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# Design and synthesis of novel sugar-oxasteroid-quinone hybrids

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A new class of sugar–oxasteroid–quinone hybrid molecules has been designed and synthesized involving an efficient enyne metathesis/Diels–Alder reaction strategy.

## Introduction

Nature continues to be the main source of inspiration for synthetic chemists in their quest to make new molecules, which can have different physical, biological and medicinal properties. It provides a range of products with varied complex molecular architecture and many of them have been routinely used as drugs against various diseases. Furthermore, Nature also makes some interesting compounds, known as hybrid natural products,[1] derived from mixed biosynthesis (Fig. 1) and some of these natural products are found to exhibit unusual physical and biological properties.[2]

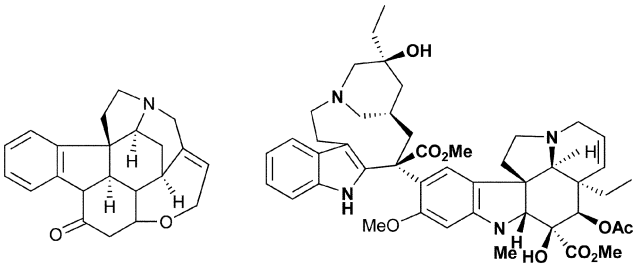



**Fig. 1**

Synthetic chemists have also successfully designed several novel hybrid natural products by combining structurally two different natural products in a single molecule leading to new classes of natural products. The chemical synthesis of hybrid natural products is a promising approach to obtain structurally diverse chemical substances for pharmacological testing. This approach coupled with combinatorial chemistry,[3] should be a powerful and practically feasible method to make thousands of compounds in a relatively short span of time.

Among the hybrid natural products, hybrids of steroid frameworks[4] have attracted great attention due to the significant biological properties and numerous therapeutic effects of steroids.[5] As a part of our research program[6] aimed at the synthesis of biologically active compounds, we developed interest in the synthesis of novel sugar–oxasteroid–quinone hybrid natural products, and herein we report our initial results. To the best of our knowledge, this is the first report on the synthesis of a new class of sugar–oxasteroid–quinone hybrid natural products having steroidal backbone and interestingly, these compounds have three different structural motifs.

Steroids represent an important class of natural products due to their high ability to penetrate cells and bind to membrane receptors. Numerous strategies[7,8] have been developed for the syntheses of this class of natural products. Similarly, owing to the importance of antineoplastic activity of anthracycline antibiotics such as daunomycinone, doxorubicin (Fig. 2) *etc.*, which have been successfully used in the treatment of cancers,[9] a few synthetic efforts have been made to synthesize simpler

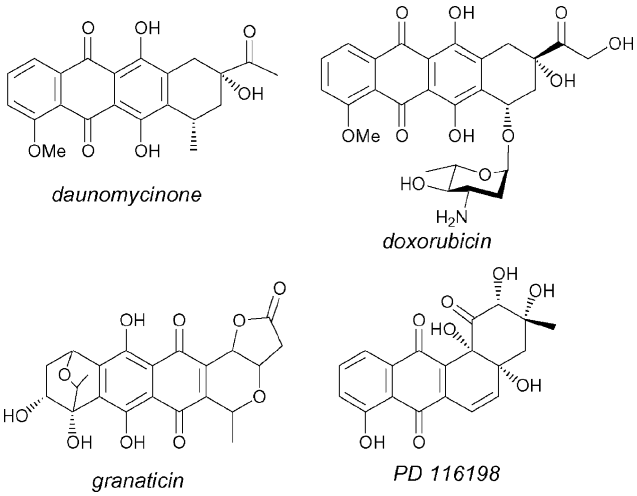



**Fig. 2** Anthraquinone anticancer agents.

analogues of these natural products.[10] In view of the importance of these two classes of natural products, we have designed a new class of hybrid structures **1** in an effort to combine the reactivity of the acetal moiety of furanose and the quinone unit with the steroidal backbone, as shown in Fig. 3. These hybrids may have significant biological activity and so, an efficient strategy to these hybrids would allow us to construct diverse hybrid analogues.

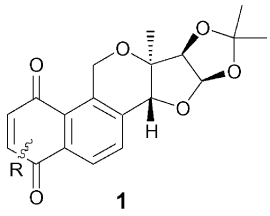
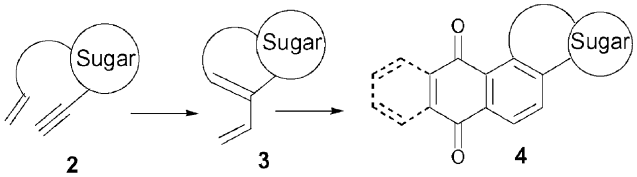



**Fig. 3** Sugar–oxasteroid–quinone hybrid.

## Results and discussion

Our proposed strategy was based on a simple and expedient sequential enyne metathesis and Diels–Alder reaction[11] of an enyne **2**, derived from a sugar unit, with a variety of 1,4-quinones to provide hybrid molecules **4** as outlined in Scheme 1.




**Scheme 1**

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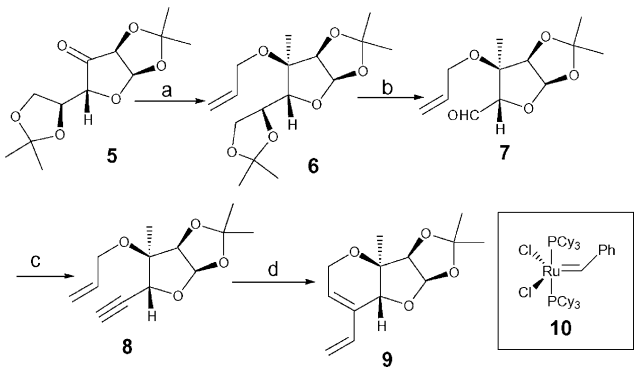
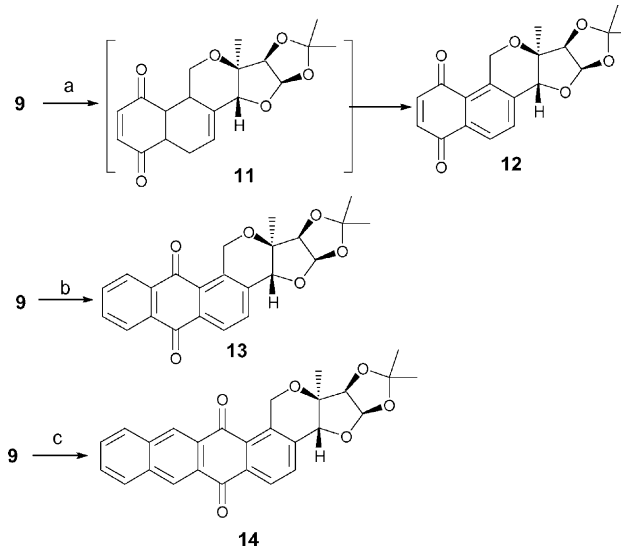
To check the feasibility of this strategy, we decided to synthesize the hybrids as shown in Schemes 2 and 3. Addition of methyl Grignard reagent to the ketone **5** followed by protection of the tertiary alcohol as its allyl ether afforded[12] **6** in good yield.




**Scheme 2** *Reagents and conditions*: (a) (i) MeMgI, diethyl ether, THF, 0 °C to RT; (ii) NaH, allyl bromide, cat. TBAI, THF, reflux, 12 h, 90% for two steps; (b) (i) 90% aq. AcOH, RT, 12 h, 83%; (ii) silica gel supported $NaIO_4$, DCM, RT, 2 h, quantitative; (c) dimethyl-1-diazo-2-oxopropylphosphonate, $K_2CO_3$, MeOH, RT, 4 h, 74%; (d) **10**, DCM, reflux, 11 h, 74%.




**Scheme 3** *Reagents and conditions*: (a) (i) toluene, 1,4-benzoquinone, reflux 12 h, (ii) triethylamine, silica gel, RT, 1 h, 49%; (b) (i) toluene, 1,4-naphthoquinone, reflux 24 h, (ii) triethylamine, silica gel, RT, 1 h, 75%; (c) (i) toluene, 1,4-anthraquinone, reflux, 24 h, (ii) triethylamine, silica gel, RT, 1 h, 65%.

Selective deprotection of the more exposed 5,6-*O*-isopropylidene group afforded a diol, which was subsequently cleaved by silica gel supported $NaIO_4$[13] to provide the aldehyde **7**. The aldehyde **7** was then easily converted into the key precursor enyne **8** by Bestmann's protocol.[14] As anticipated, the enyne **8** underwent a smooth intramolecular enyne metathesis[15] with the Grubbs' first generation catalyst **10** to yield the diene **9** in good yield.

After successfully synthesizing **9**, we then turned our attention to carry out the intermolecular Diels–Alder reaction with 1,4-benzoquinone (Scheme 3). Gratifyingly, the Diels–Alder reaction proceeded smoothly under thermal conditions to afford **11**. However, the cycloadduct seems to be unstable and attempts to purify this by silica gel column chromatography led to a mixture of aromatized product **12** and other unidentifiable products. As the cycloadduct undergoes aromatization/oxidation on a silica gel column without oxidizing agents such as DDQ, we decided to treat the crude cycloaddition product immediately with triethylamine and silica gel before purification. As expected, this protocol worked well and we could directly isolate the aromatized/oxidized cycloadduct **12** in respectable yield. This sequence was then repeated with 1,4-naphthoquinone and 1,4-anthraquinone to obtain the respective hybrid molecules **13** and **14** in good overall yield. Thus, we could establish a simple strategy to synthesize novel sugar–oxasteroid–quinone hybrid molecules

## Conclusion

We have disclosed here a versatile strategy to a new class of hybrid molecules having three different structural motifs. The reported synthesis involves an efficient sequential enyne metathesis, Diels–Alder and oxidative aromatization reactions. This approach is general and it should be possible to make a large number of such compounds starting from diverse sugar units and quinones. In ongoing studies, this methodology will be applied to the synthesis of a range of simpler analogues of this unique class of hybrid compounds and their biological activity will be studied.

## Experimental

### General experimental details

Unless otherwise noted, all starting materials and reagents were obtained from commercial suppliers and used after further purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl and toluene from sodium. Dichloromethane, hexane and pyridine were freshly distilled from calcium hydride. All solvents for routine isolation of products and chromatography were reagent grade and glass distilled. Reaction flasks were dried in an oven at 100 °C for 12 h. Air- and moisture-sensitive reactions were performed under an argon/UHP nitrogen atmosphere. Flash chromatography was performed using silica gel (100–200 mesh, Aceme) with indicated solvents. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid and heat as developing agents. Optical rotation was recorded on Jasco DIP-370 digital polarimeter. IR spectra were recorded from Thermo Nicolet Avater 320 FT-IR and Nicolete Impact 400 instruments. Mass spectra were obtained with Waters Micromass-Q-Tof micro™ (YA105) spectrometer. Elemental analyses were recorded on Thermo Finnigan Flash EA 1112. $^1H$ and $^{13}C$ NMR spectra were recorded either on Varian AS 400 or Varian ASM 300 spectrometers. Values are listed as chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, and coupling constant in hertz (Hz).

### 3-*O*-Allyl-3-*C*-methyl-1,2:5,6-di-*O*-isopropylidene-*α*-D-allofuranose 6[12]

A solution of ketone **5** (2.75 g, 10.7 mmol) in THF (60 mL) at 0 °C was treated with a solution of MeMgI (38 mmol) in diethyl ether and stirred for 2 h at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for an additional 12 h. The reaction mixture was quenched with saturated $NH_4Cl$ and extracted with ethyl acetate. The organic layer was concentrated and the crude alcohol product (2.9 g) was used for the next step without purification.

To a suspension of sodium hydride (0.85 g, 21.2 mmol, 60% dispersion in mineral oil) in dry THF (35 mL) was added a solution of alcohol (2.9 g, 10.6 mmol) in THF (20 mL) dropwise at 0 °C and the mixture was stirred for 15 min at 0 °C and then at room temperature for 30 min. To this mixture allyl bromide (2.2 mL, 26.5 mmol) was added dropwise 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 $NH_4Cl$ and extracted with ethyl acetate.

The organic layer was washed with brine, dried ($Na_2SO_4$), concentrated and purified by silica gel chromatography (10% ethyl acetate in hexanes) yielding **6** (3 g, 90%). $R_f = 0.4$ (diethyl ether–hexane, 1 : 1); $[\alpha]^{25}_D$ +53.2 (*c* 1.0, $CHCl_3$); IR (KBr) 3516, 2996, 2940, 1647, 1454, 1382, 1230, 1102 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 5.99–5.9 (m, 1H), 5.67 (d, $J = 3.6$ Hz, 1H), 5.32 (dq, $J = 12$, 1.8 Hz, 1H), 5.13 (dq, $J = 9$, 1.8 Hz, 1H), 4.25 (d, $J = 3.6$ Hz, 1H), 4.16–3.94 (m, 6H), 1.58 (s, 3H), 1.44 (s, 3H), 1.35 (s, 3H), 1.33 (s, 3H), 1.23 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 135.5, 115.7, 112.9, 109.3, 103.8, 84.1, 82.1, 81.1, 73.8, 67.1, 65.5, 27.0, 26.7, 25.4, 16.8

### 3-*O*-Allyl-5-deoxy-1,2-*O*-isopropylidene-3-*C*-methyl-α-D-riboaldofuranose 7[12]

The allyl ether **6** was stirred with 35 mL of 90% aqueous AcOH for 12 h at room temperature. After removing the solvent, the resultant diol was dissolved in $CH_2Cl_2$ (5 mL) and added to a stirred suspension of silica supported $NaIO_4$ in $CH_2Cl_2$ (10 mL). The stirring was continued at room temperature for 2 h. The solid was then filtered off. The filtrate was concentrated to afford the aldehyde **7** in quantitative yield (1.15 g, 83% for two steps).

### 5,6-Deoxy-1,2-*O*-isopropylidene-3-*O*-allyl-3-*C*-methyl-α-D-ribohex-5-ynofuranose 8

**Method A.** To a stirred suspension of activated zinc dust (0.405 g, 6.2 mmol) and triphenylphosphine (1.63 g, 6.2 mmol) in $CH_2Cl_2$ (6 mL) at 0 °C was added a solution of carbon tetrabromide (2.1 g, 6.35 mmol) in $CH_2Cl_2$ (5 mL). After being stirred for 5 min at 0 °C, a solution of aldehyde **7** (0.75 g, 3.1 mmol) in $CH_2Cl_2$ (5 mL) was added, the stirring was continued at 0 °C for 10 min and then at room temperature for 12 h. The reaction mixture was diluted with hexane (20 mL) and passed through a small pad of silica. The filtrate was concentrated and purified by flash column chromatography (silica, 5% ethyl acetate in hexanes) to afford the dibromo compound (0.9 g) in 73% yield. $R_f = 0.63$ (EtOAc–hexane, 3 : 7); $[\alpha]^{25}_D$ +14.1 (*c* 1.0, $CHCl_3$); IR (KBr) 2986, 2920, 2874, 1622,1454, 1382, 1219, 1097, 1011 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 6.43 (d, $J = 8.7$ Hz, 1H), 6.0–5.9 (m, 1H), 5.7 (d, $J = 3.65$ Hz, 1H), 5.33 (dq, $J = 11.7$, 1.8 Hz, 1H), 5.15 (dq, $J = 6$, 1.5 Hz, 1H), 4.29 (d, $J = 8.7$ Hz, 1H), 4.09–4.07 (m, 2H), 1.61 (s, 3H), 1.34 (s, 3H), 1.21 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 135.1, 133.0, 115.9, 113.3, 103.9, 95.3, 83.5, 83.1, 81.1, 65.5, 26.7, 27.0, 16.8; LRMS (ES) $[M + Na]^+$ *m/z* 418.9134; HRMS (ES) calc. for $C_{13}H_{18}Br_2O_4Na$ *m/z* 418.9457, found 418.947.

To a cooled solution of diisopropylamine in THF (56 mL) at −20 °C was added *n*-BuLi (11.3 mL of a 1.6 M solution in hexane, 17.0 mmol) dropwise. After being stirred at −20 °C for 1 h, this LDA solution was cannulated to a solution of the dibromo compound (0.9 g, 2.27 mmol) in THF (20 mL) at −78 °C. After being stirred at −78 °C for 1 h the reaction mixture was heated to room temperature and stirred for an additional 1 h. The reaction mixture was quenched with a saturated $NH_4Cl$ solution and extracted with ethyl acetate. The organic layer was concentrated and purified by silica gel column chromatography (5% ethyl acetate in hexanes) to afford the product **8** (0.42 g) in 79% yield.

**Method B.** To a solution of aldehyde **7** (350 mg, 1.4 mmol) in dry methanol (20 mL) was added anhydrous $K_2CO_3$ (0.39 g, 2.82 mmol). To this mixture dimethyl-1-diazo-2-oxopropylphosphonate (0.370 g, 1.7 mmol) was added at room temperature and stirred for 4 h. The reaction mixture was diluted with 35 mL of diethyl ether, washed (5% of aq. $NaHCO_3$) and the organic layer was concentrated. The crude product was purified in a silica gel column chromatography to yield the product **8** (0.25 g) in 74%. $R_f = 0.43$ (5% EtOAc–hexane); $[\alpha]^{25}_D$ +94.9 (*c* 1.0, $CHCl_3$); IR (KBr) 3287, 2991, 2935, 2890, 2141, 1652, 1464, 1382, 1265, 1224 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 6.0–5.9 (m, 1H), 5.74 (d, $J = 3.6$ Hz, 1H), 5.32 (dq, $J = 12$, 1.8 Hz, 1H), 5.17 (dq, $J = 6$, 1.5 Hz, 1H), 4.74 (d, $J = 2.4$ Hz, 1H), 4.32 (d, $J = 3.6$ Hz, 1H), 4.16–4.13 (m, 2H), 2.57 (d, $J = 2.1$ Hz, 1H), 1.57 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 135.0, 116.7, 113.1, 103.9, 82.7, 82.5, 78.5, 76.5, 72.5, 65.9, 26.9, 26.4, 17.2; LRMS (ES) $[M + Na]^+$ *m/z* 261.0997; HRMS (ES) calc. for $C_{13}H_{18}O_4Na$ *m/z* 261.1103, found 261.1100.

### 2,2,3b-Trimethyl-7-vinyl-3a,5,7a,8a-tetrahydro-3b*H*-1,3,4,8-tetracyclopenta[*a*]indene 9

A solution of enyne **8** (0.25 g, 1.05 mmol) was dissolved in dry $CH_2Cl_2$ (340 mL) under argon and the solution was degassed. To this mixture a solution of **10** (0.104 g, 12 mol%) in $CH_2Cl_2$ (5 mL) was added dropwise and refluxed for 11 h. The reaction mixture was cooled to room temperature and DMSO (0.45 mL, 6.3 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 (7% ethyl acetate in hexanes) gave the cyclised compound (0.19 g) in 74% yield. $R_f = 0.57$ (20% EtOAc–hexane); $[\alpha]^{25}_D$ −16.9 (*c* 1.0, $CHCl_3$); IR (neat) 3030, 1671, 1629, 1454, 1376, 1216, 1091 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 6.33–6.24 (m, 1H), 5.86 (d, $J = 3.6$ Hz, 1H), 5.75–5.69 (m, 1H), 5.57–5.52 (m, 1H), 5.16–5.12 (m, 1H), 4.73 (q, $J = 2.85$ Hz, 1H), 4.55–4.37 (m, 1H), 4.36 (d, $J = 3.6$ Hz, 1H), 1.61 (s, 3H), 1.36 (s, 3H), 1.12 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 135.7, 134.1, 123.5, 116.9, 113.4, 105.8, 81.6, 77.9, 73.6, 64.9, 26.3, 26.0, 16.0; LRMS (ES) $[M + Na]^+$ *m/z* 261.0997; HRMS (ES) calc. for $C_{13}H_{18}O_4Na$ *m/z* 261.1103, found 261.1107.

### General procedure for Diels–Alder reaction and aromatization

To a solution of quinone (1.2 mmol) in dry toluene (14 mL) was added a solution of diene **9** (1 mmol) in toluene (3 mL) at room temperature and then refluxed until the complete conversion of the diene to product. The solvent was removed and the crude product was dissolved in a minimum amount of $CHCl_3$. To this solution silica gel purged in triethylamine (2 g) was added and stirred until the complete conversion to the product. Then the solvent was removed and the product purified in a silica column to afford the corresponding aromatized adducts.

### Hybrid compound 12

Following the general procedure for Diels–Alder reaction and aromatization, combination of the diene **9** (0.045 g, 0.189 mmol) and 1,4 benzoquinone (0.025 g, 0.227 mmol) afforded the aromatized adduct **12** (0.032 g) in 49% yield. $R_f = 0.53$ (30% EtOAc–hexane); $[\alpha]^{25}_D$ −67.9 (*c* 1.0, $CHCl_3$); IR (KBr) 2991, 2946, 2869, 1683, 1581, 1377, 1326, 1270 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.14 (d, $J = 7.8$ Hz, 1H), 7.82 (d, $J = 7.8$ Hz, 1H), 6.93 (q, $J = 10.2$ Hz, 2H), 5.97 (d, $J = 3.3$ Hz, 1H), 5.57 (d, $J = 18.9$ Hz, 1H), 5.44 (d, $J = 18.9$ Hz, 1H), 5.13 (s, 1H), 4.51 (d, $J = 3.3$ Hz, 1H), 1.65 (s, 3H), 1.42 (s, 3H), 0.95 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ 186.6, 184.7, 141.9, 139.9,137.3, 136.2, 132.1, 129.0, 127.5, 126.2, 114.2, 106.7, 82.6, 76.9, 74.8, 67.0, 26.6, 26.1, 15.7; LRMS (ES) $[M + 1]^+$ *m/z* 343.1778; HRMS (ES) calc. for $C_{19}H_{19}O$ *m/z* 343.1182, found 343.1170

### Hybrid compound 13

Following the general procedure for Diels–Alder reaction and aromatization, combination of the diene **9** (0.07 g, 0.3 mmol) and 1,4-naphthoquinone (0.058 g, 0.37 mmol) afforded the aromatized adduct **13** (0.09 g) in 75% yield. $R_f = 0.47$ (30% EtOAc–hexane); $[\alpha]^{25}_D$ −41.9 (*c* 1.0, $CHCl_3$); IR (KBr) 2991, 2946, 2869, 1683, 1581, 1377, 1326, 1270 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 8.38 (d, $J = 8.1$ Hz, 1H), 8.23–8.29 (m, 2H), 7.9 (dd, $J = 6.9$, 1.2 Hz, 1H), 7.83–7.2 (m, 3H), 5.99

(d, $J$ = 3.3 Hz, 1H), 5.72 (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), 1.66 (s, 3H), 1.43 (s, 3H), 0.97 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 184.4, 182.9, 142.1, 136.8, 134.3, 134.2, 134.0, 133.8, 132.6, 129.2, 129.1, 127.4, 126.9, 126.8, 114.2, 106.7, 82.7, 76.8, 74.9, 67.5, 26.5, 26.1, 15.7; LRMS (ES) $[M + 1]^+$ $m/z$ 393.1619; HRMS (ES) calc. for $C_{23}H_{21}O_6$ $m/z$ 393.1338, found 393.1321.

#### Hybrid compound 14

Following the general procedure for Diels–Alder reaction and aromatization, the reaction of the diene **9** (0.05 g, 0.21 mmol) and 1,4 anthraquinone (0.083 g, 0.4 mmol) afforded **14** (0.06 g) in 65% yield. $R_f$ = 0.29 (30% EtOAc–hexane); $[a]^{25}_D$ −46.9 ($c$ 1.0, $CHCl_3$); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.79 (d, $J$ = 11.1 Hz, 1H), 8.46 (d, $J$ = 8.1 Hz, 1H), 8.11–8.05 (m, 2H), 7.89 (dd, $J$ = 6.6,1.2 Hz, 1H), 7.72–7.67 (m, 2H), 6.00 (d, $J$ = 3.3 Hz, 1H), 5.78 (d, $J$ = 18.9 Hz, 1H), 5.64 (d, $J$ = 18.9 Hz, 1H), 5.19 (s, 1H), 4.55 (d, $J$ = 3.3 Hz, 1H), 1.67 (s, 3H), 1.43 (s, 3H), 0.99 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 184.8, 183.8, 142.1, 137.0, 135.4, 135.1, 134.8, 130.4, 130.3, 130.2, 130.1, 129.8, 129.6, 129.5, 129.2, 128.9, 127.1, 114.2, 106.7, 82.7, 76.8, 75.0, 67.7, 26.6, 26.1, 15.8; LRMS (ES) $[M + 1]^+$ $m/z$ 443.1667; HRMS (ES) calc. for $C_{27}H_{23}O_6$ $m/z$ 443.1495, found 443.1497.

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