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Stereoselective synthesis of linear oxa-triquinanes and oxa-diquinanes *via* Lewis acid mediated nucleophilic addition to oxonium ions: study of nucleophile-dependent selectivity

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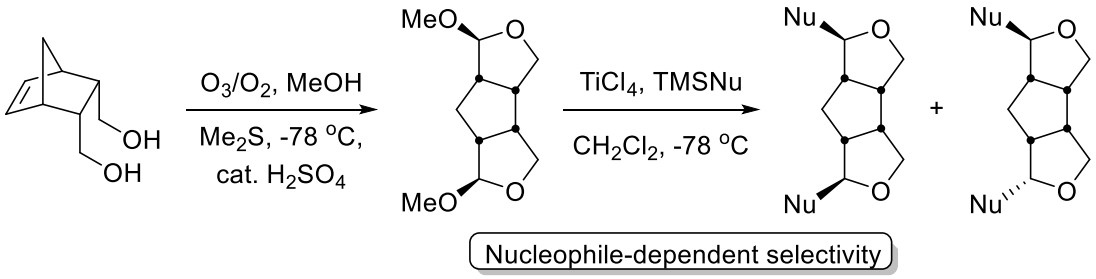
A Tribute to Prof. Sambasivarao Kotha on his 65th birthday

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Abstract

A simple and reliable approach was developed for the stereoselective construction of symmetrical linear dioxatriquinanes and oxadiquinanes *via* Lewis acid mediated nucleophilic addition to oxonium ion intermediate for etherification of dimethyl acetals. The precursors of linear triquinanes are obtained from the Diels–Alder adducts *via* ozonolysis in MeOH followed by reductive work-up and subsequent treatment with catalytic H_2SO_4 to furnish the dimethyl acetal. Further, the stereochemistry of synthesized oxa-bowls was unambiguously established by single crystal X-ray diffraction studies on its derivative.



Keywords: Dioxatriquinanes, oxadiquinanes, polycycles, nucleophiles, ozonolysis, Lewis acids

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Introduction

Triquinanes have attracted considerable attention from organic chemists due to their unique and synthetically challenging framework, which is also present in many natural products.[1-4] Generally, triquinanes are classified into three types depending on the stereochemical arrangement of the fused five-membered rings present, namely, linear-, angular-, and propellane-type (Figure 1). In addition, many of these linear triquinanes, which belong to the sesquiterpenoid family, have aroused intense interest in the recent past due to their novel molecular architecture and wide spectrum of biological activities. After the discovery and synthesis of the first polyquinane natural product, hirsutic acid C, significant progress has been made on the synthesis of carbocyclic polyquinanes. As a result, several strategies have been employed for the synthesis of linear triquinanes C-norcardanolide and Isogenine steroid based natural products.[5,6] The oxygen analogues of linear triquinanes have shown promising biological activity and proved to be useful for the treatment of leukemia, osteosarcoma, breast cancer and ovarian cancer.[7,8]

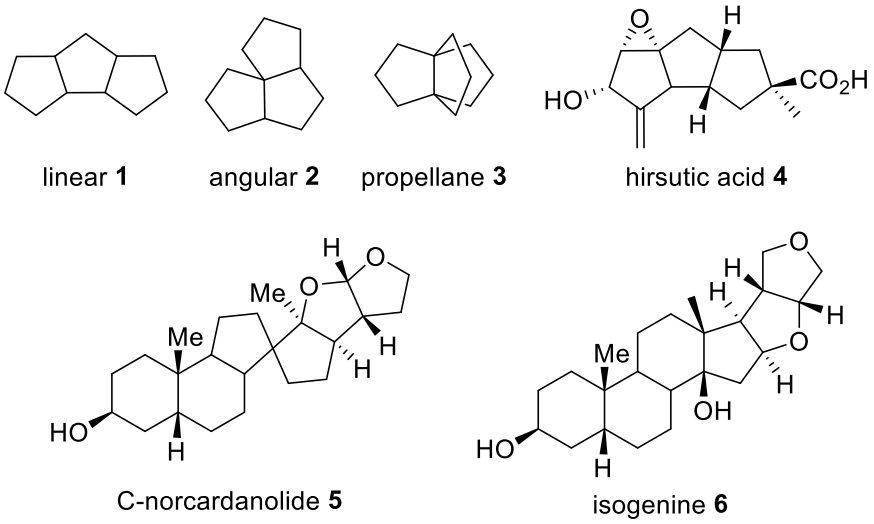


Figure 1. Fusion pattern and natural products containing triquinanes

Substantial efforts have been directed towards the synthesis of carbocyclic triquinane frameworks as they constitute the core of many sesquiterpene natural products. In contrast, the heteroatom-substituted triquinanes have attracted considerably less attention from synthetic chemists. The majority of the strategies developed in past few decades give access to unsymmetrical aza- and oxa-triquinanes.[9-23] Far less attention has been paid to develop strategies that would incorporate symmetrical dioxa-linear-triquinane. In continuation of our interest in the synthesis of oxa-, aza-bowls, cages and triquinanes, herein we describe an efficient approach to symmetrical linear dioxatriquinanes and oxadiquinanes through the stereoselective addition of nucleophiles to oxonium ion intermediate.[24-29]

Results and Discussion

A Lewis acid mediated etherification reaction based strategy conceived for the construction of symmetrical, linear oxa-triquinane structures is outlined in the Figure 2. It was envisaged that the oxa-triquinanes **7** could be

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readily prepared by addition of an appropriate nucleophile to the *bis*-oxonium ion **8** derived from the acetal **9** in the presence of Lewis acid. It was further argued that the nucleophile would preferentially add to the oxonium ion **8** from the less hindered convex face. The dimethyl acetal **9** could in turn be obtained from the diol **10** after ozonolysis. The diol **10** could be readily obtained from the reduction of Diels-Alder adduct formed between cyclopentadiene and maleic anhydride.

In order to test the feasibility of the proposed ozonolysis/Lewis acid mediated etherification strategy for the synthesis of linear dioxatriquinanes, acetal **9** was chosen as an appropriate precursor. Synthesis began with the Diels-Alder reaction between cyclopentadiene and maleic anhydride, which furnished the *endo*-adduct **11** in good yield with excellent diastereoselectivity.

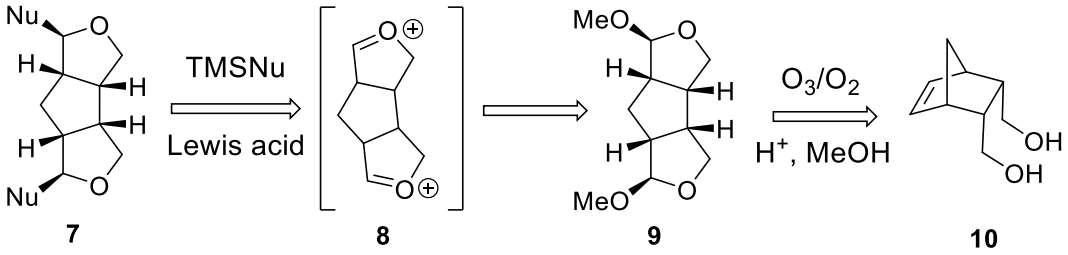
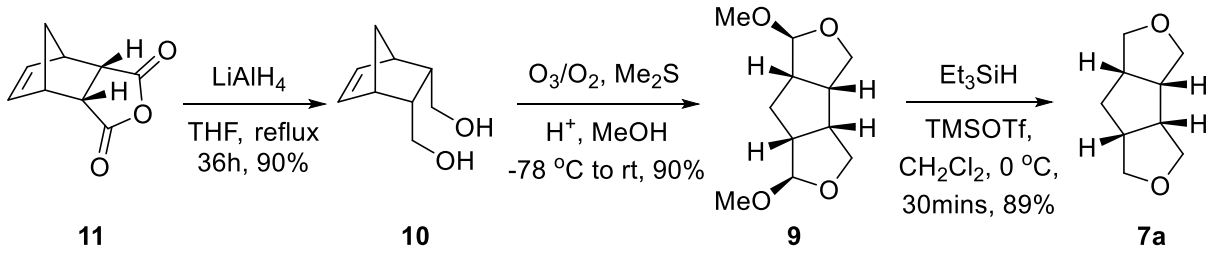


Figure 2. Retrosynthetic analysis of linear triquinanes

Reduction of the anhydride **11** using LAH in refluxing THF gave the diol **10**. The diol **10** was subjected to ozonolyzis, followed by reductive workup with dimethyl sulphide and the reaction mixture was treated with catalytic amount of H_2SO_4 in methanol to furnish the dimethyl acetal **9** in 90% yield (Scheme 1). Having the acetal **9** in hand, it was subjected to reductive etherification using triethylsilane and TMSOTf in CH_2Cl_2 at 0 °C. Gratifyingly, the reaction resulted in the formation of dioxatriquinane **7a** in 89% yield.



Scheme 1

The structure of the linear dioxatriquinane **7a** rests secured from its spectral data. Presence of molecular ion peak at m/z 155.1068 ($C_9H_{15}O_2$) in the mass spectrum suggested the formation of the product. In the ^1H NMR spectrum, presence of multiplets at δ 3.76-3.61, 2.81-2.77, 2.15-2.10 and 1.36-1.28 ppm established the structure of the product. Finally, five-line ^{13}C NMR spectrum with characteristic signals at δ 73.2 (CH_2), 69.5 (CH_2), 48.0 (CH), 46.9 (CH), 37.1(CH_2) ppm confirmed the formation of the product.

After successful demonstration of the concept by trapping the *bis*-oxonium ion with hydride as a nucleophile, a systematic study towards enhancing the scope of the reaction was carried out. Various nucleophiles were screened for their reactivity with bisoxonium ion and their stereoselectivity were monitored closely.[30-33] Initial screening of the reaction of acetal with different nucleophiles using TMSOTf as the Lewis acid

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revealed that even though the reaction worked, it was sluggish in some cases. On the other hand using $TiCl_4$ as the Lewis acid gave consistently good reactivity as well as selectivity and hence it was chosen as the Lewis acid to study the scope of the reaction with various nuclephiles. It was observed that 1,3,5-trimethoxybenzene was used as the nucleophile, trimethoxyphenyl substituted linear dioxatriquinane **7b** was obtained in good yield and excellent diastereoselectivity.

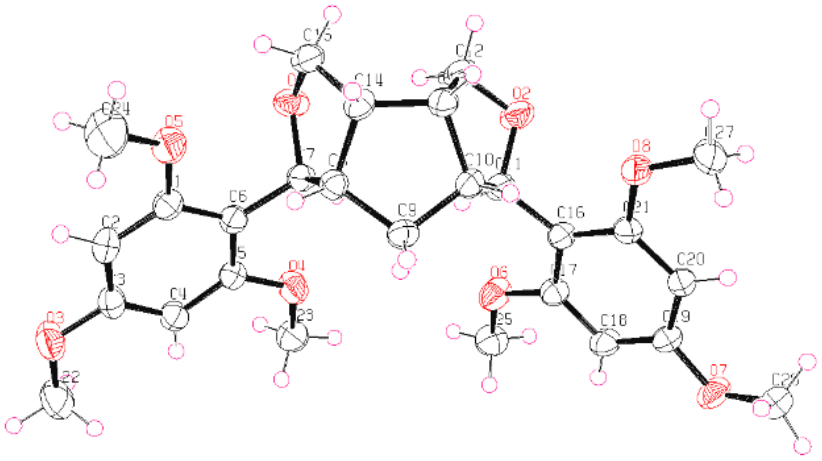
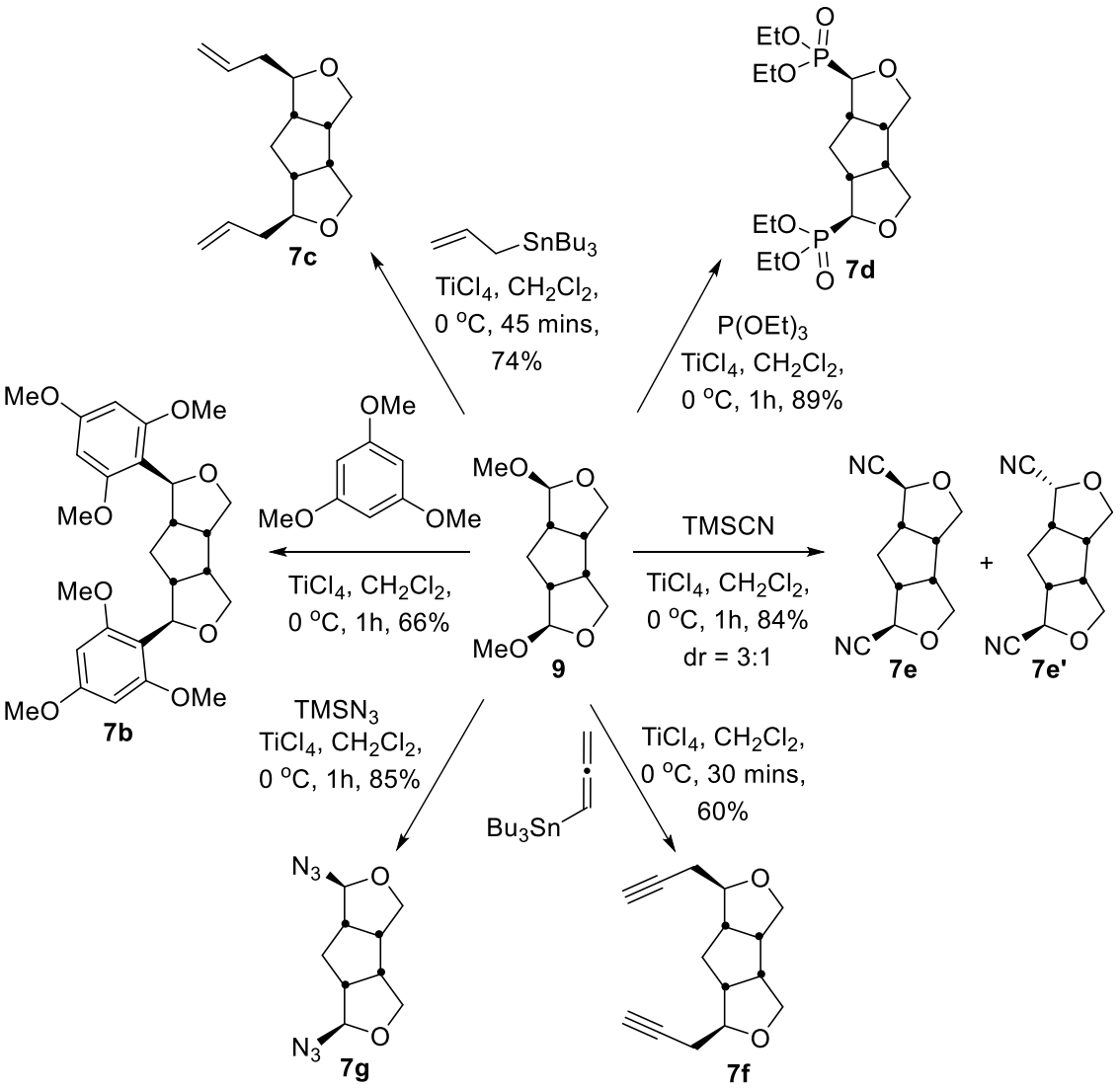


Figure 3. ORTEP picture of the 7b

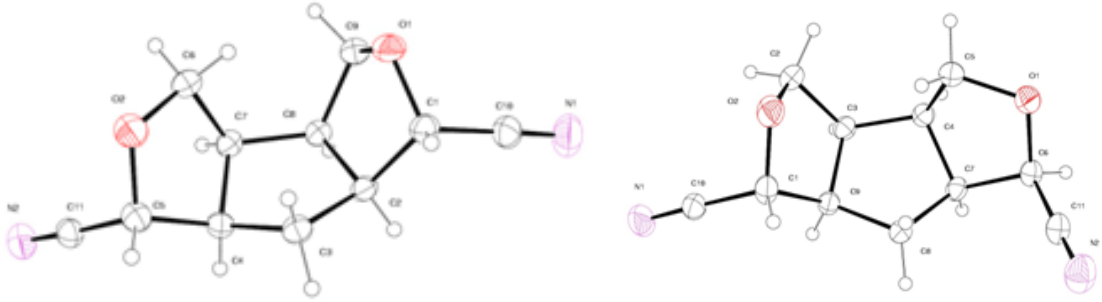
Single crystal X-ray diffraction studies (CCDC 1006760) (Figure 3) on this triquinane **7b** revealed that the aryl group had trapped the oxonium ions from the least hindered convex face. In another direction the *bis*-oxonium ion intermediate could be trapped with triethylphosphite leading to *bis*-phosphonate ester bearing triquinane **7d**. TMSCN was found to be good nucleophile and gave the corresponding triquinane **7e** and **7e'**, in good yields albeit with poor diastereoselectivity (*cis:trans* = 3:1) (Scheme 2).[34]

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Scheme 2

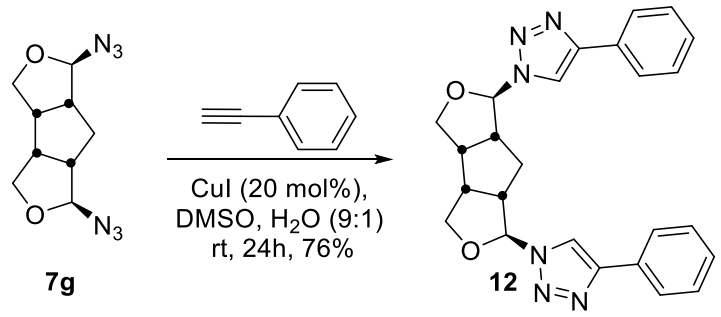
The structure of both the diastereomers **7e** and **7e'** could be unambiguously assigned based on the single crystal X-ray diffraction studies (CCDC 942151 and 1006761) (Figure 4). The bis-substituted linear triquinanes such as bis-nitriles **7e** and **7e'** could be potentially used as ligands for the synthesis of metal complexes. It was observed that allenyltributyltin and allyltributylstannane could be used as nucleophiles to furnish the triquinanes **7f** and **7c**, respectively, in good yield and excellent diatereoselectivity. On the contrary, when $TMSN_3$ was used as nucleophile the corresponding *bis*-azide **7g** was obtained in very good yield as a single detectable diastereomer.



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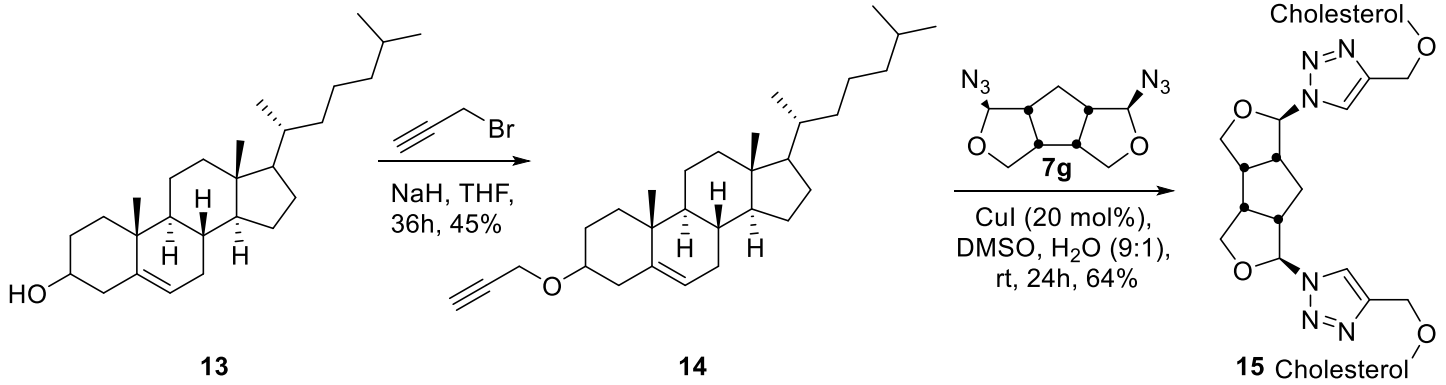
Figure 4. ORTEP picture of the **7e** and **7e'**

A Lewis acid mediated etherification reaction-based strategy was also conceived for the construction of oxa-diquinanes. Having gained access to the *bis*-azide triquinane **7g**, it was decided to study its reactivity in 1,3-dipolar cycloaddition reaction with an alkyne. Towards this end, the azide **7g** was subjected to 'click' reaction with phenyl acetylene using copper(I) iodide in DMSO-H_2O mixture as solvent. The reaction indeed gave the *bis*-triazole **12** in 76% yield (Scheme 3).[35-38]



Scheme 3

After successfully demonstrating that the triazole **12** can be prepared following the click reaction protocol, it was decided to study if triquinanes could function as spacer between two cholesterol units and if such a system will display liquid crystalline behaviour. To test this idea, synthesis of a *bis*-cholesterol derivative **15** was envisaged. Thus, cholesterol **13** was reacted with NaH and propargyl bromide to furnish the propargyl ether **14** in 45% yield.[39] The *bis*-azide **7g** was reacted with the alkyne **14** in DMSO and water (9:1) in the presence of 20 mol% of CuI at room temperature to furnish the triazole derivative **15** in good yield as a single regioisomer (Scheme 4).



Scheme 4

After synthesizing this cholesterol based triazole **15**, optical polarizing micrographs were recorded at its melting point using optical polarizing microscope as shown in Figure 5, which is a powerful tool to identify liquid crystal behaviour.[40-44] In addition, the phase transitions were studied by differential scanning calorimetry (DSC) operated at a scanning rate of 10 ^{o}C/min and the phase transitions of the compound are shown in figure 6. The textural pattern coupled with the peaks in DSC traces suggested the occurrence of liquid crystal behaviour; in

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particular, the compounds are self-assembling into a smectic phase i.e. a fluid layer structure. Further explorations are under way to understand this system better.



Figure 5. POM micrographs of cholesterol based *oxa*-triquinane **15**

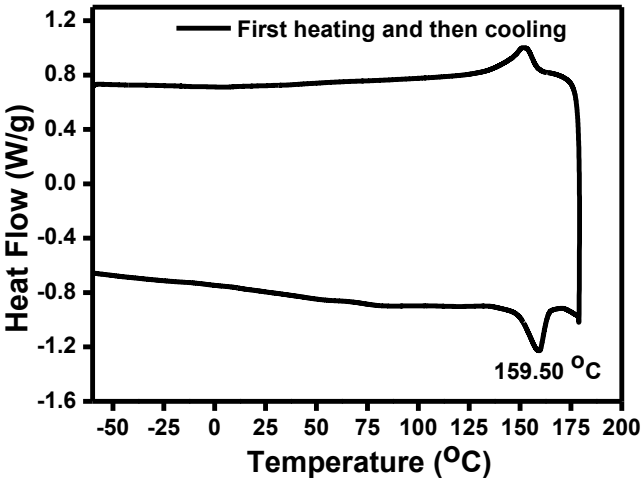
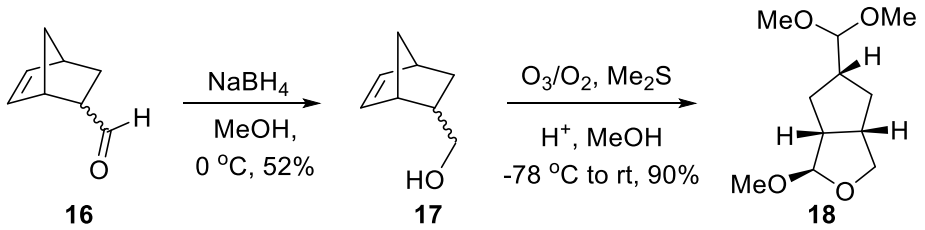


Figure 6. DSC curves of cholesterol based *oxa*-triquinane (**15**)

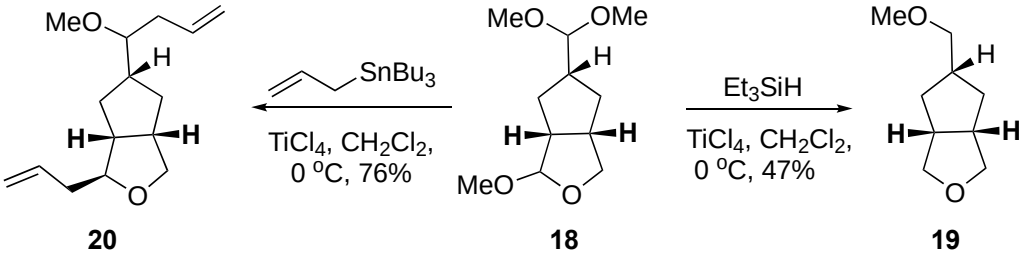
After successfully employing the ozonolysis followed by Lewis acid mediated etherification reaction for the synthesis of linear dioxa-triquinanes, study was also extended to using this method for the synthesis of oxadiquinanes. The synthesis of the requisite alcohol **17** began with $SnCl_4$ catalyzed Diels-Alder reaction of cyclopentadiene with acrolein to furnish *endo*-adduct **16** contaminated with trace amounts of *exo*-adduct **16'**. Mixture of aldehydes **16** and **16'** was subjected to reduction using $NaBH_4$ in MeOH to furnish mixture of the alcohols **17** and **17'**. No efforts were made to separate the two isomers as it was anticipated that during ozonolysis followed by the acetal formation step, only the *endo* isomer would lead to the acetal. Indeed, when the alcohol was subjected to ozonolysis followed by reductive workup with Me_2S followed by treatment with catalytic amount of H_2SO_4 in methanol, the acetal **18** was obtained as a single diasteromer in 90% yield (Scheme 5).

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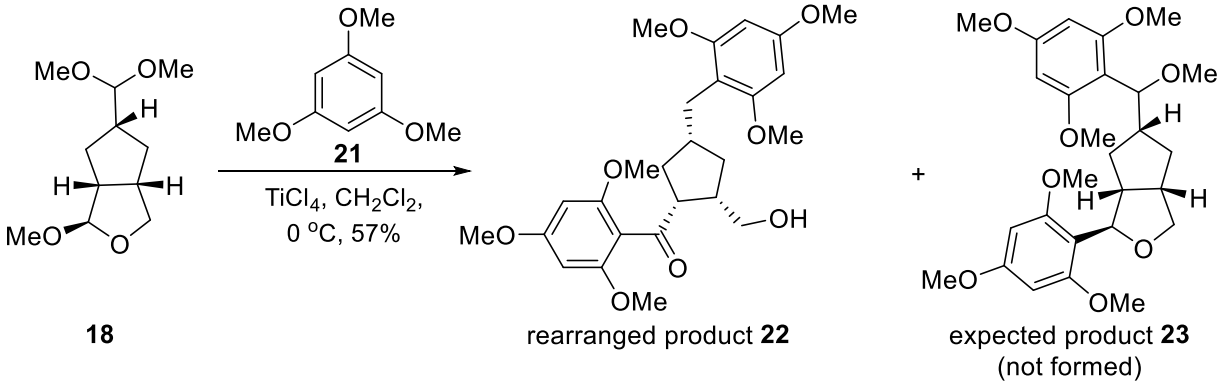
Scheme 5

After successfully synthesizing the acetal **18**, it was treated with triethylsilane and $TiCl_4$ in CH_2Cl_2 at 0 °C. The reaction resulted in the formation of the *oxa*-diquinane **19** in 47% yield (Scheme 6). The low yield is due to volatile nature of the compound. In fact, when allyltributylstannane was used as a nucleophile to trap the oxonium ion generated from the acetal **18** in the presence of $TiCl_4$, the *bis*-allyl *oxa*-diquinane **20** was obtained in 76% yield as the only detectable diastereomer. However, the stereochemistry of the final product could not be ascertained completely.



Scheme 6

The reaction of acetal **18** with electron rich aromatic nucleophiles was found to be particularly interesting. When 1,3,5-trimethoxybenzene (**21**) was reacted with acetal **18** in the presence of $TiCl_4$, rather than the oxadiaquinane **23**, a substituted cyclopentane derivative **22** was obtained in 57% yield (Scheme 7).



Scheme 7

The structure of the cyclopentane derivative **22** rests secure from its spectral data. Presence of molecular ion peak at m/z 475.2335 ($C_{26}H_{35}O_8$) in the mass spectrum and the presence of absorption band at 3055 and 1606 cm^{-1} suggested the formation of the product. In the ^1H NMR spectrum, presence of two singlets at δ 6.11

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and 6.09 ppm due to aromatic protons established the structure of the product. Finally, twenty six-line ^{13}C NMR spectrum with characteristic signals at 209.2 (C), 162.5 (C), 159.2 (C), 159.0 (C), 158.4 (C), 115.0 (C), 111.1 (C), 91.0 (CH), 90.6 (CH) ppm confirmed the formation of the keto-alcohol. It was further unambiguously confirmed based on the single crystal X-ray diffraction studies (CCDC 1006762) (Figure 7).

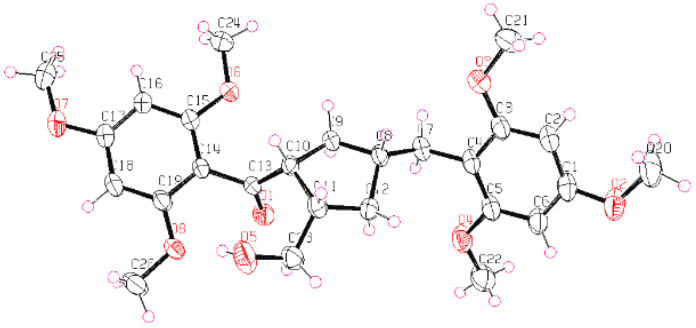
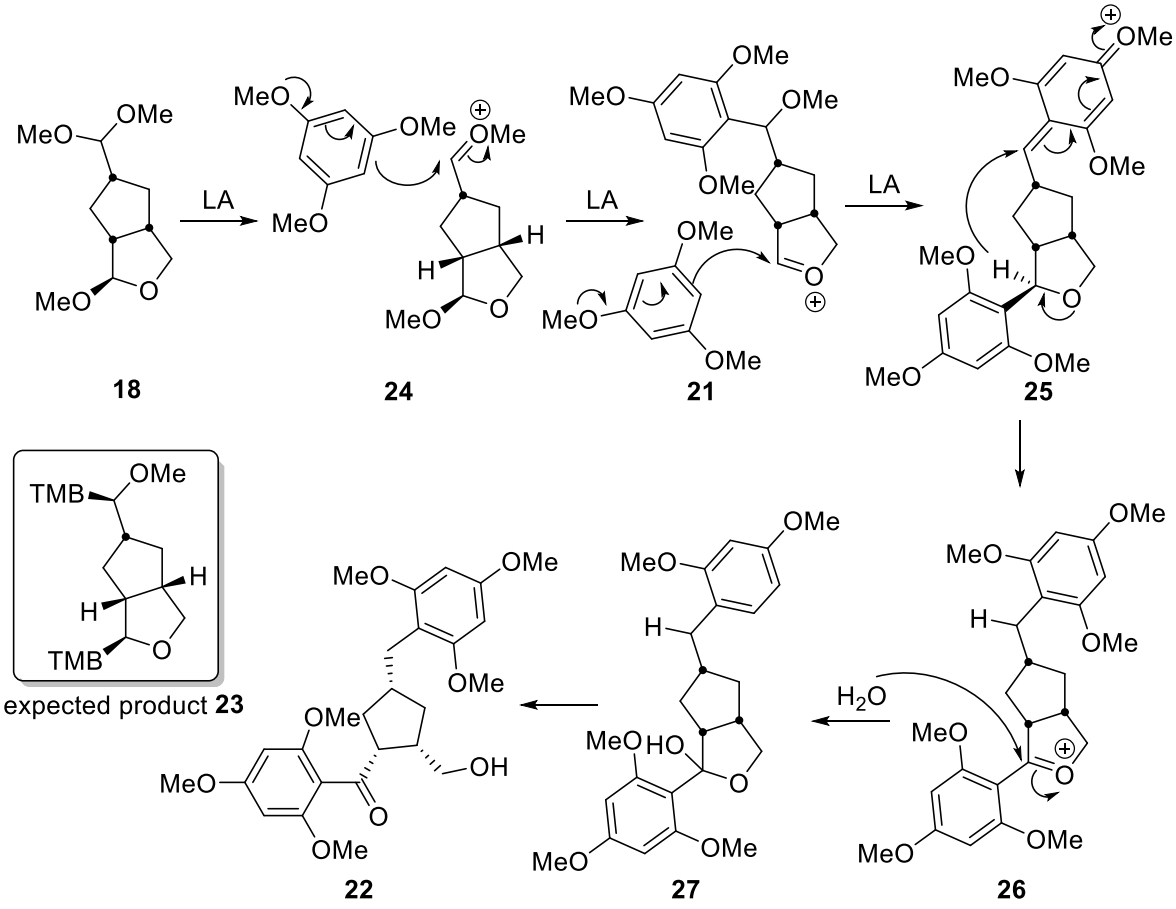


Figure 7. ORTEP picture of cyclopentane derivative **22**

Formation of the product **22** can be explained based on the mechanism involving 1,5-hydride shift. When the acetal **18** is treated with Lewis acid, initially formed oxonium ion **24** which is trapped by 1,3,5-trimethoxybenzene (**21**), leading to the formation of trimethoxyphenyl substituted oxadiquinane **23** (Scheme 7). The initially formed oxonium ion **24** further reacts with the Lewis acid, forming oxonium ion **25**, which is trapped intermolecularly by 1,3,5-trimethoxybenzene (**21**) to lead to **25**. At this stage, under the influence of the Lewis acid, benzylic methoxy group is eliminated to generate the oxonium ion **25**. This stable benzylic carbocation **25** is trapped intramolecularly with hydride by 1,5-hydride shift leading to the formation of more stable oxonium ion **26**. Trapping of this oxonium ion **26** by water molecule generates hemiacetal **27**, which leads to the formation of the keto alcohol **22.**[45-49]

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Scheme 8. Plausible mechanism for the formation of **22**

Further studies to expand the scope of this reaction and use it for the synthesis of diversely substituted cyclopentane derivatives are underway in our laboratory.

Conclusions

In conclusion, a new strategy for the stereoselective synthesis of symmetrically substituted linear dioxatriquinanes was developed based on the ozonolysis followed by Lewis acid mediated etherification strategy. The azide substituted dioxa triquinanes could be further elaborated using click chemistry to prepare cholesterol based liquid crystals. The method was extended to the synthesis of oxadiquinanes. An interesting 1,5-hydride shift was observed when electron rich aryl ring was used as a nucleophile leading to stereoselective synthesis of trisubstituted cyclopentane derivative. The *bis*-substituted linear triquinanes such as *bis*-nitriles **7e** and **7e'** could be potentially used as ligands for the synthesis of metal complexes.

Experimental Section

General. Melting points are recorded using Tempo melting point apparatus in capillary tubes and are uncorrected. IR spectra were recorded on Nicolet 6700 spectrophotometer and JASCO FT-IR-4100

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spectrophotometer. ^{1}H (400 MHz, 500 MHz) and ^{13}C (100 MHz, 125 MHz) NMR spectrums were recorded on Bruker Avance 400 spectrophotometer and Bruker Avance 500 spectrophotometer, respectively. The chemical shifts (ppm) and coupling constants (Hz) are reported in the standard fashion with reference to chloroform. In the ^{13}C NMR spectra, the nature of the carbons (C, CH, CH_2 or CH_3) was determined by recording the DEPT-135 experiment and is given in parentheses. CHN analysis was carried out using Elemental analyzer VSM-VT. High resolution mass measurements were carried out using Micromass Q-ToF instrument using direct inlet mode. Analytical thin-layer chromatography (TLC) was performed on glass plates (7.5 × 2.5 and 7.5 × 5.0 cm) coated with Merck silica gel G containing 13% calcium sulfate as binder or on pre-coated 0.2 mm thick Merck 60 F245 silica plates and various combinations of ethyl acetate and hexanes were used as eluent. Visualization of spots was accomplished by exposure to iodine vapour and UV light. All compounds were purified using silica gel [Acme's silica gel (100-200 mesh)] column chromatography. All small-scale dry reactions were carried out using standard syringe septum technique. Syringe pump was used for slow rate of addition of the reagents. All the commercial reagents were used as such without further purification.

(3aR*,4S*,7R*,7aS*)-3a,4,7,7a-Tetrahydro-4,7-methano-2-benzofuran-1,3-dione (11). Maleic anhydride (1.5 g) was dissolved in ethyl acetate (7 mL) in a 50 mL Erlenmeyer flask and was heated gently (approximately to body temperature) to get all the maleic anhydride into solution, and then hexane (7 mL) was added. To this solution, freshly prepared cyclopentadiene (1.5 mL) was added. The mixture was swirled just until the exothermic reaction was completed and crystals of the product appeared in a few minutes. The product was collected by filtration on a Büchner funnel. The crude product was taken in an Erlenmeyer flask and dissolved in toluene (6 mL) by heating on a steam bath. It was then hot filtered to remove undissolved starting materials and side products. Hexane (3 mL) was added to the filtered solution and the flask was cooled in an ice bath, and the *cis*-norbornene-5,6-*endo*-dicarboxylic anhydride **11** crystals (2.0 g, 80%) appeared after a few minutes were collected by filtration and dried under high vacuum. Physical appearance: white crystalline solid. mp 165-167 °C. IR (neat): 3015, 2982, 1770, 1337, 1292, 1227, 1190, 1118, 1082, 1054, 948, 931, 905, 844, 822, 790, 731 cm.$^{-11}$ HNMR (400 MHz, $CDCl_3$): δ 6.30 (s, 2H), 3.58 (t, *J* 2.0 Hz, 2H), 3.55-3.45 (m, 2H), 1.77 (AB, *J* 8.8 Hz, 1H), 1.57 (AB, *J* 8.8 Hz, 1H). ^{13}CNMR (100 MHz, $CDCl_3$, DEPT): δ 171.46 (2 × C), 135.65 (2 × CH), 52.87 (CH_2), 47.18 (2 × CH), 46.22 (2 × CH).

(1R*,2S*,3R*,4S*)-Bicyclo[2.2.1]hept-5-ene-2,3-diyldimethanol (10). To a stirred suspension of LAH (1.39 g, 36.58 mmol) in dry THF (60 mL) at −10 °C, the acid anhydride **11** (3.0 g., 18.29 mmol) was added portion wise with stirring. The suspension was refluxed for 36 hrs. The reaction mixture was cooled (0 °C) and wet Na_2SO_4 was slowly added with vigorous stirring. After 0.5 h milky solution appeared which was filtered through the sintered funnel and slurry was washed with additional ethyl acetate. Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate–hexanes (1:1) as eluent furnished the diol **10** (2.55 g, 90%) as a white crystalline solid. Physical appearance: white crystalline solid. mp 82-86 °C. R_f: 0.5(1:1, EtOAc:Hexanes). IR (neat): 3246, 3052, 2996, 2960, 2908, 2861, 1466, 1380, 1347, 1252, 1219, 1161, 1113, 1043, 1023, 987, 954, 913, 888, 729, 720, 690 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ 6.02 (t, *J* 1.8 Hz, 2H), 3.66 (s, 2H), 3.63 (ABX, *J* 11.0, 3.4 Hz, 2H), 3.36 (ABX, *J* 11.0, 0.0 Hz, 2H), 2.78 (t, *J* 1.8 Hz, 2H), 2.55-2.50 (m, 2H), 1.40 (ABX, *J* 8.2, 1.8 Hz, 1H), 1.37 (ABX, *J*= 8.2, 0.0 Hz, 1H). ^{13}CNMR (100 MHz, $CDCl_3$, DEPT): δ 134.92 (2 × CH), 63.60 (2 × CH_2), 50.05 (CH_2), 46.67 (2 × CH), 45.20 (2 × CH).HRMS (ESI, M+H$^+$): m/z calcd. for $C_9H_{15}O_2$ 155.1072, found 155.1070.

(1R*,3aS*,3bR*,6S*,6aS*,7aR*)-1,6-Dimethoxyoctahydro-1*H*-cyclopenta[1,2-*c*:3,4-*c*']difuran (9). A magnetically stirred solution of the diol **10** (1.5 g, 9.74 mmol) in MeOH (100 mL) was cooled to −78 °C, and ozone was bubbled through it until the solution turned light blue. Excess ozone was flushed with oxygen gas and dimethyl sulfide (9.4 mL, 126.62 mmol) and cat. H_2SO_4 (4-5 drops) were added to the reaction mixture. The

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reaction mixture allowed to warm up to rt and stirred for 24 h. Solid $NaHCO_3$ was added and the reaction mixture was concentrated under reduced pressure. The residue was taken up in water and extracted with ethyl acetate. The combined organic layer was washed with brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate hexanes (1:9) as eluent furnished the dimethyl acetal **9** (1800 mg, 90%) as a white solid. Physical appearance: white solid. mp 38-40 °C. R_f: 0.5 (1:4, EtOAc:Hexanes). IR (neat): 2951, 2890, 2829, 1468, 1450, 1366, 1295, 1267, 1221, 1201, 1165, 1131, 1080, 1062, 1000, 984, 947, 928, 909, 796, 760 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.75 (s, 2H), 3.92-3.88 (m, 2H), 3.78 (dd, *J* 8.8, 4.0 Hz, 2H), 3.29 (s, 6H), 2.93 (quin, *J* 4.0 Hz, 2H), 2.18-2.10 (m, 2H), 1.26 (AB, *J* 10.4, 1H), 1.18 (AB, *J* 10.4, 1H).

^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 109.22 (2 × CH), 68.22 (2 × CH_2), 54.55 (2 × CH_3), 53.68 (2 × CH), 45.09 (2 × CH), 32.46 (CH_2). HRMS (ESI, M+Na^+): m/z calcd. for $C_{11}H_{18}O_4Na$ 237.1103, found 237.1115.

(3aR*,3bS*,6aS*,7aR*)-Octahydro-1*H*-cyclopenta[1,2-*c*:3,4-*c*']difuran (7a). To a cold (-78 °C) magnetically stirred solution of the dimethyl acetal **9** (109 mg, 0.51 mmol) and Et_3SiH (244 µL, 1.53 mmol) in dry CH_2Cl_2 (3 mL) was added TMSOTf (184 µL, 1.02 mmol) and the resulting mixture was stirred at same temperature for 12h (TLC control). It was then quenched with saturated aq. $NaHCO_3$ (3 mL) at 0 °C and extracted with ethyl acetate. The combined organic layer was washed with brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate–hexanes (1:1) as eluent furnished linear triquinane **7a** (60 mg, 77%) as a colourless liquid. Physical appearance: colourless liquid; R_f: 0.5 (1:1, EtOAc:Hexanes). IR (neat): 2945, 2856, 2359, 2334, 1481, 1455, 1264, 1226, 1203, 1196, 1129, 1093, 1069, 1031, 995, 959, 911, 756, 712, 684 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.76-3.61 (m, 8H), 2.81-2.77 (m, 4H), 2.15-2.10 (m, 1H), 1.36-1.28 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 73.16 (2 × CH_2), 69.45 (2 × CH_2), 48.04 (2 × CH), 46.86 (2 × CH), 37.06 (CH_2). HRMS (ESI, M+H^+): m/z calcd. for $C_9H_{15}O_2$ 155.1072, found 155.1068.

(1R*,3aS*,3bR*,6S*,6aS*,7aR*)-1,6-Bis(2,4,6-trimethoxyphenyl)octahydro-1*H*-cyclopenta[1,2-*c*:3,4-*c*']difuran (7b). To a cold (0 °C) magnetically stirred solution of the dimethyl acetal **9** (140 mg, 0.65 mmol) and 1,3,5-trimethoxybenzene (327 mg, 1.94 mmol) in dry CH_2Cl_2 (5 mL) was added $TiCl_4$ (270 µL, 1.94 mmol) and the resulting mixture was stirred at same temperature for 1h (TLC control). It was then quenched with saturated aq. $NaHCO_3$ (3 mL) at 0 °C and extracted with ethyl acetate. The combined organic layer was washed with brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate–hexanes (1:1) as eluent furnished symmetric bis-trimethoxy phenyl substituted linear triquinane **7b** (207 mg, 66%) as a white solid. Physical appearance: white crystalline solid. mp 148-150 °C. R_f: 0.5(1:1, EtOAc:Hexanes). IR (neat): 2939, 2870, 2839, 1604, 1496, 1463, 1424, 1386, 1331, 1271, 1226, 1205, 1152, 1121, 1086, 1061, 1035, 1004, 988, 953, 918, 868, 814, 790, 737, 707, 667 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.13 (s, 4H), 5.40 (d, *J* 5.6 Hz, 2H), 4.14 (dd, *J* 8.8, 7.2 Hz, 2H), 3.86 (dd, *J* 8.8, 6.0 Hz, 2H), 3.81 (s, 12H), 3.80 (s, 6H), 3.21-3.12 (m, 4H), 2.06-1.98 (m, 1H), 1.64-1.70 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 160.81 (2 × C), 159.85 (4 × C), 111.04 (2 × C), 91.30 (4 × CH), 79.57 (2 × CH), 70.71 (2 × CH_2), 56.07 (4 × CH_3), 55.43 (2 × CH_3), 53.38 (2 × CH), 48.71 (2 × CH), 36.35 (CH_2). HRMS (ESI, M+H^+): m/z calcd. for $C_{27}H_{35}O_8$ 487.2332, found 487.2323.

(1R*,3aR*,3bS*,6S*,6aR*,7aS*)-1,6-Diallyloctahydro-1*H*-cyclopenta[1,2-*c*:3,4-*c*']difuran (7c). To a cold (0 °C) magnetically stirred solution of the dimethyl acetal **9** (240 mg, 1.12 mmol) and allylstannane (869 µL, 2.80 mmol) in dry CH_2Cl_2 (5 mL) was added 1M solution of $TiCl_4$ in CH_2Cl_2 (1.8 mL, 2.47 mmol) and the resulting mixture was stirred at same temperature for 40mins (TLC control). It was then quenched with saturated aq. $NaHCO_3$ (3 mL) at 0 °C and extracted with ethyl acetate.The combined organic layer was washed with brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate–hexanes (1:9) as eluent furnished symmetric bis-allyl linear triquinane **7c** (194 mg, 74%) as

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a colourless liquid. Physical appearance: colourless liquid. R_f: 0.5(1:4, EtOAc:Hexanes). IR (neat): 3075, 2932, 2865, 1640, 1482, 1432, 1366, 1206, 1091, 1044, 992, 909, 838, 709, 634 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.83-5.73 (m, 2H), 5.10-5.03 (m, 4H), 4.14-3.91 (m, 2H), 3.90-3.86 (m, 2H), 3.81-3.76 (m, 2H), 3.68 (dd, *J* 9.2, 5.6 Hz, 2H), 2.88-2.79 (m, 2H), 2.56-2.49 (m, 2H), 2.30-2.23 (m, 2H), 2.21-2.14 (m, 1H), 1.45-1.38 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 135.04 (2 × CH), 117.09 (2 × CH_2), 84.82 (2 × CH), 69.27 (2 × CH_2), 53.08 (2 × CH), 46.74 (2 × CH), 39.84 (2 × CH_2), 35.25 (CH_2). HRMS (ESI, M+H^+): m/z calcd. for $C_{15}H_{23}O_2$ 235.1698, found 235.1699.

Tetraethyl ((1R*,3aR*,3bS*,6S*,6aR*,7aS*)-octahydro-1*H*-cyclopenta[1,2-*c*:3,4-*c*']difuran-1,6-diyl)bis(phosphonate) (7d). To a cold (0 °C) magnetically stirred solution of the dimethyl acetal **9** (115 mg, 0.54 mmol) and triethylphosphite (468 µL, 2.69 mmol) in dry CH_2Cl_2 (3 mL) was added $TiCl_4$ (149 µL, 1.07 mmol) and the resulting mixture was stirred at same temperature for 1h (TLC control). It was then quenched with saturated aq. $NaHCO_3$ (3 mL) at 0 °C and extracted with ethyl acetate. The combined organic layer was washed with brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate as eluent furnished symmetric bis-phosphonate linear triquinane **7d** (202 mg, 89%) as a colourless sticky liquid as a single diasteoreomer. Physical appearance: colourless liquid. IR (neat): 2982, 2939, 2907, 1734, 1649, 1479, 1446, 1392, 1368, 1293, 1239, 1163, 1096, 1026, 967, 913, 792, 735, 700, 664 cm^{-1}.^1H NMR (400 MHz, $CDCl_3$): δ 4.21-4.10 (m, 8H), 4.07-4.03 (m, 2H), 3.98 (d, *J* 4.0 Hz, 2H), 3.79 (dd, *J* 9.2, 4.0 Hz, 2H), 3.22-3.11 (m, 2H), 3.07-3.01 (m, 2H), 2.44-2.35 (m, 1H), 1.34-1.32 (m, 1H), 1.31 (t, *J* 7.0 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 79.98 (d, *J* 165.7 Hz, 2 × CH), 70.95 (s, 2 × CH_2), 62.59 (dd, *J* 57.8, 7.0 Hz, 4 × CH_2), 48.83 (s, 2 × CH), 47.19 (s, 2 × CH), 37.50 (t, *J* 12.21 Hz, CH_2), 16.62 (s, 4 × CH_3). HRMS (ESI, M+H^+): m/z calcd. for $C_{17}H_{33}O_8P_2$ 427.1651, found 427.1667.

(1R*,3aS*,3bR*,6S*,6aS*,7aR*)-Octahydro-1*H*-cyclopenta[1,2-*c*:3,4-*c*']difuran-1,6-dicarbonitrile (7e). To a cold (0 °C) magnetically stirred solution of the dimethyl acetal **9** (96.0 mg, 0.45 mmol) and TMSCN (224.0 µL, 1.79 mmol) in dry CH_2Cl_2 (5 mL) was added 1M solutionof $TiCl_4$ in CH_2Cl_2 (723 µL, 1.36 mmol) and the resulting mixture was stirred at same temperature for 1h (TLC control). It was then quenched with saturated aq. $NaHCO_3$ (3 mL) at 0 °C and extracted with ethyl acetate. The combined organic layer was washed with brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate–hexanes (1:4) as eluent furnished symmetric bis-nitrile linear triquinane **7e** (40.0 mg, 84%) as a white solid. Physical appearance: white solid. mp 98-100 °C. R_f: 0.5(2:3, EtOAc:Hexanes). IR (neat): 2966, 2891, 2245, 1491, 1308, 1273, 1248, 1215, 1082, 989, 916, 906, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.54 (s, 2H), 4.02-3.98 (m, 2H), 3.91 (dd, *J* 9.6, 2.8 Hz, 2H), 3.16-3.13 (m, 4H), 2.44-2.39 (m, 1H), 1.41-1.33 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 118.27 (2 × C), 71.05 (2 × CH), 69.81 (2 × CH_2), 52.92 (2 × CH), 45.83 (2 × CH), 35.48 (CH_2). HRMS (ESI, M+H^+): m/z calcd. for $C_{11}H_{13}N_2O_2$ 205.0977, found 205.0983.

(1R*,3aR*,3bS*,6R*,6aR*,7aS*)-*o*ctahydro-1*H*-cyclopenta[1,2-*c*:3,4-*c*']difuran-1,6-dicarbonitrile (7e'). Physical appearance: white crystalline solid. mp 100-102 °C. R_f: 0.4(2:3, EtOAc:Hexanes). IR (neat): 2964, 2883, 2243, 1483, 1346, 1213, 1117, 1061, 1001, 991, 903, 825, 739, 635 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.63 (s, 1H), 4.56 (d, *J* 6.0 Hz, 1H), 3.98-3.94 (m, 1H), 3.88-3.84 (m, 3H), 3.27-3.19 (m, 1H), 3.15-3.10 (m, 1H), 3.09-3.02 (m, 2H), 2.40 (dt, *J* 13.2, 8.0 Hz, 1H), 1.69 (q, *J* 10.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 118.26 (C), 117.07 (C), 76.84 (CH), 70.93 (CH_2), 70.02 (CH_2), 69.34 (CH), 52.93 (CH), 49.94 (CH), 46.95 (CH), 45.02 (CH), 34.03 (CH_2).

HRMS (ESI, M+Na^+): m/z calcd. for $C_{11}H_{12}N_2O_2Na$ 227.0796, found 227.0798.

(1R*,3aR*,3bS*,6S*,6aR*,7aS*)-1,6-Di(prop-2-yn-1-yl)octahydro-1H-cyclopenta[1,2-c:3,4-c']difuran (7f). To a cold (0 °C) magnetically stirred solution of the dimethyl acetal **9** (200 mg, 0.93 mmol) and allenyltributylstannane (1.2 mg, 4.11 mmol) in dry CH_2Cl_2 (5 mL) was added 1M solution of $TiCl_4$ (1.5 mL, 2.06 mmol) and the resulting mixture was stirred at same temperature for 30 mins (TLC control). It was then quenched with saturated aq.

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$NaHCO_3$ (3 mL) at 0 °C and extracted with ethyl acetate. The combined organic layer was washed with brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate–hexanes (1:9) as eluent furnished symmetric bis-alkyne linear triquinane **7f** (136 mg, 64%) as a white solid. Physical appearance: white crystalline solid. mp 68-70 °C. R_f: 0.5(1:4, EtOAc:Hexanes).

IR (neat): 3292, 3245, 2953, 2892, 2870, 2115, 1455, 1426, 1370, 1357, 1265, 1223, 1184, 1124, 1096, 1068, 1052, 1034, 1023, 1001, 944, 910, 875, 806, 774, 739, 725, 713, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 3.98-3.92 (m, 4H), 3.74 (dd, *J* 9.2, 5.6 Hz, 2H), 2.94-2.90 (m, 2H), 2.78-2.69 (m, 2H), 2.44-2.91 (m, 2H), 2.27-2.18 (m, 2H), 1.99 (t, *J* 2.4 Hz, 2H), 1.58-1.51 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 83.41 (2 × CH), 81.18 (2 × C), 69.86 (2 × CH), 69.63 (2 × CH_2), 52.94 (2 × CH), 46.77 (2 × CH), 35.90 (CH_2), 25.04 (2 × CH_2). HRMS (ESI, M+H^+): m/z calcd. for $C_{15}H_{19}O_2$ 231.1385, found 231.1395.

(1R*,3aS*,3bR*,6S*,6aS*,7aR*)-1,6-Diazidooctahydro-1*H*-cyclopenta[1,2-*c*:3,4-*c*']difuran (7g). To a cold (0 °C) magnetically stirred solution of the dimethyl acetal **9** (150 mg, 0.69 mmol) and $TMSN_3$ (461 µL, 3.45 mmol) in dry CH_2Cl_2 (5 mL) was added $TiCl_4$ (203 µL, 1.46 mmol) and the resulting mixture was stirred at same temperature for 1h (TLC control). It was then quenched with saturated aq. $NaHCO_3$ (3 mL) at 0 °C and extracted with ethyl acetate. The combined organic layer was washed with brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate–hexanes (1:9) as eluent furnished symmetric bis-azide linear triquinane **7g** (140 mg, 85%) as a white solid. Physical appearance: white crystalline solid. R_f: 0.5(1:9, EtOAc:Hexanes). IR (neat): 2954, 2901, 2868, 2170, 2095, 2046, 2036, 2025, 1972, 1453, 1350, 1315, 1271, 1245, 1230, 1198, 1128, 1100, 1087, 1061, 1033, 997, 987, 911, 892, 782 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 5.29 (s, 2H), 4.08-4.04 (m, 2H), 3.87 (dd, *J* 9.6, 4.4 Hz, 2H), 3.01-2.97 (m, 2H), 2.67-2.60 (m, 2H), 2.24-2.17 (m, 1H), 1.33-1.25 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 96.38 (2 × CH), 69.62 (2 × CH_2), 53.74 (2 × CH), 44.91 (2 × CH), 33.19 (CH_2).

(1R*,3aS*,3bR*,6S*,6aS*,7aR*)-1,6-Bis(4-phenyl-1*H*-1,2,3-triazol-1-yl)octahydro-1*H*-cyclopenta[1,2-c:3,4-c']difuran (12). To a magnetically stirred solution of the bis-azide-linear triquinane **7g** (30.0 mg, 0.13 mmol) and phenyl acetylene (30.0 µL, 0.27 mmol) in DMSO-H_2O (9:1, 5 mL) was added CuI (5.0 mg, 0.02 mmol) and the resulting mixture was stirred at rt for 24h. The reaction mixture was then diluted with water (6 mL) and extracted with ethyl acetate. The combined organic layer was washed with brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate as eluent furnished the bis cycloaddition adduct **12** (43.0 mg, 76%) as a white solid as a single regioisomer. Physical appearance: white solid. R_f: 0.5(2:3, EtOAc:Hexanes). IR (neat):3129, 2918, 2852, 2152, 2035, 1976, 1482, 1471, 1450, 1422, 1378, 1345, 1309, 1233, 1201, 1154, 1093, 1072, 1046, 1004, 994, 973, 910, 833, 791, 761, 708, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 2H), 7.85-7.83 (m, 4H), 7.44 (t, *J* 5.6 Hz, 4H), 7.37-7.33 (m, 2H), 6.09 (s, 2H), 4.13-4.05 (m, 4H), 3.84 (q, *J* 8.4 Hz, 2H), 3.38-3.34 (m, 2H), 2.71 (dt, *J* 13.2, 8.4 Hz, 1H), 1.82-1.73 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 148.02 (2 × C), 130.38 (2 × C), 128.93 (4 × CH), 128.37 (2 × CH), 125.80 (4 × CH), 118.66 (2 × CH), 93.29 (2 × CH), 70.59 (2 × CH_2), 52.47 (2 × CH), 45.44 (2 × CH), 34.36 (CH_2). HRMS (ESI, M+H^+): m/z calcd. for $C_{25}H_{25}N_6O_2$ 441.2039, found 441.2043.

(1R*,3aS*,3bR*,6S*,6aS*,7aR*)-1,6-Bis(4-((((8R*,9R*,10S*,13S*,14R*)-10,13-Dimethyl-17-((S)-6-methylheptan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)octahydro-1H-cyclopenta[1,2-*c*:3,4-*c*']difuran (15). Reaction of the bis-azide-linear triquinane **7g** (101 mg, 0.43 mmol) with O-propargyl cholesterol (364 mg, 0.86 mmol) in presence of catalytic amount of CuI (16.0 mg, 0.09 mmol) in DMSO-H_2O (4:1, 5 mL) as described for the triazole **12** followed by purification of the residue on a silica gel column using ethyl acetate–hexanes (1:1) as eluent furnished the cycloaddition adduct **15** (297 mg, 64%) as a white solid as single regioisomer. Physical appearance:

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white solid. mp 160-162 °C. R_f: 0.5(1:1, EtOAc:Hexanes). IR (neat): 2934, 2900, 2867, 2851, 2099, 1466, 1439, 1378, 1367, 1126, 1095, 1050, 1026, 1001, 912, 844, 826, 801, 791, 740 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (s, 2H), 6.00 (s, 2H), 5.35 (s, 4H), 4.13-3.99 (m, 4H), 3.75-3.67 (m, 2H), 3.36-3.34 (m, 2H), 2.67-2.59 (m, 1H), 2.42-2.39 (m, 2H), 2.28-2.22 (m, 2H), 2.04-1.95 (m, 6H), 1.88-1.80 (m, 4H), 1.78-1.67 (m, 2H), 1.57-1.48 (m, 7H), 1.46-1.36 (m, 8H), 1.27-1.24 (m, 4H), 1.21-1.02 (m, 14H), 1.00 (br s, 12H), 0.91 (d, *J* 6.4 Hz, 10H), 0.86 (dd, *J* 6.4, 1.6 Hz, 14H), 0.67 (br s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, DEPT): δ 146.34 (2 × C), 122.01 (2 × CH), 121.47 (2 × CH), 93.37 (2 × CH), 79.17 (2 × CH), 70.63 (2 × CH_2), 61.72 (2 × CH_2), 56.92 (2 × CH), 56.31 (2 × CH), 52.69 (2 × CH), 50.32 (2 × CH), 45.54 (2 × CH), 42.48 (2 × C), 39.93 (2 × CH_2), 39.67 (2 × CH_2), 39.17 (2 × CH_2), 39.16 (2 × C), 39.16 (2 × CH_2), 37.32 (2 × CH_2), 37.01 (2 × C), 36.34 (2 × CH), 35.93 (CH_2), 34.04 (2 × CH_2), 32.10 (2 × CH_2), 32.05 (2 × CH), 28.38 (2 × CH_2), 28.16 (2 × CH), 24.44 (2 × CH_2), 23.97 (2 × CH_2), 22.96 (2 × CH_3), 22.71 (2 × CH_3), 21.22 (2 × CH_2), 19.52 (2 × CH_3),18.87 (2 × CH_3), 12.01(2 × CH_3).

HRMS (ESI, $M+H^+$): m/z calcd. for $C_{69}H_{109}N_6O_4$ 1085.8510, found 1085.8494.

(1S*, 2S*,4S*)-Bicyclo [2.2.1] hept-5-ene-2-carbaldehyde (16). Acrolein (6ml, 90.91 mmol) was added to a solution of the catalyst, stannic chloride (526 µL, 4.49 mmol) in DCM (15 ml). Then the solution of freshly prepared cyclopentadiene (6g, 90.91 mmol) in DCM (10) was added dropwise to the reaction mixture at −78 °C. The reaction was allowed to continue for 1.5h at −78 °C. After completion of the reaction, the reaction mixture was quenched with triethylamine and saturated $NaHCO_3$. Then the reaction mixture was extracted with distilled ether. Evaporation of the solvent under reduced pressure furnished the aldehyde, which was subjected to reduction without purification.

(1S*, 2S*, 4S*)-Bicyclo [2.2.1] hept-5-en-2-yl methanol (17). The Diels-Alder adduct **16** (11.45 g, 93.85mmol) was dissolved in MeOH (50 mL) and CH_2Cl_2 (30 mL). To this mixture, $NaBH_4$ (4g, 103.24 mmol) was added to the resulting solution maintaining at 0 °C and the reaction was continued for 20h (TLC control). After completion of the reaction, solvent was directly evaporated under reduced pressure. Then H_2O was added to quench $NaBH_4$ and resulting solution was extracted with EtOAc. Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate–hexanes (2:3) as eluent furnished the alcohol **17 (**6g, 52%**)** as a mixture of mixture of exo and endo isomers.

(1R*,3aS*,5R*,6aR*)-5-(Dimethoxymethyl)-1-methoxyhexahydro-1*H*-cyclopenta[*c*]furan (18). A magnetically stirred solution of the alcohol **17** (968 mg, 7.81 mmol) in MeOH (30 mL) was cooled to −78 °C, and ozone was bubbled through it until the solution turned light blue. Excess ozone was flushed with oxygen gas and dimethyl sulfide (7 mL, 101 mmol) and cat. H_2SO_4 (4-5 drops) were added to the reaction mixture. The reaction mixture allowed to warm up to rt and stirred for 24h. Solid $NaHCO_3$ was added and the reaction mixture was concentrated under reduced pressure. The residue was taken up in water and extracted with ethyl acetate. The combined organic layer was washed with brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate hexanes (1:9) as eluent furnished the acetal **18** (1160 mg, 73%) as a sticky liquid. Physical appearance: colourless liquid.R_f: 0.5(1:4, EtOAc:Hexanes). IR (neat): 2953, 2907, 2829, 1457, 1364, 1295, 1272, 1239, 1197, 1143, 1115, 1071, 989, 959, 927, 764 cm^{-1}.

^{1}HNMR (400 MHz, $CDCl_3$): δ 4.71 (s, 1H), 4.11 (d, *J* 7.2 Hz, 1H), 3.88 (dd, *J* 8.4, 6.4 Hz, 1H), 3.64 (d, *J* 9.2 Hz, 1H), 3.30 (s, 6H), 3.28 (s, 3H), 2.73-2.65 (m, 1H), 2.56 (q, *J* 9.2 Hz, 1H), 2.23-2.15 (m, 1H), 2.14-2.01 (m, 2H), 1.64-1.07 (m, 2H). ^{13}CNMR (100 MHz, $CDCl_3$, DEPT): δ 110.15 (CH), 107.92 (CH), 72.35 (CH_2), 54.35 (CH_3), 53.24 (CH_3), 53.21 (CH_3), 50.85 (CH), 44.74 (CH), 42.40 (CH), 36.10 (CH_2), 33.39 (CH_2). HRMS (ESI, M+Na): m/z calcd. for $C_{11}H_{20}O_4$ Na 239.1259, found 239.1259.

(3aR*,5R*,6aS*)-5-(Methoxymethyl)hexahydro-1*H*-cyclopenta[c]furan (19). To a cold (0 °C) magnetically stirred solution of the acetal **18** (140 mg, 0.65 mmol) and Et_3SiH (311 µL, 1.94 mmol) in dry CH_2Cl_2 (5 mL) was

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added 1M solution of $TiCl_4$ in CH_2Cl_2 (997 µL, 1.36 mmol) and the resulting mixture was stirred at same temperature for 1h (TLC control). It was then quenched with saturated aq. $NaHCO_3$ (3 mL) at 0 °C and extracted with ethyl acetate. The combined organic layer was washed with brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate–hexanes (1:19) as eluent furnished the product **19** (50 mg, 50%) as a colourless liquid. Physical appearance: colourless liquid. R_f: 0.5(1:19, EtOAc:Hexanes). IR (neat): 2950, 2927, 2854, 1475, 1459, 1388, 1365, 1242, 1193, 1144, 1123, 1089, 1017, 994, 957, 916, 734, 708 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ 3.65 (d, *J* 8.0 Hz, 2H), 3.56 (dd, *J* 8.8, 6.0 Hz, 2H), 3.33 (s, 3H), 3.31 (s, 1H), 2.68-2.64 (m, 2H), 2.15-2.07 (m, 2H), 1.25 (s, 1H),1.05-0.98 (m, 2H), 0.94-0.88 (m, 1H).

^{13}CNMR (100 MHz, $CDCl_3$, DEPT): δ 76.91 (CH_2), 74.54 (2 x CH_2), 59.03 (CH_3), 44.50 (2 x CH), 43.22 (CH), 37.42 (2 x CH_2). HRMS (ESI, M+H^+): m/z calcd. for $C_9H_{17}O_2$ 157.1229, found 157.1225.

(1S*,3aS*,5R*,6aR*)-1-Allyl-5-(1-methoxybut-3-en-1-yl)hexahydro-1*H*-cyclopenta[c]furan (20). To a cold (0 °C) magnetically stirred solution of the acetal **18** (180 mg, 0.83 mmol) and allylstannane (646 µL, 2.08 mmol) in dry CH_2Cl_2 (5 mL) was added 1M solution of $TiCl_4$ in CH_2Cl_2 (1 mL, 1.83 mmol) and the resulting mixture was stirred at same temperature for 40 mins (TLC control). It was then quenched with saturated aq. $NaHCO_3$ (3 mL) at 0 °C and extracted with ethyl acetate. The combined organic layer was washed with brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate–hexanes (1:19) as eluent furnished the bisallyl substituted oxadiquinane **20** (150 mg, 76%) as a colourless liquid. Physical appearance: colourless liquid. R_f: 0.5(1:9, EtOAc:Hexanes). IR (neat): 3072, 3051, 2936, 2855, 1641, 1442, 1353, 1268, 1095, 1000, 914, 743 cm^{-1}. ^{1}HNMR (400 MHz, $CDCl_3$): δ 5.87-5.75 (m, 2H), 5.10-5.03 (m, 4H), 3.98 (t, *J* 8.0 Hz, 1H), 3.66 (q, *J* 6.4 Hz, 1H), 3.50 (dd, *J* 8.8, 4.8 Hz, 1H), 3.35 (s, 3H), 3.06 (q, *J* 5.6 Hz, 1H), 2.74-2.64 (m, 1H), 2.38-2.56 (m, 3H), 2.24-2.16 (m, 2H), 2.14-2.04 (m, 2H), 1.89-1.83 (m, 1H), 1.24-1.03 (m, 2H). ^{13}CNMR (100 MHz, $CDCl_3$, DEPT): δ 135.20 (CH), 134.76 (CH), 116.99 (CH_2), 116.86 (CH_2), 85.57 (CH), 84.12 (CH), 73.59 (CH_2), 57.62 (CH_3), 49.85 (CH), 47.97 (CH), 45.08 (CH), 39.06 (CH_2), 36.70 (CH_2), 35 (CH_2), 34.57 (CH_2). HRMS (ESI, M+Na^+): m/z calcd. for $C_{15}H_{24}O_2Na$ 259.1674, found 259.1674.

((1R*,2S*,4R*)-2-(Hydroxymethyl)-4-(2,4,6-trimethoxybenzyl)cyclopentyl)(2,4,6-trimethoxyphenyl) methanone (22). To a cold (0 °C) magnetically stirred solution of the acetal **18** (80 mg, 0.37 mmol) and 1,3,5-trimethoxybenzene (131 mg, 0.78 mmol) in dry CH_2Cl_2 (5 mL) was added 1M solution of $TiCl_4$ in CH_2Cl_2 (596 µL, 0.81 mmol) and the resulting mixture was stirred at same temperature for 45mins (TLC control). It was then quenched with saturated aq. $NaHCO_3$ (3 mL) at 0 °C and extracted with ethyl acetate. The combined organic layer was washed with brine and dried (anhyd. Na_2SO_4). Evaporation of the solvent under reduced pressure and purification of the residue on a silica gel column using ethyl acetate–hexanes (1:1) as eluent furnished the product **22** (100 mg, 57%) as a white solid. Physical appearance: white crystalline solid. mp 110-112 °C. R_f: 0.5(1:1, EtOAc:Hexanes). IR (neat): 3055, 2987, 2965, 2940, 2839, 2686, 1733, 1681, 1606, 1497, 1466, 1456, 1438, 1420, 1337, 1265, 1228, 1205, 1186, 1155, 1129, 1059, 1043, 1006, 949, 916, 896, 873, 850, 841, 736, 709, 705 cm^{-1}.

^{1}HNMR (400 MHz, $CDCl_3$): δ 6.11 (s, 2H), 6.09 (s, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.78 (s, 6H), 3.76 (s, 6H), 3.74-3.53 (m, 3H), 3.49-3.42 (m, 1H), 2.68-2.63 (m, 1H), 2.44-2.35 (m, 2H), 3.49-3.42 (m, 1H), 2.12-2.01(m, 1H),2.10-1.92 (m, 1H), 1.80-1.73 (m, 1H), 1.46-1.38 (m, 1H). ^{13}CNMR (100 MHz, $CDCl_3$, DEPT): δ 209.21(C), 162.49 (C), 159.16 (C), 158.98 (2 x C), 158.37 (2 x C), 114.92 (C), 111.14 (C), 90.96 (2 x CH), 90.56 (2 x CH), 63.90 (CH_2), 56.02 (2 x CH_3), 55.67 (2 x CH_3), 55.53 (CH_3), 55.38 (CH_3), 55.08 (CH), 45.79 (CH), 39.97 (CH), 38.40 (CH_2), 35.75 (CH_2), 27.50 (CH_2).

HRMS (ESI, M+H^+): m/z calcd. for $C_{26}H_{35}O_8$ 475.2332, found 475.2335.

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Supplementary Material

^{1}H and ^{13}C NMR characterization data of products.

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