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A relay ring-closing metathesis/Diels–Alder approach to sugar-derived pluramycin-hybrids†‡

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Herein, we present a general approach for synthesizing pluramycin hybrids, which are analogous to the pluramycinone carbocyclic skeleton. This method involves a sequence of relay ring-closing enyne metathesis, Diels–Alder and oxidative aromatization reactions to synthesize pluramycinone-sugar hybrids. As part of our ongoing research, we have successfully synthesized two pluramycin hybrid analogues by carefully monitoring the late-stage oxidative aromatization steps, which depend on the stereo-orientation of the Diels–Alder cycloadduct at the C-4 center. The undesired ring-opening product can also serve as a C-glycoside analog, providing a versatile convergent route to access both types of hybrids and highlighting the significance of this strategy.

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Introduction

Natural products have historically provided crucial insights into biological processes due to their intricate chemical makeup and have been comprehensively investigated in relation to their biosynthesis and mechanisms of action. It is worth noting that numerous natural products have proven to be valuable substances or starting compounds in various industries, including fragrances, crop science, and pharmaceuticals.

In fact, over 40% of recently approved drugs are either natural products or derived from them.¹ However, many traditional drugs have become ineffective due to multidrug resistance (MDR), posing a significant challenge in the field. To overcome this obstacle, scientists have made significant progress in identifying new synthetic compounds with enhanced therapeutic properties. Among the various strategies for rapidly synthesizing a diverse range of molecules, the hybrid approach has emerged as one of the methods, as it combines structural features from different classes of compounds to produce distinct compounds with modified or unprecedented biological activities in a short time frame.^{2,3} The drive for the creation of these hybrids has been derived from nature, which employs mixed biosynthesis pathways to produce various bioactive natural products (Fig. 1),^{4–6} for example, an intricate indole alkaloid, such as strychnine (1), which is derived from the amino acid tryptophan and the monoterpene precursor

loganin,^{5a,b} and ansa antibiotics, such as rifamycins (3)^{5c,d} in which the aromatic core is derived from shikimate and the ansa chain from polyketides. On the other hand, glycoproteins, chlorophyll-a (2), vitamin E (4), and vinblastine (5) (Fig. 1) are notable examples of naturally occurring hybrid molecules, where different segments of the molecule have diverse biosynthetic origins but are firmly bonded together to form a functional unit.^{5,6} Drawing on this natural process, synthetic chemists have designed and synthesized several hybrid compounds comprising both natural and unnatural elements with various biological functions. These hybrid molecules, existing as dimers or polymers, may exhibit a behaviour that is distinct from those of their monomeric counterparts.

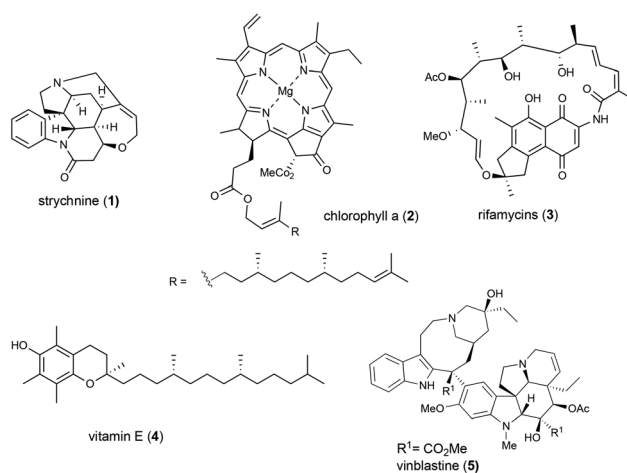


Fig. 1 Representative examples of hybrid natural products derived from biosynthetic pathways.

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† Dedicated with respect to Prof. Sukh Dev on the occasion of his 100th birthday.

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Anthrapyran antibiotics constitute a diverse range of natural products obtained from various terrestrial and marine *Streptomyces* sp. strains as secondary metabolites. These compounds feature a distinct 4*H*-anthra[1,2-*b*]-pyran-4,7,12-trione nucleus (Fig. 2) and exhibit versatile and potent biological activities, making them appealing synthetic targets (6–10).^{7a,c–e} Apart from their significant biological activity profile, it has been found that these families of natural products display prominent chemical instability. They are sensitive to heat and decompose when exposed to temperatures exceeding 60 °C.^{7b}

In addition, a considerable portion of these compounds was discovered to be unstable when exposed to ultraviolet light or sunlight.^{7b,c} They also exhibit high cytotoxicity and low solubility issues. Due to these factors, they have not been investigated much in clinical trials despite exhibiting widespread biological activities, including antitumor properties. Given our laboratory's interest in the total synthesis of biologically active natural products and their analogues, we have designed and synthesised several interesting classes of hybrid molecules derived from sugar as the chiral backbone.⁸ In this work, we report a general approach by exploring the RRCM (relay ring-closing enyne metathesis) as a key step to access the pluramycinone family of natural product analogues.

Results and discussion

The synthesis of hybrid natural products using chemical methods offers a means for rapidly accessing diverse structural compounds ready for pharmacological testing. Our strategy includes a sequential relay ring-closing enyne metathesis/Diels–Alder approach to synthesize the required tetracyclic core skeleton 3,4-dihydro-2*H*-anthra[1,2-*b*]-pyran-7,12-dione, as depicted in Scheme 1.

Retrosynthetic analysis of diene 11

We anticipated that the chiral diene 11 could be accessed by a relay ring-closing enyne metathesis (RRCM) from the enyne

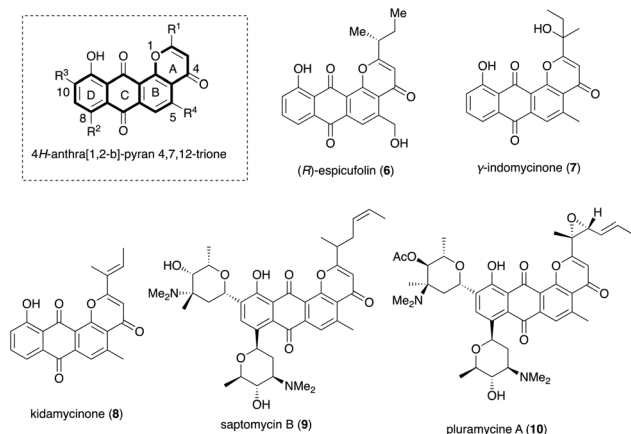
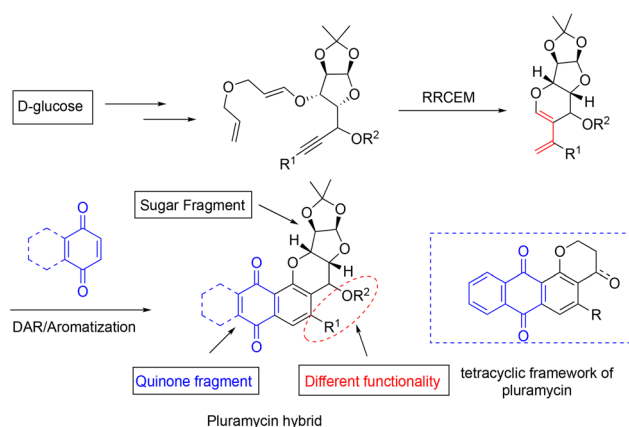


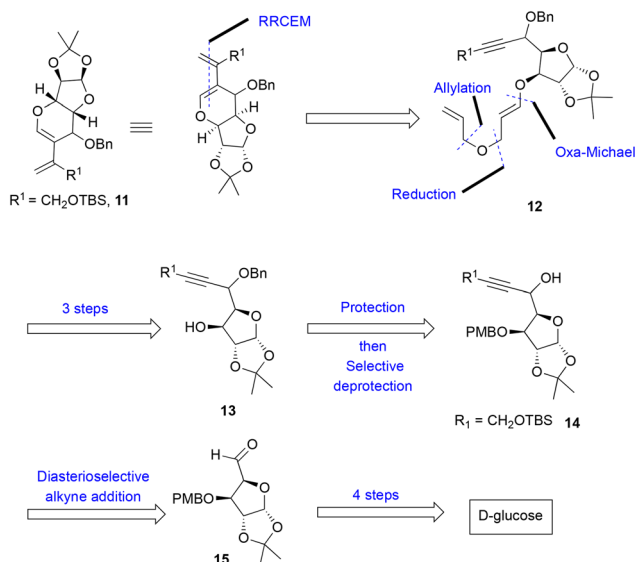
Fig. 2 Selected examples of pluramycin/pluramycinone natural products.



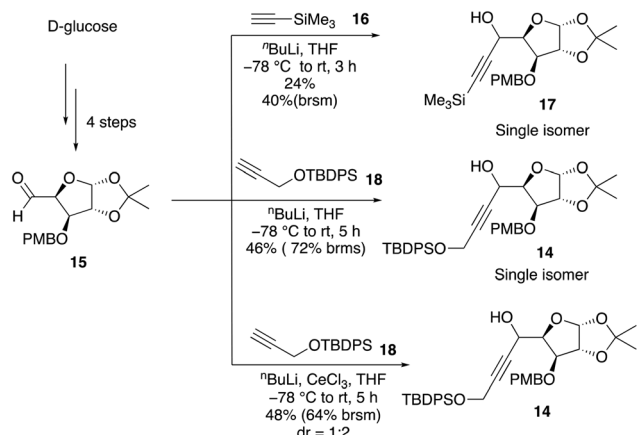
Scheme 1 Relay ring-closing enyne metathesis/Diels–Alder approach.

precursor 12, which, in turn, could be accessed in three steps from alkyne 13 *via* a diastereoselective oxa-Michael addition with ethyl propiolate and the reduction of the resultant ester to primary alcohol followed by *O*-allylation reaction. Alcohol 13 could be synthesized in two steps from alkynol 14 *via* protection of alkynol and removal of the PMB group. The alkyne functionality on alcohol 14 could be installed by diastereoselective nucleophilic addition of the terminal alkyne into the known aldehyde 15, which in turn could be prepared from commercially available D-glucose in four steps (Scheme 2) by following known literature procedure (see the ESI†).⁹

Our synthesis began with the incorporation of the alkyne functionality into the known aldehyde 15 through a diastereoselective nucleophilic addition reaction. The addition of the lithium anion of TMS acetylene 16 with *n*-BuLi resulted in only 24% yield of the addition product 17 (Scheme 3). However, when TBDPS-protected propargylic alcohol 18 was employed



Scheme 2 Retrosynthetic analysis for diene 11.

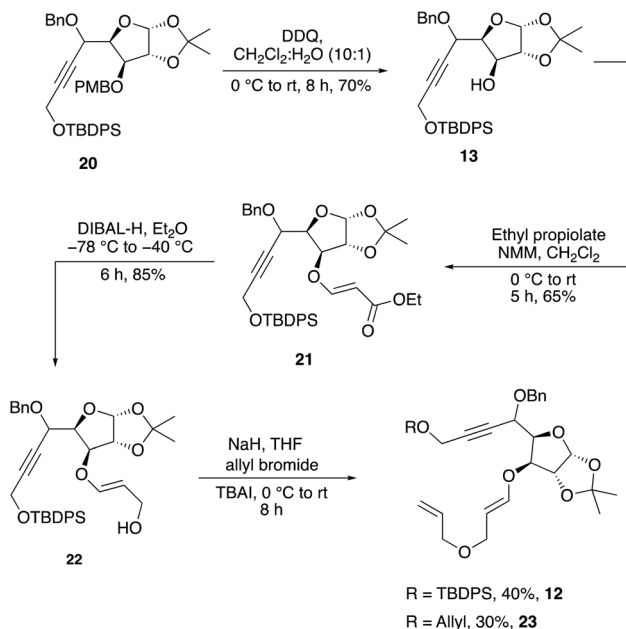


Scheme 3 Synthesis of propargylic alcohols 17 and 14.

under the same conditions, alcohol 14 was obtained in 46% yield as a single isomer. Attempts to use an *in situ* generated organocerium reagent (prepared from anhydrous cerium chloride and *n*-BuLi) did not improve the yield and diastereoselectivity of the product. So, we decided to move further with alcohol 14 obtained in a moderate yield. Attempts to protect the alcohol as MOM ether under different conditions did not give a good yield of the expected product. Thus, efforts were redirected towards using a less sterically hindered ether-protecting group, such as benzyl, which was smoothly incorporated by using benzyl bromide with NaH in DMF to provide the desired benzyl ether product 20 (Scheme 4).

The next objective was to selectively remove the PMB group of 20, which was easily achieved by treating with DDQ to provide alcohol 13 in 70% yield. The oxa-Michael addition reaction of 13 with ethyl propiolate in the presence of *N*-methylmorpholine (NMM) delivered ester 21, which was immediately reduced with DIBAL-H to furnish the allylic alcohol 22 in 85% yield (Scheme 5).

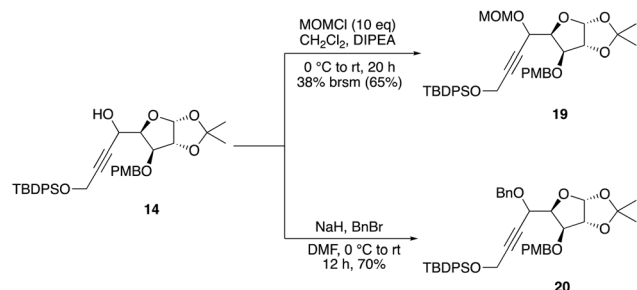
When 22 was subjected to *O*-allylation by treating it with NaH and allyl bromide, the key enyne precursor 12 was obtained only in 40% yield. It was observed that a minor undesired double *O*-allylated product, 23, was formed during this reaction. This unwanted by-product resulted from the deprotection of the TBDPS group under basic conditions followed by a second allylation (Scheme 5). After multiple



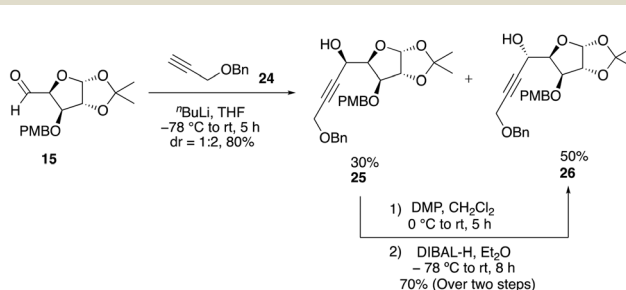
Scheme 5 Synthesis of the enyne precursor 12.

attempts to prevent the formation of the unwanted product 23 using various bases, including NaH, potassium *tert*-butoxide and solvents such as DMF and THF, we were unsuccessful in controlling the formation of 23. The low yield and decomposition of the starting materials appeared to have forced us to abandon this route.

At this stage, it became evident that a stable protecting group was crucial to overcome this problem to obtain a substantial quantity of the enyne precursor product. Consequently, we chose to replace the TBDPS protecting group with the robust benzyl group. Subsequently, we performed nucleophilic addition of the benzyl-protected propargylic alcohol 24 to aldehyde 15, which resulted in the formation of a mixture of diastereomers 25 and 26 (dr = 1:2), with a combined yield of 80% (Scheme 6). The conversion of the minor isomer 25 into the major isomer 26 was achieved exclusively through sequence of oxidation and reduction reactions. Initially, the minor diastereomer was oxidized using DMP oxidation, which resulted in the formation of an alkynone product, which was subsequently reduced using various redu-



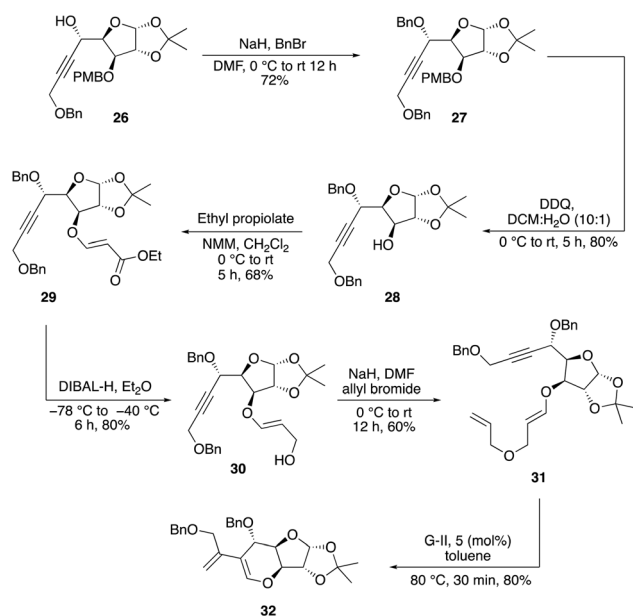
Scheme 4 Synthesis of compounds 19 and 20.



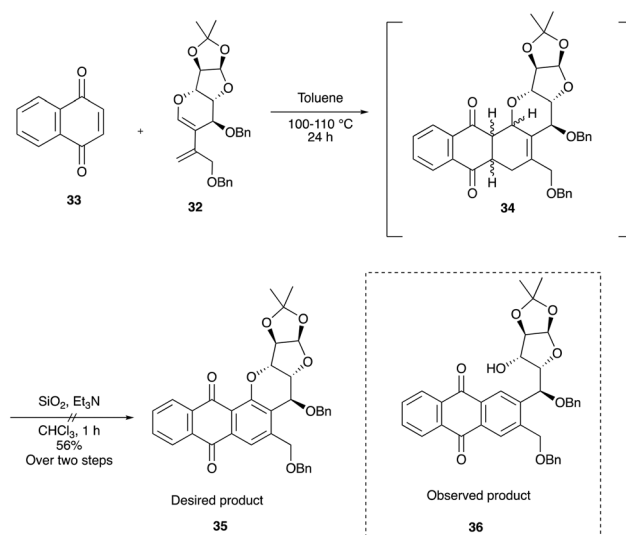
Scheme 6 Synthesis of alcohols 25 and 26.

cing reagents with the aim of obtaining a single isomer of alcohol **26** (see the ESI†) (Scheme 6). Among the various options, diisobutylaluminium hydride (DIBAL-H), a sterically hindered electrophilic hydride donor, was found to be much more efficient and predominantly produced a single isomer of alcohol **26**. The major isomer of **26** was then protected as benzyl ether **27** in 72% yield. Now, the chemo-selective removal of the PMB group with DDQ proceeded smoothly to afford alcohol **28** in 80% yield. The oxa-Michael addition of alcohol **28** with ethyl propiolate in the presence of *N*-methylmorpholine furnished the conjugate ester **29** in 68% yield. Reduction of **29** with DIBAL-H afforded the allylic alcohol **30**, which, upon *O*-allylation using NaH and allyl bromide, afforded the *O*-alkylated product **31** in good yield *via* two steps. Having sufficient quantity of the enyne precursor **31** in hand, we proceeded to carry out the first key step (relay ring-closing enyne metathesis) with the Grubbs' second-generation catalyst (G-II). To our delight, this reaction worked well to afford the desired diene product **32** in 80% yield within 30 min (Scheme 7).

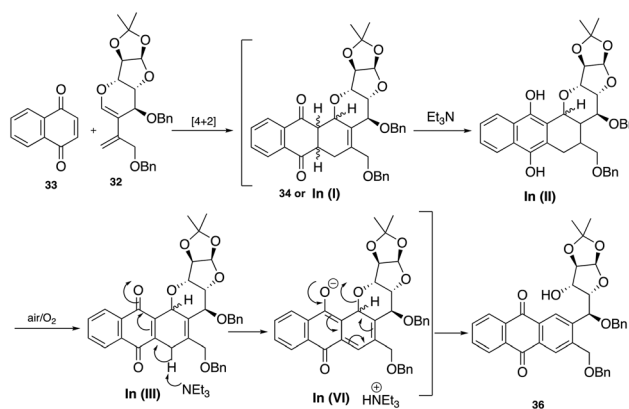
With diene **32** in hand, we next focused our efforts on the sequential Diels–Alder–aromatization reaction by exposing it to various quinone dienophiles to obtain the tetracyclic framework of pluramycin hybrids. Initially, diene **32** was heated in toluene at 100 to 110 °C with commercially available 1,4-naphthoquinone **33**, which resulted in a crude cycloadduct **34** in 24 h. However, when this crude product was subjected to aromatization under air and the SiO₂–Et₃N reagent mixture, contrary to our expected tetracycle **35**, we observed the formation of the ring-cleaved aromatized product **36** (Scheme 8). The plausible mechanism for ring opening product is shown in Scheme 9.



Scheme 7 Synthesis of diene **32**.



Scheme 8 Attempted conditions for tetracycle **35**.

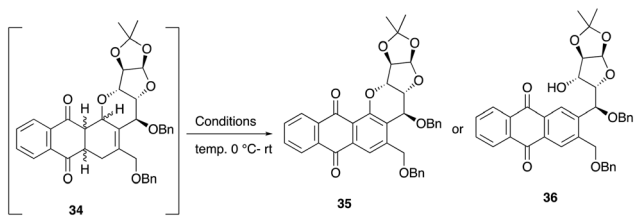


Scheme 9 Plausible reaction mechanism for the aromatization of cycloadduct **34**.

The formation of Cycloadduct intermediate **34** was confirmed by high resolution mass spectrometry (HRMS) data (see the ESI†) and at this stage we realized that the Diels–Alder reaction proceeded smoothly, but further optimization is required for the aromatization step.

The use of milder bases, such as Et₃N (entry 1) and K₂CO₃ (entry 2), did not yield the desired aromatic tetracyclic product **35**; instead, it provided the ring-cleaved product **36** exclusively. At this point, it became apparent that basic conditions may not be suitable for obtaining the desired product, as C–O bond cleavage is more facile under basic conditions due to its better-leaving group capability. As a result, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)¹⁰ was used to provide the expected tetracycle, but this reagent also unfortunately provided a complex mixture (entry 3, Table 1). Since direct aromatization of cycloadduct **34** was unsuccessful under various conditions, we anticipated that prior functionalization of the cyclohexene intermediate **34**, before aromatization, might

Table 1 Attempted conditions for aromatization



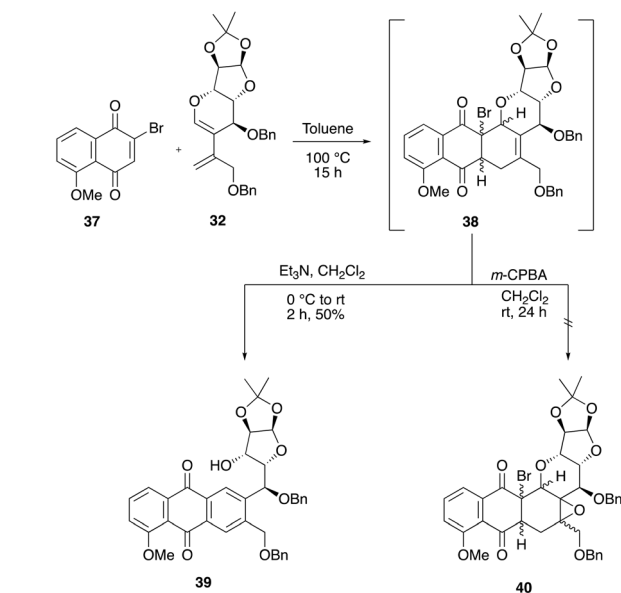
Entry	Reaction conditions	Time	Result
1	Et ₃ N, SiO ₂ , CHCl ₃	1 h	36 (56%) ^a
2	K ₂ CO ₃ , MeOH	2 h	36 (50%) ^a
3	DDQ, CH ₂ Cl ₂	12 h	Complex mixture
4	NBS, THF : H ₂ O (5 : 1) then Et ₃ N, CH ₂ Cl ₂	8 h	Complex mixture
5	OsO ₄ , NMO, acetone : H ₂ O (5 : 1)	24 h	36 (45%) ^a
6	<i>m</i> -CPBA, NaHCO ₃ , CH ₂ Cl ₂	24 h	NR ^b

^a Isolated overall yield. NR = no reaction. ^b Only the starting material remains.

facilitate the process to provide the desired product 35. Thus, attempts were made to form the bromohydrin intermediate *via* a bromonium ion (entry 4, Table 1), but this reaction also led to a complex mixture. Inspired by the seminal work done by Krohn and co-workers,^{11a} we subjected the crude cycloadduct 34 to hydroxylation by exposing it to a catalytic amount of osmium tetroxide along with the co-oxidant *N*-methylmorpholine-*N*-oxide (NMO) (entry 5, Table 1).

The NMR analysis of the crude mixture revealed that a product with ring cleavage and aromatization was formed during the hydroxylation step. We presumed that the *in situ* generation of *N*-methylmorpholine would have facilitated the elimination process by means of a base-induced elimination process. Recently, Collet and co-workers reported a strategy wherein the Diels–Alder cycloadduct intermediate was subjected to a one-pot epoxidation followed by aromatization to furnish the aromatic tetracyclic natural product.^{11b} However, our attempts to use similar conditions to synthesize the anthrapyran analogue from the cyclohexene intermediate 34 with *m*-CPBA in dichloromethane (entry 6) were unsuccessful.¹² Further, when we carried out the Diels–Alder reaction of 32 with a known and activated brominated dienophile 37, the required crude cycloadduct intermediate was obtained in 15 h. However, the addition of a triethyl amine base resulted in the immediate formation of the C–O bond cleavage product 39 in 50% yield over two steps (Scheme 10). Efforts to epoxidize the cyclohexene adducts 38 were unsuccessful despite repeated attempts. Furthermore, our efforts to isolate the cyclohexene intermediate 38 using silica gel or neutral alumina column chromatography were unsuccessful, as it seems to be unstable during purification and hence immediately subjected to aromatization conditions after the consumption of diene 32 (Scheme 10).

We presumed that the presence of two bulky benzyloxy groups around the cyclohexene double bond of 38 might be



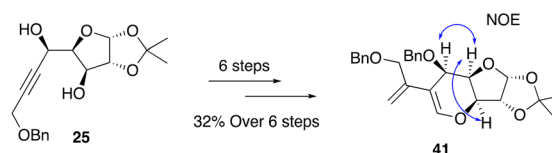
Scheme 10 Attempted aromatization conditions with tetracycle 38.

blocking the epoxidation from both faces of the alkene. As a result, we redirected our attention towards synthesizing an epimer of diene 32 to address this issue.

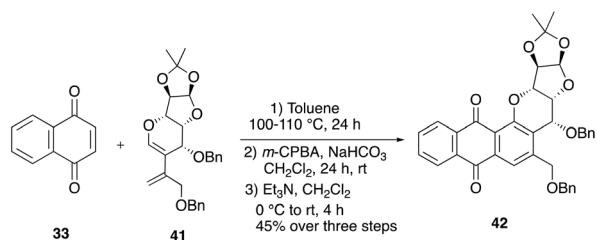
Following a similar reaction sequence, diene 41 was successfully synthesized from alcohol 25 in 6 steps in an overall yield of 32% (Scheme 11). At this stage, the stereochemical orientation of the newly formed stereocenter in the synthesis of 25 and 26 (Scheme 6) was confirmed by NOE NMR analysis of 41 (see the ESI†), which also resolves the relative configuration of the key intermediate 32 and all compounds derived further.

Synthesis of hybrid 42

When the minor diastereomer of diene, *i.e.* 41, was subjected to Diels–Alder reaction conditions with the commercially available 1,4-naphthaquinone 33, the crude cycloadduct product was delivered within 24 h. The crude cyclohexene adduct was then directly used for epoxidation with *m*-CPBA in DCM. After 12 h, to our delight, TLC showed complete consumption of the starting materials, and we were pleased to observe the formation of the epoxide product. After consumption of the starting material, the crude epoxide was then directly treated with excess triethylamine in the same pot under an open-air atmosphere, resulting in the desired tetracyclic analogue 42 in an overall yield of 45% over three steps (Scheme 12).



Scheme 11 Synthesis of the minor diene isomer 41 from alcohol 25.

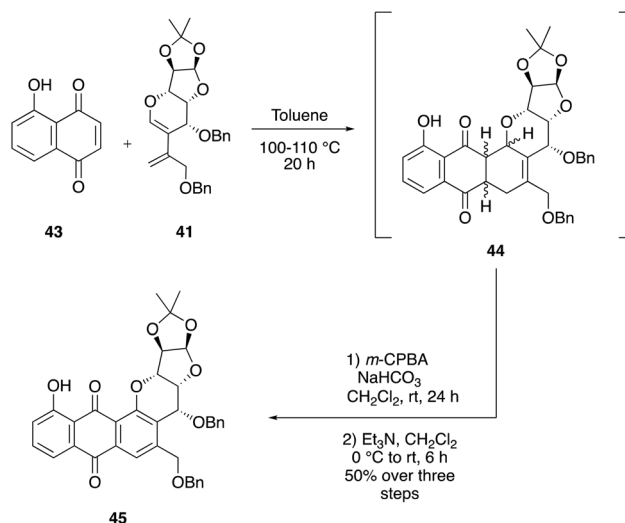
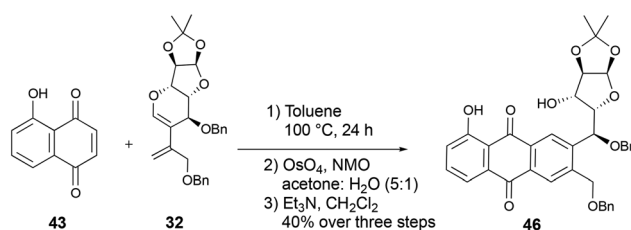
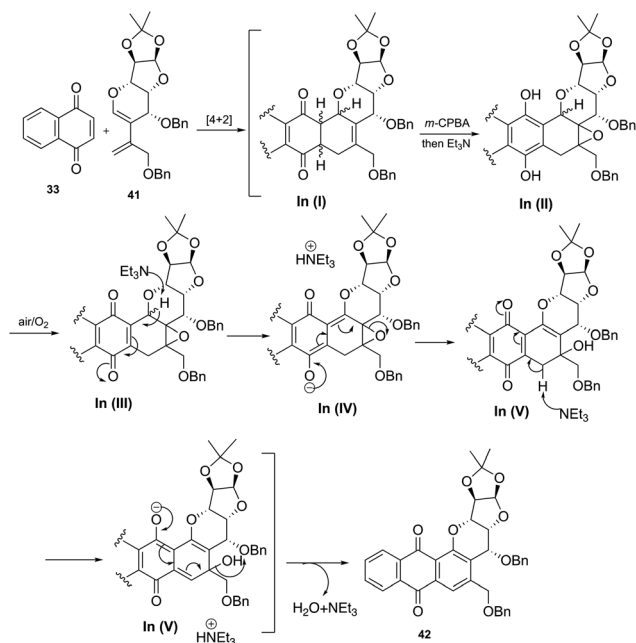
Scheme 12 Synthesis of the pluramycin-sugar hybrid **42**.

The plausible reaction mechanism for the aromatization *via* epoxide ring opening reaction is depicted in Scheme 13.

Synthesis of hybrid **45**

Given the biological importance of juglone **43** and the presence of hydroxyl groups in numerous natural products from the pluramycin family, we were motivated to create a sugar hybrid analog of juglone. To achieve this aim, juglone **43** was subjected to optimized Diels–Alder reaction conditions with diene **41** in toluene at 100 to 110 °C, resulting in the formation of the cycloadduct intermediate **44** within 20 h. The crude cycloadduct mixture was dried under vacuum and re-dissolved in dichloromethane and then treated with *m*-CPBA, and it led to the formation of a crude epoxide mixture. This mixture was then immediately subjected to aromatization within the same pot by adding an excess of Et₃N to the reaction mixture in an open-air atmosphere, resulting in the desired pluramycin-sugar hybrid **45** in 50% overall yield over three steps (Scheme 14).

However, when the same sequence was attempted with the major diene **32**, the C–O bond cleaved product **46** was obtained in 40% yield over three steps (Scheme 15).

Scheme 14 Synthesis of the pluramycin-sugar hybrid **45**.Scheme 15 Synthesis of the sugar-quinone hybrid **46**.

Scheme 13 Plausible reaction mechanism for the aromatization step.

In this study, our attempts to isolate any of the cycloadducts seem challenging, as they either lead to the ring-opening product or the decomposition of the product. Therefore, we decided to subject them immediately to subsequent steps after their formation.

Conclusions

In conclusion, we have developed a simple convergent strategy for the synthesis of a new class of sugar-derived pluramycin hybrids, which share similarity to the pluramycinone carbocyclic skeleton. This approach involves key steps, namely sequential relay ring-closing enyne metathesis (RRCM) and Diels–Alder and oxidative aromatization reactions. This methodology opens up interesting possibilities for the synthesis of such hybrids by using diverse sugar units and quinones as starting materials. Ongoing studies in our laboratory will apply this methodology to synthesize various simpler analogues of pluramycinone natural products. In this study, we have successfully synthesized two hybrid molecules, **42** and **45**, exhibiting an oxa-tetracyclic framework of pluramycin natural products by successfully controlling the challenging late-stage aromatization reaction with a minor isomer of diene **41** in overall 14 longest linear steps (LLS). In addition to the inherent stability

of C-glycosidic natural products *in vitro*, the late-stage C–O bond cleavage products derived from the major diene **32** could also serve as novel C-glycoside analogues of sugar-quinone hybrids. Hence, these efforts have led to a divergent route for the synthesis of both types of analogues and have potential for further discovery. Efforts to synthesize other different sugar-derived quinone-hybrid molecules and study their biological activities are currently underway in our laboratory.

Experimental section

General information

Unless otherwise noted, all starting materials and reagents were obtained from commercial suppliers and used after further purification. THF was distilled from sodium benzophenone ketyl and toluene from sodium. DCM and DMF were freshly distilled from calcium hydride. All solvents for routine isolation of products and chromatography were of reagent grade and glass distilled. Reaction flasks were dried in an 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 the indicated solvents. Thin-layer chromatography (TLC) was conducted with Merck silica gel 60 F254 percolated plates (0.25 mm) and visualized with UV, KMnO₄, and ceric ammonium molybdate. IR spectra were recorded with PerkinElmer Spectrum One and JASCO V-570 spectrophotometers. Mass spectra were obtained with a Bruker ESI-QTOF spectrometer recorded on Bruker Maxis Impact S No. 282001.0008 and Agilent spectrometers. ¹H NMR spectra were recorded on Bruker 400 MHz and Bruker 500 MHz spectrometers and are reported in ppm using a solvent as an internal standard (CDCl₃ at 7.26 ppm). Proton-decoupled ¹³C NMR spectra were recorded on Bruker 400 MHz and Bruker 500 MHz spectrometers and have been reported using a solvent as an internal standard (CDCl₃ at 77.2 ppm). Optical rotations were measured at 20 °C using an Autopol IV polarimeter.

Experimental data and characterization of products

1-((3aR,5R,6S,6aR)-6-((4-Methoxybenzyl)oxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-3-(trimethylsilyl)prop-2-yn-1-ol (17). To a solution of the trimethylsilyl acetylene **16** (0.157 g, 1.60 mmol) in dry THF (7 mL) at –78 °C was added *n*-BuLi (2.0 mL, 1.6 M in hexane, 3.2 mmol) over 5 min, and the reaction mixture was allowed to be stirred at the same temperature for 45 min. Aldehyde **15** (0.2 g, 0.64 mmol) in THF (10 mL) was added to the solution of alkyne at –78 °C, and the reaction was further kept at the same temperature for 1 h, and then stirred at room temperature for 6 h. The reaction mixture was quenched with sat. aqueous NH₄Cl solution, and the organic layer was extracted with EtOAc (3 × 15 mL), washed with brine solution, dried over anhydrous Na₂SO₄, concentrated under reduced pressure, and further purification was done through silica gel column chromatography (1:4 EtOAc/hexane) to

obtain **17** (0.064 g, 24% yield, 40% brsm) as a single isomer. **Physical appearance:** Sticky yellow liquid; *R*_f: 0.6 (30% EtOAc/hexane × 2); **IR** (neat, cm^{–1}): 3468, 2957, 2348, 1613, 1515, 1466, 1375, 1302, 1251, 1215, 1165, 1121, 1077, 1029, 845, 760; $[\alpha]_D^{20}$: –42.3 (*c* = 1.00, CHCl₃); **¹H NMR** (400 MHz, CDCl₃): δ 7.27 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.94 (d, *J* = 3.6, 1H), 4.71 (d, *J* = 8.5 Hz, 1H), 4.57–4.47 (m, 3H), 4.30 (dd, *J* = 8.4 Hz, 3.6 Hz, 1H), 4.07 (d, *J* = 3.3 Hz, 1H), 3.79 (s, 3H), 2.55 (br, 1H), 1.51 (s, 3H), 1.31 (s, 3H), 0.17 (s, 9H); **¹³C NMR** (100 MHz, CDCl₃): δ 159.4, 129.4, 129.2, 128.5, 113.8, 112.18, 105.6, 102.5, 90.7, 83.9, 82.4, 72.9, 62.4, 55.2, 26.8, 26.3, –0.24; **HRMS** (ESI-QTOF): [M + Na]⁺ calcd for C₂₁H₃₀NaO₆Si 429.1709; found 429.1704.

4-((tert-Butyldiphenylsilyl)oxy)-1-((3aR,5R,6S,6aR)-6-((4-methoxybenzyl)oxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)but-2-yn-1-ol (14). To a solution of alkyne **18** (0.47 g, 1.60 mmol) in dry THF (15 mL) at –78 °C was added *n*-BuLi (2.0 mL, 1.6 M in hexane, 3.2 mmol) over 5 min, and the reaction mixture was allowed to be stirred at the same temperature for 1 h. Aldehyde **15** (0.2 g, 0.64 mmol) in THF (10 mL) was added to the solution of alkyne at –78 °C, and the reaction was further kept at the same temperature for 1 h and then stirred at room temperature for 4 h. The reaction mixture was quenched with sat. aqueous NH₄Cl solution, and the organic layer was extracted with EtOAc (3 × 15 mL), washed with brine solution, dried over anhydrous Na₂SO₄, concentrated under reduced pressure, and further purification was done through silica gel column chromatography (1:45 EtOAc/hexane) to obtain **14** (0.18 g, 46% yield, 72% brsm) as a single isomer. **Physical appearance:** Sticky yellow liquid; *R*_f: 0.5 (30% EtOAc/hexane × 2); **IR** (neat, cm^{–1}): 3467, 2933, 2858, 2345, 1613, 1514, 1472, 1428, 1374, 1302, 1215, 1165, 1112, 1075, 1019, 890, 825, 755, 704, 614, 506; $[\alpha]_D^{20}$: –37.4 (*c* = 1.00, CHCl₃); **¹H NMR** (400 MHz, CDCl₃): δ 7.71–7.69 (m, 4H), 7.43–7.36 (m, 6H), 7.23 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.95 (d, *J* = 3.6 Hz, 1H), 4.70 (d, *J* = 7.8 Hz, 1H), 4.57 (d, *J* = 3.6 Hz, 1H), 4.53 (d, *J* = 10.9 Hz, 1H), 4.44 (d, *J* = 10.9 Hz, 1H), 4.35 (d, *J* = 1.6 Hz, 1H), 4.34 (d, *J* = 1.6 Hz, 1H), 4.23 (dd, *J* = 8.3 Hz, 3.2 Hz, 1H), 4.01 (d, *J* = 3.2 Hz, 1H), 3.75 (s, 3H), 2.42 (br, 1H), 1.52 (s, 3H), 1.33 (s, 3H), 1.05 (s, 9H); **¹³C NMR** (100 MHz, CDCl₃): δ 159.5, 135.7, 135.7, 133.0, 130.0, 129.7, 129.3, 127.9, 113.9, 112.3, 105.7, 84.4, 83.8, 82.6, 82.2, 82.0, 72.7, 62.0, 55.3, 52.7, 27.0, 26.8, 26.5, 19.2; **HRMS** (ESI-QTOF): [M + Na]⁺ calcd for C₃₅H₄₂NaO₇Si 625.2596; found 625.2592.

5-((3aR,5R,6S,6aR)-6-((4-Methoxybenzyl)oxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-11,11-dimethyl-10,10-diphenyl-2,4,9-trioxo-10-siladodec-6-yne (19). To a solution of **14** (0.15 g, 0.25 mol) in CH₂Cl₂ (10 mL) at 0 °C was added DIPEA (0.12 g, 0.99 mmol) followed by freshly prepared MOMCl (0.82 mL, 3 M in toluene). The reaction was monitored by TLC, and after 20 h, the reaction mixture was quenched with water (10 mL). Then the organic layer was extracted with EtOAc (2 × 15 mL), washed with brine solution, dried over anhydrous Na₂SO₄, concentrated under reduced pressure, and further purified *via* silica gel chromatography (1:5 EtOAc/hexane) to obtain **19** (0.062 g, 38% yield, 65% brsm). **Physical appearance:**

Colourless oily liquid; R_f : 0.5 (25% EtOAc/hexane); **IR** (neat, cm^{-1}): 2932, 2858, 2057, 1737, 1613, 1587, 1471, 1428, 1374, 1302, 1250, 1214, 1163, 1111, 1076, 1030, 946, 917, 824, 757, 704, 624, 505; $[\alpha]_D^{20}$: -1.7 ($c = 1.00$, CHCl_3); **^1H NMR** (500 MHz, CDCl_3): δ 7.68 (d, $J = 7.5$ Hz, 4H), 7.44–7.36 (m, 6H), 7.23 (d, $J = 8.6$ Hz, 2H), 6.82 (d, $J = 8.6$ Hz, 2H), 5.95 (d, $J = 3.6$ Hz, 1H), 4.86 (d, $J = 6.7$ Hz, 1H), 4.66 (dd, $J = 6.7$ Hz, 8.8 Hz, 2H), 4.53 (d, $J = 3.6$ Hz, 1H), 4.50 (d, $J = 10.8$ Hz, 1H), 4.45 (d, $J = 10.8$ Hz, 1H), 4.35–4.31 (m, 3H), 4.02 (d, $J = 3.1$ Hz, 1H), 3.75 (s, 3H), 3.39 (s, 3H), 1.63 (br, 1H), 1.52 (s, 3H), 1.32 (s, 3H), 1.03 (s, 9H); **^{13}C NMR** (125 MHz, CDCl_3) δ 159.3, 135.5, 135.5, 132.8, 132.8, 129.8, 126.7, 129.2, 127.7, 113.7, 111.9, 105.7, 94.2, 84.6, 82.5, 82.2, 81.8, 80.5, 72.5, 65.3, 55.6, 55.2, 52.5, 26.9, 26.6, 26.3, 19.1; **HRMS** (ESI-QTOF): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{37}\text{H}_{46}\text{O}_8\text{Si}$ 669.2842 found 669.2854.

((4-(Benzyloxy)-4-((3*R*,5*R*,6*S*,6*aR*)-6-((4-methoxybenzyl)oxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)but-2-yn-1-yl)oxy)(*tert*-butyl)diphenylsilane (**20**). NaH (30 mg, 60% in mineral oil, 0.75 mmol) was charged into a flame dried two-neck round bottomed flask and diluted with anhydrous DMF (7 mL). After cooling down to 0 °C, a solution of alcohols **14** (0.3 g, 0.50 mmol) in DMF (10 mL) was added in a drop-wise manner, and the resulting suspension was stirred at the same temperature for 40 min. Finally, benzyl bromide (0.09 mL, 0.75 mmol) was added, and the resulting mixture was stirred at room temperature over 12 h. After complete consumption of the starting material, the reaction was quenched with saturated NH_4Cl solution, and the product was extracted with (2 × 10 mL). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and then concentrated to obtain the crude product. Purification was done through silica gel column chromatography (1:20 EtOAc/hexane) to obtain the benzylated compound **20** (70%, 0.245 g). **Physical appearance**: Sticky colourless liquid; R_f : 0.8 (20% EtOAc/hexane); **IR** (neat, cm^{-1}): 3071, 3015, 2933, 2858, 1612, 1588, 1514, 1471, 1427, 1374, 1303, 1251, 1216, 1164, 1174, 1112, 1078, 1035, 936, 910, 823, 758, 703, 667, 614, 505; $[\alpha]_D^{20}$: -2.3 ($c = 1.00$, CHCl_3); **^1H NMR** (500 MHz, CDCl_3) δ 7.73 (d, $J = 7.2$ Hz, 4H), 7.46–7.43 (m, 2H), 7.41–7.38 (m, 6H), 7.35–7.32 (m, 2H), 7.28 (d, $J = 7.1$ Hz, 1H), 7.24 (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 5.99 (d, $J = 3.7$ Hz, 1H), 5.78 (d, $J = 12.1$ Hz, 1H), 4.60 (d, $J = 12.1$ Hz, 1H), 4.55–4.47 (m, 4H), 4.42 (dd, $J = 3.1$ Hz, 8.5 Hz, 1H), 4.38–4.37 (m, 2H), 4.07 (d, $J = 3.21$ Hz, 1H), 3.77 (s, 3H), 1.54 (s, 3H), 1.34 (s, 3H), 1.08 (s, 9H); **^{13}C NMR** (125 MHz, CDCl_3) δ 159.2, 137.7, 135.5, 135.4, 132.8, 132.8, 129.8, 129.5, 129.3, 128.1, 127.9, 127.7, 127.7, 127.4, 113.6, 111.8, 105.8, 85.0, 82.4, 82.3, 81.7, 81.0, 72.4, 70.7, 68.6, 55.1, 52.5, 26.8, 26.6, 26.3, 19.1; **HRMS** (ESI-QTOF): $[\text{M} + \text{K}]^+$ calcd for $\text{C}_{42}\text{H}_{48}\text{KO}_7\text{Si}$ 731.2797; found 731.2801.

(3*R*,5*S*,6*S*,6*aR*)-5-(1-(Benzyloxy)-4-((*tert*-butyldiphenylsilyl)oxy)but-2-yn-1-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-ol (**13**). To a solution of 4-methoxybenzyl ether **20** (0.24 g, 0.34 mmol) in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (20 mL 10:1) cooled to 0 °C was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.19 g, 0.85 mmol) and the solution was stirred at 25 °C for 8 h. The reaction mixture was quenched with sat. NaHCO_3

(20 mL) and the mixture was extracted with EtOAc (20 mL × 3). The organic layer was washed with water and brine solution, dried over Na_2SO_4 , and then concentrated under reduced pressure to obtain the crude product, which was further purified by silica gel column chromatography (1:4 EtOAc/hexane) to obtain alcohol **13** (70%, 0.138 g). **Physical appearance**: Sticky colourless liquid; R_f : 0.2 (30% EtOAc/hexane); **IR** (neat, cm^{-1}): 3463, 2932, 2858, 1961, 1471, 1454, 1428, 1374, 1313, 1259, 1216, 1163, 1112, 1070, 1013, 956, 887, 854, 823, 754, 702, 614, 702, 614, 505; $[\alpha]_D^{20}$: $+36.5$ ($c = 1.00$, CHCl_3); **^1H NMR** (400 MHz, CDCl_3) δ 7.76 (d, $J = 6.8$ Hz, 4H), 7.48–7.41 (m, 6H), 7.37–7.31 (m, 5H), 6.0 (d, $J = 3.5$ Hz, 1H), 4.79 (d, $J = 11.7$ Hz, 1H), 4.57 (d, $J = 11.8$ Hz, 1H), 4.49–4.42 (m, 4H), 4.28–4.25 (m, 2H), 2.66 (br, 1H), 1.52 (s, 3H), 1.34 (s, 3H), 1.10 (s, 9H); **^{13}C NMR** (100 MHz, CDCl_3) δ 136.9, 135.4, 132.8, 129.8, 128.3, 128.1, 127.7, 127.7, 113.7, 111.7, 105.2, 86.2, 84.681.6, 80.3, 75.7, 70.6, 67.9, 52.5, 26.7, 26.5, 26.2, 19.0; **HRMS** (ESI-QTOF): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{34}\text{H}_{40}\text{NaO}_6\text{Si}$ 595.2476; found 595.2486.

(*E*)-Ethyl-3-(((3*R*,5*R*,6*S*,6*aR*)-5-(1-(benzyloxy)-4-((*tert*-butyldiphenylsilyl)oxy)but-2-yn-1-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl)oxy)acrylate (**21**). To a solution of alcohol **13** (0.32 g, 0.56 mmol) in anhydrous CH_2Cl_2 (20 mL) was added ethyl propiolate (62 μL , 0.62 mmol) under N_2 and stirred for 5 min. Then, *N*-methyl morpholine (56.6 μL , 0.56 mmol) was added at 0 °C using a micro syringe. The resulting mixture was stirred for 5 h. The reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography (1:10 EtOAc/hexane) to obtain ester **21** (0.25 g, 65%). **Physical appearance**: Sticky colourless liquid; R_f : 0.6 (20% EtOAc/hexane); **IR** (neat, cm^{-1}): 2933, 2861, 1712, 1624, 1515, 1463, 1371, 1329, 1253, 1217, 1136, 1039, 966, 852, 824, 757, 702, 610, 505; $[\alpha]_D^{20}$: $+14.5$ ($c = 1.00$, CHCl_3); **^1H NMR** (500 MHz, CDCl_3) δ 7.72–7.69 (m, 4H), 7.45–7.38 (m, 6H), 7.38–7.37 (m, 3H), 7.33 (t, $J = 7.6$ Hz, 2H), 7.30 (d, $J = 12.7$ Hz, 1H), 5.96 (d, $J = 3.81$ Hz, 1H), 5.30 (d, $J = 12.7$ Hz, 1H), 4.90 (d, $J = 11.8$ Hz, 1H), 4.55 (d, $J = 11.8$ Hz, 1H), 4.50 (d, $J = 3.8$ Hz, 1H), 4.45–4.42 (m, 2H), 4.43–4.37 (m, 3H), 4.14 (qt, $J = 7.1$ Hz, 2H), 1.32 (s, 3H), 1.25 (t, $J = 7.9$ Hz, 3H), 1.07 (s, 9H); **^{13}C NMR** (125 MHz, CDCl_3) δ 166.9, 160.0, 137.4, 135.5, 135.5, 132.8, 132.8, 129.8, 128.2, 127.9, 127.7, 127.7, 127.6, 112.4, 105.5, 98.8, 86.0, 83.6, 81.4, 81.2, 79.7, 70.7, 67.6, 59.9, 52.4, 26.6, 26.6, 26.3, 19.0, 14.2; **HRMS** (ESI-QTOF): $[\text{M} + \text{K}]^+$ calcd for $\text{C}_{39}\text{H}_{46}\text{KO}_8\text{Si}$ 709.2594; found 709.2592.

(*E*)-3-(((3*R*,5*R*,6*S*,6*aR*)-5-(1-(Benzyloxy)-4-((*tert*-butyldiphenylsilyl)oxy)but-2-yn-1-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl)oxy)prop-2-en-1-ol (**22**). A solution of DIBAL-H {1 M in toluene} (0.6 mL, 0.60 mmol) was added *via* a syringe to a stirred mixture of ester **21** (160 mg, 0.238 mmol) in Et_2O (5.0 mL) at -78 °C. After 1 h, the reaction flask was warmed to -40 °C and further stirred for 4 h. The reaction mixture was quenched using sat. aqueous solution of Rochelle's salt, and the stirring was continued for 1 h. The reaction mixture was then extracted with EtOAc (20 mL × 3), and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure, and further purified by column chromatography using silica gel (1:3 EtOAc/hexanes) to obtain the

allylic alcohol **22** (128 mg, 85%). **Physical appearance:** Sticky colourless oil; R_f : 0.4 (25% EtOAc/hexanes); **IR** (neat, cm^{-1}): 3485, 2932, 2861, 1961, 1889, 1825, 1667, 1651, 1455, 1428, 1373, 1306, 1260, 1216, 1165, 1023, 939, 854, 739, 702, 613, 506; $[\alpha]_D^{20}$: +79.9 ($c = 0.50$, CHCl_3); **^1H NMR** (400 MHz, CDCl_3): δ 7.75–7.69 (m, 4H), 7.48–7.26 (m, 11H), 6.31 (d, $J = 12.7$ Hz, 1H), 5.96 (d, $J = 3.8$ Hz, 1H), 5.13 (dt, $J = 12.7, 7.3$ Hz, 1H), 4.76 (d, $J = 11.8$ Hz, 1H), 4.56 (dd, $J = 10.1, 8.0$ Hz, 2H), 4.47–4.30 (m, 5H), 3.97 (d, $J = 7.2$ Hz, 2H), 1.54 (s, 3H), 1.32 (s, 3H), 1.08 (s, 9H); **^{13}C NMR** (100 MHz, CDCl_3) δ 147.9, 137.7, 135.7, 135.6, 133.0, 132.9, 130.0, 128.4, 128.1, 127.9, 127.9, 127.7, 112.3, 105.8, 105.7, 85.6, 82.3, 81.7, 81.6, 80.5, 70.8, 68.1, 60.3, 52.7, 26.9, 26.8, 26.5, 19.3; **HRMS** (ESI-QTOF): $[\text{M} + \text{K}]^+$ calcd for $\text{C}_{37}\text{H}_{44}\text{KO}_7\text{Si}$ 667.2488; found 667.2487

((4-((3aR,5R,6S,6aR)-6-(((E)-3-(allyloxy)prop-1-en-1-yl)oxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)-4-(benzyloxy)but-2-yn-1-yl)oxy)(tertbutyl)diphenylsilane (**12**). A flame dried two-neck round-bottomed flask was charged with NaH (10 mg, 0.24 mmol, 60% in mineral oil) and anhydrous DMF (5 mL) was added. After cooling to 0 °C, a solution of alcohol **21** (0.1 g, 0.16 mmol) in DMF (5 mL) was added in a drop-wise manner and the resulting solution was stirred for 40 min at the same temperature. Finally, allyl bromide (20.7 μL , 0.24 mmol) was added at 0 °C using a micro syringe, and the resulting mixture was allowed to be stirred at room temperature for 8 h. The reaction was quenched with saturated NH_4Cl solution, and work-up was done with EtOAc to obtain the crude mixture. Purification was done through silica gel column chromatography (1:7 EtOAc/hexane) to obtain the RRCEM precursor **12** (42 mg, 40%) and the minor compound **23** (31 mg, 30%).

Data for compound (12). **Physical appearance:** Sticky colourless oil; R_f : 0.6 (20% EtOAc/hexane); **IR** (neat, cm^{-1}): 3077, 2932, 2867, 1653, 1456, 1429, 1374, 1261, 1217, 1164, 1114, 1070, 1020, 936, 856, 826, 741, 703, 614, 506; $[\alpha]_D^{20}$: +18.7 ($c = 0.5$, CHCl_3); **^1H NMR** (400 MHz, CDCl_3) δ 7.71 (dt, $J = 8.0, 1.8$ Hz, 4H), 7.45–7.35 (m, 8H), 7.35–7.27 (m, 3H), 6.30 (d, $J = 12.7$ Hz, 1H), 5.95 (d, $J = 3.8$ Hz, 1H), 5.93–5.83 (m, 1H), 5.25 (dd, $J = 17.2, 1.6$ Hz, 1H), 5.17 (dd, $J = 10.4, 1.4$ Hz, 1H), 5.05 (dt, $J = 12.7, 7.3$ Hz, 1H), 4.76 (d, $J = 11.9$ Hz, 1H), 4.60–4.52 (m, 2H), 4.45–4.39 (m, 2H), 4.36 (s, 2H), 4.33 (d, $J = 2.6$ Hz, 1H), 3.91 (dd, $J = 4.0, 2.8$ Hz, 2H), 3.82 (d, $J = 7.2$ Hz, 2H), 1.53 (s, 3H), 1.32 (s, 3H), 1.07 (s, 9H); **^{13}C NMR** (100 MHz, CDCl_3) δ 148.4, 135.7, 135.7, 134.9, 133.1, 130.1, 128.5, 128.2, 127.9, 127.9, 127.7, 117.3, 112.4, 105.9, 102.9, 85.7, 82.4, 81.8, 81.6, 80.4, 70.9, 70.8, 68.1, 67.4, 52.7, 26.9, 26.8, 26.5, 19.3; **HRMS** (ESI-QTOF): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{40}\text{H}_{48}\text{NaO}_7\text{Si}$ 691.3063; found 691.3062.

(3aR,5R,6S,6aR)-5-(4-(allyloxy)-1-(benzyloxy)but-2-yn-1-yl)-6-(((E)-3-(allyloxy)prop-1-en-1-yl)oxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole (**23**)

Data for compound (23). **Physical appearance:** Sticky colourless oil; R_f : 0.7 (30% EtOAc/hexane); **IR** (neat, cm^{-1}): 3079, 2930, 2866, 1663, 1450, 1429, 1374, 1261, 1217, 1164, 1113, 1072, 1010, 932, 944, 856 826, 826, 741, 703, 645, 614, 502; $[\alpha]_D^{20}$: +26.7 ($c = 0.5$, CHCl_3); **^1H NMR** (500 MHz, CDCl_3) δ

7.44–7.26 (m, 5H), 6.38 (d, $J = 12.7$ Hz, 1H), 5.95 (d, $J = 3.7$ Hz, 1H), 5.95–5.83 (m, 2H), 5.30 (d, $J = 13.5$ Hz, 1H), 5.27 (d, $J = 14.6$ Hz, 1H), 5.22 (d, $J = 10.4$ Hz, 1H), 5.19 (d, $J = 10.4$ Hz, 1H), 5.14–5.06 (m, 1H), 4.82 (d, $J = 11.9$ Hz, 1H), 4.65 (d, $J = 11.9$ Hz, 1H), 4.56 (d, $J = 3.7$ Hz, 1H), 4.50–4.42 (m, 2H), 4.41 (d, $J = 2.4$ Hz, 1H), 4.19 (s, 2H), 4.03 (d, $J = 5.5$ Hz, 2H), 3.95 (d, $J = 5.6$ Hz, 2H), 3.88 (d, $J = 7.3$ Hz, 2H), 1.51 (s, 3H), 1.31 (s, 3H); **^{13}C NMR** (100 MHz, CDCl_3) δ 148.4, 137.7, 134.8, 134.0, 128.4, 128.1, 127.8, 118.0, 117.35, 112.4, 105.1, 102.9, 82.3, 81.8, 81.5, 71.2, 70.8, 70.7, 68.2, 67.4, 57.4, 26.9, 26.5; **HRMS** (ESI-QTOF): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{27}\text{H}_{34}\text{NaO}_7$ 493.2206; found 493.2208.

(S)-4-(benzyloxy)-1-((3aR,5R,6S,6aR)-6-((4-methoxybenzyl)oxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)but-2-yn-1-ol (**26**). To a solution of alkyne **24** (2.13 g, 14.5 mmol) in dry THF (20 mL) at –78 °C was added *n*-BuLi (9.0 mL, 1.6 M in hexane, 3.2 mmol) over 10 min, and the reaction mixture was allowed to be stirred at the same temperature for 1 h. Aldehyde **15** (3 g, 9.72 mmol) in THF (15 mL) was added to the solution of alkyne at –78 °C, and the reaction was further kept at the same temperature for 1 h, then stirred at room temperature for 4 h. The reaction mixture was quenched with sat. aqueous NH_4Cl solution, and the organic layer was extracted with EtOAc (3 $\times$ 30 mL), washed with brine solution, dried over anhydrous Na_2SO_4 , concentrated under reduced pressure, and further purification was done through silica gel column chromatography (1:45 EtOAc/hexane) to obtain alcohols **26** (2.21 g, 50%) and **25** (1.34 g, 30%).

Data for major diastereomers (26). **Physical appearance:** Sticky yellow liquid; R_f : 0.5 (30% EtOAc/hexane $\times$ 2); **IR** (neat, cm^{-1}): 3467, 2933, 2858, 2345, 1613, 1514, 1472, 1428, 1374, 1302, 1215, 1165, 1112, 1075, 1019, 890, 825, 755, 704, 614, 506; $[\alpha]_D^{20}$: –37.4 ($c = 1.00$, CHCl_3); **^1H NMR** (400 MHz, CDCl_3) δ 7.36–7.28 (m, 5H), 7.26 (d, $J = 8.5$ Hz, 2H), 6.85 (d, $J = 8.5$ Hz, 2H), 5.97 (d, $J = 3.6$ Hz, 1H), 4.78 (d, $J = 8.1$ Hz, 1H), 4.61 (dd, $J = 7.4, 3.8$ Hz, 2H), 4.57 (s, 2H), 4.48 (d, $J = 11.2$ Hz, 1H), 4.31 (dd, $J = 8.0, 3.3$ Hz, 1H), 4.19 (s, 2H), 4.08 (d, $J = 3.3$ Hz, 1H), 2.54 (brs, 1H), 1.51 (s, 3H), 1.33 (s, 3H); **^{13}C NMR** (100 MHz, CDCl_3) δ 159.6, 137.5, 129.7, 129.2, 128.6, 128.16 128.0, 114.0, 112.4, 105.7, 83.8, 83.7, 82.6, 82.1, 81.9, 72.5, 71.8, 62.0, 57.5, 55.4, 27.0, 26.5; **HRMS** (ESI-QTOF): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{26}\text{H}_{30}\text{NaO}_7$ 477.1884; found 477.1888.

(R)-4-(benzyloxy)-1-((3aR,5R,6S,6aR)-6-((4-methoxybenzyl)oxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5-yl)but-2-yn-1-ol (**25**)

Data for minor diastereomers (25). **Physical appearance:** Sticky yellow liquid; R_f : 0.6 (30% EtOAc/hexane $\times$ 2); **IR** (neat, cm^{-1}): 3461, 2989, 2932, 2323, 1720, 1610, 1513, 1454, 1380, 1354, 1300, 1254, 1219, 1164, 1073, 1029, 888, 839, 756, 699, 666, 636, 590, 517; $[\alpha]_D^{20}$: –45.80 ($c = 2.00$, CHCl_3); **^1H NMR** (400 MHz, CDCl_3) δ 7.34–7.27 (m, 5H), 7.25 (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 6.01 (d, $J = 3.8$ Hz, 1H), 4.80–4.73 (m, 1H), 4.63 (d, $J = 11.1$ Hz, 1H), 4.59 (d, $J = 3.8$ Hz, 1H), 4.56 (s, 2H), 4.49 (d, $J = 11.1$ Hz, 1H), 4.29–4.22 (m, 2H), 4.16 (d, $J = 1.4$ Hz, 2H), 3.75 (s, 3H), 3.46 (d, $J = 9.2$ Hz, 1H), 1.48 (s, 3H), 1.31 (s, 3H); **^{13}C NMR** (100 MHz, CDCl_3) δ 159.8, 137.5, 130.0, 128.6, 128.2, 128.0, 114.2, 112.1, 105.7, 85.1, 83.4, 82.0, 81.8,

81.1, 72.5, 71.8, 61.5, 57.5, 55.4, 27.0, 26.4; **HRMS (ESI-QTOF)**: $[M + Na]^+$ calcd for $C_{26}H_{30}NaO_7$ 477.1884; found 477.1867.

(3aR,5R,6S,6aR)-5-(1,4-Bis(benzyloxy)but-2-yn-1-yl)-6-((4-methoxybenzyl)oxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole (27). NaH (660 mg, 60% in mineral oil, 16.5 mmol) was charged into a flame dried two-neck round-bottomed flask and diluted with anhydrous DMF (15 mL). After cooling down to 0 °C, a solution of **26** (5 g, 11.0 mmol) in DMF (50 mL) was added in a drop-wise manner, and the resulting suspension was stirred at the same temperature for 40 min. Finally, benzyl bromide (1.95 mL, 16.5 mmol) was added and the resulting mixture was stirred at room temperature over 12 h. After complete consumption of the starting material, the reaction mixture was quenched with saturated NH_4Cl solution and the product was extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4 and then concentrated to obtain the crude product. Purification was done through silica gel column chromatography (1 : 10 EtOAc/hexane) to obtain the benzylated compound **27** (72%, 4.35 g). **Physical appearance**: Sticky colourless liquid; R_f : 0.7 (20% EtOAc/hexane); **IR (neat, cm^{-1})**: 3071, 3015, 2933, 2858, 1612, 1588, 1514, 1471, 1427, 1374, 1303, 1251, 1216, 1164, 1174, 1112, 1078, 1035, 936, 910, 823, 758, 703, 667, 614, 505; $[\alpha]_D^{20}$: -35.3 ($c = 1.00$, $CHCl_3$); **1H NMR (400 MHz, $CDCl_3$)** δ 7.45–7.26 (m, 10H), 7.18 (d, $J = 8.6$ Hz, 2H), 6.83 (d, $J = 8.6$ Hz, 2H), 5.97 (d, $J = 3.6$ Hz, 1H), 4.90 (d, $J = 11.3$ Hz, 1H), 4.69–4.61 (m, 3H), 4.61–4.42 (m, 4H), 4.38 (dd, $J = 9.1, 3.0$ Hz, 1H), 4.31 (d, $J = 1.4$ Hz, 2H), 4.09 (d, $J = 2.9$ Hz, 1H), 3.78 (s, 3H), 1.53 (s, 3H), 1.34 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 139.2, 131.5, 123.8, 123.3, 77.2, 77.0, 76.7, 59.1, 39.4, 26.2, 25.5, 17.5, 16.1; **HRMS (ESI-QTOF)**: $[M + Na]^+$ calcd for $C_{33}H_{36}NaO_7$ 567.2354; found 567.2353.

(3aR,5S,6S,6aR)-5-(1,4-Bis(benzyloxy)but-2-yn-1-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-ol (28). To a solution of the 4-methoxybenzyl ether **27** (2.7 g, 4.9 mmol) in CH_2Cl_2/H_2O (50 mL 10 : 1) cooled to 0 °C was added DDQ (2.82 g, 12.4 mmol) and the solution was stirred at 25 °C for 5 h. The reaction mixture was quenched with sat. $NaHCO_3$ (20 mL) which was added at 0 °C, and the mixture was extracted with ethyl acetate (20 mL × 3). The organic layer was washed with water, followed by brine, dried over $NaSO_4$, and then concentrated to obtain the crude product. The crude product was purified through silica gel column chromatography (1 : 3 EtOAc/hexane) to obtain alcohol **28** (80%, 1.5 g). **Physical appearance**: Sticky colourless liquid; R_f : 0.25 (30% EtOAc/hexane); **IR (neat, cm^{-1})**: 3540, 2932, 2858, 1961, 1471, 1454, 1428, 1374, 1313, 1259, 1216, 1163, 1112, 1070, 1013, 956, 887, 854, 823, 754, 702, 614, 702, 614, 505; $[\alpha]_D^{20}$: +38.5 ($c = 1.00$, $CHCl_3$); **1H NMR (500 MHz, $CDCl_3$)** δ 7.46–7.26 (m, 10H), 6.02 (d, $J = 3.6$ Hz, 1H), 4.90 (d, $J = 11.8$ Hz, 1H), 4.69 (d, $J = 11.8$ Hz, 1H), 4.63 (s, 2H), 4.56 (d, $J = 6.2$ Hz, 1H), 4.50 (d, $J = 3.6$ Hz, 1H), 4.40–4.33 (m, 2H), 4.27 (d, $J = 1.3$ Hz, 2H), 1.53 (s, 3H), 1.34 (s, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 137.0, 136.9, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 111.8, 105.3, 84.7, 83.8, 81.8, 81.6, 77.2, 77.0, 76.7, 75.8, 71.7, 71.0, 68.1, 57.2, 26.7, 26.2; **HRMS (ESI-QTOF)**: $[M + Na]^+$ calcd for $C_{25}H_{28}NaO_6$ 447.1774; found 447.1778.

Ethyl(E)-3-(((3aR,5R,6S,6aR)-5-(1,4-bis(benzyloxy)but-2-yn-1-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)acrylate (29). To a solution of alcohol **28** (1 g, 2.30 mmol) in anhydrous CH_2Cl_2 (20 mL) was added ethyl propiolate (0.25 mL, 2.53 mmol) under N_2 and stirred for 5 min. Then, *N*-methyl morpholine (2.33 mL, 2.30 mmol) was added at 0 °C using a micro syringe. The resulting mixture was stirred for 5 h. The reaction mixture was concentrated and purified by silica gel chromatography (1 : 10 EtOAc/hexane) to obtain ester **29** (0.82 g, 68%). **Physical appearance**: Sticky colourless liquid; R_f : 0.5 (20% EtOAc/hexanes); **IR (neat, cm^{-1})**: 3032, 2933, 2861, 1712, 1624, 1515, 1463, 1371, 1329, 1253, 1217, 1136, 1039, 966, 852, 824, 757, 702, 610, 505; $[\alpha]_D^{20}$: +24.5 ($c = 1.00$, $CHCl_3$); **1H NMR (400 MHz, $CDCl_3$)** δ 7.51 (d, $J = 12.7$ Hz, 1H), 7.43–7.23 (m, 10H), 5.99 (d, $J = 3.8$ Hz, 1H), 5.37 (d, $J = 12.7$ Hz, 1H), 4.84 (d, $J = 11.9$ Hz, 1H), 4.66 (d, $J = 11.9$ Hz, 1H), 4.54 (ddd, $J = 10.3, 6.2, 2.3$ Hz, 5H), 4.47 (t, $J = 4.7$ Hz, 1H), 4.29–4.18 (m, 2H), 4.14 (q, $J = 7.1$ Hz, 2H), 1.53 (s, 3H), 1.32 (s, 3H), 1.25 (t, $J = 7.1$ Hz, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 166.9, 160.1, 137.3, 137.1, 128.3, 128.2, 127.9, 127.8, 127.6, 112.5, 105.5, 98.9, 83.9, 83.6, 81.5, 81.4, 81.3, 77.3, 77.0, 76.6, 71.6, 71.0, 67.8, 59.9, 57.1, 26.6, 26.2, 14.2; **HRMS (ESI-QTOF)**: $[M + Na]^+$ calcd for $C_{30}H_{34}NaO_8$ 545.2146; found 545.2146.

(E)-3-(((3aR,5R,6S,6aR)-5-(1,4-Bis(benzyloxy)but-2-yn-1-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-6-yl)oxy)prop-2-en-1-ol (30). A solution of DIBAL-H {1 M in toluene} (3.82 mL) was added *via* a syringe to a stirred mixture of ester **29** (0.8 g, 1.53 mmol) in Et_2O (5.0 mL) at -78 °C. After 1 h, the reaction flask was warmed to -40 °C and further stirred for 5 h. The reaction mixture was quenched using a sat. aqueous solution of Rochelle's salt, and the stirring was continued for 1 h. The reaction mixture was then extracted with EtOAc (40 mL × 2). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel (1 : 25 EtOAc/hexanes) to obtain the allylic alcohol **30** (585 mg, 80%). **Physical appearance**: sticky colourless oil; R_f : 0.3 (25% EtOAc/hexane); **IR (neat, cm^{-1})**: 3485, 3021, 2932, 2861, 1632, 1455, 1428, 1373, 1306, 1260, 1216, 1165, 1023, 939, 854, 739, 702, 613, 506; $[\alpha]_D^{20}$: +79.9 ($c = 0.50$, $CHCl_3$); **1H NMR (400 MHz, $CDCl_3$)** δ 7.52–7.15 (m, 10H), 6.37 (d, $J = 12.7$ Hz, 1H), 5.98 (d, $J = 3.8$ Hz, 1H), 5.16 (dd, $J = 7.1, 5.6$ Hz, 1H), 4.84 (d, $J = 11.9$ Hz, 1H), 4.67 (d, $J = 11.9$ Hz, 1H), 4.58 (s, 2H), 4.56 (d, $J = 3.8$ Hz, 1H), 4.50 (d, $J = 2.8$ Hz, 2H), 4.43 (d, $J = 2.4$ Hz, 1H), 4.22 (d, $J = 0.7$ Hz, 2H), 3.95 (d, $J = 7.2$ Hz, 2H), 1.53 (s, 3H), 1.32 (s, 3H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 147.8, 137.6, 137.2, 128.5, 128.4, 128.1, 128.0, 127.7, 112.3, 105.8, 105.7, 83.1, 82.4, 82.1, 81.9, 81.6, 71.7, 71.1, 68.3, 60.1, 57.3, 26.8, 26.4; **HRMS (ESI-QTOF)**: $[M + Na]^+$ calcd for $C_{28}H_{32}NaO_7$ 503.2040; found 503.2040.

(3aR,5R,6S,6aR)-6-(((E)-3-(Allyloxy)prop-1-en-1-yl)oxy)-5-(1,4-bis(benzyloxy)but-2-yn-1-yl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole (31). A flame-dried two neck round-bottomed flask was charged with NaH (60 mg, 1.45 mmol, 60% in mineral oil) and anhydrous DMF (15 mL) was added. After cooling to 0 °C, a solution of alcohol **30** (450 mg, 0.936 mmol) in DMF (10 mL) was added in a drop-wise manner, and the resulting solution

was stirred for 40 min at the same temperature. Finally, allyl bromide (0.125 mL, 1.45 mmol) was added at 0 °C, and the resulting mixture was stirred to room temperature for 12 h. The reaction was quenched with saturated NH_4Cl solution, and work-up was done with EtOAc to obtain the crude mixture. Purification was done through silica gel column chromatography (1 : 9 EtOAc/hexane) to obtain the RRCEM precursor **31** (300 mg, 60%). **Physical appearance:** sticky colourless oil; R_f : 0.5 (20% EtOAc/hexane); **IR** (neat, cm^{-1}): 3077, 2932, 2867, 1653, 1456, 1429, 1374, 1261, 1217, 1164, 1114, 1070, 1020, 936, 856, 826, 741, 703, 614, 506; $[\alpha]_D^{20}$: +28.7 ($c = 0.5$, CHCl_3); **^1H NMR** (500 MHz, CDCl_3) δ 7.41 (d, $J = 7.3$ Hz, 2H), 7.39–7.30 (m, 7H), 7.28 (d, $J = 7.3$ Hz, 1H), 6.39 (d, $J = 12.7$ Hz, 1H), 5.97 (d, $J = 3.8$ Hz, 1H), 5.89 (ddd, $J = 22.8, 10.8, 5.6$ Hz, 1H), 5.25 (dd, $J = 17.2, 1.4$ Hz, 1H), 5.17 (d, $J = 10.4$ Hz, 1H), 5.11 (dt, $J = 12.9, 7.3$ Hz, 1H), 4.84 (d, $J = 11.9$ Hz, 1H), 4.67 (d, $J = 11.9$ Hz, 1H), 4.57 (s, 3H), 4.49 (d, $J = 3.0$ Hz, 2H), 4.43 (d, $J = 2.5$ Hz, 1H), 4.22 (s, 2H), 3.92 (d, $J = 5.7$ Hz, 2H), 3.83 (d, $J = 7.3$ Hz, 2H), 1.53 (s, 3H), 1.32 (s, 3H); **^{13}C NMR** (125 MHz, CDCl_3) δ 148.4, 137.7, 137.4, 134.8, 128.6, 128.4, 128.1, 128.1, 128.0, 127.8, 117.2, 112.4, 105.9, 102.9, 83.2, 82.1, 82.1, 81.9, 81.1, 71.7, 71.2, 70.8, 68.3, 67.3, 57.4, 26.9, 26.5; **HRMS** (ESI-QTOF): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{31}\text{H}_{36}\text{NaO}_7$ 543.2368; found 543.2353.

(3aR,3bS,7aR,8aR)-7-(Benzyloxy)-6-(3-(benzyloxy)prop-1-en-2-yl)-2,2-dimethyl-3a,3b,7a,8a-tetrahydro-7H-[1,3]di-oxo-lo[4',5':4,5]furo[3,2-*b*]pyran (32). A solution of the RRCEM precursor **31** (190 mg, 0.36 mmol) in toluene (80 mL) was degassed under argon; the G-II catalyst (21.3 mg, 7 mol%) was added and the solution was stirred at reflux under an argon atmosphere for 30 min. After completion of the reaction, the solution was cooled to room temperature and the solvent was evaporated under reduced pressure. The resulting crude mixture was washed with pentane and purified by column chromatography (1 : 12 EtOAc/hexane) to obtain the corresponding 1,3-diene **32** (132 mg, 80%). **Physical appearance:** Sticky colourless oil; R_f : 0.6 (20% EtOAc/hexane); $[\alpha]_D^{20}$: +21.82 ($c = 1.5$, CHCl_3); **IR** (neat, cm^{-1}): 3077, 2939, 2867, 1634, 1450, 1429, 1374, 1261, 1217, 1164, 1114, 1070, 1020, 936, 856, 826, 741, 703, 614, 506; **^1H NMR** (500 MHz, CDCl_3) δ 7.39–7.27 (m, 10H), 6.86 (s, 1H), 5.89 (d, $J = 3.6$ Hz, 1H), 5.12 (s, 1H), 5.07 (s, 1H), 4.71 (d, $J = 11.5$ Hz, 1H), 4.69 (d, $J = 3.6$ Hz, 1H), 4.63 (d, $J = 11.5$ Hz, 1H), 4.54–4.51 (m, 1H), 4.48 (d, $J = 0.8$ Hz, 2H), 4.39 (d, $J = 2.0$ Hz, 1H), 4.38 (d, $J = 1.5$ Hz, 1H), 4.21–4.11 (m, 2H), 1.54 (s, 3H), 1.36 (s, 3H); **^{13}C NMR** (100 MHz, CDCl_3) δ 143.6, 140.2, 138.3, 138.0, 128.5, 128.4, 128.0, 127.9, 127.7, 112.4, 111.7, 109.9, 104.8, 83.8, 74.8, 74.24, 72.0, 71.6, 71.4, 66.8, 26.8, 26.3; **HRMS** (ESI-QTOF): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{27}\text{H}_{30}\text{NaO}_6$ 473.1935; found 473.1929.

2-((Benzyloxy)((3aR,5S,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)methyl)-3-((benzyloxy)methyl)anthracene-9,10-dione (36). A mixture of diene **32** (80 mg, 0.177 mmol) and quinone **33** (33.5 g, 0.212 mmol) in toluene (1.5 mL) was heated to 100–110 °C for 24 h. After complete consumption of diene **32**, the resulting mixture was concentrated under reduced pressure to give the crude cycloadduct product **34**. The crude cycloadduct product was re-dissolved in

CHCl_3 (7 mL); then Et_3N (0.5 mL) purged with SiO_2 (2 g) was added in one portion and stirred for 1 h at room temperature. The reaction mixture was concentrated and purified by column chromatography (2 : 5 EtOAc/hexane), affording the aromatized product **36** (60 mg, 56%). **Physical appearance:** Yellow-orange powder solid; R_f : 0.4 (30% EtOAc/hexane $\times$ 2); **IR** (KBr, cm^{-1}): 3432, 3077, 2932, 2867, 1456, 1429, 1374, 1261, 1217, 1164, 1114, 1070, 1020, 936, 856, 826, 741, 703, 614, 506; $[\alpha]_D^{20}$: +20.7 ($c = 0.5$, CHCl_3); **^1H NMR** (500 MHz, CDCl_3) δ 8.61 (s, 1H), 8.35–8.28 (m, 2H), 8.23 (s, 1H), 7.84–7.79 (m, 2H), 7.40–7.20 (m, 10H), 6.03 (d, $J = 3.7$ Hz, 1H), 5.11 (d, $J = 5.8$ Hz, 1H), 4.55 (d, $J = 2.5$ Hz, 1H), 4.54–4.51 (m, 2H), 4.49 (dd, $J = 5.5, 2.6$ Hz, 1H), 4.48 (dd, $J = 11.3, 4.3$ Hz, 2H), 4.42 (d, $J = 3.7$ Hz, 1H), 4.36 (d, $J = 12.0$ Hz, 1H), 3.86 (d, $J = 2.3$ Hz, 1H), 1.43 (s, 3H), 1.27 (s, 3H); **^{13}C NMR** (125 MHz, CDCl_3) δ 182.7, 182.5, 144.0, 143.2, 141.7, 137.0, 136.5, 134.3, 134.2, 133.6, 133.4, 132.9, 128.9, 128.6, 128.5, 128.3, 128.2, 128.1, 128.0, 128.0, 127.3, 127.2, 111.7, 105.0, 84.9, 82.5, 77.3, 77.0, 76.7, 75.4, 73.2, 71.3, 69.4, 26.7, 26.1; **HRMS** (ESI-QTOF): $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{37}\text{H}_{34}\text{NaO}_8$ 629.2254; found 629.2252.

6-((S)-(Benzyloxy)((3aR,5S,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)methyl)-7-((benzyloxy)methyl)-1-methoxyanthracene-9,10-dione (39). A mixture of diene **32** (50 mg, 0.11 mmol) and quinone **37** (35 mg, 0.13 mmol) in toluene (1.5 mL) was heated to 100 °C for 15 h. After complete consumption of diene **32**, the resulting mixture was concentrated under reduced pressure to give the crude cycloadduct product **38**. The crude cycloadduct product was re-dissolved in CH_2Cl_2 (10 mL); then Et_3N (0.5 mL) was added at 0 °C and stirred for 2 h at room temperature. The reaction mixture was concentrated and purified by column chromatography (2 : 5 EtOAc/hexane), affording the aromatized product **39** (35 mg, 50%). **Physical appearance:** Yellow-orange sticky solid; R_f : 0.5 (30% EtOAc/hexane); **IR** (KBr, cm^{-1}): 3528, 3423, 2922, 2847, 1752, 1674, 1605, 1591, 1446, 1216, 1163, 1147, 1020, 976, 790, 668; $[\alpha]_D^{20}$: +85.40 ($c = 0.4$, CHCl_3); **^1H NMR** (500 MHz, CDCl_3) δ 8.52 (s, 1H), 8.29 (s, 1H), 7.95 (d, $J = 7.4$ Hz, 1H), 7.70 (t, $J = 8.0$ Hz, 1H), 7.37–7.31 (m, 5H), 7.28–7.24 (m, 2H), 7.22 (dd, $J = 7.4, 5.2$ Hz, 3H), 5.80 (d, $J = 3.5$ Hz, 1H), 5.12 (d, $J = 7.2$ Hz, 1H), 4.75 (d, $J = 12.4$ Hz, 1H), 4.57 (s, 2H), 4.52 (dd, $J = 12.2, 7.4$ Hz, 2H), 4.44 (d, $J = 3.5$ Hz, 1H), 4.31 (s, 1H), 4.24–4.18 (m, 2H), 4.03 (s, 3H), 1.31 (s, 3H), 1.21 (s, 3H); **^{13}C NMR** (125 MHz, CDCl_3) δ 183.2, 182.4, 160.5, 144.1, 143.7, 137.7, 137.3, 135.9, 135.2, 134.6, 132.5, 128.8, 128.6, 128.4, 128.2, 128.1, 128.0, 128.0, 125.8, 121.6, 120.0, 118.1, 111.8; **HRMS** (ESI-QTOF): $[\text{M} + \text{K}]^+$ calcd for $\text{C}_{38}\text{H}_{36}\text{O}_9$ 675.1962; found 675.1962.

6-((S)-(Benzyloxy)((3aR,5S,6S,6aR)-6-hydroxy-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)methyl)-7-((benzyloxy)methyl)-1-methoxyanthracene-9,10-dione (46). A mixture of diene **32** (30 mg, 0.06 mmol) and quinone **43** (14 mg, 0.08 mmol) in toluene (1 mL) was heated to 100 °C for 24 h. After complete consumption of diene **32**, the resulting mixture was concentrated under reduced pressure to give a crude cycloadduct product, which was re-dissolved in a mixture of acetone (2.5 mL) and water (5 : 1) and treated with OsO_4 (1 mol%) and *N*-methylmorpholine *N*-oxide (26.3 μL , 0.24 mmol) at room

temperature. The reaction mixture was then allowed to stir for 8 h. After the consumption of the starting material, the reaction temperature was brought to 0 °C, and an excess of Et₃N (0.5 mL) was added in a drop-wise manner and stirred at rt for 12 h. After completion of the reaction, the solvent was evaporated, and the residue was purified using silica gel column chromatography (1 : 4 EtOAc/hexane), affording compound **46** (20 mg, 40%). **Physical appearance:** Yellow-orange sticky solid; *R_f*: 0.5 (20% EtOAc/hexane × 2); **IR (neat) cm⁻¹**: 3427, 2922, 2857, 1674, 1639, 1603, 1456, 1354, 1291, 1212, 1166, 1070, 1015, 914, 885, 863, 760, 699, 607; [α]_D²⁰: +34.48 (*c* = 1.5, CHCl₃); **¹H NMR (400 MHz, CDCl₃)** δ 12.62 (s, 1H), 8.63 (s, 1H), 8.23 (s, 1H), 7.84 (d, *J* = 7.5 Hz, 1H), 7.70 (t, *J* = 8.0 Hz, 1H), 7.43–7.37 (m, 3H), 7.36–7.29 (m, 7H), 7.27–7.22 (m, 2H), 6.05 (d, *J* = 3.7 Hz, 1H), 5.14 (d, *J* = 5.5 Hz, 1H), 4.56 (d, *J* = 11.9 Hz, 3H), 4.52–4.47 (m, 3H), 4.44 (d, *J* = 3.8 Hz, 1H), 4.39 (d, *J* = 12.0 Hz, 1H), 4.18 (d, *J* = 3.1 Hz, 1H), 3.92 (s, 1H), 1.44 (s, 3H), 1.30 (s, 4H); **¹³C NMR (100 MHz, CDCl₃)** δ 188.1, 182.1, 162.7, 144.3, 142.4, 137.0, 136.9, 136.6, 133.5, 133.4, 133.1, 129.1, 128.8, 128.7, 128.4, 128.3, 128.3, 128.2, 128.1, 124.7, 119.7, 116.3, 111.8, 105.1, 85.1, 82.4, 75.7, 73.4, 71.5, 69.5, 26.9, 26.3; **HRMS (ESI-QTOF):** [*M* + Na]⁺ calcd for C₃₇H₃₄NaO₉ 645.2047; found 645.2047.

(3aR,5R,6S,6aR)-5-((R)-1,4-Bis(benzyloxy)but-2-yn-1-yl)-6-((4-methoxybenzyl)oxy)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (S4). NaH (462 mg, 60% in mineral oil, 11.5 mmol) was charged into a flame dried two-neck round bottomed flask and diluted with anhydrous DMF (20 mL). After cooling down to 0 °C, a solution of alcohol **25** (3.5 g, 7.70 mmol) in DMF (40 mL) was added in a dropwise manner, and the resulting suspension was stirred at the same temperature for 40 min. Finally, benzyl bromide (1.36 mL, 11.5 mmol) was added, and the resulting mixture was stirred at room temperature over 12 h. After complete consumption of the starting material, the reaction mixture was quenched with saturated NH₄Cl solution, and the product was extracted with EtOAc (2 × 40 mL). The combined organic layer was washed with water, dried over anhydrous Na₂SO₄ and then concentrated to obtain the crude product. Purification was done through silica gel column chromatography (1 : 10 EtOAc/hexane) to obtain the benzyolated compound **S4** (80%, 3.3 g). **Physical appearance:** Sticky yellow liquid; *R_f*: 0.7 (25% EtOAc/hexane); **IR (neat, cm⁻¹)**: = 3461, 2989, 2932, 2227, 1720, 1610, 1584, 1513, 1454, 1380, 1354, 1300, 1254, 1164, 1073, 1029, 839, 756, 699, 666, 636, 590, 517; [α]_D²⁰: +31.53 (*c* = 0.5, CHCl₃); **¹H NMR (400 MHz, CDCl₃)** δ 7.45–7.26 (m, 10H), 7.18 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 5.97 (d, *J* = 3.6 Hz, 1H), 4.90 (d, *J* = 11.3 Hz, 1H), 4.68–4.61 (m, 3H), 4.58 (t, *J* = 7.7 Hz, 2H), 4.50 (d, *J* = 11.3 Hz, 1H), 4.46 (d, *J* = 11.4 Hz, 1H), 4.37 (dd, *J* = 9.1, 2.9 Hz, 1H), 4.30 (d, *J* = 1.3 Hz, 2H), 4.09 (d, *J* = 2.9 Hz, 1H), 3.78 (s, 3H), 1.53 (s, 3H), 1.34 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 159.4, 137.7, 137.6, 129.7, 129.2, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 113.9, 112.0, 105.3, 83.9, 83.2, 82.3, 81.3, 80.8, 72.1, 71.4, 70.9, 66.6, 57.6, 55.3, 26.9, 26.4; **HRMS (ESI-QTOF):** [*M* + Na]⁺ calcd for C₃₃H₃₆NaO₇ 567.2354; found 567.2353.

(3aR,5S,6S,6aR)-5-((R)-1,4-Bis(benzyloxy)but-2-yn-1-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-ol (S5). To a solution of the 4-methoxybenzyl ether **S4** (3 g, 7.0 mmol) in CH₂Cl₂/H₂O (50 mL 10 : 1) cooled to 0 °C was added DDQ (4.72 g, 17.5 mmol) and the solution was stirred at 25 °C for 4 h. The reaction mixture was quenched with sat. NaHCO₃ (30 mL) and the mixture was extracted with ethyl acetate (30 mL × 3). The organic layer was washed with water followed by brine, dried over Na₂SO₄, and then concentrated to obtain the crude product, which was further purified through silica gel column chromatography (1 : 35 EtOAc/hexane) to obtain the alcohol **S5** (90%, 2.1 g). **Physical appearance:** Sticky colorless liquid; *R_f*: 0.2 (30% EtOAc/hexane); **IR (neat, cm⁻¹)**: 3471, 3089, 2988, 2931, 2861, 2237, 1957, 1723, 1630, 1606, 1496, 1454, 1375, 1354, 1315, 1216, 1164, 1081, 1020, 947, 884, 858, 750, 699, 638, 605, 540, 520; [α]_D²⁰: −52.56 (*c* = 3.0, CHCl₃); **¹H NMR (400 MHz, CDCl₃)** δ 7.39–7.28 (m, 10H), 5.98 (d, *J* = 3.6 Hz, 1H), 4.87 (d, *J* = 11.7 Hz, 1H), 4.65–4.59 (m, 4H), 4.50 (d, *J* = 3.6 Hz, 1H), 4.45 (d, *J* = 2.2 Hz, 1H), 4.28 (dd, *J* = 6.5, 2.1 Hz, 3H), 1.68 (br s, 1H), 1.50 (s, 3H), 1.32 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 137.3, 136.6, 128.8, 128.6, 128.4, 128.3, 128.1, 112.0, 105.3, 84.9, 84.4, 81.9, 81.1, 75.5, 71.9, 71.6, 67.8, 57.5, 27.0, 26.3; **HRMS (ESI-QTOF):** [*M* + K]⁺ calcd for C₂₅H₂₈KO₆ 463.1482; found 463.1481.

Ethyl(E)-3-(((3aR,5R,6S,6aR)-5-((R)-1,4-bis(benzyloxy)but-2-yn-1-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl)oxy)acrylate (S6). To a solution of alcohol **S5** (1 g, 2.3 mmol) in anhydrous CH₂Cl₂ (20 mL) was added ethyl propiolate (0.25 mL, 2.53 mmol) under N₂ and stirred for 5 min. Then, *N*-methyl morpholine (0.23 mL, 2.3 mmol) was added at 0 °C. The resulting mixture was stirred for 12 h. The reaction mixture was concentrated and purified by silica gel chromatography (1 : 12 EtOAc/hexane) to obtain the ester **S6** (0.92 g, 75%). **Physical appearance:** Sticky colourless liquid; *R_f*: 0.5 (20% EtOAc/hexanes); **IR (neat, cm⁻¹)**: 3030, 2980, 2850, 1713, 1645, 1626, 1496, 1454, 1374, 1324, 1285, 1260, 1216, 1194, 1166, 1138, 1067, 1048, 1024, 949, 907, 884, 853, 755, 699, 667, 644, 519; [α]_D²⁰: +87.41 (*c* = 1.5, CHCl₃); **¹H NMR (400 MHz, CDCl₃)** δ 7.42–7.27 (m, 10H), 5.93 (d, *J* = 3.7 Hz, 1H), 5.33 (d, *J* = 12.2 Hz, 1H), 4.80 (d, *J* = 12.2 Hz, 1H), 4.65 (s, 2H), 4.54 (d, *J* = 3.8 Hz, 1H), 4.48 (t, *J* = 7.2 Hz, 2H), 4.43–4.33 (m, 2H), 4.29 (d, *J* = 1.4 Hz, 2H), 4.23–4.13 (m, 2H), 1.51 (s, 3H), 1.31 (s, 3H), 1.28 (s, 3H); **¹³C NMR (100 MHz, CDCl₃)** δ 167.2, 160.6, 137.4, 136.8, 128.7, 128.5, 128.5, 128.3, 128.24, 128.0, 112.6, 105.2, 99.0, 83.6, 83.0, 82.9, 82.1, 80.5, 71.6, 70.9, 65.5, 60.1, 57.5, 26.7, 26.4, 14.4; **HRMS (ESI-QTOF):** [*M* + K]⁺ calcd for C₃₀H₃₄KO₈ 561.1851; found 561.1851.

(E)-3-(((3aR,5R,6S,6aR)-5-((R)-1,4-Bis(benzyloxy)but-2-yn-1-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl)oxy) prop-2-en-1-ol (S7). A solution of DIBAL-H {1M in toluene} (10.25 mL) was added *via* a syringe to a stirred mixture of ester **S6** (2 g, 4.1 mmol) in Et₂O (25 mL) at −78 °C. After 1 h, the reaction flask was warmed to −40 °C and further stirred for 2 h. The reaction mixture was quenched using a sat. aqueous solution of Rochelle's salt, and the stirring was continued for 1 h. The reaction mixture was then extracted with EtOAc (30 mL × 2).

The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography using silica gel chromatography (1:3 EtOAc/hexanes) to obtain the allylic alcohol **S7** (1.6 g, 90%). **Physical appearance:** Sticky colourless oil; *R*_f: 0.35 (20% EtOAc/hexane); **IR** (neat, cm⁻¹): 3475, 3064, 2989, 2935, 2345, 1876, 1808, 1670, 1652, 1496, 1454, 1375, 1310, 1218, 1167, 1107, 1073, 1025, 941, 854, 755, 699, 638, 517; [α]_D²⁰: -48.37 (*c* = 5.0, CHCl₃); **¹H NMR** (500 MHz, CDCl₃) δ 7.45–7.22 (m, 10H), 6.32 (d, *J* = 12.6 Hz, 1H), 5.96–5.85 (m, 2H), 5.27 (d, *J* = 17.2 Hz, 1H), 5.19 (d, *J* = 10.4 Hz, 1H), 5.16–5.05 (m, 1H), 4.82 (d, *J* = 11.3 Hz, 1H), 4.64 (s, 2H), 4.58 (d, *J* = 3.3 Hz, 1H), 4.49 (d, *J* = 11.3 Hz, 1H), 4.44 (d, *J* = 9.4 Hz, 1H), 4.40–4.33 (m, 2H), 4.28 (s, 2H), 3.95 (d, *J* = 5.3 Hz, 2H), 3.87 (d, *J* = 7.0 Hz, 2H), 1.51 (s, 3H), 1.31 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 148.7, 137.5, 137.4, 134.9, 128.6, 128.5, 128.4, 128.0, 117.2, 112.4, 105.3, 102.7, 83.5, 83.3, 82.1, 81.1, 80.8, 77.2, 71.6, 71.0, 70.8, 67.3, 66.0, 57.6, 26.9, 26.5; **HRMS** (ESI-QTOF): [*M* + Na]⁺ calcd for C₂₈H₃₂NaO₇ 503.2040; found 503.2040.

(3*aR*,5*R*,6*S*,6*aR*)-6-((*E*)-3-(Allyloxy)prop-1-en-1-yl)oxy)-5-((*R*)-1,4-bis(benzyloxy)but-2-yn-1-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxole (**S8**). A flame-dried two-neck round-bottomed flask was charged with NaH (37.4 mg, 0.93 mmol, 60% in mineral oil) and anhydrous DMF (7 mL) was added. After cooling to 0 °C, a solution of alcohol **S7** (300 mg, 0.62 mmol) in DMF (5 mL) was added in a drop-wise manner, and the resulting solution was stirred for 30 min at the same temperature. Finally, allyl bromide (82 μ L, 0.95 mmol) was added, and the resulting mixture was stirred to room temperature for 12 h. The reaction was quenched with saturated NH₄Cl solution, and work-up was done with EtOAc to obtain the crude mixture. Purification was done through silica gel column chromatography (1:10 EtOAc/hexane) to obtain the RRCEM precursor **S8** (240 mg, 70%). **Physical appearance:** Sticky colourless oil; *R*_f: 0.6 (20% EtOAc/hexane); **IR** (neat, cm⁻¹): 3031, 2938, 2850, 2345, 1725, 1493, 1452, 1386, 1216, 1163, 1097, 1072, 1017, 946, 883, 885, 756, 699, 670, 521; [α]_D²⁰: 14.63 (*c* = 0.6, CHCl₃); **¹H NMR** (500 MHz, CDCl₃) δ 7.41–7.27 (m, 10H), 6.32 (d, *J* = 12.6 Hz, 1H), 5.95–5.87 (m, 2H), 5.27 (d, *J* = 17.2 Hz, 1H), 5.19 (d, *J* = 10.4 Hz, 1H), 5.16–5.07 (m, 1H), 4.82 (d, *J* = 11.3 Hz, 1H), 4.64 (s, 2H), 4.58 (d, *J* = 3.3 Hz, 1H), 4.49 (d, *J* = 11.3 Hz, 1H), 4.44 (d, *J* = 9.4 Hz, 1H), 4.40–4.33 (m, 2H), 4.28 (s, 2H), 3.95 (d, *J* = 5.3 Hz, 2H), 3.87 (d, *J* = 7.0 Hz, 2H), 1.51 (s, 3H), 1.31 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 148.6, 137.4, 137.2, 134.7, 128.4, 128.3, 128.2, 127.8, 117.1, 112.2, 105.1, 102.6, 83.3, 83.1, 81.9, 80.9, 80.6, 71.4, 70.8, 70.6, 67.2, 65.8, 57.4, 26.7, 26.3; **HRMS** (ESI-QTOF): [*M* + Na]⁺ calcd for C₃₁H₃₆NaO₇ 543.2312; found 543.2312.

(3*aR*,3*bS*,7*R*,7*aR*,8*aR*)-7-(Benzyloxy)-6-(3-(benzyloxy)prop-1-en-2-yl)-2,2-dimethyl-3*a*,3*b*,7*a*,8*a*-tetrahydro-7*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-*b*]pyran (**41**). A solution of the RRCEM precursor **S8** (200 mg, 0.38 mmol) in toluene (80 mL) was degassed under argon; the G-II catalyst (22.5 mg, 7 mol%) was added in one portion and the solution was stirred at reflux under an argon atmosphere for 2 h. After completion of the reaction, the solution was cooled to room temperature, and then the reaction

mixture was evaporated to dryness. The resulting crude mixture was washed with pentane and purified by column chromatography (1:12 EtOAc/hexane) to obtain the corresponding 1,3-diene **41** (160 mg, 85%). **Physical appearance:** Sticky colourless oil; *R*_f: 0.5 (20% EtOAc/hexane); [α]_D²⁰: +21.82 (*c* = 1.5, CHCl₃); **IR** (neat, cm⁻¹): 3037, 2983, 2928, 1725, 1637, 1496, 1454, 1380, 1379, 1283, 1264, 1215, 1164, 1082, 1024, 890, 865, 843, 756, 699, 666, 604; **¹H NMR** (400 MHz, CDCl₃) δ 7.40–7.26 (m, 10H), 6.63 (s, 1H), 6.03 (d, *J* = 3.7 Hz, 1H), 5.20 (d, *J* = 1.4 Hz, 1H), 5.07 (d, *J* = 1.4 Hz, 1H), 4.76 (d, *J* = 11.5 Hz, 1H), 4.69 (dd, *J* = 3.7, 0.9 Hz, 1H), 4.64 (dd, *J* = 5.0, 2.3 Hz, 1H), 4.59 (s, 1H), 4.53 (d, *J* = 17.7 Hz, 1H), 4.45 (d, *J* = 25.8 Hz, 1H), 4.38 (d, *J* = 7.8 Hz, 1H), 4.24 (d, *J* = 12.2 Hz, 1H), 4.06 (d, *J* = 12.3 Hz, 1H), 1.54 (s, 3H), 1.36 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 142.1, 140.4, 138.3, 137.9, 128.4, 128.4, 128.1, 128.0, 127.7, 127.7, 113.5, 112.7, 112.3, 104.8, 83.6, 78.4, 72.3, 72.3, 71.7, 70.4, 67.6, 26.8, 26.4; **HRMS** (ESI-QTOF): [*M* + Na]⁺ calcd for C₂₇H₃₀NaO₆ 473.1894; found 473.1893.

(8*R*,8*aR*,9*aR*,12*aR*,12*bS*)-8-(Benzyloxy)-7-((benzyloxy)methyl)-11,11-dimethyl-8*a*,9*a*,12*a*,12*b*-tetrahydro-8*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-*b*]naphtho[2,3-*h*]chromene-5,14-dione (**42**). A mixture of diene **41** (50 mg, 0.11 mmol) and quinone **33** (21 mg, 0.133 mmol) in toluene (1.5 mL) was heated to 100–110 °C for 24 h. After complete consumption of diene **41**, the resulting mixture was concentrated under reduced pressure to give a crude cycloadduct product. The crude cycloadduct product was re-dissolved in CH₂Cl₂ (10 mL) and *m*-CPBA (60 mg) was added portion-wise at room temperature, followed by NaHCO₃ (40 mg). The mixture was stirred at room temperature for 24 h, and then Et₃N (0.8 mL) was added at room temperature in an open-air atmosphere and further kept stirring at room temperature for 4 h. After completion of the reaction, the residue was concentrated under reduced pressure and purified by column chromatography (1:4 EtOAc/hexane), affording the aromatized product **42** (38 mg, 45%). **Physical appearance:** Yellow-orange powder solid; *R*_f: 0.5 (30% EtOAc/hexane); **IR** (KBr, cm⁻¹): 3055, 2926, 2857, 2349, 1729, 1673, 1589, 1455, 1381, 1324, 1265, 1216, 1163, 1094, 1024, 890, 755, 717, 700; [α]_D²⁰: -26.94 (*c* = 1.00 CHCl₃); **¹H NMR** (400 MHz, CDCl₃) δ 8.23 (d, *J* = 7.4 Hz, 2H), 8.11 (s, 1H), 7.80–7.70 (m, 2H), 7.40–7.30 (m, 10H), 6.08 (d, *J* = 3.8 Hz, 1H), 5.16–5.11 (m, 1H), 5.02 (d, *J* = 4.8 Hz, 1H), 4.86–4.81 (m, 1H), 4.77 (d, *J* = 11.0 Hz, 1H), 4.74 (s, 1H), 4.72 (d, *J* = 9.6 Hz, 1H), 4.64 (d, *J* = 13.5 Hz, 1H), 4.57 (d, *J* = 11.0 Hz, 1H), 4.54 (s, 2H), 1.56 (s, 3H), 1.41 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 183.1, 181.9, 154.9, 145.9, 137.8, 137.1, 135.1, 134.7, 134.4, 133.5, 132.6, 128.7, 128.5, 128.3, 128.0, 128.0, 127.3, 126.8, 126.7, 120.5, 113.0, 105.3, 84.7, 79.4, 73.1, 72.5, 71.3, 70.5, 69.0, 27.1, 26.6. **HRMS** (ESI-QTOF): [*M* + H]⁺ calcd for C₃₇H₃₃O₈ 605.2170; found 605.2163.

(8*R*,8*aR*,9*aR*,12*aR*,12*bS*)-8-(Benzyloxy)-7-((benzyloxy)methyl)-1-hydroxy-11,11-dimethyl-8*a*,9*a*,12*a*,12*b*-tetrahydro-8*H*-[1,3]dioxolo[4',5':4,5]furo[3,2-*b*]naphtho[2,3-*h*]chromene-5,14-dione (**45**). A mixture of diene **41** (50 mg, 0.11 mmol) and dienophile **43** (23 mg, 1.33 mmol) in toluene (1 mL) was heated to 100–110 °C for 20 h. After complete consumption of diene **41**,

the resulting mixture was concentrated under reduced pressure to give the crude cycloadduct product **44**. The crude cycloadduct product was re-dissolved in CH₂Cl₂ (10 mL) and *m*-CPBA (60 mg) followed by NaHCO₃ (40 mg) were added portion-wise at room temperature. The mixture was stirred at room temperature for 24 h, and then Et₃N (0.8 mL) was added at room temperature in an open-air atmosphere and further kept stirring at room temperature for 6 h. After completion of the reaction, the residue was concentrated under reduced pressure and purified by column chromatography (1 : 5 EtOAc/hexane), affording the aromatized product **45** (35 mg, 50%). **Physical appearance**: Yellow sticky solid; *R*_f: 0.5 (20% EtOAc/hexane); **IR** (KBr, cm⁻¹): 3502, 3040, 2926, 2864, 1672, 1638, 1592, 1512, 1454, 1372, 1318, 1262, 1161, 1098, 1023, 890, 836, 756, 699, 670; [α]_D²⁰: -56.80 (*c* = 0.65, CHCl₃); **¹H NMR** (500 MHz, CDCl₃) δ 12.96 (s, 1H), 8.10 (s, 1H), 7.79–7.73 (m, 1H), 7.61 (t, *J* = 7.9 Hz, 1H), 7.40–7.27 (m, 11H), 6.09 (d, *J* = 3.8 Hz, 1H), 5.12 (d, *J* = 3.8 Hz, 1H), 5.01 (d, *J* = 4.6 Hz, 1H), 4.85–4.80 (m, 1H), 4.74 (d, *J* = 11.4 Hz, 2H), 4.69 (d, *J* = 13.5 Hz, 1H), 4.62 (d, *J* = 13.5 Hz, 1H), 4.55 (d, *J* = 11.2 Hz, 1H), 4.53 (s, 2H), 3.81 (s, 1H), 1.56 (s, 3H), 1.42 (s, 3H); **¹³C NMR** (125 MHz, CDCl₃) δ 188.2, 182.4, 162.6, 155.4, 146.6, 137.7, 137.0, 136.0, 134.7, 132.8, 128.7, 128.4, 128.3, 128.1, 128.0, 127.2, 124.9, 120.8, 120.0, 119.0, 117.2, 113.2, 105.3, 84.9, 79.8, 77.4, 77.2, 76.9, 73.2, 72.9, 71.4, 70.3, 69.0, 27.2, 26.8; **HRMS** (ESI-QTOF): [*M* + Na]⁺ calcd for C₃₇H₃₂NaO₉ 643.1894; found 643.1894.

Data availability

All of the data related to new compounds pertaining to this manuscript are available in the ESI.†

Conflicts of interest

There are no conflicts to declare.

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- 12 It was observed that in the epoxidation attempts of the major diene isomer **32** using *m*-CPBA in DCM, **32** did not react at all, even after adding an excess of reagents and extending the reaction time.