (TLC) was conducted with silica gel 60 F_{254} precoated plates (0.25 mm) and visualized with UV, potassium permanganate, ceric ammonium molybdate, or iodine staining as appropriate. All ^1H NMR spectra were recorded on 400 and 500 MHz spectrometers and have been reported in ppm using solvents as internal standards ($CDCl_3$ at 7.26 ppm). All proton-decoupled ^{13}C NMR spectra were recorded at 100 and 125 MHz and have been reported in ppm using solvents as internal standards ($CDCl_3$ at 77.2 ppm). Compounds were analyzed for HRMS on an ESI-QTOF mass spectrometer using electrospray ionization in the positive ion mode. IR spectra were recorded with KBr on an FT-IR

spectrometer and have been reported in wavenumber (cm^{-1}). For all the solid compounds melting points were measured on a Buchi micromelting point apparatus. A few general procedures were followed during the course of reactions, and they are explained later. Splitting patterns are designated as s, singlet; d, doublet; dd, doublet of doublet; t, triplet; q, quartet; quin, quintet; m, multiplet. Optical rotations were measured at 25 °C on Autopol IV polarimeter.

General procedure for Diels-Alder reaction and aromatization

Method A: To a solution of quinone (0.65 mmol, 1.2 equiv) in dry toluene (10 mL) was added a solution of diene (0.5 mmol, 1 equiv) in toluene (3 mL) at RT and then refluxed till the complete disappearance of diene. Then the solvent was removed under vacuum. The crude product was dissolved in minimum amount of $CHCl_3$. To this solution silica gel (2 g) purged in triethylamine (0.6 mL) was added and stirred till the complete conversion to product was observed. Then the solvent was removed in rotavapor and purified by a silica gel column chromatography to afford the corresponding aromatized hybrid.

Method B: A solution of diene (1 mmol) in dry toluene (10 mL) was treated with DMAD (1.2 mmol) at RT and then heated at 80 °C until the complete conversion of the diene to product was observed. The solvent was removed under reduced pressure and the crude product was dissolved in CH_2Cl_2 (20 mL) and treated with MnO_2 (10 mmol) under refluxing conditions. After 12 h, the reaction mixture was passed through a small pad of Celite and the filtrate was concentrated and purified by column chromatography to afford the corresponding aromatized adducts. **Note:** For experimental details and spectral data of compounds **28b**-**18** and **37**, **39** see reference (10).

Compound 17: A solution of enyne **24** (0.23 g, 1.03 mmol) was dissolved in dry CH_2Cl_2 (30 mL) under argon and the solution was degassed. To this mixture a solution of **26** (0.059 g, 7 mol%) in CH_2Cl_2 (5 mL) was added dropwise and refluxed for 12 h. The reaction mixture was cooled to room temperature and DMSO (0.36 mL, 5.15 mmol) was added to quench the excess of catalyst and stirred for 6 h at room temperature. Evaporation of solvent and purification by silica gel column chromatography (5% ethyl acetate in hexanes) gave the cyclized compound **17** (0.17 g) as colourless syrup in 77% yield. *Rf* = 0.6 (15% EtOAc/hexane); $[\alpha]^{25}_D$ = +1.58 (c 2.4, $CHCl_3$); IR (neat) 3030, 1671, 1629, 1454, 1376, 1216, 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (dd, J = 17.7, 10.8 Hz, 1H), 5.98 (d, *J* = 3.7 Hz, 1H), 5.95–5.94 (m, 1H), 5.50 (d, *J* = 17.5 Hz, 1H), 5.18 (d, *J* = 10.8 Hz, 1H), 4.60–4.58 (m, 2H), 4.29 (dd, *J* = 17.7 , 4.1 Hz, 1H), 4.19 (d, *J* = 17.7 Hz, 1H), 3.97 (d, *J* = 2.4 Hz, 1H), 1.53 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 131.7, 129.2, 114.7, 111.5, 105.3, 83.7, 79.0, 70.8, 64.8, 26.9, 26.2; HRMS (ESI) calc. for $C_{12}H_{16}O_4Na$ $(M+Na)^+$ 247.0946, found 247.0949.

(3a*R*,5*R*,6*R*,6a*R*)-6-(allyloxy)-5-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-6-phenyltetrahydrofuro[3,2-d][1,3]dioxole (28a) : A solution of PhMgBr (7.2 g, 42.8 mmol) in ether (50 mL) was added to a solution of the ketone **27** (3 g, 10.7 mmol) in THF (60 mL) at 0 °C. Stirring was continued for 2 h at 0 °C and then at room temperature for 12 h. The reaction mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate (3 x 50 mL). Organic layer was concentrated and the crude product (2.7 g) was used for next step without purification. To a suspension of sodium hydride (0.45 g, 18.6 mmol, 60% dispersion in mineral oil) in dry THF (35 mL) was added a solution of alcohol (2.5 g, 7.44 mmol) in THF (17 mL) drop wise at 0 °C and the mixture was stirred for 15 min., then at room temperature for 30 min. To this mixture allyl bromide (2.9 g, 18.6 mmol) was added drop wise followed by a catalytic amount of TBAI and the reaction mixture was stirred at 0 °C for 10 min., and then refluxed for 12 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with ethyl acetate (3 x 50 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified by silica gel column chromatography (25% EtOAc/hexane) yielded 2 g of **28a** as colourless syrup in 74% yield over two steps. R_f = 0.6 (40% EtOAc/hexane); $[\alpha]^{25}_D$ = +106.0 (*c* 1.2, $CHCl_3$); IR (neat) 3017, 1646, 1496, 1427, 1373, 1219, 1023 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.42 (m, 3H), 7.25–7.22 (m, 2H), 6.11 (d, *J* = 3.8 Hz 1H), 6.25– 5.91 (m,1H), 5.38 (dd, *J* = 17.2, 1.9 Hz, 1H), 5.18 (dd, *J* = 7.7, 1.6 Hz, 1H), 4.75 (d, *J* = 3.8 Hz, 1H), 4.44 (d, *J* = 4.2 Hz, 1H), 4.17–4.13 (m, 1H), 3.87 (ddt, *J* = 12.4, 7.2, 1.7 Hz, 1H), 3.77–3.73 (m, 1H), 3.24, (dd, *J* = 8.4, 6.4 Hz, 1H), 1.66 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H) , 1.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 134.9 128.7, 128.5, 126.9, 115.9, 112.7, 108.4, 105.3, 86.7, 83.2, 82.3, 74.2, 66.2, 64.5, 27, 26.8, 26.6, 25.5; HRMS (ESI) calcd. for $C_{21}H_{28}O_6Na$ $(M+Na)^+$ 399.1784, found 399.1782.

(3a*R*,5*R*,6*R*,6a*R*)-6-(allyloxy)-2,2-dimethyl-6-phenyltetrahydrofuro [3,2-d][1,3]dioxole-5 carbaldehyde (29a): The allyl ether **28a** (2 g, 5.31 mmol) was stirred with 35 mL of 90% aqueous AcOH for 12 h at room temperature. The reaction mixture was concentrated azeotropically to provide a diol (1.4 g) as syrup in 70% yield. The resultant diol was dissolved in DCM (5 mL) and added to a stirred suspension of silica supported $NaIO_4$ in DCM (10 mL). The stirring was continued at room temperature for 8 h. The solid was filtered off. The filtrate was concentrated to afford the aldehyde **29a** in quantitative yield. R_f = 0.5 (20% EtOAc/hexane); $[\alpha]^{25}_D$ = +87.2 (*c* 1.0, $CHCl_3$); IR (neat) 3021, 2927, 2857, 1728, 1671, 1591, 1278, 1216, 1021 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 7.42–7.36 (m, 2H), 7.36–7.31 (m, 1H), 7.24–7.15 (m, 1H), 6.22 (d, *J* = 3.6 Hz, 1H), 6.04–5.92 (m, 1H), 5.37 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.21 (dq, *J* = 10.4, 1.6 Hz, 1H), 4.83 (d, *J* = 3.5 Hz, 1H), 4.71 (d, *J* = 1.5 Hz, 1H), 4.14 (ddt, *J* = 12.0, 5.5, 1.5 Hz, 1H), 3.92 (ddt, *J* = 12.0, 5.5, 1.5 Hz, 1H), 2.86 (dd, *J* = 8.4, 6.5 Hz, 1H), 1.66 (s, 3H), 1.44 (s 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 135.6, 134.3, 129.1, 128.9, 126.6, 116.9, 113.5, 105.9, 87.9, 85.9, 83.4, 66.6, 27.1, 26.8; HRMS (ESI) calcd. for $C_{17}H_{20}O_5Na$ $(M+Na)^+$ 327.1208, found 327.1221.

(3a*R*,5*R*,6*R*,6a*R*)-6-(allyloxy)-5-ethynyl-2,2-dimethyl-6-phenyltetra hydrofuro[3,2 d][1,3] dioxole (30a): To a solution of aldehyde **29a** (0.3 g, 0.98 mmol) in dry methanol (21 mL) was added anhydrous K_2CO_3

(0.34 g). To this mixture dimethyl-1-diazo-2-oxopropylphosphonate **25** was added at room temperature and stirred for 4 h. The reaction mixture was diluted with 35 mL of ether, washed with 5% of aqueous $NaHCO_3$ and the organic layer was concentrated. The crude product was purified by a silica gel column chromatography (5% EtOAc/hexane) to afford the **30a** (0.2 g) as a white gummy solid in 71% yield. R_f =0.7 (10% EtOAc/hexane); $[\alpha]^{25}_D$ = +64.5 (*c* 0.78, $CHCl_3$); IR (neat) 3019, 2400, 1522, 1425, 1219, 1097, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52–5.48 (m, 2H), 7.44–7.33 (m, 3H), 6.03–5.94 (m, 1H), 5.93 (d, *J* = 3.7 Hz, 1H), 5.33 (dq, *J* = 17.2, 1.7Hz, 1H), 5.21 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.11 (d, *J* = 2.3 Hz, 1H), 4.71 (d, *J* = 3.6 Hz, 1H), 4.12 (ddt, *J* = 12.0, 5.6, 1.4 Hz, 1H), 3.92 (ddt, *J* = 12.0, 5.6, 1.4 Hz, 1H), 2.40 (s, 1 H), 1.65 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6, 134.6, 128.6, 127.6, 117.0, 113.4, 104.6, 87.5, 83.5, 78.4, 78.3, 73.3, 67.0, 27.1, 26.6; HRMS (ESI) calcd. for $C_{18}H_{20}O_4Na$ $(M+Na)^+$ 323.1259, found 323.1266.

Compound 19: A solution of enyne **30a** (0.3 g, 1.05 mmol) in dry CH_2Cl_2 (340 mL) under Argon was degassed and to this mixture a solution of Grubbs' catalyst **26** (0.052 g, 7 mol %) in CH_2Cl_2 (5 mL) was added drop wise and refluxed for 11 h. The reaction mixture was cooled to room temperature and DMSO (5.9 mmol) was added to quench the catalyst and stirred for 6 h at room temperature. Evaporation of the solvent and purification by silica gel column chromatography (8% EtOAc/hexane) gave **19** (0.24 g) as a white gummy solid in 80% yield. R_f =0.7 (10% EtOAc/hexane); $[\alpha]^{25}_D$ = +265.9 (*c* 0.46, $CHCl_3$); IR (neat) 2939, 1657, 1451, 1376, 1215, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65–7.59 (m, 2H), 7.36–7.24 (m, 3H), 6.30 (dd, *J* = 17.5, 11.1 Hz, 1H,), 5.90 (d, 17.4 Hz, 1H), 5.71 (d, *J* = 3.3 Hz, 1H), 5.31–5.21 (m, 3H), 4.52 (d, *J* = 3.3 Hz, 1H), 4.43 (d, *J* = 18.6 Hz, 1H), 3.97 (d, *J* = 2.5 Hz, 1H), 1.67 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 136.8, 134.3, 134.2, 128.5, 128.2, 127.9, 123.6, 117.5, 117.4, 114.1, 106.0, 83.0, 75.2, 65.7, 26.8, 26.3; HRMS (ESI) calcd. for $C_{18}H_{20}O_4Na$ $(M+Na)^+$ 323.1259, found 323.1264.

Hybrid compound 31 : Following the general procedure (method A) for Diels-Alder reaction between the diene **17** (0.112 g, 0.5 mmol) and 1, 4-naphthoquinone **11** (0.102 g, 0.65 mmol) afforded 0.128 g of the aromatized adduct **31** in 68% yield as a yellow solid after silica gel column chromatography (8% EtOAc/hexane): mp = 172–174 °C; R_f = 0.6 (15% EtOAc/hexane); $[\alpha]^{25}_D$ = +215 (*c* 1.1, $CHCl_3$); IR (neat) 3021, 2929,1675, 1412, 1217, 1086, 1017 cm^{-1}; ^1H NMR (400 MHz,$CDCl_3$) δ 8.34, (d, *J* = 8.0 Hz, 1H), 8.29–8.26 (m, 1H), 8.25–8.10 (m, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 7.84–7.77 (m, 2H), 6.02 (d, *J* = 3.7 Hz, 1H), 5.60 (d, *J* = 17.8 Hz, 1H), 5.07 (d, *J* = 17.8 Hz, 1H), 5.04 (s, 1H), 4.79 (d, *J* = 3.8 Hz, 1H), 4.22 (d, *J* = 2.3 Hz, 1H), 1.61 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.0, 183.0, 139.4, 136.9, 136.4, 134.8, 134.5, 134.3, 134.2, 132.7, 129.8, 127.4, 127.1, 126.6, 112.2, 105.4, 84.8, 78.8, 73.8, 68.0, 27.0, 26.3; HRMS (ESI) calcd. for $C_{22}H_{19}O_6$ $(M+H)^+$ *m/z* 379.1182, found 379.1167.

Hybrid compound 32 : Following the general procedure (method A) for Diels-Alder reaction between the diene **17** (0.112 g, 0.5 mmol) and 1,4-dihydroxy naphthoquinone **12** (0.123, 0.65 mmol) afforded 0.137 g of the aromatized adduct **32** in 67% yield as a brown solid after silica gel column chromatography (8% EtOAc/hexane) : mp = 186–188 °C ; R_f = 0.5 (15% EtOAc/hexane); $[\alpha]^{25}_D$ = +142 (*c* 0.8, $CHCl_3$); IR (neat) 3469, 2924, 1617, 1418, 1352, 1218, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.84 (s, 2H), 8.39, (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.31 (s, 2H), 6.04 (d, *J* = 4.0 Hz, 1H), 5.68 (d, *J* = 17.6 Hz, 1H), 5.08 (d, *J* = 17.6 Hz, 1H), 5.06 (d, *J* = 2.0 Hz, 1H), 4.81 (d, *J* = 4.0 Hz, 1H), 4.22 (d, *J* = 2.4 Hz, 1H), 1.62 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9, 186.6, 139.9, 157.5, 136.9, 134.8, 129.9, 129.7, 129.3, 126.3, 112.4, 112.3, 105.4, 84.8, 78.7, 73.8, 68.1, 29.9, 27.0, 26.3; HRMS (ESI) calcl. For $C_{22}H_{19}O_8$ $(M+H)^+$ 411.1080, found 411.1100.

Hybrid compound 33 : Following the general procedure (method A) for Diels-Alder reaction between the diene **17** (0.112 g, 0.5 mmol) and 1,4-dihydroxy naphthoquinone **13** (0.135 g, 0.65mmol) afforded 0.150 g of the aromatized adduct **33** in 71% yield as a brown solid after silica gel column chromatography (8% EtOAc/hexane) : mp = 179–181 °C; R_f = 0.5 (15% EtOAc/hexane); $[\alpha]^{25}_D$ = –87.17 (*c* 0.39, $CHCl_3$); IR (neat) 3464, 3020, 1732, 1645, 1375, 1215, 1094 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 8.77, (s,1H), 8.41 (d, *J* = 8.0 Hz, 1H), 8.11–8.06 (m, 2H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.67–7.30 (m, 2H), 6.03 (d, *J* = 3.8 Hz, 1H), 5.65 (d, *J* = 17.5 Hz, 1H), 5.11 (d, *J* = 17.5 Hz, 1H), 5.05 (d, *J* = 2.0 Hz, 1H), 4.80 (d, *J* = 3.5 Hz, 1H), 4.24 (d, *J* = 2.2 Hz, 1H), 1.62 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.6, 182.7, 139.5, 136.9, 136.4, 135.7, 135.4, 135.1, 130.8, 130.3, 130.2, 130.2, 129.7, 129.6, 129.4, 128.9, 126.7, 112.2, 105.4, 84.8, 78.7, 73.8, 68.2, 27.0, 26.3; HRMS (ESI) calcl. For $C_{26}H_{21}O_6$ $(M+H)^+$ 429.1338, found 429.1331.

Hybrid compound 34 : Following the general procedure (method A) for Diels-Alder reaction between the diene **17** (0.112 g, 0.5 mmol) and 5-hydroxy 1,4-naphthoquinone **14** (0.113 g, 0.65 mmol) afforded 0.164 g of the aromatized adduct **34** in 80% yield (inseparable mixture of diastereomers (d.r = 2.2:1)) as a brown solid after silica gel column chromatography (8% EtOAc/hexane) : mp = 187–189 °C ; R_f = 0.6 (15% EtOAc/hexane); $[\alpha]^{25}_D$ = –89.9 (*c* 1.3, $CHCl_3$); IR (neat) 3472, 2927, 2854, 1966, 1732, 1673, 1636, 1456, 1313, 1216, 1096 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 12.46 (s, 0.65H), 12.39 (s, 0.3H), 8.28–8.25 (m, 1H), 7.93–7.87 (m,1H), 7.78 (dd, *J* = 7.4, 1.1 Hz, 0.7H), 7.69 (dd, *J* = 7.5, 1.2 Hz, 0.3H), 7.66–7.63 (m, 1H), 7.29–7.25 (m, 1H), 6.02–6.01 (m, 1H), 5.59–5.49 (m, 1H), 4.99–4.98 (m, 2H), 4.78 (d, *J* = 3.6 Hz, 1H), 4.18 (s, 1H), 1.62 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 187.9, 183.8, 181.9, 162.3, 161.1, 139.4, 137.9, 136.9, 136.8, 136.6, 136.2, 134.5, 134.1, 133.8, 132.4, 129.6, 129.1, 126.4, 125.9, 124.6, 123.9, 119.4, 119.2, 116.4,115.3, 112, 105.2, 84.5, 78.5, 78.4, 73.6, 73.5 67.8, 67.7, 26.8, 26.1; HRMS (ESI) calcl. For $C_{22}H_{18}O_7Na$ $(M+Na)^+$ 417.0950, found 417.0931.

Hybrid compound 35 : Following the general procedure (method A) for Diels-Alder reaction between the diene **17** (0.112 g, 0.5 mmol) and 4-nitronaphthoquinone **15** (0.132 g, 0.65 mmol) afforded 0.164 g of the aromatized adduct **35** in 75% yield as a yellow solid (inseparable mixture of diastereomers (d.r = 6.3:1)) after silica gel column chromatography (9% EtOAc/hexane): mp = 218–220 °C ; R_f = 0.4 (15% EtOAc/hexane);

$[\alpha]^{25}_D$ = –79.5 (*c* 0.27, $CHCl_3$); IR (neat) 2923, 2858, 1631, 1546, 1528, 1376, 1211, 1094, 1015 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.43, (dd, *J* = 7.9, 0.95 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 7.99–7.95 (m, 1H), 7.94–7.89 (m, 1H), 7.76 (dd, *J* = 7.8, 1 Hz, 1H), 6.01 (d, *J* = 3.7 Hz, 1H), 5.55 (d, *J* = 17.6 Hz, 1H), 5.01–5.08 (m, 2H), 4.78 (d, *J* = 3.6 Hz, 1H), 4.21 (d, *J* = 1.2 Hz, 1H), 1.60 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.4, 179.7, 148.7, 139.6, 139.5, 137.6, 137.0, 136.8, 134.9, 134.8, 134.4, 134.2, 129.7, 129.5, 128.5, 128.1, 127.5, 126.8, 126.5, 123.9, 112.1, 112.0, 105.2, 84.5, 78.7, 78.6, 73.4, 67.6, 67.4, 26.8, 26.1; HRMS (ESI) calcd. For $C_{22}H_{17}NNaO_8$ $(M+Na)^+$ 446.0846, found 446.0841.

Hybrid compound 36 : Following the general procedure (method B) for Diels-Alder reaction between the diene **17** (0.112 g, 0.5 mmol) and DMAD **16** (0.092 g, 0.65 mmol) afforded 0.133 g of the aromatized adduct **36** in 73% yield as a white solid after silica gel column chromatography (30% EtOAc/hexane) : mp = 154–156 °C ; R_f = 0.6 (30% EtOAc/hexane); $[\alpha]^{25}_D$ = -155 (*c* 0.91, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 5.98 (d, *J* = 3.8 Hz, 1H), 4.99 (d, *J* = 2.3 Hz, 1H), 4.81 (d, *J* = 15.6 Hz, 1H), 4.73 (d, *J* = 3.8 Hz, 1H), 4.66 (d, *J* = 15.6 Hz, 1H), 4.17 (d, *J* = 2.4 Hz, 1H), 3.91 (s, 3H), 3.89 (s, 3H),1.59 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 166.0, 134.6, 133.3, 132.1, 131.6, 128.9, 128.7, 112.1, 105.3, 84.7, 79.7, 73.0, 65.5, 52.9, 52.8, 26.9, 26.3; IR (neat) 3019, 2929, 1733, 1449, 1216, 1018 cm^{-1}; HRMS (ESI) calcd. for $C_{18}H_{20}O_8Na$ $(M+Na)^+$ 387.1050 found 387.1049.

Hybrid compound 38 : Following the general procedure (method A) for Diels-Alder reaction between the diene **18** (0.119 g, 0.5 mmol) and 5, 8-dihydroxynaphthoquinone **12** (0.123 g, 0.65 mmol) afforded 0.131 g of the aromatized adduct **38** in 62% yield as a red solid after silica gel column chromatography (9% EtOAc/hexane) : mp = 192–194 °C; R_f = 0.65 (15% EtOAc/hexane); $[\alpha]^{25}_D$ = +36.1 (*c* 0.5, $CHCl_3$); IR (KBr) 3413, 2930, 2862, 1967, 1616, 1455, 1248, 1217, 1090, 1038 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.89 (s, 2H), 8.43 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.31(s, 2 H), 5.98 (d, *J* = 3.2 Hz, 1H), 5.74 (d, *J* = 19.2 Hz, 1H), 5.58 (d, *J* = 19.2 Hz, 1H,), 5.17 (s, 1H), 4.53 (d, *J* = 3.3 Hz, 1H), 1.69 (s, 3H), 1.24 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9, 186.7, 157.9, 157.6, 142.8, 137.6, 133.8, 129.8, 129.7, 129.4, 129.1, 126.8, 114.4, 113.5, 112.4, 106.8, 82.7, 77.40, 75.0, 67.7, 26.7, 26.2, 15.8; HRMS (ESI) calcd. for $C_{23}H_{20}O_8$ *m/z* $(M+H)^+$ 425.1236, found 425.1240.

Hybrid compound 40 : Following the general procedure (method A) for Diels-Alder reaction between the diene **18** (0.119 g, 0.5 mmol) and 5-hydroxynaphthoquinone **14** (0.113 g, 0.65 mmol) afforded 0.171 g of the aromatized adduct **40** in 84% yield as a yellow solid (mixture of inseparable regioisomers d.r. = 2.2:1) after silica gel column chromatography (13% EtOAc/hexane): mp = 183–185 °C; R_f = 0.6 (25% EtOAc/hexane); $[\alpha]^{25}_D$ = +247 (*c* 0.75, $CHCl_3$); IR (neat) 2923, 2853, 1669, 1634, 1455, 1374, 1216, 1087, 1049 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 12.59 (s, 0.7H), 12.5 (s, 0.3H), 8.35 (d, *J* = 7.9 Hz, 1H), 7.86 (dd, *J* = 16.8, 0.9 Hz, 1H), 7.63–7.70 (m, 1H), 7.27–7.33 (m, 1H), 5.99 (d, *J* = 3.3 Hz, 1H), 5.67 (dd, *J* = 19.1, 6.9 Hz, 1H), 5.56 (dd, *J* = 19.1, 8.9 Hz, 1H), 5.16 (s, 1H), 4.54 (dd, *J* = 3.3, 1.6 Hz, 1H), 1.66 (s, 3H), 1.43 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 188.3, 184.1, 182.4, 162.6, 162.3, 142.9, 142.4, 137.3, 137.0, 136.7, 134.2, 133.9, 133.5, 132.7, 129.8, 129.4, 129.3, 129.1, 127.2, 126.6, 124.8, 124.0, 119.3, 116.8, 115.6, 114.3, 106.8, 82.7, 75.0, 74.9, 67.6, 26.6, 26.2, 15.9, 15.8; HRMS (ESI) calcd. For $C_{23}H_{21}O_7$ *m/z* $(M+H)^+$ 409.1287, found 409.1271.

Hybrid compound 41 : Following the general procedure (method A) for Diels-Alder reaction between the diene **18** (0.119 g, 0.5 mmol) and 5-nitronaphthoquinone **15** (0.132 g, 0.65 mmol) afforded 0.183 g of the aromatized adduct **41** in 81% yield as a yellow solid (as a mixture of inseparable diastereomers d.r = 3.1:1) after silica gel column chromatography (8% EtOAc/hexane) : mp = 176–178 °C , R_f = 0.6 (15% EtOAc/hexane); $[\alpha]^{25}_D$ = +5.3 (*c* 0.46, $CHCl_3$); IR (neat) 2926, 2854, 1966, 1605, 1571, 1545, 1514, 1365, 1216, 1082 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 7.9 Hz, 1H), 7.45 (dd, *J* = 8.2 Hz, 1H), 6.95 (dd, *J* = 8.3,1.0 Hz, 1H), 5.97 (d, *J* = 3.3 Hz, 1H), 5.67 (d, *J* = 18.9 Hz, 1H), 5.53 (d, *J* = 18.8 Hz, 1H), 5.15 (s, 1H), 4.51 (d, *J* = 3.3 Hz, 1H), 1.65 (s, 3H), 1.41 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.0, 184.7, 181.4, 150.7, 143.2, 140.9, 137.4, 136.3, 135.2, 135, 134.9, 134.4, 133.6, 132.6, 129.8, 129.5, 129, 128.9, 128, 127, 126.4, 122.6, 117.3, 114.3, 114.1, 113, 106.6, 82.6, 82.5, 74.9, 74.8,67.5, 67, 26.53, 26.1, 26, 15.8, 15.7; HRMS (ESI) calcd. For $C_{23}H_{19}NNaO_8$ $(M+Na)^+$ 460.1003, found 409.1000.

Hybrid compound 42 : Following the general procedure (method B) for Diels-Alder reaction between the diene **18** (0.119 g, 0.5 mmol) and DMAD (0.092 g, 0.65 mmol) afforded 0.130 g of the aromatized adduct **42** in 61% yield as a white yellow solid after silica gel column chromatography (13% EtOAc/hexane) : mp = 162–164 °C ; R_f = 0.6 (25% EtOAc/hexane); $[\alpha]^{25}_D$ = −50.4 (*c* 1.3, $CHCl_3$); IR (neat) 2926, 1735, 1639, 1374, 1250, 1098, 1025, 945 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 5.94 (d, *J* = 3.7 Hz, 1H), 5.04-5.12 (m, 2H), 4.93 (d, *J* = 16.2 Hz, 1H), 4.45 (d, *J* = 3.2 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 1.62 (s, 3H), 1.39 (s, 3H), 0.87 (s, 3H);; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 165.8, 139.9, 137.2, 130.1, 127.9, 127.5, 125.7, 112.3, 105.3, 84.5, 80.1, 70.3, 67.4, 52.9, 52.8, 27.2, 26.7; HRMS (ESI) calcd. For $C_{19}H_{22}O_8Na$ $(M+Na)^+$ 401.1207, found 401.1207.

Hybrid compound 43 : Following the general procedure (method A) for Diels-Alder reaction of the diene **19** (0.150 g, 0.5 mmol) and 1,4-naphthoquinone **11** (0.101 g, 0.65 mmol) afforded 0.186 g of the aromatized adduct **43** in 82% yield as a dark yellow solid after silica gel column chromatography (8% EtOAc/hexane): mp = 186–188 °C; R_f = 0.5 (10% EtOAc/hexane); $[\alpha]^{25}_D$ = −23.4 (*c* 1.6, $CHCl_3$); IR (KBr) 2983, 1671, 1591, 1566, 1449, 1375, 1322, 1215, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.36, (d, *J* = 7.9 Hz, 1H), 8.17−8.23 (m, 1H), 8.08−8.15 (m, 1 H), 8.14 (dd, *J* = 7.9, 1 Hz, 1H), 7.68−7.75 (m, 2H), 7.48−7.53 (m, 2H), 7.10−7.22 (m, 3H), 5.90 (d, *J* = 3.1 Hz, 1H), 5.73 (d, *J* = 4.3 Hz, 1H), 5.69 (s, 1H), 5.16 (d, 1H, *J* = 18.8 Hz), 4.67 (d, *J* = 3.12 Hz, 1H), 1.72 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.6, 183.1, 143, 136.8, 136.6, 134.3, 134.1, 134, 133.6, 132.6, 129.3, 128.8, 128.7, 127.4, 127,

115.1, 107.0, 84.0, 81.1, 76.4, 68.4, 27.0, 26.4; HRMS (ESI) calcd. for $C_{28}H_{22}O_6Na$ $(M+Na)^+$ 455.1495, found 455.1496.

Hybrid compound 44 : Following the general procedure (method A) for Diels-Alder reaction of the diene **19** (0.150 g, 0.5 mmol) and 5,8-dihydroxynaphthoquinone **12** (0.12 g, 0.65 mmol) afforded 0.153 g of the aromatized adduct **44** in 63% yield as a red solid after silica gel column chromatography (6% EtOAc/hexane): mp = 228–230 °C; R_f = 0.7 (10% EtOAc/hexane); $[\alpha]^{25}_D$ = –116.8 (*c* 1.3, $CHCl_3$); IR (KBr) 3439, 2924, 2854, 1618, 1455, 1248, 1095, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.85 (s, 1H), 12.77 (s, 1H), 8.41 (d, *J* = 7.96 Hz, 1H), 8.09 (d, *J* = 1.08 Hz, 1H), 7.50 (d, *J* = 1.56 Hz, 1H), 7.25 (s, 1H), 7.12–7.22 (m, 5H), 5.90 (d, *J* = 3.12 Hz, 1H), 5.73 (s, 1H), 5.72 (d, *J* = 18.9 Hz, 1H), 5.16, (d, *J* = 18.9 Hz, 1H), 4.67, (d, 3.16 Hz, 1H), 1.72 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 186.6, 157.7, 143.6, 137.3, 136.4, 133.4, 129.6, 129.3, 129.2, 129.0, 128.7, 128.3, 128.2, 126.6, 115.1, 113.4, 112.2, 107.0, 84.1, 81.0, 68.3, 27.0, 26.3; HRMS (ESI) calcd. for $C_{28}H_{23}O_8$ *m/z* $(M+H)^+$ 487.1393, found 487.1401.

Hybrid compound 45 : Following the general procedure (method A) for Diels-Alder reaction of the diene **19** (0.150 g, 0.5 mmol) and 1,4-anthraquinone **13** (0.135 g, 0.65 mmol) afforded 0.224 g of the aromatized adduct **45** in 89% yield as a yellow solid after silica gel column chromatography (9% EtOAc/hexane) : mp = 198–200 °C; R_f = 0.7 (15% EtOAc/hexane); $[\alpha]^{25}_D$ = –46.16 (*c* 0.50, $CHCl_3$); IR (KBr) 2930, 1672, 1619, 1588, 1458, 1297, 1206, 1093, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.75 (s, 1H), 8.65 (s, 1H), 8.45 (d, *J* = 7.9 Hz, 1H), 8.05–8.12 (m, 3H), 7.63–7.66 (m, 2H), 7.52–7.54 (m, 2H), 7.10–7.22 (m, 3H), 5.92 (d, *J* = 3.1 Hz, 1H), 5.78 (d, *J* = 18.6 Hz, 1H), 5.74 (s, 1H), 5.22 (d, *J* = 18.6 Hz, 1H), 4.68, (d, 3.1Hz, 1H), 1.73 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.5, 183, 142.9, 137, 136.6, 135.4, 135.1, 134.7, 130.4, 130.2, 129.8, 129.6, 129.2, 129, 128.8, 128.7, 128.2, 127.2, 115.0, 107.0, 84.2, 81.1, 68.5, 27.0, 26.4 ; HRMS (ESI) calcd. for $C_{32}H_{24}O_6$ $(M+H)^+$ 505.1651, found 505.1661.

Hybrid compound 46 : Following the general procedure (method A) for Diels-Alder reaction of the diene **19** (0.150 g, 0.5 mmol) and 5-hydroxy 1,4-naphthoquinone **14** (0.113 g, 0.65 mmol) afforded 0.172 g of the aromatized adduct **46** in 71% yield as a yellow solid (mixture of inseparable regioisomers d.r. = 2.1:1) after silica gel column chromatography (8% EtOAc/hexane): mp = 204–206 °C; R_f = 0.75 (15% EtOAc/hexane); $[\alpha]^{25}_D$ = – 85.5 (*c* 1.19, $CHCl_3$); IR (KBr) 3429, 2933, 1966, 1669, 1636, 1586, 1454, 1277, 1217, 1095, 1014 cm^{-1} ;^1H NMR (500 MHz, $CDCl_3$) δ 12.49, (d, 1H, *J* = 4.2 Hz), 8.20–8.39 (m, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 7.4 Hz, 1H), 7.66–7.76 (m, 1H), 7.48–7.53 (m, 2 H), 7.12–7.25 (m, 4H), 5.90 (d, 1 H, *J* = 2.9 Hz), 5.64–5.75 (m, 2H), 5.14 (d, 1H, *J* = 18.6 Hz), 4.67 (d, 1H, *J* = 2.9 Hz), 1.72 (s, 3 H), 1.43 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 182.4, 162.6, 143.2, 136.9, 136.7, 136.5, 136.3, 133.5, 132.5, 129.2, 128.9, 128.5, 128.1, 128, 126.9, 126.4, 124.5, 123.7, 119.4, 119, 116.6, 114.9, 107.07, 84.1, 81.09, 80.9, 76.2, 76.1, 68.1, 26.8, 26.2; HRMS (ES) calcd. for $C_{28}H_{23}O_7$ $(M+H)^+$ 471.1444, found 471.1440.

Hybrid compound 47 : Following the general procedure (method A) for Diels-Alder reaction of the diene **19** (0.150 g, 0.5 mmol) and 5-nitro naphthoquinone **15** (0.132 g, 0.65 mmol) afforded 0.216 g of the aromatized adduct **47** in 84% yield as a yellow solid (as mixture of inseparable diastereomers d.r. = 1.7:1) after silica gel column chromatography (8% EtOAc/hexane), R_f = 0.6 (15% EtOAc/hexane): mp = 196–198 °C; $[\alpha]^{25}_D$ = −9.5 (*c* 0.9, $CHCl_3$); IR (KBr) 2926, 1738, 1634, 1605, 1570, 1544, 1457, 1376, 1322, 1275, 1259, 1095, 1015 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.25–8.35 (m, 2H), 8.06 (dd, *J* = 7.8, 1 Hz, 1H), 7.66 (dd, *J* = 7.8, 0.95 Hz, 1H), 7.44–7.53 (m, 2H), 7.11–7.22 (m, 4H), 5.90 (m, 1H), 5.64–5.75 (m, 2H), 5.09−5.14 (m, 1H), 4.64−4.66 (m, 1H), 1.72 (s, 3 H), 1.39 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.7, 184.6, 182, 179.6, 150.5, 148.7, 143.7, 141.6, 137, 136.5, 136.1, 134.9, 134.8, 134.7, 134.5, 133.1, 129.7, 129.3, 128.8, 128.6, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.4, 127.2, 126.2, 124.0, 122.4, 117.1, 114.9, 114.8, 106.9, 106.8, 83.9, 83.8, 81, 80.9, 76.2, 76.1, 68.2, 67.9, 26.7, 26.2; HRMS (ESI) calcd. for $C_{28}H_{21}NNaO_7$ $(M+Na)^+$ 522.1159, found 522.1158.

Hybrid compound 48 : Following the general procedure (method B) for Diels-Alder reaction of the diene **19** (0.150 g, 0.5 mmol) and DMAD (0.092 g, 0.65 mmol) afforded 0.165 g of the aromatized adduct **48** in 75% yield as colourless solid after silica gel column chromatography (40% EtOAc/hexane). R_f = 0.52 (20% EtOAc/hexane): mp = 175–177 °C $[\alpha]^{25}_D$ = −29.9 (*c* 1.5, $CHCl_3$); IR (neat) 3020, 2929, 1733, 1449, 1216, 1018 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31, (d, *J* = 8.2 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.34–7.44 (m, 5H), 5.20 (d, *J* = 2.9 Hz, 1H), 4.90 (d, *J* = 16.3 Hz, 1H), 4.80 (d, *J* = 16.3 Hz, 1H), 4.52 (d, *J* = 2.88 Hz, 1H), 3.91 (s, 3H), 3.90 (s, 3H), 1.29 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz $CDCl_3$) δ 168.4, 166.2, 132.6, 129.5, 129.0, 128.9, 128.7, 127.6, 112.7, 104.3, 88.8, 60.8, 55.3, 53.2, 27.1, 27.0; HRMS (ESI) calcd. For $C_{24}H_{25}O_8$ $(M+H)^+$ 441.1549, found 441.1537.

Hybrid compound 49 : Following the general procedure (method A) for Diels-Alder reaction between the diene **20** (0.112 g, 0.5 mmol) and 1,4-naphthoquinone **11** (0.102 g, 0.65 mmol) afforded 0.145 g of the aromatized adduct **49** in 77% yield as a pale yellow solid after silica gel column chromatography (11% EtOAc/hexane: mp = 152–154 °C; R_f = 0.6 (20% EtOAc/hexane); $[\alpha]^{25}_D$ = +129 (*c* 1.2, $CHCl_3$); IR (neat) 2926, 2854, 1674, 1592, 1324, 1286, 1217, 1164, 1069 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.30−8.40 (m, 2H), 8.21−8.29 (m, 1H), 7.77−7.79 (m, 2H), 7.49 (d, *J* = 8.0 Hz, 1H), 6.22 (d, *J* = 2.0 Hz, 1H), 6.03 (d, *J* = 3.7 Hz, 1H), 4.91−4.96 (m, 1H), 4.82−4.88 (m, 1H), 4.68−4.77 (m, 1H), 4.24 (d, 1H, *J* = 2.1 Hz), 1.82 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.0, 183.2, 142.3, 134.7, 134.5, 133.9, 132.5, 131.2, 130.2, 128.3, 128.2, 126.8, 112.6, 105.1, 84.3, 79.9, 70.8, 67.8, 27.35, 27.0; HRMS (ESI) calcl. For $C_{22}H_{19}O_6$ $(M+H)^+$ 379.1182, found 379.1194.

Hybrid compound 50 : Following the general procedure (method A) for Diels-Alder reaction between the diene **20** (0.112 g, 0.5 mmol) and 1,4-dihydroxy naphthoquinone **12** (0.123 g, 0.65 mmol) afforded 0.096 g of the aromatized adduct **50** in 63% yield as a brown solid after silica gel column chromatography (8% EtOAc/hexane): mp = 177–179 °C; R_f = 0.5

(15% EtOAc/hexane); $[\alpha]^{25}_{D}$ = +51.3 (*c* 0.37, $CHCl_3$); IR (neat) 3432, 2923, 2857, 1671, 1583, 1322, 1283, 1211, 1165, 1065 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 13.02 (s, 1H), 12.9 (s, 1H), 8.42 (d, *J* = 8 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.28−7.33 (m, 2H), 6.2 (d, *J* = 1.3 Hz, 1H), 6.03 (d, *J* = 3.5 Hz, 1H), 4.96 (d, *J* = 16 Hz, 1H),4.87 (d, *J* = 16 Hz, 1H), 4.73 (d, 1H, *J* = 3.5 Hz), 4.23 (d, 1H, *J* = 1.5 Hz), 1.76 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.2, 186.2, 158.0, 157.4, 134.8, 131.8, 131.5, 130.6, 130, 128.9, 127.8, 113.4, 112.6, 112.1, 104.9, 83.9, 79.5, 70.6, 67.7, 27.1, 26.8; HRMS (ESI) calcl. For $C_{22}H_{18}NaO_8$ $(M+Na)^+$ 433.0894, found 433.0896.

Hybrid compound 51 : Following the general procedure (method A) for Diels-Alder reaction between the diene **20** (0.112 g, 0.5 mmol) and 1,4-anthraquinone **13** (0.135 g, 0.65 mmol) afforded 0.161 g of the aromatized adduct **51** in 76% yield as a yellow solid after silica gel column chromatography (10% EtOAc/hexane): mp = 166–168 °C; R_f = 0.5 (15% EtOAc/hexane); $[\alpha]^{25}_{D}$ = +89 (*c* 1.0, $CHCl_3$); IR (neat) 2929, 2851, 1674, 1581, 1317, 1286, 1215, 1162, 1059 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.88 (s, 1H), 8.78 (s, 1H), 8.44 (d, *J* = 8 Hz, 1H), 8.07−8.08 (m, 2H), 7.68 (d, *J* = 3.2 Hz, 1H), 7.67 (d, *J* = 3.1 Hz, 1H), 7.49 (d, *J* = 8 Hz, 1H), 6.30 (s, 1H), 6.04 (d, *J* = 3.6 Hz, 1H), 4.96 (d, *J* = 15.7 Hz, 1H), 4.86 (d, *J* = 15.7 Hz, 1H), 4.74 (d, *J* = 3.6 Hz, 1H), 4.25 (d, 1H, *J* = 1.6 Hz), 1.85 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ183.7, 182.6, 142.2, 135.4, 134.9, 132.7, 131.6, 130.3, 129.4, 129.3, 128.8, 128.3, 118.4, 104.9, 84.1, 79.8, 70.6, 67.7, 27.2, 26.8; HRMS (ESI) calcl. For $C_{26}H_{20}NaO_6$ $(M+Na)^+$ 451.1158, found 451.1158.

Hybrid compound 52 : Following the general procedure (method A) for Diels-Alder reaction between the diene **20** (0.112 g, 0.5 mmol) and 5-hydroxynaphthoquinone (0.113 g, 0.65 mmol) afforded 0.147 g of the aromatized adduct **52** in 72 % yield as a yellow solid (mixture of regioisomers d. r. = 3.6:1) after silica gel column chromatography (12% EtOAc/hexane): mp = 164–166 °C; R_f = 0.6 (25% EtOAc/hexane); $[\alpha]^{25}_{D}$ = +121 (*c* 1.1, $CHCl_3$); IR (neat) IR (neat) 3490, 3021, 2929, 1669, 1217, 1099, 1021, 940 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.1 (s, 1H), 8.34 (d, *J* = 8.04 Hz, 1H), 7.78 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.65 (m, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.32 (dd, *J* =8.4, 1.2 Hz, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 6.12 (d, *J* = 2.0 Hz, 1H), 6.02 (d, *J* = 3.7 Hz, 1H), 4.94 (d, *J* = 15.9 Hz, 1H), 4.86 (d, *J* = 15.9 Hz, 1H), 4.73 (d, 1H, *J* = 3.70 Hz), 4.23 (d, 1H, *J* = 2.2 Hz), 1.77 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 182.4, 162.8, 142.6, 136.6, 134.6, 132.5, 131.7, 131.5, 130.9, 128.4, 127.9, 125.1, 120.5, 119.2, 117.1, 112.7, 105.1, 84.2, 84.1, 79.7, 70.8, 70.7, 67.9, 27.3, 27.0; HRMS (ESI) calcl. For $C_{22}H_{18}O_8Na$ $(M+Na)^+$ 433.0899, found 433.0878.

Hybrid compound 53 : Following the general procedure (method A) for Diels-Alder reaction between the diene **20** (0.112 g, 0.5 mmol) and 5-nitronaphthoquinone (0.132, 0.65 mmol) afforded 0.138 g the aromatized adduct **53** in 63% yield as a yellow solid (mixture of regioisomers d. r. = 2.6:1) after silica gel column chromatography (8% EtOAc/hexane): mp = 142–144 °C; R_f = 0.6 (15% EtOAc/hexane); $[\alpha]^{25}_{D}$ = +194 (*c* 1.2, $CHCl_3$); IR (neat); IR (neat) 3024, 2925, 2851, 1774, 1678, 1601, 1570, 1515, 1456, 1215, 1085, 1024, 940 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (dd, *J* = 7.9, 1.0 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 7.89 (dd, *J* = 7.9, 7.8 Hz, 1H), 7.72−7.74 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 6.10 (d, *J* = 1.8 Hz, 1H), 6.0 (d, *J* = 4 Hz, 1H), 4.94 (d, *J* = 12 Hz, 1H), 4.82 (d, *J* = 12 Hz, 1H), 4.72 (d, 1H, *J* = 3.70 Hz), 4.23 (d, 1H, *J* = 2.2 Hz), 1.78 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.5, 179.7, 148.9, 148.2 135.5, 134.6, 133.4 130.9, 130.8, 130.4, 128.9, 123.3, 122.8, 112.4, 104.2, 84.9, 79.7, 70.4, 67.6, 27.4, 26.8 ; HRMS (ESI) calcl. For $C_{22}H_{17}O_8NNa$ $(M+Na)^+$ 446.0850, found 446.0850.

Hybrid compound 54 : Following the general procedure (method B) for Diels-Alder reaction between the diene **20** (0.112 g, 0.5 mmol) and DMAD (0.092 g, 0.65 mmol) afforded 0.138 g of the aromatized adduct **54** in 76% yield as a pale yellow solid after silica gel column chromatography (13% EtOAc/hexane): mp = 127–129 °C; R_f = 0.6 (25% EtOAc/hexane); $[\alpha]^{25}_{D}$ = −210 (*c* 0.95, $CHCl_3$); IR (neat) 2927, 1733, 1441, 1279, 1216, 1019, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.1 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 5.95 (d, *J* = 3.7 Hz, 1H), 5.18 (d, *J* = 2.3 Hz, 1H), 4.85 (d, *J* = 15.1 Hz, 1H), 4.70 (d, *J* = 15.7 Hz, 1H), 4.67 (s, 1H), 4.16 (d, *J* = 2.4 Hz, 1H), 3.96 (s, 3H), 3.90 (s, 3H), 1.56 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 165.8, 139.9, 137.2, 130.1, 127.9, 127.5, 125.7, 112.3, 105.3, 84.5, 80.1, 70.3, 67.4, 52.9, 52.8, 27.2, 26.7; HRMS (ESI) calcl. For $C_{18}H_{20}O_8Na$ $(M+Na)^+$ 387.1056, found 387.1075.

Hybrid compound 61 : Following the general procedure (method A) for Diels-Alder reaction between the diene **21** (0.084 g, 0.5 mmol) and 1,4-naphthoquinone **11** (0.102 g, 0.64 mmol) afforded 0.122 g of the aromatized adduct **61** in 64% yield as a pale orange solid after silica gel column chromatography (5% EtOAc/hexane): mp = 117–119 °C; R_f = 0.5 (10% EtOAc/hexane); $[\alpha]^{25}_{D}$ = +308.5 (*c* 0.56, $CHCl_3$); IR (KBr) 2929, 1669, 1587, 1450, 1340, 1329, 1293, 1214, 1103, 1057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.4 Hz, 1H), 8.08−8.28 (m, 2H), 7.76−7.86 (m, 2H), 7.23 (d, *J* = 8.4Hz, 1H), 6.47 (d, *J* = 4.7 Hz, 1H), 6.34 (d, *J* = 4.7 Hz, 1H), 1.58 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.5, 181.9, 164.4, 134.4, 134.02, 133.6, 133.5, 132.6, 131.3, 128.2, 127.4, 127.3, 126.0, 116.1, 114.1, 109.3, 80.7, 28.0, 27.7; HRMS (ESI) calcd. for $C_{19}H_{14}O_5$ $(M+H)^+$ 323.0919, found 323.0916.

Hybrid compound 62 : Following the general procedure (method A) for Diels-Alder reaction between the diene **21** (0.084, 0.5 mmol) and 5,8-dihydroxynaphthoquinone **12** (0.123 g, 0.65 mmol) afforded 0.109 g of the aromatized adduct **62** in 52% yield as a red solid after silica gel column chromatography (6-8% EtOAc/hexane): mp = 146–148 °C ; R_f = 0.6 (10% EtOAc/hexane); $[\alpha]^{25}_{D}$ = +109 (*c* 2.5, $CHCl_3$); IR (neat) 3447, 2927, 1966, 1673, 1618, 1458, 1292, 1215, 1093, 1023, 920 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.98 (s, 1H), 8.40 (d, *J* = 8 Hz, 1H), 7.97 (d, *J* = 8 Hz, 1H), 7.31 (s, 2H), 6.03 (d, 1H, *J* = 4 Hz), 5.68 (d, 1H, *J* = 17.6 Hz), 5.0−5.12 (m, 2H), 4.80 (d, *J* = 4 Hz, 1H), 1.62 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9, 186.5, 157.8, 157.7, 139.9, 137.5, 136.9, 134.7, 129.9, 129.7, 129.2, 126.3, 112.3, 112.2, 105.4, 84.8, 78.6, 73.8, 67.0, 27.0, 26.3; HRMS (ESI) calcd. for $C_{19}H_{15}O_7$ $(M+H)^+$ 355.0818, found 355.0816.

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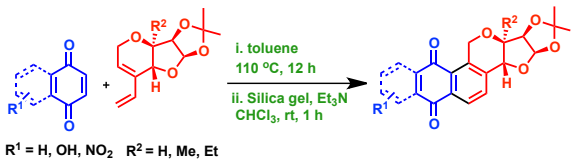

26 examples of Sugar-oxasteroid-quinone hybrids

Scalable

62-89% isolated yields

Key Topic*

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